SPECIAL ISSUE: **WHAT'S NEXT IN CANCER CARE**

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# Evidence-Based ONCOLOGY™

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## ALSO IN THIS ISSUE


**A MANDATORY MODEL?** HHS Secretary Alex Azar, JD, warned in November that a mandatory model for radiation oncology is coming. Azar said CMS would rethink its policy on bundled payments after abandoning several models under his predecessor, Tom Price, MD. For more, SP572.

**PLOTTING CANCER TRENDS.** Contributor Robin Gelburd, JD, the president of FAIR Health, offers an overview of who gets cancer with an eye toward who will get cancer in the future, based on a review of the group's vast claims database, SP538-SP541.

**ONCOLOGY IN PRACTICE.** Barbara McAneny, MD, well-known for developing the COME HOME model, visited with *Evidence-Based Oncology*™ during her tenure as president of the American Medical Association. She discussed how ever-changing regulations are creating challenges for the practicing oncologist, SP546-SP547.

**COA PAYER EXCHANGE SUMMIT.** From cultural and regulatory roadblocks to value-based agreements, to movement toward Oncology Payment Model 2.0, read our complete coverage from Tysons, Virginia, SP548-SP556.

**CARVE-OUT FOR CAR T.** A presentation at Academy of Managed Care Pharmacy Nexus 2018 outlined how Massachusetts' Medicaid program designed an innovative reimbursement solution for chimeric antigen receptor (CAR) T-cell therapy, SP556.

## POPULATION HEALTH

### Increasing Rates of Cancer Screening

*John B. Kisiel, MD, and Philip Parks, MD, MPH*

#### Introduction

**CANCER REMAINS THE SECOND** leading cause of death in the United States.[1] As 2018 comes to a close, an estimated 1,735,350 new cancer cases will have been diagnosed and 609,640 individuals will have died from the disease.[2] Although cancer therapies continue to improve outcomes, more effective screening technologies—enabling more people to get screened and more cancers detected at an earlier, more curable stage—are needed. Better and more convenient screening tools for a variety of cancer types will help us achieve the targets set forth by leading healthcare organizations. Screening for common cancers is generally cost-effective,[3-5] and an increase in screening rates accompanied by earlier detection of cancer and improved treatment regimens offer the potential to reduce the cancer-related healthcare cost burden through improving outcomes and survival.[6,7]

Staff at Exact Sciences test customer stool samples to screen for colorectal cancer.

CONTINUED ON SP586

## PAYING FOR INNOVATION

### Renting Health vs Buying Cures: How New Financing Tools Can Boost Cancer Therapy Development

*Andrew Smith*

**ANDREW W. LO, PHD,** the Charles E. and Susan T. Harris Professor at the MIT Sloan School of Management, has a wide variety of research interests. He's best known in the healthcare world for ideas that could greatly increase the development of new drugs and access to expensive cures. The director of the MIT Laboratory for Financial Engineering, Lo is a principal investigator at the MIT Computer Science and Artificial Intelligence Laboratory and an affiliated faculty member of the MIT Department of Electrical Engineering and Computer Science. He is a past winner of the Batterymarch, Guggenheim, and Sloan fellowships and has been named one of the 100 most influential people in the world by *TIME*.[1]

CONTINUED ON SP589

## COMMENTARY

### The Future of Cancer Care

*Joseph Alvarnas, MD*

**ONE CAN GET AN EXCELLENT** sense of the pace of cancer care innovation and the controversies and failures that are part of this grand narrative by tracking cancer-related cover stories in *TIME* magazine.[1-10] Dating back 70 years, these cover stories have told the dynamic story of the failed promises, bold advances, and unintended consequences of advances in cancer treatment and their impact upon patients affected by this diverse set of disorders. In reading this series of stories, it is difficult not to wonder how this narrative will continue to evolve over the next 10 to 20 years.

CONTINUED ON SP596

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FROM THE EDITOR-IN-CHIEF


ALVARNAS

# Why the Future Never Arrives

**FOR A RECENT ARTICLE** in *Wired*, "25 Years of WIRED Predictions: Why the Future Never Arrives," David Karpf reviewed every issue in chronological order to get a sense of how accurately the magazine had predicted the future.[1] He found experts and sages to have a relatively poor track record for predicting what will happen. "The mistake that seems most glaring is the magazine's confidence that technology and the economics of abundance would erase social and economic inequality," he wrote.

Karpf's key finding is worth remembering as we consider the future of cancer care. In a time of unprecedented innovation in oncology therapeutics and genomic diagnostics, it is easy for our excitement at these technologies to obscure our view of the gaps in patient access to equitable cancer care, the challenges of paying for ever more expensive treatments, and the lack of transparency around care outcomes. As advances in diagnostic and therapeutic cancer care technologies offer promise to patients in need, without an effective system that can deliver them to patients in a sustainable way, there will be no way to ensure that the promise of these advances translates into realty for patients who need them most.

As Karpf realized, technology alone will not save us. The future of cancer care requires a delivery system that fosters greater patient engagement, including more effective cancer screening; more creative and sustainable ways of funding continued advances; sustainable reimbursement models for innovative therapeutics; and the creation of a more patient-centered ecosystem for care delivery that more effectively meets patients' needs and overcomes barriers to care delivery, including those related to social determinants of health.

In this issue of *Evidence Based Oncology*™, we take the opportunity to both look at the impact of these advances in cancer care and at how our systems of care will need to evolve. Robin Gelburd, JD, president of FAIR Health, reviews claims data to better understand who gets cancer and who is likely to get cancer in the future. In a complementary article, we get a perspective from authors at Mayo Clinic and Exact Sciences on the future of cancer screening. In Andrew Smith's interview with Professor Andrew Lo, of the MIT Sloan School of Management, we learn of some new models for funding drug innovation that may point to a future in which greater patient needs, particularly among patients with rare tumors, may be addressed through a model that differs from that of traditional pharmaceutical research and development. We also have 2 articles that speak toward how we might meet some of the challenges of the high cost of anticancer drugs. Finally, we get both the perspective of the Community Oncology Alliance and Barbara McAneny, MD, a medical oncologist and the current president of the American Medical Association, on their work to foster more effective ecosystems for delivering cancer care.

At the recent Patient Centered Oncology Care® meeting, several expert participants voiced a common sentiment: As oncologists, we are inherently optimistic about the future. The possibilities for patients with cancer have never been brighter. Innovations and diagnosis and cancer therapeutics have changed the prognosis for many patients with advanced cancers and point toward a future with an even more dynamic pace of innovation. As we work together to navigate the challenges of care cost and create more patient-centric systems for care delivery, I am deeply optimistic that patients and their families will benefit tremendously from these advances. A key part of the mission of *Evidence-Based Oncology*™ is to foster discussions among the many cancer care stakeholders whose coordinated efforts are required to achieve this vision of the future. Throughout the next year, we look forward to bringing more of these conversations to you. ◆

*Joseph Alvarnas, MD*
EDITOR-IN-CHIEF

**REFERENCE**

1. Karpf D. 25 years of WIRED predictions: why the future never arrives. *Wired*. September 18, 2018. wired.com/story/wired25-david-karpf-issues-tech-predictions/. Accessed November 28, 2018.

EDITORIAL MISSION

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

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

# Along the MBC journey*– explore Verzenio[1]

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

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

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

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

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

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

**Select Important Safety Information**

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

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

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

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

Lilly

For women with HR+, HER2− MBC

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

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

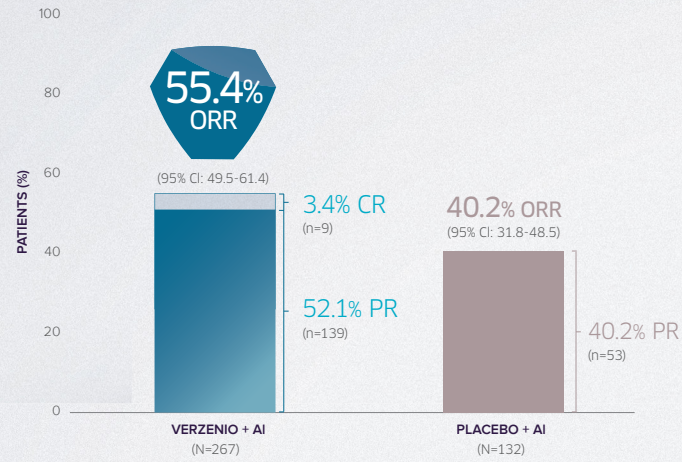
**ITT[1]**

**28.2 months mPFS**

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

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

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




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

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

Exploratory subgroup analyses

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

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

**Liver metastases[13]**

**15.0 months**

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

**Treatment-free interval <36 months[14]**

**29.5 months**

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

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

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

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

## Select Important Safety Information (cont'd)

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

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

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

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

For women with HR+, HER2− MBC

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

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

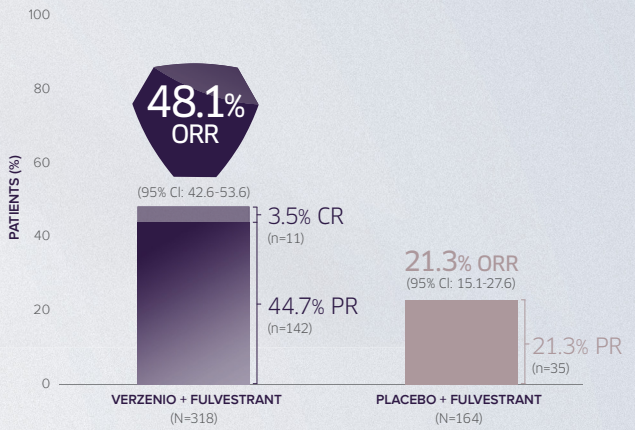
**ITT[1]**

**16.4 months mPFS**

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

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

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




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

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

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

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

### Primary resistance[16]

**15.3 months**

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

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

### Visceral disease[16]

**14.7 months**

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

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

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

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

## Select Important Safety Information (cont'd)

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

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

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

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

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

For heavily pretreated women with HR+, HER2− MBC

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

## ORR[1]

**19.7% ORR**

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

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

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

## Median duration of response (mDoR)[1†]


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

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

## Select Important Safety Information (cont'd)

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

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

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

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

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

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

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

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

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

## CATEGORY 1*

### Abemaciclib (Verzenio) + fulvestrant[19†]

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

### Abemaciclib (Verzenio) + an AI[19†]

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

## CATEGORY 2A‡

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

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

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

## Select Important Safety Information (cont'd)

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

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

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

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

**Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.** Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

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

AL HCP ISI 29AUG2018

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

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

DISCOVER MORE DATA AT
verzenio.com/hcp

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

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



Lilly

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

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

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

## INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

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

**CONTRAINDICATIONS:** None

## WARNINGS AND PRECAUTIONS

### Diarrhea

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

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

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

### Neutropenia

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

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

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

### Hepatotoxicity

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

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

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

### Venous Thromboembolism

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

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



### Embryo-Fetal Toxicity

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

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

## ADVERSE REACTIONS

### Clinical Studies Experience

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

MONARCH 3: VERZENIO in Combination with an Aromatase Inhibitor (Anastrozole or Letrozole) as Initial Endocrine-Based Therapy

*Postmenopausal Women with HR-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting*

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

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

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

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

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

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

| | VERZENIO plus Anastrozole or Letrozole N=327 | | | Placebo plus Anastrozole or Letrozole N=161 | | |
|---|---|---|---|---|---|---|
| | All Grades % | Grade 3 % | Grade 4 % | All Grades % | Grade 3 % | Grade 4 % |
| **Gastrointestinal Disorders** | | | | | | |
| Diarrhea | 81 | 9 | 0 | 30 | 1 | 0 |
| Nausea | 39 | <1 | 0 | 20 | 1 | 0 |
| Abdominal pain | 29 | 1 | 0 | 12 | 1 | 0 |
| Vomiting | 28 | 1 | 0 | 12 | 2 | 0 |
| Constipation | 16 | <1 | 0 | 12 | 0 | 0 |
| **Infections and Infestations** | | | | | | |
| Infections[a] | 39 | 4 | <1 | 29 | 2 | <1 |
| **Blood and Lymphatic System Disorders** | | | | | | |
| Neutropenia | 41 | 20 | 2 | 2 | <1 | <1 |
| Anemia | 28 | 6 | 0 | 5 | 1 | 0 |
| Leukopenia | 21 | 7 | <1 | 2 | 0 | <1 |
| Thrombocytopenia | 10 | 2 | <1 | 2 | <1 | 0 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 40 | 2 | 0 | 32 | 0 | 0 |
| Influenza like illness | 10 | 0 | 0 | 8 | 0 | 0 |

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

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

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

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

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

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

*Creatinine Increased*

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

MONARCH 2: VERZENIO in Combination with Fulvestrant

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

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

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

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



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

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

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

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

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

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

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

[c] Includes neutropenia, neutrophil count decreased.

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

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

[f] Includes platelet count decreased, thrombocytopenia.

[g] Includes asthenia, fatigue.

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

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

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

*Creatinine Increased*

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

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

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

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

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

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

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

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

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



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

| | VERZENIO N=132 | | |
|---|---|---|---|
| | All Grades % | Grade 3 % | Grade 4 % |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | |
| Cough | 19 | 0 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | |
| Arthralgia | 15 | 0 | 0 |
| **Nervous System Disorders** | | | |
| Headache | 20 | 0 | 0 |
| Dysgeusia | 12 | 0 | 0 |
| Dizziness | 11 | 0 | 0 |
| **Skin and Subcutaneous Tissue Disorders** | | | |
| Alopecia | 12 | 0 | 0 |
| **Investigations** | | | |
| Creatinine increased | 13 | <1 | 0 |
| Weight decreased | 14 | 0 | 0 |

[a] Includes asthenia, fatigue.
[b] Includes neutropenia, neutrophil count decreased.
[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[d] Includes platelet count decreased, thrombocytopenia.
[e] Includes leukopenia, white blood cell count decreased.

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

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

*Creatinine Increased*

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

## DRUG INTERACTIONS

### Effect of Other Drugs on VERZENIO

CYP3A Inhibitors

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

*Ketoconazole*

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

*Other Strong CYP3A Inhibitors*

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

*Moderate CYP3A Inhibitors*

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements, if necessary.

Strong and Moderate CYP3A Inducers

Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (*see* Data). Advise pregnant women of the potential risk to a fetus.

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

Data

*Animal Data*

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

### Lactation

Risk Summary

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

### Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

*Females*

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

Infertility

*Males*

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

### Pediatric Use

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

### Geriatric Use

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

### Renal Impairment

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

### Hepatic Impairment

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

## OVERDOSAGE

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

Rx only.

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

**Eli Lilly and Company, Indianapolis, IN 46285, USA**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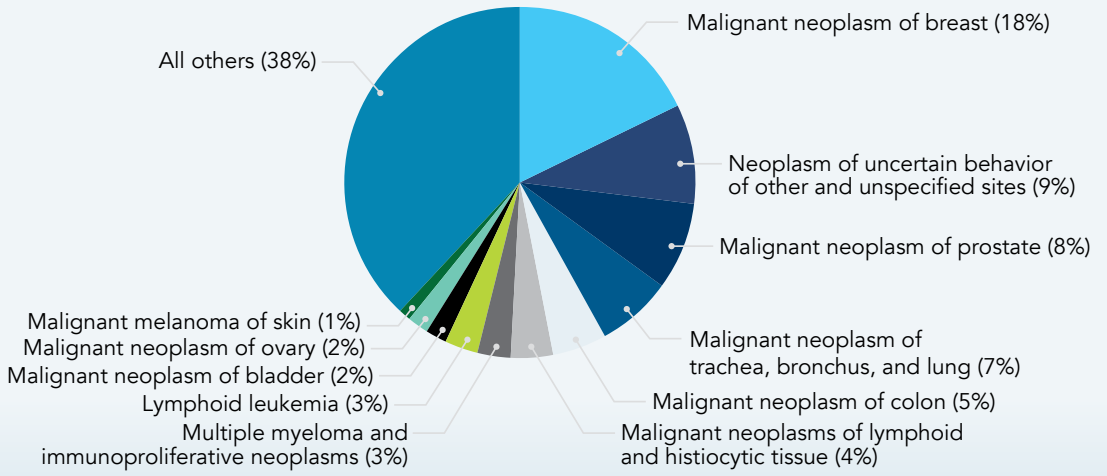


Distribution of Claim Lines With Cancer Diagnoses, 2007-2017
Source: FAIR Health database

PIE CHART SOURCE: FAIR HEALTH DATABASE

## FEATURES



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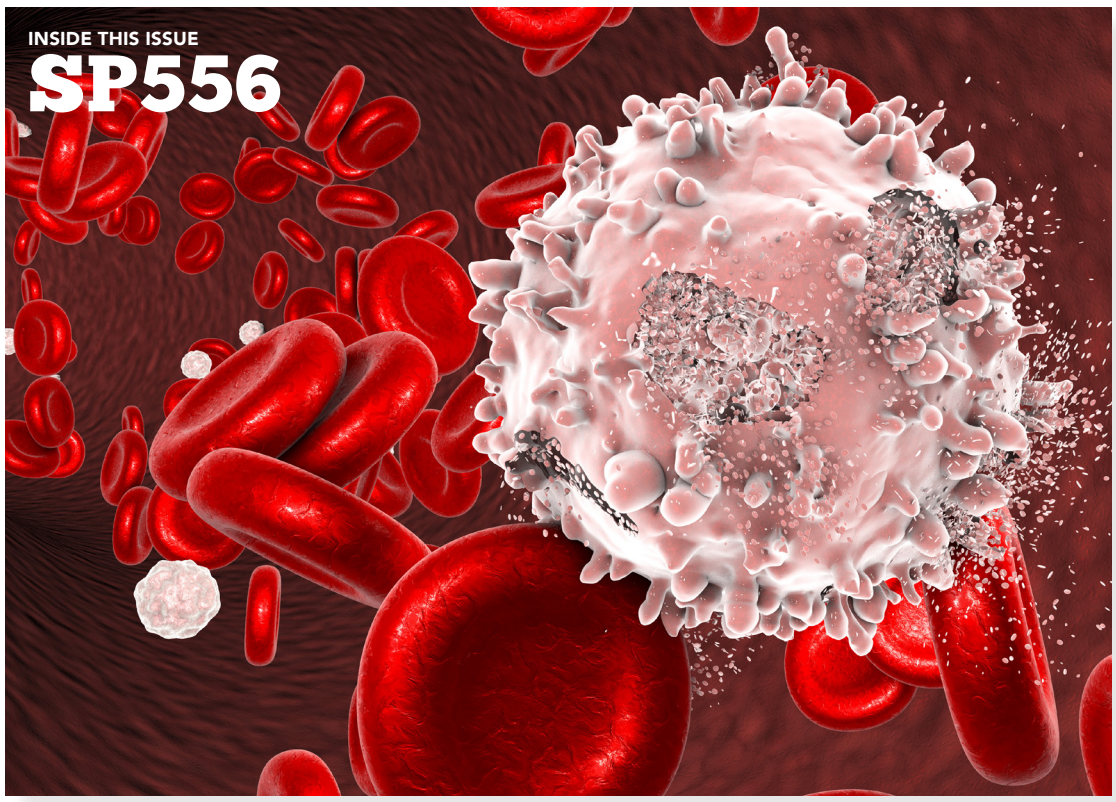


A leukemia cancer cell in the blood stream. Chimeric antigen receptor T-cell therapy is poised to revolutionize treatment of certain treatment resistant leukemias and lymphomas, but at a high cost to state Medicaid programs.





FROM THE CHAIRMAN

# In Cancer Care, New Treatments, New Players, New Ways to Pay

**CANCER CARE, TO PUT IT SIMPLY,** is not what it used to be. Our editor-in-chief Joseph Alvarnas, MD, chronicles the journey of cancer from an acute, terminal condition to, for many, a chronic disease that can be managed for years. Today, he writes, we are making the next leap. With cell and gene therapies, the age of the 1-time treatment has arrived; more and more, we can give cancer a powerful punch that lasts for years or even a lifetime. Technology leaders, like the founders of Flatiron Health, which didn't exist a decade ago, now help oncologists tailor treatment plans, conduct research, and keep up with changes in government reimbursement systems.

Cutting-edge treatments, which include customized chimeric antigen receptor T-cell therapies, come with a few catches, however. They are tricky to administer, and they are not cheap. So far, science is racing ahead faster than the payment models, including those run by the government. As Novartis CEO Vas Narasimhan said recently, the new treatments are pushing the limits of the old system, and the healthcare community is split on how to move forward with a value-based replacement.[1]

As we read in this issue about future cancer care models, new thinkers are stepping up. Andrew W. Lo, PhD, of MIT, has tested models for spreading the risk of developing new treatments across a portfolio so that hard-to-finance pediatric treatments can find investors. Value-based contracts may be designed with payment terms that resemble mortgages so that paying for a cure does not mean bankruptcy. More cancer care and preventive services are being built with the consumer in mind. As our Oncology Stakeholders Summit revealed, younger patients will demand solutions, like hearing from their doctor via email or getting care at their local pharmacy.

Getting from today's payment system to tomorrow's will not be easy. Physicians are experiencing burnout as hours with electronic health records replace those with patients and government leaders design payment models around erroneous assumptions about life in a small oncology practice. American Medical Association President McAneny, MD, who visited our office for an interview with *Evidence-Based Oncology*™, explained how physicians are being asked to take on financial risk for things they cannot control or even predict. As Dr Alvarnas warns, if we cannot fix the reimbursement conundrum, we risk slowing the tide of innovation.

The wonders of cancer care offer much to excite us. A century after scientists first conceived of harnessing the immune system to battle tumors, the word "cure" is heard, if quietly. But as we relish the knowledge gained, we must pause before we lose the human infrastructure our country will need to bring the future to everyone. ◆

REFERENCE

1. Narasimhan V. Novartis CEO says four factors can help with pricing and payment of lifesaving cell and gene therapies. CNBC website. www.cnbc.com/2018/11/26/novartis-ceo-on-how-to-price-lifesaving-cell-and-gene-therapies.html. Published and accessed November 26, 2018.

Sincerely,

*Mike Hennessy, Sr*
CHAIRMAN AND CEO

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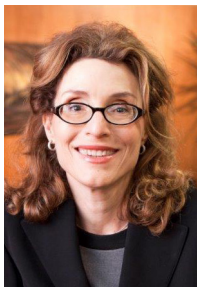
# Cancer Today and Cancer Tomorrow: Analysis of US Cancer Claims, 2007-2017

*Robin Gelburd, JD*



**GELBURD**

*Robin Gelburd, JD, is the president of FAIR Health.*

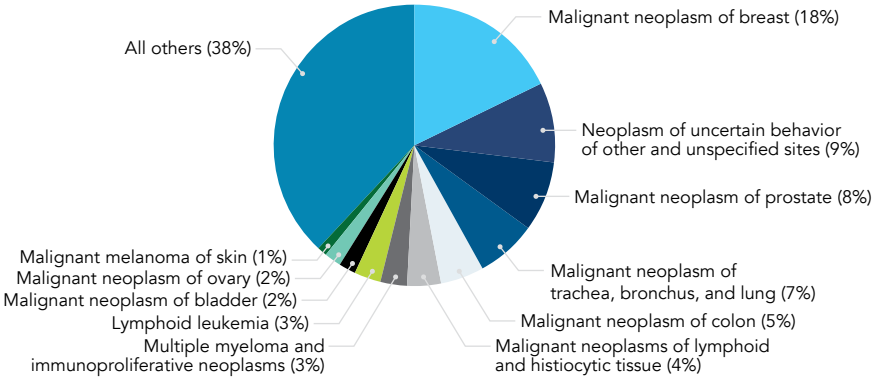
**CANCER IS THE SECOND** leading cause of death in the United States and a major public health concern.[1,2] Claims data from private payers can illuminate many aspects of cancer prevalence and trends over the past decade. In this article, we use data from our FAIR Health database of over 27 billion privately billed healthcare claims to identify the cancer diagnosis categories with the highest percentage of claim lines among all cancer diagnosis categories. As indicators of trends that may continue into the future, we also identify the cancer diagnosis categories with the greatest recent increases in relative claim line volume. In addition, we use claims data to shed light on patterns related to geography, gender, and age from pediatric patients to senior citizens. These patterns include the states with the most, and fewest, claims for certain cancer diagnoses as a percentage of all other medical claims in 2007 and 2017; the state referenced is the state where the services were performed and not where the patient resides.

## Most Common Cancers Associated With Private Claims, 2007-2017

As shown in **Figure 1**, from 2007 to 2017, the most common cancer diagnoses associated with private insurance claim lines were, in order from most to least common:

1. Breast cancer
2. Prostate cancer
3. Cancer of the trachea, bronchus, and lung
4. Colon cancer
5. Cancer of lymphoid and histiocytic tissue
6. Multiple myeloma and immunoproliferative cancer
7. Lymphoid leukemia
8. Bladder cancer
9. Ovarian cancer, and
10. Malignant melanoma of skin

**FIGURE 1.** Distribution of Claim Lines With Cancer Diagnoses, 2007-2017




Source: FAIR Health database

**FIGURE 2.** Most Frequently Listed Cancer Diagnoses on Claim Lines for Services by Year, 2007-2017




Source: FAIR Health database

Breast cancer, at 18%, had the highest percentage of all cancer diagnosis claim lines from 2007 to 2017. Prostate cancer; trachea, bronchus, and lung cancer; and colon cancer, respectively, were second, third and fourth, with 8%, 7%, and 5% of all cancer claim lines. We did not include the category "neoplasms of uncertain behavior" as these lesions may or may not become malignant over time.

As in our list, the American Cancer Society (ACS) places breast cancer at the top of its list of specific cancers by estimated new cases in 2018.[3] In the ACS list, lung and bronchus cancer rank second and prostate cancer is third compared with third and second, respectively, in our list. These and other variances may be attributable to differences in methodology or in the data underlying the studies. For example, although the ACS statistics are based on cancer registry data on unique individuals with a cancer diagnosis, we measured the number of claim lines representing services rendered to individuals with a particular cancer diagnosis.

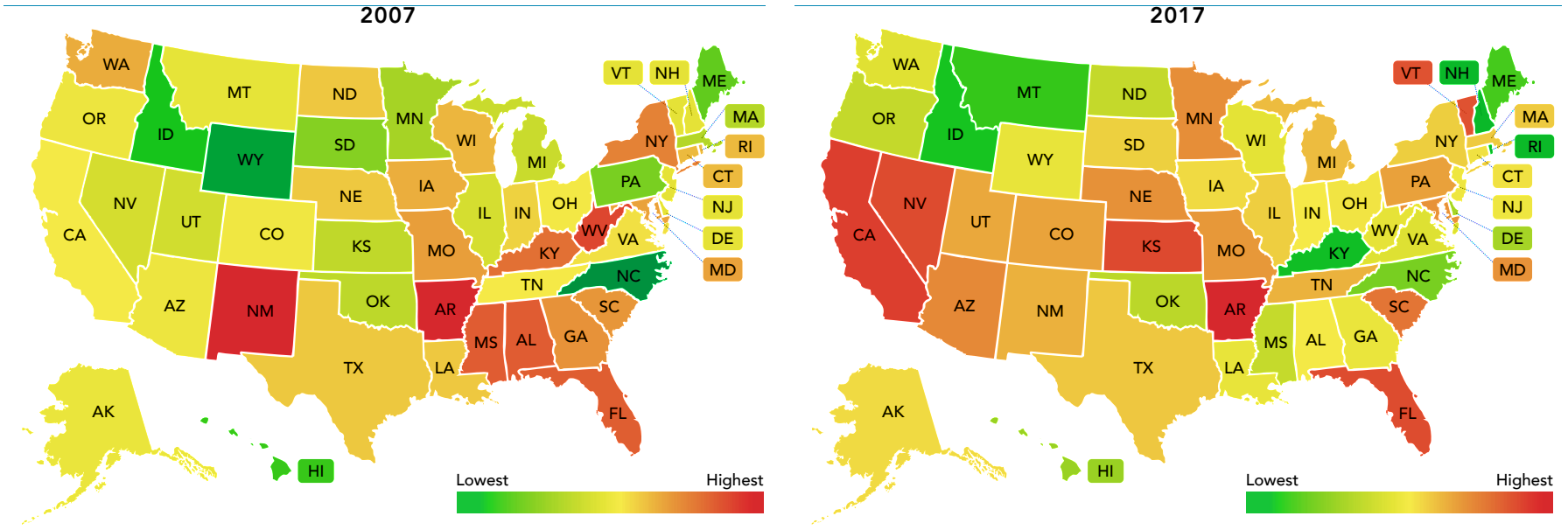
Our analysis shows that, for the most part, there was only slight variation from 2007 to 2017 in the services associated with the most frequently occurring cancer diagnoses (**Figure 2**). The category that has shown the greatest increase in the number of claim lines at 51% is "multiple myeloma and immunoproliferative cancers," a category that includes lymphoma and a variety of leukemia. One other category, lymphoid leukemia, had a slight increase in claim lines.

## Breast Cancer

The maps below show the state-by-state distribution of breast cancer claim lines in 2007 and 2017 (**Figures 3** and **4**). Breast cancer diagnosis claim lines in 2007 were widely dispersed across the country. The states with the highest number of claim lines associated with breast cancer diagnoses as a percentage of all medical claim lines were New Mexico, Arkansas, West Virginia, and Mississippi. Washington, DC also made this list.

In 2017, although breast cancer diagnosis–related claim lines were still widely distributed, the dispersal of cases was somewhat different. The highest percentage of claim lines were seen in Arkansas; California; Washington, DC; Kansas; and Nevada.

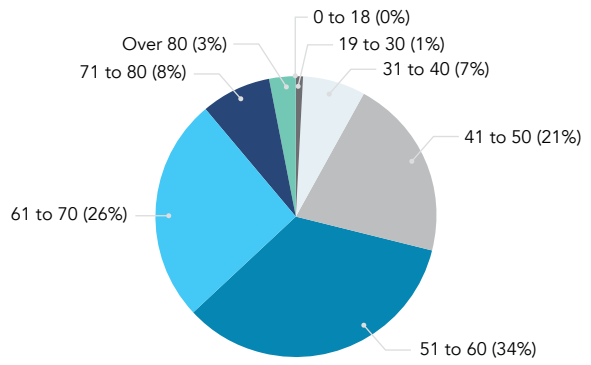
**FIGURES 3 AND 4.** Claim Lines Associated With Breast Cancer Diagnoses by State




The above figures reflect cancer claims as a percentage of all medical claim lines by state, 2007 and 2017

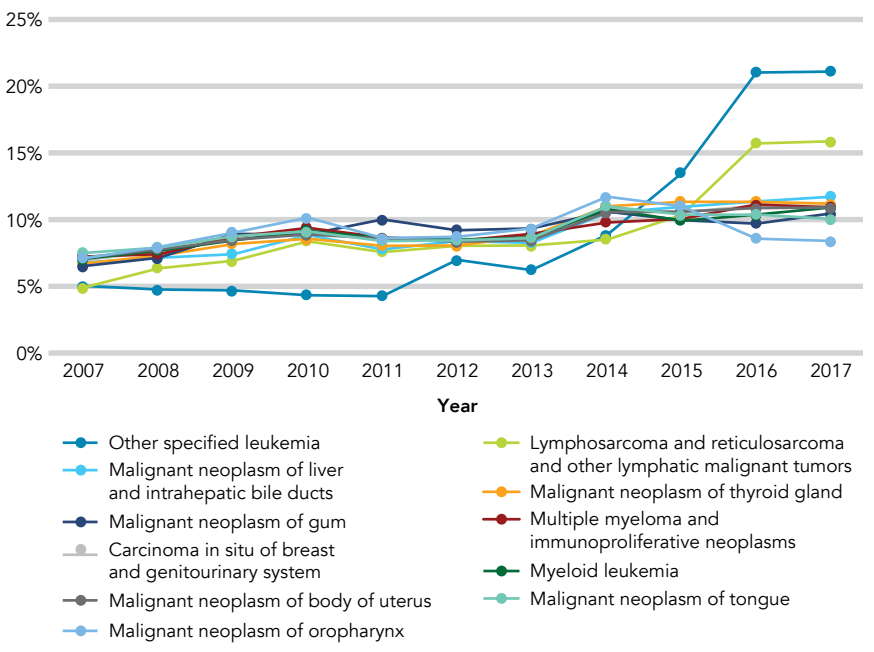
Source: FAIR Health database

**FIGURE 5.** Claim Lines With Breast Cancer Diagnoses by Age Group (in Years), 2017




Source: FAIR Health database

**FIGURE 6.** Cancer Diagnoses With the Greatest Increase in Claim Lines, 2007-2017




Source: FAIR Health database

As seen in **Figure 5**, in 2017, claim lines associated with breast cancer diagnoses were submitted most frequently for patients 51 to 60 years of age; 34% of total claim lines were associated with that age group. Individuals 61 to 70 years of age accounted for 26% of claim lines, followed by those 41 to 50 years of age, with 21% of claim lines. (Note that the claims data analyzed in this article do not include traditional Medicare but rather private insurance, including Medicare Advantage. If traditional Medicare data were included, claim line distribution might differ.)

## Prostate Cancer

ACS statistics show that 6 of 10 cases of prostate cancer are diagnosed in men 65 and older and that this cancer is rarely seen in men under 40.[4] Our data likewise support the association of prostate cancer with an older age group. In our analysis, claim lines for individuals 61 to 70 years dominate prostate cancer–related claims, representing 43% of the total. Claim lines for individuals over age 70 make up 32% of the distribution, and claim lines for individuals 51 to 60 years constitute 23%. Individuals younger than age 50 represent just 2.2% of total prostate cancer claim lines.

## Trachea, Bronchus, and Lung Cancer

In 2007, the highest number of claim lines associated with diagnoses of trachea, bronchus, and lung cancer as a percentage of the total claim lines was found in Kentucky, Arkansas, Vermont, Delaware, and Nevada. In 2017, the states with the most claim lines associated with these diagnoses were Arkansas, Vermont, Iowa, Kansas, and Pennsylvania; Kentucky fell to number 16 in the list. This correlates with Surveillance, Epidemiology, and End Results Program data showing lung cancer incidence in Kentucky has decreased markedly since 2010.[5]

## Colon Cancer

In 2007, colon cancer–related claim lines were somewhat geographically concentrated. The 5 states with the highest percentage of colon cancer–associated claim lines were Arkansas, Mississippi, Kentucky, West Virginia, and New Mexico, with all but New Mexico located in the South. Colon cancer claim lines were more widely dispersed in 2017, when the 5 states with the highest prevalence were Michigan, Arkansas, Kansas, Pennsylvania, and Florida.

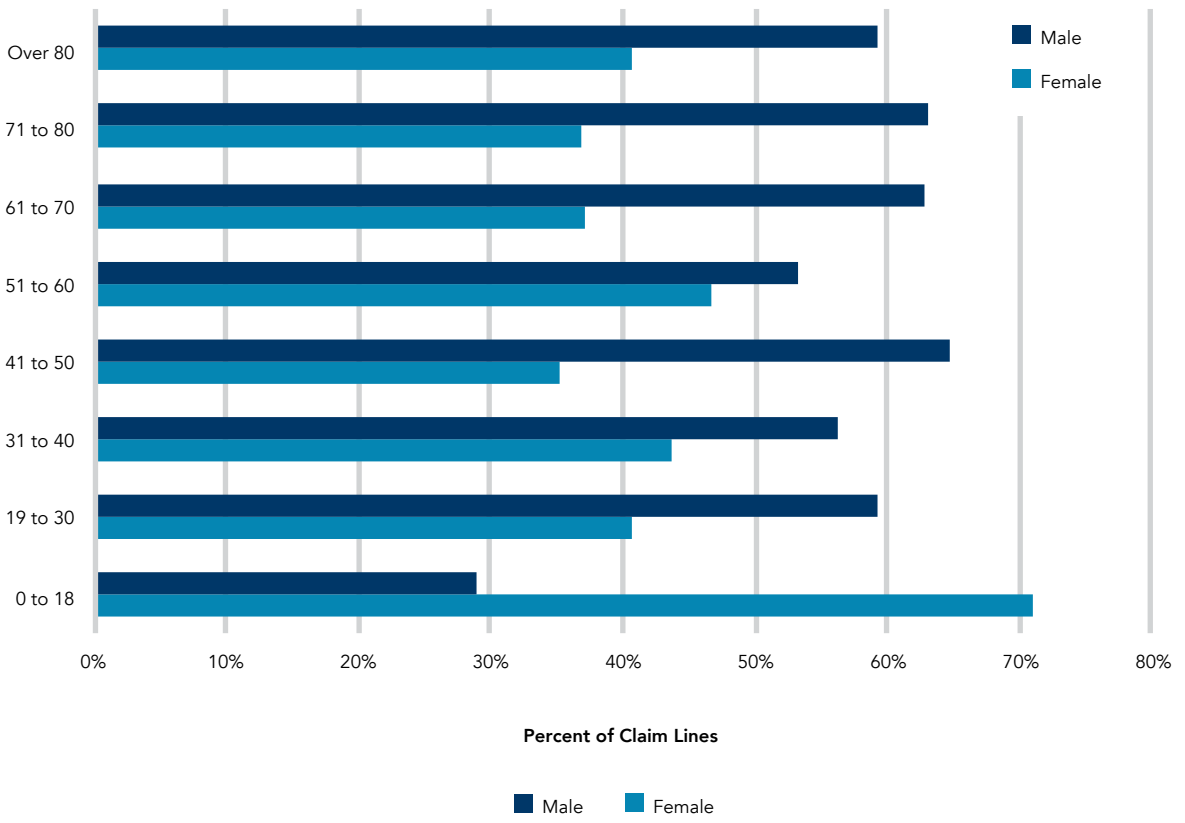
In 2017, individuals in the 51-to-60 age group accounted for 34% of claim lines associated with colon cancer diagnoses; individuals in the 61-to-70 age group accounted for 27%. At 16% of the total, colon cancer–associated claim lines were less common but still notable in the 41-to-50 age group.

Colon cancer is more prevalent in males than in females in every age category, with males taking a 54% share of the claim lines among all age groups.

## Cancers With the Greatest Increase in Claim Lines, 2007-2017

The sharpest growth in claim lines from 2007 to 2017 occurred in 2 cancer categories (**Figure 6**). With a 328% increase, claim lines associated with "other specified »

**FIGURE 7.** Distribution of Claim Lines for Other Leukemias of Specified Cell Type by Age Group (in Years) and Gender




Source: FAIR Health database

leukemia," which includes erythremia and megakaryocytic leukemia, had the greatest growth of all categories. The second greatest increase in this period was in "lymphosarcoma and reticulosarcoma and other lymphatic malignant tumors," which increased 230%.

Claim lines for liver, thyroid, and gum cancer increased 75%, 65%, and 64%, respectively, from 2007 to 2017. Claim lines related to a diagnosis of "multiple myeloma and immunoproliferative neoplasms" increased 51%. This diagnosis is also found among the most common cancer diagnoses associated with private insurance claim lines.

## Other Specified Leukemias

Our data show a distinctive gender pattern for "other specified leukemias," which includes tumors of the hematopoietic and lymphoid tissues (**Figure 7**). In this diagnostic group, pediatric patients (aged 0-18) are overwhelmingly female (71%) and all other age groups are predominantly male (55%-65%).

Pediatric patients account for 16% of diagnosis-related claims in the other specified leukemias category. The 51-to-60, 61-to-70, and 71-to-80 age groups have similar distributions, accounting for 17%, 23%, and 14% of claim lines, respectively. The diagnosis appears to be uncommon in individuals 19 to 50 years of age.

## Lymphosarcoma and Reticulosarcoma

In 2007, the highest percentage of medical claim lines related to the diagnosis "lymphosarcoma and reticulosarcoma and other lymphatic malignant tumors" was found in Iowa; Wisconsin; Washington, DC; Louisiana; and Texas (**Figure 8**). The lowest percentages were found in Wyoming, Hawaii, Maine, Montana, Vermont, and North Carolina.

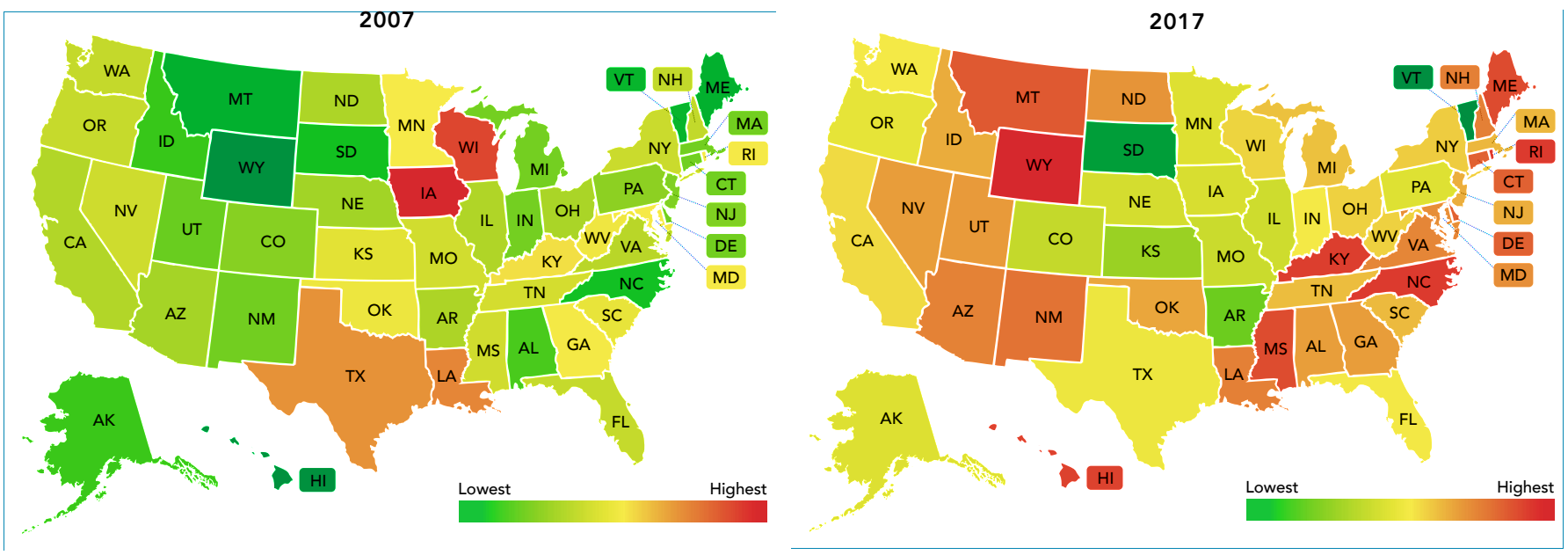
In 2017, claim lines for this diagnosis were much more widely dispersed. The states with the highest percentage of claim lines for this category were Rhode Island, Wyoming, North Carolina, Kentucky, and Hawaii (**Figure 9**). Interestingly, Wyoming, North Carolina, and Hawaii were among the states with the fewest claims for this category in 2007.

## Liver Cancer

"Neoplasms of the liver and intrahepatic bile ducts," liver cancer, is a diagnostic category in which the landscape has changed greatly in the last decade. In 2007, diagnosis-related claim lines were not widespread and were seen most frequently in Vermont; Nevada; Washington, DC; Arkansas; and New York (**Figure 10**). By 2017, liver cancer–related claims were dispersed throughout the country (**Figure 11**). The states with the highest prevalence in 2017 were South Dakota, New Hampshire, North Dakota, Rhode Island, and Mississippi. The change in distribution may be related to an increase in medical services available for liver cancer.

Claims data show liver cancer is found most frequently in individuals aged 61 to 70 years, who

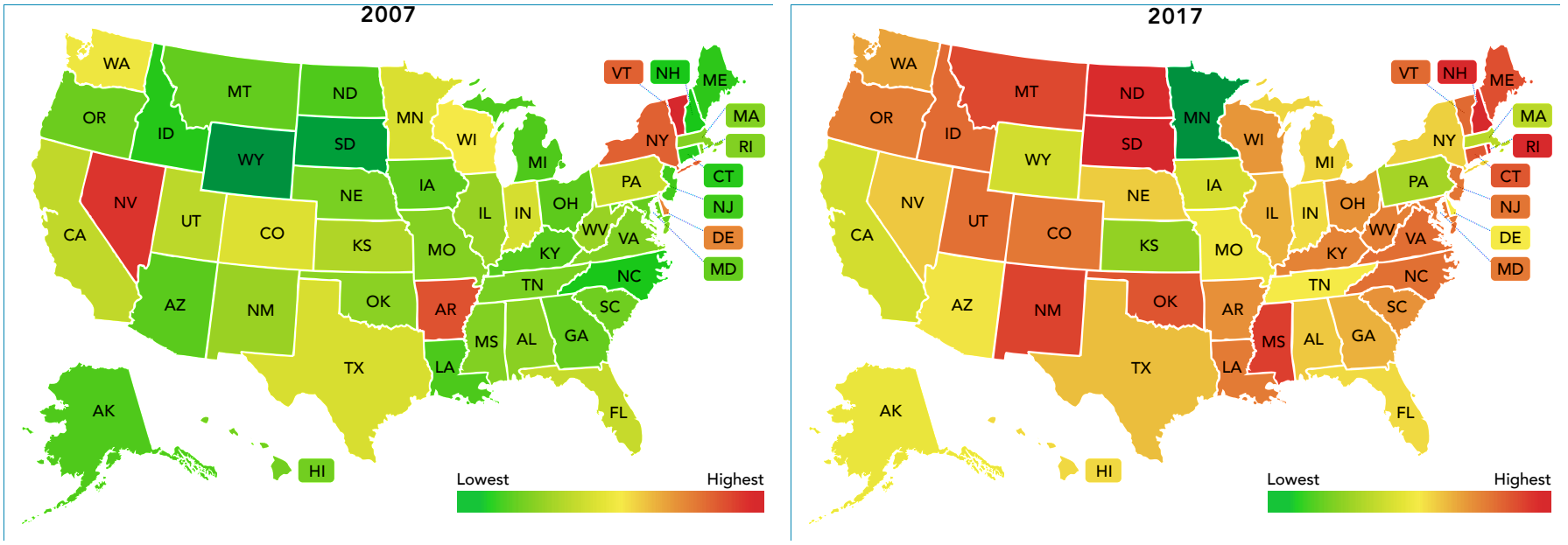
**FIGURES 8 AND 9.** Claim Lines Associated With Lymphosarcoma and Reticulosarcoma and Other Lymphatic Malignant Tumors Diagnoses




The above figures reflect claims as a percentage of all medical claim lines by state, 2007 and 2017

Source: FAIR Health database

**FIGURES 10 AND 11.** Claim Lines Associated With Liver Cancer Diagnoses as a Percentage of Medical Claim Lines by State




Source: FAIR Health database

**FIGURE 12.** Claim Lines With Liver Cancer Diagnoses by Age Group (in Years), 2017

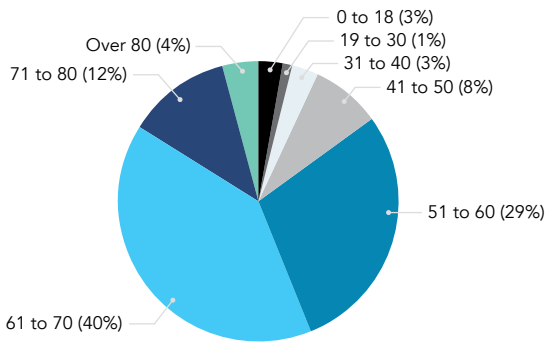
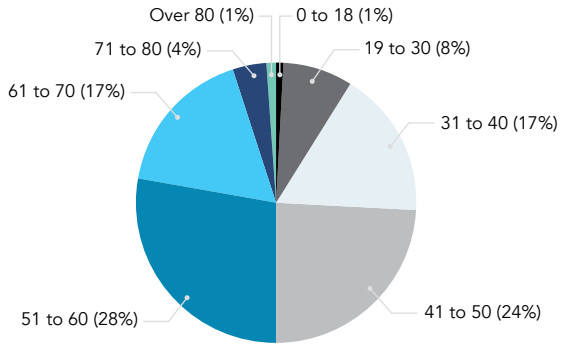



**FIGURE 13.** Claim Lines With Thyroid Cancer Diagnoses by Age Group (in Years), 2017




Source: FAIR Health database

account for 40% of the total (**Figure 12**). Individuals 51 to 60 years of account for another 29% of claims. Risk of liver cancer is increased by chronic hepatitis C (HCV) infection, the prevalence of which has been found to be highest among adults born from 1945 to 1965 due to the large number of HCV infections that occurred during the 1970s and 1980s.[6]

## Thyroid Cancer

Individuals in the 41-to-50 and 51-to-60 age groups together account for 52% of claims (**Figure 13**). Individuals in the 19-to-30 and 31-to-40 age groups account for 25% of claims, which is high for those demographics compared with the percentage of new cancers overall in younger adults: SEER data show individuals aged 20 to 44 years account for only about 8% of new cancers.[7] Thyroid cancer is found overwhelmingly in females (75% of all diagnosis-related claim lines) compared with males. This correlates with data from the American Society of Clinical Oncology, which show females account for 3 of 4 thyroid cancer diagnoses and two-thirds of all thyroid cancers are diagnosed in individuals aged 20 to 55.[8]

## Conclusions

Today, breast cancer leads the list of the most common cancer diagnoses, as reflected in private healthcare claims across the country. From 2007 to 2017, there has been only slight variation in the frequency of claim lines for those diagnoses. How cancer will change tomorrow is uncertain, but from 2007 to 2017, the highest growth in claim lines for cancer was in the categories "other specified leukemia" and "lymphosarcoma and reticulosarcoma and other lymphatic malignant tumors." FAIR Health releases findings from our comprehensive claims collection in order to help fuel further research. ◆

### AUTHOR INFORMATION

Robin Gelburd, JD, is the president of FAIR Health, a national independent nonprofit organization with the mission of bringing transparency to healthcare costs and health insurance information. FAIR Health possesses the nation's largest collection of private healthcare claims data, which includes over 27 billion claim records contributed by payers and administrators who insure or process claims for private insurance plans covering more than 150 million individuals. FAIR Health also holds separate data representing the experiences of all individuals enrolled in traditional Medicare, from 2013 to the present, as well as Medicare Advantage enrollees represented in its private claims data. Certified by the Centers for Medicare & Medicaid Services as a Qualified Entity, FAIR Health receives all of Medicare Parts A, B, and D claims data for use in nationwide transparency efforts. Ms. Gelburd is a nationally recognized expert on healthcare policy, data and transparency.

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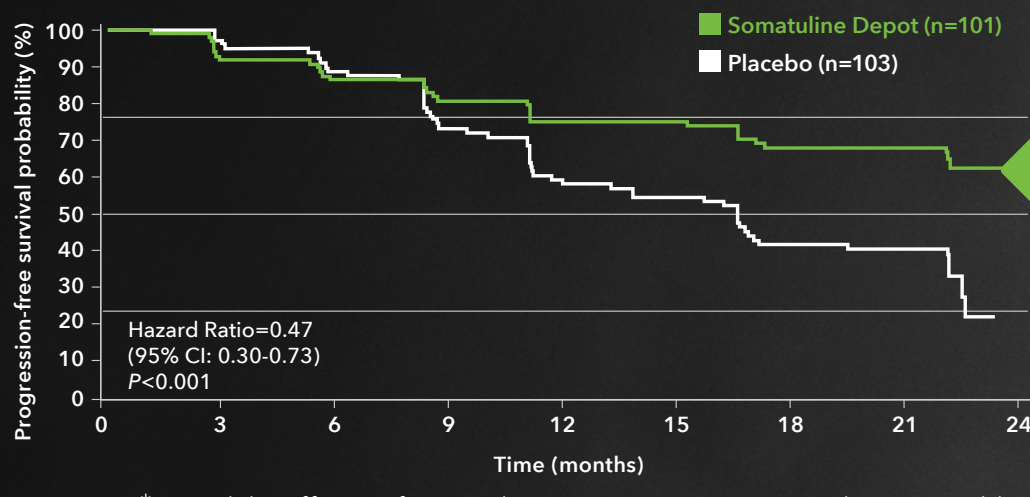
## 1 PFS IN GEP-NETs

### Progression-free Survival (PFS) in Adult Patients With Unresectable, Well- or Moderately-Differentiated, Locally Advanced or Metastatic GEP-NETs[1]

Primary Endpoint: Median PFS for Somatuline Depot vs Placebo[1,2]




**53%**
reduction in risk of progression or death with Somatuline Depot vs placebo[1]

CLARINET* tested the efficacy of Somatuline Depot in 204 patients with unresectable, well- or moderately-differentiated, metastatic or locally advanced GEP-NETs. Patients received Somatuline Depot 120 mg or placebo every 4 weeks until disease progression, unacceptable toxicity, or a maximum of 96 treatment weeks. Patients were required to have nonfunctioning tumors without hormone-related symptoms. Primary efficacy outcome was PFS, defined as time to either disease progression† or death.[1,2]

- The median PFS for Somatuline Depot was not yet reached at 22 months (95% CI: NE-NE) vs 16.6 months for placebo (95% CI: 11.2-22.1); HR=0.47 (95% CI: 0.30-0.73; *P*<0.001); number of events with Somatuline Depot=32 (31.7%) vs placebo=60 (58.3%)[1]

**Adverse Reactions Reported in CLARINET Study**

The adverse reactions occurring in ≥5% of Somatuline Depot patients and at a higher rate than placebo were abdominal pain (34%), musculoskeletal pain (19%), vomiting (19%), headache (16%), injection site reaction (15%), hyperglycemia (14%), hypertension (14%), cholelithiasis (14%), dizziness (9%), depression (7%), and dyspnea (6%).[1]

*CLARINET: **C**ontrolled Study of **L**anreotide **A**ntiproliferative **R**esponse **I**n **N**euro**E**ndocrine **T**umors, a randomized, double-blind, placebo-controlled trial.
†Assessed by a central independent radiological review in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

## IMPORTANT SAFETY INFORMATION

**Contraindications**

- SOMATULINE DEPOT is contraindicated in patients with hypersensitivity to lanreotide. Allergic reactions (including angioedema and anaphylaxis) have been reported following administration of lanreotide.

**Warnings and Precautions**

- **Cholelithiasis and Gallbladder Sludge**
  - SOMATULINE DEPOT may reduce gallbladder motility and lead to gallstone formation.
  - Periodic monitoring may be needed.
- **Hypoglycemia or Hyperglycemia**
  - Pharmacological studies show that SOMATULINE DEPOT, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Patients treated with SOMATULINE DEPOT may experience hypoglycemia or hyperglycemia.
  - Blood glucose levels should be monitored when SOMATULINE DEPOT treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.
- **Cardiovascular Abnormalities**
  - SOMATULINE DEPOT may decrease heart rate.
  - In patients in the GEP-NET pivotal trial, 23% of SOMATULINE DEPOT-treated patients had a heart rate of less than 60 bpm compared to 16% of placebo-treated patients. The incidence of bradycardia was similar in the treatment groups. Initiate appropriate medical management in patients with symptomatic bradycardia.
  - In patients without underlying cardiac disease, SOMATULINE DEPOT may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to treatment, sinus bradycardia may occur. Care should be taken when initiating treatment in patients with bradycardia.

## The 1st and Only SSA‡ That Is FDA-approved to Treat Both[1]:

- Adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival; **and**
- Adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy

‡SSA=somatostatin analog.

# 2 CARCINOID SYNDROME

### Reducing the Frequency of Short-acting SSA Rescue Therapy[1]

Somatuline Depot is FDA-approved to treat adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

Carcinoid syndrome trial adverse events (AEs) occurring in ≥5% of Somatuline Depot-treated patients and ≥5% more than in placebo-treated patients were headache (12%), dizziness (7%), and muscle spasm (5%); AEs were generally similar to those in the GEP-NETs trial.

# 3 DELIVERY

### Deep Subcutaneous Injection[1]

- Provided in a prefilled, low-volume, single-use syringe
- The recommended dose is 120 mg/0.5 mL, administered by a healthcare provider every 4 weeks
- No reconstitution required
- If your patient is already being treated for GEP-NETs, do not administer an additional dose for the treatment of carcinoid syndrome

Safe'n'Sound® syringe technology

Safe'n'Sound is a registered trademark of *NEMERA LA VERPILLIERE SAS.*

Not actual size.

## IMPORTANT SAFETY INFORMATION (continued)

**Most Common Adverse Reactions**

- **GEP-NETs:** Adverse reactions occurring in greater than 10% of patients who received SOMATULINE DEPOT in the GEP-NET trial were abdominal pain (34%), musculoskeletal pain (19%), vomiting (19%), headache (16%), injection site reaction (15%), hyperglycemia (14%), hypertension (14%), and cholelithiasis (14%).
- **Carcinoid Syndrome:** Adverse reactions occurring in the carcinoid syndrome trial were generally similar to those in the GEP-NET trial. Adverse reactions occurring in greater than 5% of patients who received SOMATULINE DEPOT in the carcinoid syndrome trial and occurring at least 5% greater than placebo were headache (12%), dizziness (7%) and muscle spasm (5%).

**Drug Interactions:** SOMATULINE DEPOT may decrease the absorption of cyclosporine (dosage adjustment may be needed); increase the absorption of bromocriptine; and require dosage adjustment for bradycardia-inducing drugs (e.g., beta-blockers).

**Special Populations**

- **Lactation:** Advise women not to breastfeed during treatment and for 6 months after the last dose.

**To report SUSPECTED ADVERSE REACTIONS,** contact Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

**Learn more at SomatulineDepotHCP.com**

IPSEN Innovation for patient care

Somatuline® Depot (lanreotide) Injection 120 mg

**SOMATULINE® DEPOT (lanreotide) injection, for subcutaneous use**

**Brief Summary of full Prescribing Information—GEP-NETs and Carcinoid Syndrome. See full Prescribing Information. Rx Only.**

## INDICATIONS AND USAGE:

**Gastroenteropancreatic Neuroendocrine Tumors:** for the treatment of adults with unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

**Carcinoid Syndrome:** for the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy.

## DOSAGE AND ADMINISTRATION

**Important Administration Instructions** *For deep subcutaneous injection only;* intended for administration by a healthcare provider. The recommended dosage of SOMATULINE DEPOT is 120 mg administered every 4 weeks by deep subcutaneous injection. If patients are already being treated with SOMATULINE DEPOT for GEP-NETs, do not administer an additional dose for the treatment of carcinoid syndrome. For preparation and administration instructions, refer to the full Prescribing Information.

**CONTRAINDICATIONS:** SOMATULINE DEPOT is contraindicated in patients with history of a hypersensitivity to lanreotide. Allergic reactions (including angioedema and anaphylaxis) have been reported following administration.

## WARNINGS AND PRECAUTIONS

**Cholelithiasis and Gallbladder Sludge:** SOMATULINE DEPOT may reduce gallbladder motility and lead to gallstone formation; therefore, patients may need to be monitored periodically.

**Hyperglycemia and Hypoglycemia:** Patients treated with SOMATULINE DEPOT may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

**Cardiovascular Abnormalities:** In patients without underlying cardiac disease, SOMATULINE DEPOT may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to SOMATULINE DEPOT treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with SOMATULINE DEPOT in patients with bradycardia. Cases of hypertension have been reported. In 81 patients with GEP-NETs and baseline heart rates of 60 beats per minute (bpm) or greater treated with SOMATULINE DEPOT, the incidence of heart rate less than 60 bpm was 23% (19/81) as compared to 16% (15/94) of placebo treated patients; 10 patients (12%) had documented heart rates less than 60 bpm on more than one visit. The incidence of documented episodes of heart rate less than 50 bpm as well as the incidence of bradycardia reported as an adverse event was 1% in each treatment group. Initiate appropriate medical management in patients who develop symptomatic bradycardia.

## ADVERSE REACTIONS

GEP-NETs: The safety of SOMATULINE DEPOT 120 mg for the treatment of patients with GEP-NETs was evaluated in a double-blind, placebo-controlled trial. Patients were randomized to receive SOMATULINE DEPOT (N=101) or placebo (N=103) administered by deep subcutaneous injection once every 4 weeks. The data below reflect exposure to SOMATULINE DEPOT in 101 patients with GEP-NETs, including 87 patients exposed for at least 6 months and 72 patients exposed for at least 1 year (median duration of exposure 22 months). Patients treated with SOMATULINE DEPOT had a median age of 64 years (range 30 to 83 years), 53% were men and 96% were Caucasian. Eighty-one percent of patients (83/101) in the SOMATULINE DEPOT arm and 82% of patients (82/103) in the placebo arm did not have disease progression within 6 months of enrollment and had not received prior therapy for GEP-NETs. The rates of discontinuation due to treatment-emergent adverse reactions were 5% (5/101 patients) in the SOMATULINE DEPOT arm and 3% (3/103 patients) in the placebo arm. **Adverse reactions occurring in 5% and greater of patients receiving SOMATULINE DEPOT 120 mg (N=101)** rated as either Any or Severe (defined as hazardous to well-being, significant impairment of function or incapacitation) **and at a higher rate than Placebo (N=103)**, also rated as either Any or Severe, respectively, were: **Any Adverse Reactions (88%, 26%, 90%, 31%)**; Abdominal pain: includes upper/lower, abdominal discomfort (34%*, 6%*, 24%*, 4%); Musculoskeletal pain: includes myalgia, musculoskeletal discomfort, musculoskeletal pain, back pain (19%*, 2%*, 13%*, 2%*); Vomiting (19%*, 2%*, 9%*, 2%*); Headache (16%, 0%, 11%, 1%); Injection site reaction: includes infusion site extravasation, injection site discomfort, injection site granuloma, injections site hematoma, injection site hemorrhage, injection site induration, injection site mass, injections site nodule, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling (15%, 0%, 7%, 0%); Hyperglycemia: includes diabetes mellitus, glucose tolerance impaired, hyperglycemia, type 2 diabetes mellitus (14%*, 0%, 5%, 0%); Hypertension: includes hypertensive crisis (14%*, 1%*, 5%, 0%); Cholelithiasis (14%*, 1%*, 7%, 0%); Dizziness (9%, 0%, 2%*, 0%); Depression: includes depressed mood (7%, 0%, 1%, 0%); Dyspnea (6%, 0%, 1%, 0%).
* Includes one or more serious adverse events (SAEs) defined as any event that results in death, is life threatening, results in hospitalization or prolongation of hospitalization, results in persistent or significant disability, results in congenital anomaly/birth defect, or may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed.

Carcinoid Syndrome**:** The safety of SOMATULINE DEPOT 120 mg in patients with histopathologically confirmed neuroendocrine tumors and a history of carcinoid syndrome (flushing and/or diarrhea) was evaluated in a double-blind, placebo-controlled trial. Patients were randomized to receive SOMATULINE DEPOT (N=59) or placebo (N=56) administered by deep subcutaneous injection once every 4 weeks. Patients in both arms had access to subcutaneous octreotide as rescue medication for symptom control. Adverse reactions reported were generally similar to those reported for the GEP-NETs population. Adverse reactions occurring in 5% and greater of SOMATULINE DEPOT-treated patients and occurring at least 5% more than in placebo-treated patients were headache (12% vs 5%, respectively), dizziness (7% vs 0%, respectively), and muscle spasm (5% vs 0%, respectively) by week 16.

**Immunogenicity:** As with all peptides, there is 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 to lanreotide with the incidence of antibodies in other studies or to other products may be misleading. Development of anti-lanreotide antibodies was assessed using a radioimmuno-precipitation assay. In patients with GEP-NETs receiving SOMATULINE DEPOT, the incidence of anti-lanreotide antibodies was 4% (3 of 82) at 24 weeks, 10% (7 of 67) at 48 weeks, 11% (6 of 57) at 72 weeks, and 10% (8 of 84) at 96 weeks. Assessment for neutralizing antibodies was not conducted. Less than 2% (2 of 108) of the carcinoid syndrome patients treated with SOMATULINE DEPOT developed anti-lanreotide antibodies.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of SOMATULINE DEPOT. Because these

reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Hepatobiliary:* Steatorrhea, cholecystitis, pancreatitis; *Body as a Whole:* angioedema and anaphylaxis.

## DRUG INTERACTIONS

**Insulin and Oral Hypoglycemic Drugs:** Lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Blood glucose levels should be monitored when SOMATULINE DEPOT treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

**Cyclosporine:** Concomitant administration of cyclosporine with SOMATULINE DEPOT may decrease the absorption of cyclosporine, and therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic drug concentrations.

**Bromocriptine:** Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the absorption of bromocriptine.

**Bradycardia-Inducing Drugs:** Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with lanreotide. Dosage adjustments of concomitant drugs may be necessary.

**Drug Metabolism Interactions:** The limited published data available indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that SOMATULINE DEPOT may have this effect, avoid other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine). Drugs metabolized by the liver may be metabolized more slowly during SOMATULINE DEPOT treatment and dose reductions of the concomitantly administered medications should be considered.

## USE IN SPECIFIC POPULATIONS

**Pregnancy:** Limited available data based on postmarketing case reports with SOMATULINE DEPOT use in pregnant women are not sufficient to determine a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, decreased embryo/fetal survival was observed in pregnant rats and rabbits at subcutaneous doses 5- and 2-times the maximum recommended human dose (MRHD) of 120 mg, respectively.

**Lactation:** There is no information available on the presence of lanreotide in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions in breastfed infants from SOMATULINE DEPOT, including effects on glucose metabolism and bradycardia, advise women not to breastfeed during treatment with SOMATULINE DEPOT and for 6 months (6 half-lives) following the last dose.

**Females and Males of Reproductive Potential:** *Infertility (Females)* Based on results from animal studies conducted in female rats, SOMATULINE DEPOT may reduce fertility in females of reproductive potential.

**Pediatric Use:** The safety and effectiveness of SOMATULINE DEPOT in pediatric patients have not been established.

**Geriatric Use:** Studies conducted in patients with neuroendocrine tumors, did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Renal Impairment:** GEP-NETs No effect was observed in total clearance of lanreotide in patients with mild to moderate renal impairment receiving SOMATULINE DEPOT 120 mg. Patients with severe renal impairment were not studied.

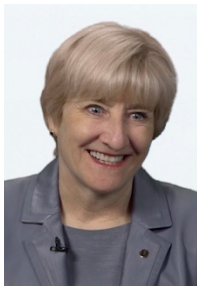
**Hepatic Impairment:** GEP-NETs SOMATULINE DEPOT has not been studied in patients with GEP-NETs and hepatic impairment.

**References: 1.** Somatuline Depot (lanreotide) Injection [Prescribing Information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; September 2017. **2.** Caplin ME, Pavel M, Ćwikła JB, et al, for the CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371(3):224-233.

LEADERSHIP

# McAneny Discusses OCM, Community Practices, and Building the Right Rewards

*Based on an interview with Surabhi Dangi-Garimella, PhD*



**MCANENY**

*Barbara McAneny, MD, a board-certified medical oncologist/hematologist, is the current president of the American Medical Association.*

**THESE ARE CHANGING TIMES** in oncology care. Breakthroughs in science have been tempered by the cost of treatments and CMS policy shifts over the past year, and leaders of major physician organizations were kept busy responding to various proposals to change Medicare reimbursement.[1,2] Together with discussions about changing the way the government pays for prescription drugs[3] and the possibility of a mandatory payment model in radiation oncology,[4] the cancer care community is facing a time of unprecedented upheaval.

But oncologists have the right voice in the right place. In June, oncologist Barbara McAneny, MD, became the 173rd president of the American Medical Association (AMA),[5] bringing her years of leadership in payment reform as the originator of the community oncology medical home (COME HOME) model[6] to a broader advocacy role. Today, McAneny is taking on the AMA's agenda of improving health outcomes, creating sustainable practice environments, advancing medical education, and attacking the opioid epidemic. Oncology, however, is never far from her mind, as it was in a recent interview with Surabhi Dangi-Garimella, PhD, associate editorial director for *The American Journal of Managed Care®*.

"We have a lot of work to do," McAneny said. "There are a lot more changes to come, but I'm optimistic that the AMA is going to be able to help create the healthcare system of the future that is deserving of doctors' work and patients' respect, so that we don't have the burnout issue and we can deliver better healthcare to patients at a lower cost."

## Developing Alternative Payment Models

McAneny discussed the need for CMS and other payers to build relationships with physicians, with a shared goal of delivering the best care to patients at the lowest possible cost. "We need to have that trusting partnership between the physicians and CMS and the other payers, instead of the adversarial relationship that it's been in the past," she said.

The movement away from fee-for-service reimbursement toward more alternative payment models (APMs) has created a process, through the Quality Payment Program, to develop more APMs. Not every model will look alike. "What works for inflammatory bowel disease may not be the same model that works for diabetes or cancer or heart disease," McAneny said. "So, we need to have as many smart people as possible across the country thinking about this and coming up with models that CMS can test to be able to change this payment structure."

CMS wants accountability, she said. "Patients are going broke out there. And we have to help them with that, as well."

## Care Coordination and the OCM

McAneny became known for her efforts as chief medical officer of New Mexico Oncology Hematology Consultants, where she developed the COME HOME model, which put a priority on improving outcomes and keeping patients out of the emergency department (ED) with expanded care coordination and 24/7 practice access. COME HOME was funded by the Center for Medicare and Medicaid Innovation and was a forerunner to the Oncology Care Model (OCM).[6] COME HOME saved an average of $2100 per cancer patient by reducing ED and hospital visits, and delivering antibiotics or fluids in the office.

Besides the savings, quality of life improved. "Patients do not want to spend their time in the hospital," McAneny said.

She sees the fruits of those efforts playing out in practices today. "I think that care management is focusing now on the low-hanging fruit of keeping people out of the hospital and keeping people out of the emergency departments."

"There will always be cancer patients in the hospital, we will never get to zero on that," McAneny continued. "But, if we set up our practices so that we can manage a lot of the side effects of cancer and its treatment in the lower-cost physician office setting, we can save significant amount of money."

**"I highly value community oncology. I think it is the low-cost, high-quality alternative to hospital-based systems, because under the hospital outpatient prospective payment system, that automatically costs the system twice as much. We're the most expensive healthcare system on the planet. We cannot afford to pay twice as much for the same service."**

—Barbara McAneny, MD,
President, American Medical Association

## Helping Community Practices Thrive

The challenge, however, is connecting improved care to the right rewards structure. Community oncology practices have said they are under pressure from a reimbursement structure that is forcing many practices to close or merge with hopsitals.[7] McAneny said it is "crucial" to help community practices thrive.

"I highly value community oncology. I think it is the low-cost, high-quality alternative to hospital-based systems, because under the hospital outpatient prospective payment system, that automatically costs the system twice as much," McAneny said. "We're the most expensive healthcare system on the planet. We cannot afford to pay twice as much for the same service.…In addition, 40% of Americans live in rural areas. There are not going to be large, integrated systems in rural areas."

To do this, she said, "We have to have a system that does not penalize physicians for doing the right thing for the right patient. The OCM has a practice adjuster that tries to look for how efficient they were before and has an early adopter factor that they put in for people who are using the new biologic agents, which are much better than standard chemotherapy. [They are] much less toxic [and have] better outcomes, so ethically we absolutely have to use those drugs. But they are also very expensive."

McAneny repeated complaints of other oncologists, that the adjustment mechanisms in OCM do not go far enough to compensate practices that are using the most innovative therapies, which are, by definition, the most expensive.[8]

"The first thing we have to do, if we're going to preserve community oncology, is to reward physicians, not penalize them for doing the right thing for patients."

**The Community Oncology Medical Home (COME HOME) model builds on the concept of a patient-centered medical home with 7 components**

An ongoing relationship with a personal physician to provide first contact, continuous and comprehensive care

Physician-directed team care

Whole person orientation

Integrated/ coordinated care

Evidence-based medicine and performance measurement to assure quality and safety

Enhanced access

Payment to recognize the value-added of a medical home

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Payers must also consider that community practices must hire nurses with the same training levels as those at hospitals, along with professionals in data analytics—a need that did not exist a decade ago. "I now need technical people who can keep the [electronic health record] running," she said. "So, the expense of practices has gone up significantly, but the payment from Medicare has not.…We are penalized for trying to adapt. If they want practices to evolve, from fee-for-service into some sort of alternative payment model, CMS and the payers have to recognize that that evolution takes resources. We really need a system that will allow physician practices to have that margin so that we can invest in the future."

To adapt, physician-owned practices have joined forces to create a National Cancer Care Alliance that provides what McAneny calls "bandwith" for managing functions such as information technology, HIPAA security, scheduling efficiency, and maximizing the effectiveness of electronic health records.

"If we band together, then we can delegate thinking about one of those problems to one of the people in the practice and then share the outcomes. So, that will really help us. And I think that's going to be a good model for the future."

## Pathways to Success

CMS recently announced it sought to speed up the timetable for getting accountable care organizations (ACOs) to take on downside risk, through a revamped program called Pathways for Success.[9] McAneny said the AMA expressed concerns about such a rapid transition. For starters, the ACOs that have only taken on 1-sided risk were saving more money than those taking on 2-sided risk.

"Since the goal of the ACOs is to deliver better healthcare at a lower price, we think that switching from the group that's more successful at that and forcing everyone into a model where it hasn't performed as well may be problematic," she said.

Another AMA concern is CMS' rapid move to let Medicare Advantage plans move to step therapy, which McAneny called a "fail first" program. "People often change their Medicare Advantage plans every year or 2 or plans change what they put as first-line drugs depending on the economics of what they purchase it for. That is incredibly disruptive for patients.

"For [patients with cancer], if we have to have patients fail first on the old-fashioned, less-expensive chemotherapy before they can get to the stuff that's going to make a difference in their life, we're going to do damage to people."

The Trump administration has said it seeks to reduce paperwork and administrative burdens, which the AMA applauds, McAneny said. "But if now I have to go through this process, every time I treat a patient on a Medicare Advantage plan, to plead with them to let me give the patient the drugs that I think are better, they have just increased my documentation and physician burnout risk significantly."

"We would like to be able to work with the administration to find better ways to save money. We absolutely agree that we need to save money in this system. We understand that physicians need to be held accountable for the quality of the care that we deliver," she said. "We just think there are better ways to do it than the prior authorization process or the fail-first processes."

## Understanding Social Determinants of Health

Most people do not realize that the most important factor in determining a person's health outcome is their ZIP code, McAneny said. It can determine whether the patient has a caregiver, whether the person can afford copays and deductibles—and yet these "social determinants of health" are not being measured.

"One of the things that the AMA is taking on, which I think is incredibly important, is how do we measure that? And how do we code for that in a respectful fashion, so that we can look at what that problem is?" she asked. "You can't address a problem until you know how to define it and what the magnitude is."

The AMA is working on a coding system, but it will take years. "We're working to develop a coding system that will allow us to be able to stratify patients according to those risk factors, as well as what is your tumor type and are you also diabetic and all the other medical risk factors that are part of it. Because then we can truly judge whether or not a physician is doing the job we're hoping they're doing.

"You know, if they're starting out with someone whose hemoglobin A1C is 14, and then get it down to 9, they're doing a great job. But they would still be penalized under our current system." ◆

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*Coverage by Surabhi Dangi-Garimella, PhD; and Mary Caffrey*

# Priority Health's Payment Reform Model Shows How Buy-in Matters

**A COLLABORATION BETWEEN** a regional commercial payer in Michigan and community-based practices, which piloted in 2011, was developed[1] with the sole objective of improving care delivery in the oncology space and moving away from the fee-for-service model.

FOX

The model was extremely successful, and to speak about its success and ongoing development after 6 years, John Fox, MD, medical director at Priority Health, joined Dennis Zoet, chief business development officer at Cancer and Hematology Centers of Western Michigan, during the Community Oncology Alliance Payer Exchange Summit, October 29-30, 2018, in Tysons, Virginia.

Fox told the audience that the model was a version of an oncology medical home model, that does away with episodic care. The 3-pronged focus included:

- Payment reform: The transition to a performance-based care delivery system included changes within drug reimbursement, addition of a care management fee, shared savings, infrastructure development, and enhanced services.
- Care redesign: This included agreement on preferred regimens, care management, advance care planning (ACP), and survivorship
- Performance measurement

"We realized that change is hard; it takes time, experience, and commitment; and it takes money," Fox said. Zoet's practice has successfully adopted these changes for 6 years.

Although implementing changes to adopt the pilot was easy, using that as a stepping stone to participate in the Oncology Care Model (OCM) was much harder, Zoet said. "Our staff thought [the Priority Health pilot] was a one-off, so they bought in to some extent. What changed the deal was OCM participation. That was a big change, as it looped in 60% of our patients," he said.

Zoet explained that internal champions for these programs played an important role. "We had both physician and administrative champions," he said. The practice saw staff that didn't buy-in to these changes leave the practice. "But those who were sold stayed on and moved forward with us."

The practice had to add staff to their payroll to implement some of the required changes, including a same-day care clinic and moving over to OncoEMR[2], the platform from Flatiron Health.

The conversation then shifted to the important role of data in practice transformation. Zoet explained that his practice extracted data through 2 vendors in addition to the claims data that CMS provides, "because they all look at the same data differently." He emphasized that data transparency was key. Physicians reviewed the data as a group as well as individually. Additionally, the data were sorted based on each specialty, which is key in oncology.

Zoet then provided a case study of how data analysis helped them realize that the hospital that was conveniently located across the street from their practice had a 65% admission rate among the practices' patients who visited the hospital's emergency department (ED), about 40% higher than another hospital that was a little farther away.

The practice also hired social workers and encouraged ACP discussions, which he said have evolved into care coordination programs.

"We have started having frequent conversations with our physicians on the cost of drugs," Zoet said, because physicians have, traditionally, not been aware of drug prices.

"Now that they have to pay for it, they are," Fox said.

It's not a win-win situation, however, and the practice continues to face challenges with the model and continues to evolve as well. Zoet indicated care coordination, ED inpatient visits, and data exchange as their top challenges.

But he is also hopeful that changes such as exploring artificial intelligence and hiring an internist, which the practice is planning to adopt, will make a difference. ◆

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# Experts Discuss Regulatory, Cultural Roadblocks to Progress With Value-Based Agreements

**"CONGRESS CONTINUES TO ASK** us the same questions [about cost of healthcare], and we continue looking for different answers. Value-based agreements are the current innovative solution" to improving quality and reducing healthcare costs, said Jeff Mortier, partner at Farragut Partners. Mortier was speaking on the second day of the Community Oncology Alliance (COA) Payer Exchange Summit, held October 29-30, 2018, in Tysons, Virginia.

Historically, HHS linked 80% of Medicare payments to value. A trigger for the current movement could have been the revelation that, in 2012, US expenditures for poor care coordination and administrative burdens and fraud crossed $1 trillion, Mortier explained. "Adequate treatment and adherence in chronic conditions can save $213 billion," he explained.

MORTIER

But there are barriers to operationalizing value-based agreements (VBAs), said Mortier, which echoed the thoughts of Bo Gamble, director of strategic practice initiatives, COA, who highlighted regulatory and cultural challenges as a hurdle to VBAs during a session on the first day of the meeting.

Operational challenges, which include antikickback laws, drug pricing proposals, administrative burdens, and government pricing "all add layers of complexity to existing structural impediments," Mortier explained.

He listed a few structural impediments to VBAs, including rebates for commercial payers, which adds downward pressure and reduces provider reimbursement; best price policy, which includes negotiations for a single lowest price; and increased 340 B liability for manufacturers.

Mortier explained that HHS' focus on lowering list prices and introducing competition within the Medicare Part B space via step therapy[1] are some of the operational challenges that manufacturers face. He highlighted the contradiction between the government wanting to lower drug list prices and introducing value-based contracts. UnitedHealthcare's pilot study[2] that was launched in 2010 reported substantial savings (34%) in cancer costs over the 3-year period of the program, "but the drug cost went up 179%," said Mortier. "So, we are a little bit at odds with this administration that wants to adopt value-based models, but [also wants] to lower the list price [of drugs]."

There is a need, he said, to fill Congress' knowledge gap in the space.

"Additionally, data and reporting challenges continue to mar provider practices that don't necessarily have the time to dedicate a team for doing this," Mortier said. "Interoperability and meaningful use, or 'meaningless use' as some like to call it, continue to burden practice economics as they try to engage in VBAs."

Mortier underscored the changing cancer landscape, which has moved from 88% to 50% in the community, which he believes has caught the attention of Congress. "When you are on a safety raft, you don't really focus on VBAs," he said.

### Big Pharma's Input on VBAs

Following this policy update by Mortier was a surprise panel that COA convened: An all-pharma panel discussed the progress and challenges with VBAs from the drug manufacturer's outlook. Gamble told the audience that the panel

was the product of a series of meetings that COA held with multiple manufacturers as part of the organization's focus on value-based oncology care.

Participants included Erin Darling, executive director, Merck; Prasun Subedi, MD, senior director, Patient and Health Impact, Center for Health Systems Innovation Leadership, Pfizer; Tamar Thompson, MHS, Government Affairs, Alliance Development, and Policy, Bristol-Myers Squibb; and Eric Turowski, director, Oncology Payer Marketing, Pricing, and Market Access, Eli Lilly and Company.

When asked to describe their major learnings from the VBA meetings, Turowski said that VBAs are a major priority for Eli Lilly and that he realized at the meetings that it's the same for other drug manufacturers. "The meetings helped us understand where there are alignments between us, COA [providers], payers, and employers as well."

Thompson agreed, adding that the meetings drew attention to patient-centricity and quality measures in a meaningful way.

Although such arrangements, historically, have been between manufacturers and payers, "It was interesting to learn that providers want to be a significant part of this conversation," said Darling.

Subedi added that as VBAs stand today, stakeholders want to answer specific questions about the value of a particular treatment. He believes that access to patients and the opportunity to create data are vital to the process. According to Subedi, the best VBAs are the ones that clearly articulate the relation between the product and its value. "Simplicity is key," he said.

One learning for Turowski was that providers have interest in getting down to the individual patient-level performance, not just the aggregate comparisons that VBAs today are built to measure.

Although data are vital to this conversation, Subedi said that providers don't need to have all the answers when they come to the table; rather, they should be patient and gain an understanding of the process, which may not be very fast paced.

### Obstacles to the Process

Darling pointed out that current guardrails, such as the federal antikickback statutes that were instituted a long time ago, are a major roadblock to innovation in the value-based care process, because of associated legal and business risks. "It prevents us from providing value to our stakeholders: patients, providers, and payers," she said. "We need safe harbors in the space to help us pull through collaborations that will be good for patients, but we cannot [do so] within the current frameworks of the law."

Thompson pointed to waivers that were introduced for payers and providers to allow accountable care organization (ACO) collaborations and also for launching the Oncology Care Model (OCM). She pointed how important it is for manufacturers to understand the government's position on what they can or cannot do, similar to changes that facilitated collaborations in the ACO and OCM environment.

"Once we have support on that front, there will be a baseline of comfort to start bigger arrangements," Thompson said.

Whereas manufacturers have figured out ways to work on agreements within the existing guidance, "These are very simple agreements, and so we cannot innovate," Darling told the audience. She urged the providers and payers in the room for assistance to develop a more meaningful process.

Additionally, cultural barriers include that the manufacturer–physician relationship has always existed within the sales or marketing environment, Thompson said. So, infusing policy conversations into the space would require a big cultural shift.

The panelists agreed that we have traveled only a small section of this path and a lot lies ahead, primarily because of the lack of support from infrastructure, technology, and regulatory rules. Darling believes that we require shifts along those dimensions and that with growing capabilities, we will move quicker.

The patient needs to be the central component of the design of these agreements. Subedi urged providers to step up and represent their patients' perspectives when participating in these conversations.

"We have different views of value, but we need to find the center of the Venn diagram, because that's where the patient sits," Darling said. ◆

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# COA's OCM 2.0: Moving Toward a Universal Payment Model

**THE COMMUNITY ONCOLOGY ALLIANCE** (COA) has been working with its member practices and some payer partners who have successfully implemented innovative care delivery and payment models to develop a 2.0 version of CMS' Oncology Care Model (OCM). A progress report was presented at COA's Payer Exchange Summit held October 29-30 in Tysons, Virginia.

Moderated by Kavita Patel, MD, MS, co-founder, Tuple Health, and nonresident fellow, Brookings Institution, participants included Bo Gamble, director of strategic practice initiatives, COA; Bruce Gould, MD, president, COA, and medical director, Northwest Georgia Oncology Centers; and Lalan Wilfong, MD, vice president of quality programs, Texas Oncology.

WILFONG

Patel clarified that COA's OCM 2.0 is not a CMS-developed model. "We are thinking of a more universal approach to develop models that can be used for Medicare and by commercial payers."

Wilfong reiterated Patel's explanation, saying that the goal of their collaboration was to develop a payment model template that can be used to frame a new payment system for patients with cancer that can be used by Medicare, commercial plans, and self-insured employers, irrespective of their type or size, whose ultimate mission is to provide cost-effective quality care.

He added that the focus of their meetings and discussions was what they liked or did not like about current payment models and learning experiences for practices that have not been through value-based models or have not negotiated contracts or looked at reconciliation reports.

Wilfong then highlighted some of the key features of OCM 2.0. It is vital, he explained, to maintain a consistent and frequent channel of communication among collaborators. Open, timely, and frequent communications and reporting are vital to fine-tune, implement, and monitor the model, with a goal to meet at least on a quarterly basis. Trust among collaborators is vital for this model to work.

A few of the other considerations within the model include:

- Identifying the target population receiving the treatment, with details on population size, depending on reporting capabilities
- Trigger via submission of G-code, rather than depend on retrospective claims data
- Attribution for patients with corresponding G-code and reconciled with payer
- Making episodes easier to report: They should be based on the calendar year and can start any time after January 1; patient remains on the roster for 90 days after last treatment or until death
- A monthly care management fee for every patient that is attributed to the participating care team
- Include clinical trial participants

Wilfong said that the model should have a base of 5 to 7 base quality measures and additional measures can be included following a payer–provider agreement. These measures have to be patient-centered, he said, and can be used as a multiplier when calculating payment.

Risk adjustments in this model would be based on grouping by primary International Classification of Diseases, 10th revision diagnosis codes with the

CONTINUED ON SP555 »

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

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

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

## IMPORTANT SAFETY INFORMATION

**WARNING: DIFFERENTIATION SYNDROME**

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

### WARNINGS AND PRECAUTIONS

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

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

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

agios

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

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

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

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

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

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

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

## ADVERSE REACTIONS

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

## DRUG INTERACTIONS

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

**Strong CYP3A4 Inducers:** Avoid concomitant use with TIBSOVO.

**Sensitive CYP3A4 Substrates:** Avoid concomitant use with TIBSOVO.

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

## LACTATION

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

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

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

TIBSOVO® (ivosidenib) 250 mg tablets

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

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

## INDICATIONS AND USAGE

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

## DOSAGE AND ADMINISTRATION

### Patient Selection

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

### Recommended Dosage

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

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

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

### Monitoring and Dose Modifications for Toxicities

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

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

**Table 1. Recommended Dose Modifications for TIBSOVO**

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

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

### Dose Modification for Use with Strong CYP3A4 Inhibitors

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

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

## ADVERSE REACTIONS

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

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

## CLINICAL TRIALS EXPERIENCE

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

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

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

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

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

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

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

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

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

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

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

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

## DRUG INTERACTIONS

### Effect of Other Drugs on Ivosidenib

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

### Effect of Ivosidenib on Other Drugs

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary

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

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

Data

*Animal Data*

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

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

**Lactation**

Risk Summary

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

**Pediatric Use**

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

**Geriatric Use**

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

**PATIENT COUNSELING INFORMATION**

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

Differentiation Syndrome

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

QTc Interval Prolongation

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

Drug Interactions

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

Guillain-Barré Syndrome

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

Tumor Lysis Syndrome

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

Gastrointestinal Adverse Reactions

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

Lactation

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

Dosing and Storage Instructions

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

**Please see Full Prescribing Information, including Boxed WARNING, at TibsovoPro.com.**

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CONTINUED FROM SP549

same first 3 digits. Finally, shared savings would be allocated to payer, provider, and the employer associated with the patient care team.

Following a preview of the universal payment model, Gould highlighted key features of CMS' OCM model that providers appreciate. "We like that it's open to all payers. Also, there are no boundaries on when an episode may begin for a patient," he said. Currently, the episode begins when the patient receives treatment for the first time.

"The monthly enhanced oncology services payment is vital to help practices transition to cost-effective and efficient care and enhanced services.".

Finally, winsorization, whereby the Center for Medicare and Medicaid Innovation makes adjustments when calculating performance-based payments (PBPs) so practices that are 5% or lower or 95% and higher, their costs of care are not included when calculating their PBPs.

However, OCM as it currently exists has several problems, Gould explained and listed them for the audience:

1. OCM is prescriptive. "We would recommend a more comprehensive model that follows Oncology Medical Home[1] [OMH] accreditation, which has been developed by COA." Key elements of a comprehensive OMH are:
   - Patient engagement/education: who the care team is, including midlevel caregivers
   - Expanded access: extended hours, substitute for emergency department visits, 24-hour telephone service
   - Evidence-based care: predicated on guidelines
   - Comprehensive team-based care
   - Continuous quality improvement
   - Chemotherapy safety and adverse event monitoring: ensuring the right patient gets the drug at the right time and that there is appropriate chemotherapy storage
2. Attribution remains a significant issue, Gould said, and it can be overcome by using G codes: practice can register patients, so it's clear that the patient belongs to that specific practice.
3. Reporting and measures are problems that have evolved from poor technology interfaces, too much data entry, and too many measures. A solution for this is better coordination with CMS and their contractors to develop seamless, user-friendly interfaces and harmonization of measures.
4. Performance-based payments are a problem, too, because they are based on claims data, not clinical data. "Baseline prices do not reflect true drug costs, and the solution lies in considering both clinical and claims data when calculating baseline prices and for risk adjustment," Gould said. "It is important that the model keeps up with real-time changes in indications and [the] price of a drug. Also, a shared savings model might be a better calculator than a gains savings model. We like a lot of what we have experienced with OCM 1.0, and we'd like to see it improve," Gould said.

Finally, Gamble spoke to the audience about drugs and their value proposition in OCM 2.0.

He said that COA has had several meetings with pharmaceutical manufacturers to understand their progress and approach to explain the value of their product. "They have a different set of challenges that are both regulatory and cultural in nature," he said. Additionally, manufacturers are also wrestling with measures for "value."

Gamble listed a few key considerations for drugs and value-based arrangements (VBAs) in COA's universal payment model:

- Can patients be involved in this conversation, along with providers and employers?
- Not all payers are involved in VBAs
- Payers usually do not want providers involved or aware of a VBA with a drug company
- Outcomes measures are difficult to define. Are we looking at the total cost of care or the difference between overall survival and progression-free survival? Are we ready to define cost of outcomes in a unique way?

"COA wants to be a facilitator for these discussions with providers, for payers and the pharmaceutical industry," Gamble said. ◆

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# Community Practices Continue to Struggle With Emergency Department Use, Risk Stratification in OCM

**AT THE COMMUNITY ONCOLOGY ALLIANCE** (COA) Payer Exchange Summit in Tysons, Virginia, October 29-30, a small group practice and a midsize practice shared their experiences and learnings from the first 2 years of being in the Oncology Care Model[1] (OCM) and provided feedback to the moderator from CMS in the form of struggles and missed opportunities in the model as it currently functions.

Ellen Lukens, division director, specialty payment models, CMS, facilitated the conversation between Kashyap Patel, MD, CEO, Carolina Blood and Cancer Care, and Barry Russo, CEO, The Center for Cancer and Blood Disorders.

LUKENS

Explaining the objective of the panel, Lukens said that the audience can hope to draw perspectives from payer and provider learnings over the past two-and-a-half years of being in the OCM and where the future lies for this model. She hoped that the conversation would provide adequate guidance for oncology practices and health insurance plans who haven't participated in the OCM yet.

"OCM was a brave effort from all of us, and it's much bigger than what any of us anticipated at launch [of the program]," Lukens said.

Considering the complexity of cancer care, "We need a model that can manage [this complex disease] and is responsive for this level of care," she said. Emphasizing the need for partnership among stakeholders, Lukens said that CMS continues to receive feedback on the OCM from COA, the American Medical Association, and the Association of Community Cancer Centers, among other, "which has been tremendously valuable to the [Center for Medicare and Medicaid Innovation], and it helps improve the model."

Anecdotal evidence has suggested that practices have performed well with care transformation, access, and communication, she said. "[Although] 25% of participating practices achieved a performance-based payment [PBP] in performance period 1, [and] 40% did so in performance period 2, which is impressive," Lukens told the audience. "Additionally, 75% of practices beat their benchmark in performance period 2: 85% if we minus the care management fee."

These are internal analyses, and independent evaluation results for the second performance period are expected by year-end.

"We are open to suggestions at the two-and-a-half-year mark to improve the model," Lukens said.

She then invited Patel to share his practice's experience with OCM, who explained his clinic's motivation to initiate practice transformation.[2] "We started this process in 2013 for accreditation as a patient-centered specialty practice," following advice from their payer partner, commercial Blue Cross Blue Shield of North Carolina (BCBSNC). The process stemmed from a threat that the clinic faced as a result of 2 big healthcare systems that were buying up practices in the surrounding area.

The transformation process required changes at multiple levels, including same-day appointments, walk-in access, and an up-front triage process to appropriately direct patients. But the most vital part of the process, in addition to adding to the practices' head count, was employee buy-in, Patel emphasized.

"We brought in external stakeholders to speak to our employees on why we should bring about this change," he said, which was followed by their initiating a pilot model with BCBSNC, before participating in the OCM. »

They identified emergency department (ED) visits and hospitalizations as the biggest challenges in their patient population, especially because of the rural population that their practice served, and educated their patients to call the clinic first in case of an emergency. "We added slots to our daily and weekend schedules to be able to see patients the same day."

Since a lot of their patients were Medicaid-assisted, the practice looked at external sources of funding and raised about $1.6 million from foundation and agency grants, "which was our second patient-centered move," Patel said.

Additionally, his practice moved 100% of its patients to biosimilar filgrastim[3] instead of the reference product, which led to additional cost savings.

"Patient triage, same-day visits, and the use of biosimilars together had a big impact," Patel said.

Also, to address the challenge of after-hours care, the clinic partnered with a local urgent care center, which added a second tier of support for patients who did not have life-threatening emergency.

However, the rural location of the practice remains a challenge, Patel said. Their analysis of high utilizers has identified a patient stereotype: Most only have Medicare, they live alone, and they typically lack access to transportation.

Patel recommended that social complexities of patients should be included as a risk factor in the model.

Russo's practice had experience with several value-based care models for almost a decade prior to entering into the OCM pilot, including the COME HOME model and Aetna's value-based care program. He listed similar practice transformation efforts as Patel's clinic, including after-hours and weekend care and a centralized triage pathway system, in addition to a lot of support services, including on-site dietitians, massage therapy, acupuncture, and navigators for educating patients. "This support team is vital," he said.

How do you pay for these supportive care services? Although the monthly enhanced oncology services payments help fund these services, "We have reached out to outside foundations to receive financial support related to services that we do not charge for," Russo said.

He also described some new programs that their practice implemented: a prehab program aimed at reducing falls in patients who are at a higher risk of falling after discharge. "It's also had an impact on keeping patients on therapy after discharge," he said.

One of their biggest challenges is the rural location of their practice. "We have made some dents in ED utilization, especially in some more urban areas, but our problem is that the ED is the rural population's primary care provider," he said. They continue to struggle with this issue despite consistent patient education against visiting the ED.

To better equip their practice for risk stratification, another one of their ongoing challenges, The Center for Cancer and Blood Disorders has partnered with an artificial intelligence system that has 7 vectors: depression, pain, risk for ED admission, risk for readmission, risk for 30-day mortality, and risk for 60-day morbidity. These vectors are meant to help identify, in a succinct way, where the risk for patients in the practice lies. "This tool has made a big difference," he said.

Finally, Russo pointed out that the lack of aligned incentives creates significant barriers for their cost-saving efforts.

In closing, he said, "We need all hands on deck for the success of this transformation—everyone from the front desk to the coders to the nurses. They all have to understand that this affects everyone's day-to-day activities as well as financial well-being." ◆

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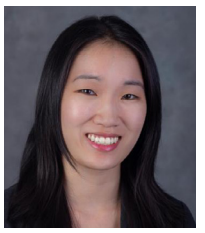
# Massachusetts Medicaid Finds CAR T-Cell Payment Solution While Waiting on CMS

**EXCITEMENT OVER CHIMERIC ANTIGEN** receptor (CAR) T-cell therapies has been matched only by the frustration at figuring out how to pay for these unique, expensive, and hard-to-administer treatments. CMS ended an early value-based agreement with Novartis that covered the first therapy, tisagenlecleucel (Kymriah), which lists at $475,000.[1] Federal policymakers are in the midst of a National Coverage Analysis that will produce a decision memo in February 2019.[2] In the meantime, the science races ahead, with more treatments and more indications expected, as well as the prospect that CAR T-cell therapy will advance from autologous to allogeneic treatments.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What can payers and institutions do in the meantime? At least 1 Medicaid program isn't waiting, as a pair of speakers discussed October 24, 2018, at the Academy of Managed Care Pharmacy Nexus 2018 in Orlando, Florida. Therese Mulvey, MD, director of quality safety and value at Massachusetts General Hospital in Boston, and Stephanie Tran, PharmD, a clinical consultant pharmacist for the University of Massachusetts Medical School, covered the clinical and financial challenges that CAR T-cell therapy presents and how the commonwealth has addressed them with a carve-out initiative through the pharmacy benefit.

First, Mulvey reviewed data from the ZUMA-1 trial for axicabtagene ciloleucel (Yescarta),[3] which is approved to treat diffuse large B-cell lymphoma (DLBCL) at a cost of $373,000, and the JULIET trial for tisagenlecleucel,[4] approved initially for pediatric acute lymphoblastic leukemia (ALL). As she explained, the patients in the trials who had success with these therapies had run out of options, and the results were astounding. Because these are "living drugs," functioning cells that are modified to fight cancer, they keep working after a single treatment. "These are drugs that are very expensive, but if the patients have a response, and the responses are durable, the folks won't require additional treatment."

She contrasted this with multiple myeloma, which now has many treatments options and much improved survival rates and can cost $2.2 million per patient over the first 3 years. Clinical trials for CAR T-cell therapy in multiple myeloma are ongoing, Mulvey said.

A big challenge for CAR T-cell therapy is toxicity, notably cytokine release syndrome (CRS), which Mulvey said is usually manageable and reversible but can emerge up to 50 days after the infusion. The other toxicity is financial, as the price tag for CAR T-cell therapy "has definitely shattered oncology pricing norms," Mulvey said. Some estimates have put the total price, including inpatient costs, at $1 million.[5]

Medicare and Medicaid frameworks are not designed for this, and that's a problem, given that roughly 50% of the DLBCL population will be in Medicare (and CMS is pushing more of them into Medicare Advantage). Among the pediatric ALL population, 40% are eligible for Medicaid. Given the need for inpatient infusion, the possibility of CRS, and the administrative burden involved, Mulvey asked rhetorically, "Why should a facility or a provider take the time to do this work?"

She called on payers and policymakers, including the National Comprehensive Cancer Network, to develop policies to grant equal access, to ensure that patients who are poor or live in remote areas can be reimbursed for travel. There's a need to address the timing of payments, as well, because the risk to institutions is great. A life-saving therapy "should not bankrupt the system."

Tran then gave a detailed overview of how Massachusetts' Medicaid program, MassHealth, designed a special reimbursement plan, or "carveout," with the CMS approval to cover CAR T-cell therapies. A carveout was considered when it became clear that CAR T-cell treatments were so costly that they rose above the "outlier" policy that reimbursed 85% of normal adjudicated rates. The decision was made to develop a carveout in November 2017; providers were notified in February 2018, and the carveout became effective

in March 2018. CMS gave its approval on June 22, 2018, with an effective date of March 1, 2018.

Under the policy, providers bill separately for the therapy, which is not included in the normal adjudicated rate. But treatment centers are still at risk for some ancillary costs, including the initial leukapheresis or treatments for CRS. The therapy is managed as part of the pharmacy benefit, Tran said.

A CAR T-cell therapy monitoring program carefully tracks how patients are doing and gets biweekly updates on outcomes. Under an agreement with Novartis, if the tisagenlecleucel therapy is not working at 30 days, MassHealth does not pay for the therapy carveout.

Future considerations for all stakeholders include:

- At the 1-year mark of therapy approval, there will be more data, which could have an effect on prices.
- New indications may change affordability of the treatments.
- Payers will have to consider how to change the administrative process to improve work flow. ◆

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# Drug Market to See More Competition, Launch of Biosimilars in 2019

**IF COMPETITION IS KEY** to finding savings in drug pricing, then the next 2 years should bring plenty of opportunities, according to Aimee Tharaldson, PharmD, senior consultant for emerging therapeutics for Express Scripts, who gave her overview of the specialty pharmacy landscape on October 23, 2018, at the Academy of Managed Care Pharmacy Nexus 2018 in Orlando, Florida.

THARALDSON

Rising competition across specialty pharmacy classes, the launch of more biosimilars, and approvals of rare disease therapies will create a dynamic landscape, Tharaldson said, although there will still be many new treatments that hit the market at prices of $300,000 a year or higher. She reviewed activity on treatments for HIV, hemophilia, multiple sclerosis (MS), various inflammatory conditions, cancer, and rare diseases. The trend of specialty pharmacy dominating what America spends on drugs will continue, Tharaldson said. According to her presentation, Express Scripts' data show specialty pharmacy accounted for 41% of the drug spend in 2017, and she predicts this share will rise to 50% by 2019, even though only a fraction of those who take prescription drugs use these medications.

## Biosimilars

Tharaldson reviewed existing approvals as well as the legal challenges that have kept several promising products from reaching the US market. But she also listed target launch dates for some key products, including July 2019 for bevacizumab-awwb (Mvasi), which has indications in several common forms of cancer, and June 2019 for trastuzumab-dkst (Ogivri), a common treatment for breast cancer. She listed 8 more biosimilars with approvals pending before the end of 2018, including treatments for neutropenia, products that reference trastuzumab, and a treatment that references rituximab for non-Hodgkin's lymphoma.

Of note, Tharaldson said, the FDA is working hard to develop policies to promote the biosimilars market by making it more difficult for branded drug manufacturers to extend patents and stifle competition. "Eventually, this will lead to cost savings," she said.

## Cancer Therapies

At the time of her talk, the FDA had approved 12 cancer therapies in 2018 and 4 more were anticipated. Many forms of cancer have been transformed to chronic conditions, Tharaldson said, and the 25% reduction in death rates is due to both better treatments and better detection, as well as less smoking.[1] However, "even though we are seeing new niche products, we are not bringing the prices down very much," she said, and $150,000 a year for a cancer therapy is fairly common. Drug developers are finding success in treatments for rare cancers, and 30% of the treatments approved for disease that affect 200,000 or fewer patients become blockbusters,[2] she said.

## Specialty Drug Spending

Data from Express Scripts show that spending on inflammatory conditions, such as rheumatoid arthritis (RA) or psoriasis, outranks all other categories and is twice that of cancer. Spending for hepatitis C now trails HIV, cancer, and MS. Total specialty pharmacy spending was $444 per member per year. And with 39 new specialty drugs in the pipeline, there's no sign of that slowing down, Tharaldson said. She highlighted new therapies for HIV-1, metastatic melanoma, cystic fibrosis, RA, and acute myeloid leukemia.

## In the Pipeline

Tharaldson discussed therapies across multiple classes that are on track for approval over the next 2 years. Four therapies for inflammatory conditions—risankizumab and bimekizumab for psoriasis, and upadacitinib and filgotinib for RA—are anticipated through 2020, while 4 therapies in the pipeline for MS—cladribine, siponimod, monomethyl fumarate, and ozanimod—are all on track for approval in 2019. A 2017 study found that MS affects about 1 million people in the United States.[3]

As she has in the past, Tharaldson drew attention to nonalcoholic steatohepatitis, or NASH, which is associated with high cholesterol and type 2 diabetes (T2D) and causes liver damage when fat develops in the liver. There are no real treatments, although some may be coming, including a few approved for other indications. Novo Nordisk's semaglutide is already approved for T2D and is in trials for NASH, and Gilead's selonsertib and Intercept Pharmaceutical's obeticholic acid could be on track for approval in 2019. Eight other therapies are under development for approval beyond 2020.

Alzheimer disease, meanwhile, continues to baffle researchers amid growing need, as 5.5 million people have the disease and more will receive this diagnosis as they age. Tharaldson listed 9 treatments under study, but, "So far, these drugs just haven't been able to demonstrate that they are effective," she said. "It's a very high-risk, high-reward class."

## Drugs to Watch

The audience gasped when Tharaldson said she has her eye on an intravenous drug under development by Novartis, now listed as AVSX-101, for spinal muscular atrophy, which could cost $1 million to $3 million for a single infusion. By contrast, Pfizer's tafamidis, which could be approved next year to treat transthyretin amyloid cardiomyopathy, will be an important treatment, as it promises to greatly reduce hospitalizations and thus could save health plans money. ◆

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TREATING MYELOMA CAN SEEM LIKE A MARATHON

# WOULD YOU TAKE OFF YOUR SHOE WHEN RUNNING A MARATHON?

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

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

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

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

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

## Important Safety Information

### Warnings and Precautions

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

### Adverse Reactions

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

### Special Populations

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

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

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

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**Please see accompanying Brief Summary.**

Takeda ONCOLOGY

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

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

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

## 1 INDICATION

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

## 5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

## 6 ADVERSE REACTIONS

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

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

### 6.1 CLINICAL TRIALS EXPERIENCE

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

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

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

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

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

**Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.**
*Represents a pooling of preferred terms

(Continued on next page)

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

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

Herpes Zoster

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

Eye Disorders

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

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

**7 DRUG INTERACTIONS**

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

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy:**

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

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

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

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

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

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

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

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

**17 PATIENT COUNSELING INFORMATION**

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

*Dosing Instructions*

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

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

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

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

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

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

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

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

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

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

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



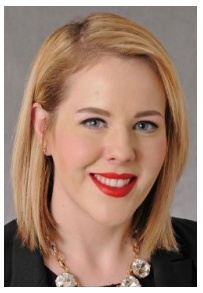
AUG 2018 MAT-US-IXA-18-00351

# Patient Perspectives Must Meaningfully Inform Healthcare Value Measurement

*Jennifer Bright, MPA, and Elizabeth Franklin, LGSW, ACSW*

**BRIGHT**

*Jennifer Bright, MPA, is executive director for the Innovation and Value Initiative.*



**FRANKLIN**

*Elizabeth Franklin, LGSW, ACSW, is executive director, the Cancer Policy Institute at the Cancer Support Community, Washington, DC.*

**THE UNITED STATES HAS** the most expensive healthcare system in the world, as well as a growing number of patients living with chronic illnesses.[1] Further, there is an ever-expanding number of available treatment options, many of which have limited differences in efficacy and toxicity.[2] In addition to rising societal costs, many patients are increasingly experiencing financial toxicity.[3] High out-of-pocket (OOP) costs associated with healthcare can put patients at physical, emotional, and financial risk as they may opt to skip doses, or ultimately lose their savings and/or face bankruptcy.[4] As a result, there has been a growing focus on the concept of "value" in healthcare. Yet, there is lack of consensus on a definition of value.[5] Although patient-centricity has been a steady refrain in healthcare, we question whether the values, needs, and preferences of patients have been meaningfully incorporated into value assessments thus far.

Perfunctory statements are often made regarding the consideration of patient viewpoints in value assessment, but meaningful action is another matter. There is not yet agreement—or even substantial serious conversation—about processes for measuring what patients truly value in healthcare. Without collaboration and routine efforts focused on how to build patient perspectives into such assessments, we will continue to engage in sporadic and superficial conversations with patients instead of capturing meaningful data that can contribute to a healthcare system which truly places them at the center.

There are encouraging trends that show patient viewpoints and participation are beginning to be prioritized. The FDA is now conducting patient-focused drug development in order to systematically obtain the patient perspective on diseases and their treatments.[6] In a survey of pharmaceutical industry representatives last year, 77% said embracing patient-centricity is extremely important to their company.[7] Additionally, in a recent report by the Center for Workforce Health and Performance examining employer use of research-based evidence in health, the authors recommended that employers look beyond cost and use evidence-based research to assess what is most important to their employees.[8]

When patient perspectives are sought as part of value assessment, a vital understanding regarding what is most important to patients (such as productivity, OOP spending, convenience, and the promise of hope among many other concerns) is unlocked and can be considered in value calculations. This gives healthcare decision makers—from clinical trial designers to employee benefit designers—more insight into factors affecting choice and adherence to treatment, which have an impact on outcomes. Moreover, these stakeholders gain the advantage of having more precise tools to assess how diagnostics and therapies may work for individuals, rather than being limited to population-based averages, which may overlook crucial differences in patient response. In the decentralized and increasingly value-based US healthcare marketplace, use of data, analysis, and a real-world understanding of the covered population is imperative.

Patients and patient advocates have long understood that value means more than just efficacy and cost, and it differs according to the individual being treated. Oncology is a perfect example. Oncology care is more expensive than for any other disease; with a rapidly increasing array of treatment and imaging options[9,10] and many patients having numerous therapy options, there are a host of factors and trade-off decisions that influence patient choice. Cancer is a disease area that demonstrates how value factors can go beyond a therapy's cost.

Government agencies like the FDA are increasingly interested in patient-centered drug design and incorporation of patient-centered measures in clinical trials, but these efforts remain in their infancy. Several organizations—including the National Health Council, Pharmaceutical Research and Manufacturers of America, Avalere/FasterCures, and National Pharmaceutical Council—have called for patient engagement in developing value frameworks, but significant room for improvement exists in order to incorporate ongoing, meaningful, and systematic patient feedback.

**Perfunctory statements are often made regarding the consideration of patient viewpoints in value assessment, but meaningful action is another matter. There is not yet agreement—or even substantial serious conversation—about processes for measuring what patients truly value in healthcare.**

Existing frameworks tend to focus on clinical and economic outcomes, overlooking key concepts of importance to patients. Research has found that identifying the value to the individual patient is considered by many to be the most important factor in any assessment; yet, individual patient disease characteristics are not considered by many of the frameworks.[11] Many frameworks overlook concepts such as quality of life, severity of disease, and daily functioning.[12] Simply put, value is not comprehensively assessed when patients are not partners in the process.

But still the question persists: How should patient information be collected and incorporated into value assessment?

The Innovation and Value Initiative (IVI) makes incorporation of patients' perspectives a priority in developing open-source, transparent value models, with multiple opportunities for patients to participate in model development and provide feedback.

Incorporating these perspectives into IVI's mathematical models is often challenged by a lack of detailed data—although increasing use of patient-reported outcomes and patient experience metrics in trials and studies could begin to change this. However, IVI has demonstrated how robust qualitative research utilizing focus groups and in-depth, structured interviews, leads to the collection and incorporation of patient experiences and perspectives.

IVI recently released qualitative research on patients with metastatic nonsquamous non–small cell lung cancer (NSCLC) who had received systemic therapy within the past 5 years.[13] This research explored drivers of value, preferences in treatment, and other key contextual questions, which helped inform the structure and content of IVI's Open-Source Value Platform (OSVP) decision models for assessing the relative value of sequential treatments for epidermal growth factor receptor–positive NSCLC.

According to the research, patients reported valuing treatments that would help increase overall or progression-free survival, help

stop or slow progression of their disease, as well as the degree to which treatment efficacy would allow them to maintain functional ability and their quality of life with minimal adverse effects.

Incorporating these findings into IVI's OSVP model from the onset is an important development for the science and implementation of value assessment and a step that those involved in assessing risk, value, and cost should analyze.

Still, the fact that best practices to collect real-world patient experience and preference data are not defined is evidence enough that we must prioritize ways to systematically capture and measure what is most meaningful to patients. It is no longer acceptable to say that this data is "messy" or challenging to quantify. If we are assessing a treatment or test specific to a patient population, it is our responsibility to collaborate with one another to better understand what the patients who are being impacted by these assessments have experienced and what they value most.

Value is not just the catch phrase of the moment in healthcare; rather, it has a direct impact on the lives of patients. All stakeholders need to step forward and embrace the challenge to find a way to routinely measure and include patient experiences and perspectives in treatment development and surveillance, and, ultimately, in value assessment. Accelerating action will ensure we can deliver better results for employers, plans, providers, and most importantly, patients. ◆

**AUTHOR INFORMATION**

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# The New Oncology Bundle Model: What We Know and Don't Know

*Alyssa Dahl, MPH, CPH*

**IT'S ALWAYS EXCITING TO SEE** new episodic bundling models being considered, as it's indicative of the industry's movement toward getting better value out of the healthcare system. It's also a validation of all the work of early adopters of bundled payment models over the past 5 years (See **SP572**). With HHS Secretary Alex Azar's November 8, 2018, announcement of an upcoming bundle in radiation oncology,[1] CMS is showing its continued commitment to creating innovative ways of transforming care.


DAHL

CMS' announcement wasn't a surprise—the payer has been vocal that their work in oncology isn't done yet. However, it has been heartening to see that, despite political changes in the Trump administration and the time taken to re-evaluate these programs and how they're being implemented, the play button for bundled payment models has been pressed again.

Here is what we know so far:

This new bundle will be specific to patients undergoing radiation treatment. Patients being treated with radiation therapy alone are currently excluded from the Oncology Care Model (OCM), and patients who may be undergoing both chemotherapy and radiation can have periods of their cancer journey omitted from an OCM episode. Having a radiation oncology bundle will help oncology practices cover a larger pool of patients in a care transformation model. Radiation oncology episodes will also likely be shorter in duration than OCM episodes, to reflect the length of radiology treatment regimens and a period of monitoring for complications.

The 2 major unknowns:

1. A looming question is: Will this bundle remain mandatory, as Azar stated during his announcement? It's an aggressive decision because CMS hasn't developed this kind of bundle in the past, and the agency does not have the benefit of experience from participants in a voluntary version to serve as a foundation. There are a few radiation oncology bundles in the private sector that could dissuade CMS from making this model mandatory, but we will have to wait and see how those play out.

2. Questions remain around the alignment of this bundle with the current OCM. If the models run concurrently, some patients may fall into both an OCM and radiation oncology episode. CMS will need to determine how to calculate savings and how to allow for cross-participation across the 2 models. Episode attribution to either program will not be as simple as when the Comprehensive Care for Joint Replacement program was introduced while the original Bundled Payments for Care Improvement program was still running. For these 2 oncology bundles, there are many ways CMS could go.

Participants should stay tuned to see if there is anything in CMS' rulemaking that could possibly exclude their participation or affect their attributed OCM population. If there is, they may want to provide commentary to CMS to help shape the future of both programs. Over the coming weeks, we will be evaluating what can be modeled using the current and forthcoming program details; we encourage participants to be ready to have conversations around any new information we receive about this program in the coming weeks. ◆

**AUTHOR INFORMATION**

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# Data and Collaboration Are Key for Value-Based Care Success

*Laura Joszt*

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**PAGE**

*Ray D. Page, DO, PhD, FACOI, medical oncologist at The Center for Cancer and Blood Disorders*

**GALLO**

*Tom Gallo, MS, executive director, Virginia Cancer Institute; president, Association of Community Cancer Centers*

**BRILLSTEIN**

*Lili Brillstein, MPH, director, episodes of care, Horizon Blue Cross Blue Shield of New Jersey*

**ALTHOUGH THE UNITED STATES** now spends almost twice as much on healthcare compared with peer nations, this spending was much closer to other nations just a few decades ago. The biggest culprit: prices, explained Sibel Blau, MD, medical oncologist at Northwest Medical Specialties, PLLC, at the November 7 meeting of *The American Journal of Managed Care*®'s The Institute for Value-Based Medicine®. The dinner discussion, "Advancing Quality in Oncology Care" was held in Seattle, Washington.

Blau kicked off the meeting with an overview of the economics of cancer care in the United States, highlighting that the cancer market is lucrative for investors and cancer care far exceeds any other disease with drug costs and hospital prices as major contributors to cost inflation, when looking at all healthcare expenditures.

By 2026, there will be an estimated 20.3 million cancer survivors, an increase of 16% from 2016, and those survivors will be feeling the burden of the cost of their treatments.

"There are a lot of [patients with cancer who] are going to be living longer because of all the discoveries and drugs and advances; but it's expensive, so up to one-third of those patients will incur medical debt and up to 78% will face financial hardship," Blau said.

Although CMS has mandated the transition from volume- to value-based care, these programs are not perfect, as the following panelists discussed.

## The Value Equation

Ray D. Page, DO, PhD, FACOI, medical oncologist at The Center for Cancer and Blood Disorders (CCBD), noted that the old system was definitely not working. Not only did it drive up costs for patients, but the traditional system also led to community oncology practices closing at a fast rate. Data from the Community Oncology Alliance have shown that more than 400 practices closed a site in 2017 and more than 600 were acquired by a hospital.

"In the traditional buy-and-bill system, if you're going to stay in that system and not make transformational changes … an oncology practice will die under a fee-for-service plan, buy-and-bill method alone," Page said.

Currently, practices are stuck between 2 worlds, said Tom Gallo, MS, executive director of Virginia Cancer Institute (VCI) and president of the Association of Community Cancer Centers. As long as the transition to value-based care is incomplete, some of what practices do for value-based care could hurt them in fee-for-service and vice versa. So, although people are trying to be encouraged to seek care at lower-cost sites of care, hospitals are still incentivized by having bodies in the beds.

"You really have this dichotomy going on as we go through this transition," Gallo said.

The challenge, as practices continue to get squeezed between the colliding universes of fee-for-service and value-based care, is that the equation for calculating value has gotten more complicated. The simple, widely held view is that value equals quality at the lowest cost. But the government has far more difficult equations it uses to calculate value, according to the Medicare Access and CHIP Reauthorization Act and the Oncology Care Model (OCM).

"It's not unlike your IRS tax forms," Page said. The final equation becomes a massive calculation across multiple lines on a spreadsheet, with equations to figure out individual aspects of a larger, final equation.

He ran through multiple slides that outlined how if practices want to figure their target price for a given episode, they first have to calculate the baseline price, the trend factor, the novel therapies adjustment, and the OCM discount rate.

What the OCM equation misses are things like the art of medicine, compassion, personalized medicine, and social determinants of health, Page noted.

**"None of these programs are perfect, but we thought it was important to be involved in the beginning. If you're not at the table, you're on the menu."**

—Tom Gallo, MS, executive director, Virginia Cancer Institute; president, Association of Community Cancer Centers

After 2 performance period results from the OCM, he admitted that his practice, which worked with UnitedHealthcare for an episode-fee pilot program and was 1 of 3 practices in Aetna's Medical Home Shared Savings program and 1 of 7 practices in the COME HOME program, was still in the red. Although they're currently in performance period 5, practices just received results from the second period, highlighting the huge lag time until practices receive data about what they're doing. Once performance period 7 hits, CCBD will have to entertain going into a 2-sided risk model as part of the OCM's structure that moves practices out of 1-sided risk and into 2-sided risk if they have not achieved performance-based payments by the time of performance period 4 reconciliation (expected to take place around the middle of 2019).

Both Gallo and Page noted that participating in the OCM and other value-based models requires large practice transformation in order to be successful.

"When you start thinking about [value-based care], the first question is, do you first go out and get value-based care contracts? Or do you undertake practice transformation and process improvement first?" Gallo asked. "It's a really difficult question to answer."

He pointed out that since a lot of programs use historical costs as a benchmark and to create a target, practices with higher costs have the most potential for shared savings.

"So, if you do process improvement first, you reduce your costs, you've already taken care of a lot of the low-hanging fruit," Gallo. "It actually makes it more difficult for you to achieve success, at least financial success, in a number of these models."

Ultimately, Gallo's group had made many changes before the first value-based care contracts and well before the OCM. The practice introduced financial counselors to help patients make payments, instituted a same-day clinic and weekend hours,

utilized National Comprehensive Cancer Network distress assessments, and implemented follow-up calls after the first chemotherapy session.

VCI also formed an accountable care organization with 20 other practices in the market. Not only does this improve care, but it allows practices to stay independent, which maintains a strong referral base.

"What we've done through this organization is really be able to communicate much better with each other in terms of looking at our overall costs, brainstorming ways to reduce those costs, and actually implementing it," Gallo said.

## Practice Transformation

Some of the major practice transformations CCBD has made to manage its patients with cancer included implementing oncology clinical pathways and triage/symptom management pathways; hiring nurse navigators to educate patients on insurance requirements, the triage process, and support services; gotten actuarial support to understand the OCM data and make improvement changes; utilized a risk-stratification tool that uses artificial intelligence to analyze 30-day mortality, decline in 6 months, depression, pain, and emergency department (ED) risk; and added support services to mitigate risk from peripheral problems.

Now that the practices have implemented changes, both Page and Gallo noted that they are using the data from CMS under the OCM to identify new opportunities. Gallo called the OCM a "treasure trove of data."

He said that VCI is now more cognizant of the cost of prescription drugs; has a pathways committee that looks at efficacy, cost, and financial burden; and has taken a look at end-of-life care, including deaths in hospital with no hospice and the proportion of patients enrolled in hospice while in the hospital.

Page acknowledged that his practice doesn't maximize the evaluation and management codes to get paid for all the services it provides. It also wants to improve palliative care coordination and utilize more telemedicine, especially in rural areas since the analysis of OCM data showed issues among rural patients who go to the ED when they have health concerns because they don't have access to the right resources where they live. The practice is also investigating home visits and how to better coordinate care with specialists.

He finished by emphasizing the need for collaboration. CCBD and VCI are both part of the Quality Cancer Care Alliance, one of a number of national supergroups that have formed to pool information and share best practices.

"To stay alive…you can't do it on your own," Page said. "This is a team sport, so we have to share our knowledge…"

Gallo added that collaboration is important because the value-based care movement is affecting everyone. It isn't just affecting oncology, either, and practices in the community can learn best practices from one another.

"We'll try anything when it comes to these programs to see what works and what doesn't when it comes to reducing costs," he said.

Both Page and Gallo noted that the OCM, and most value-based care programs, are not perfect. Page said that the OCM has a lot of flaws and still needs to be tweaked. Gallo agreed, saying that his group finds flaws with the program every day. Regardless, participating in it is critical.

"None of these programs are perfect, but we thought it was important to be involved in the beginning," Gallo said and quoted the old maxim, "If you're not at the table, you're on the menu. We wanted to be at the table."

## The Payer's Role

The meeting closed out with a payer perspective as Lili Brillstein, MPH, director of episodes of care at Horizon Blue Cross Blue Shield of New Jersey, highlighted how the payer had collaborated with its providers to build a model for value-based care.

She explained that under fee-for-service, all parties would come to the table with their "dukes up," fight, negotiate, and come away with a decision that made no one happy, all without mentioning the patient. Then the parties don't speak for another 3 years, until they go through the process again. The focus in this type of contracting is on all the care rendered by 1 physician or practice without considering whether the patient gotten better or had a good experience.

In contrast, value-based care relies on communication and collaboration between all parties in order to be successful. Instead of focusing on care from 1 physician, these contracts focus on "care rendered to 1 patient across the continuum," Brillstein explained.

Under the episodes-of-care model Horizon uses to engage specialists, physicians are accountable for all care rendered to the patient, which is much more difficult and requires more information, which the payers provide in a format that allows physicians to see across the continuum of care and where there are opportunities to make changes.

However, Brillstein acknowledged that stil, nothing is built to support value-based care models. "Everything is still built on the fee-for-service chassis." As a result, Brillstein is a big proponent of upside-only models, which allows for extra time for all parties to work out the kinks.

The Horizon episode-of-care model sits on a fee-for-service chassis that began as a retrospective, upside-only model. If there are no savings, Horizon and the providers can work together to find out where opportunities were missed. The next stage is to move to a low-risk model that has downside risk capped.

Horizon is also working on an oncology medical home that is in response to New Jersey providers in the OCM who weren't performing well. Horizon built an OCM-like model with no risk that provides a per member per month payment. There will also be a stage with low risk, and if all goes well, the model may move to full risk—although Brillstein acknowledges they may never get to that.

She also took time to discuss that value-based care provides opportunities, although people rarely talk about it, to bring in complimentary therapies. However, if these value-based care models are done right, there should be enough money saved from some of the activities done to be successful that healthcare can fund things like Uber to get patients to the doctor's office, medical nutrition, meditation, and yoga.

"All sorts of things that in a fee-for-service model would never even be considered," Brillstein said. "But in a value-based model, the focus is on the outcomes. What has the biggest impact on the patient's outcome for the lowest cost?" ◆

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Rubraca® (rucaparib) tablets:

# TWO INDICATIONS. MORE PATIENT TYPES.

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

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MAINTENANCE

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

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

**Select Important Safety Information**

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

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

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

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

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

CLOVIS ONCOLOGY

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

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


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

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

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

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

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

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

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

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

Rubraca® (rucaparib) tablets

**RUBRACA® (rucaparib) tablets, for oral use**

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

## INDICATIONS AND USAGE

### Maintenance Treatment of Recurrent Ovarian Cancer

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

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

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

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Myelodysplastic Syndrome/Acute Myeloid Leukemia

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

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

### Embryo-Fetal Toxicity

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

## ADVERSE REACTIONS

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

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

### Clinical Trials Experience

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

#### Maintenance Treatment of Recurrent Ovarian Cancer

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## DRUG INTERACTIONS

### Effect of Rucaparib on Cytochrome p450 (CYP) Substrates

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

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy

***Risk Summary***

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

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

### Data

Animal Data

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

### Lactation

***Risk Summary***

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

### Females and Males of Reproductive Potential

***Pregnancy Testing***

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

***Contraception***

Females

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

### Pediatric Use

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

### Geriatric Use

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

### Hepatic Impairment

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

### Renal Impairment

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

## OVERDOSAGE

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

## PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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# Getting the Patient's Viewpoint in the Oncology Quality Equation

*Mary Caffrey*

**LOPEZ**

*Ana Maria Lopez, MD, MPH, vice chair, medical oncology; chief, New Jersey Division, Sidney Kimmel Cancer Center at Thomas Jefferson University*

**PATEL**

*Kashyap Patel, MD president and CEO, Carolina Blood and Cancer Care Associates*

**RUIZ DE SOMOCURCIO**

*Michael Ruiz de Somocurcio, vice presdient for payer and provider collaboration, Regional Cancer Care Associates*

**CSIK**

*Valerie P. Csik, MPH, CPPS, project director for practice transformation, Sidney Kimmel Cancer Center at Thomas Jefferson University*

**IF PHYSICIANS CAN DEMONSTRATE** they delivered good care, but the patient is left feeling unhappy, what does that tell us about quality?

According to Ana Maria Lopez, MD, MPH, vice chair of medical oncology and chief of the New Jersey Division of the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, Pennsylvania, it may mean that physicians are using the classic value equation of quality over cost—although an update would factor in customer service.

Lopez led the discussion at the Philadelphia meeting of the Institute for Value-Based Medicine®, an initiative of *The American Journal of Managed Care®*, which also featured Kashyap Patel, MD, president and CEO, Carolina Blood and Cancer Care Associates (CBCCA); Michael Ruiz de Somocurcio, vice president for payer and provider collaboration at New Jersey-based Regional Cancer Care Associates (RCCA); and Valerie P. Csik, MPH, CPPS, project director for practice transformation, Sidney Kimmel Cancer Center at Thomas Jefferson University.

According to Lopez, it's important to ask how cost is defined. What factors are considered? Before service was part of the equation, she said, sometimes "patients were still not happy with the care they were receiving, although we could say demonstrably that it was quality care."

From the perspective of a physician, the things that mattered—improved clinical indicators, fewer adverse effects—might not be the things that mattered to patients when they were asked. Often, patients being treated for cancer mentioned things that had nothing to do with their medical care: less time waiting, no problems parking the car, good food in the cafeteria.

As an oncologist, Lopez said, "That has nothing to do with me and quality care, but it has to do with quality of life. And we have the data that improvements in quality of life improve outcomes."

So, as the population ages, and more people receive a cancer diagnosis—as the disease is diagnosed earlier and treatment costs rise because patients live with the disease for longer periods—quality of life and patient experiences are rising on the radar. If a patient has a rough time parking every time they come to the clinic, and has checkups every 3 to 6 months for several years, that's a problem.

What can be done? Lopez said the future lies in integrated practice units, which identify conditions and map out the delivery process as far out as possible. "When you do that, you realize care crosses department lines and service lines, and really needs lots of coordination," she said. Integrated care allows the health system to ensure that the right care is delivered to the right patient at the right location. A single electronic health record (EHR) is key to a better experience.

It's also important to help the patient become more effective and responsible for their own care, Lopez said. "This really is a partnership," she said. "We really want to engage the patient, so they can be a part of this experience."

Using metrics to measure quality, service, and cost—and to reward innovation—will require that health systems do what's in the patient's best interest, even if it sometimes means competitors within a given market work together, Lopez said. But as practices in the Oncology Care Model (OCM) have seen, when clinicians get the opportunity to see how they compare with their peers, they will say, "I don't want to be the most expensive person."

Pathways help decrease variability and cost, she said; the adherence target should be in the range of 70% to 85%, so there is allowance for individual circumstances and adaptation to new knowledge. Health systems must ask what processes their pathways use to incorporate innovation.

But Lopez offered a word of caution about metrics.

"Often," she said, "we measure what is easy and most accessible, and that may not be what's giving us the most value."

## Better Patient Access: the "Lowest-Hanging Fruit"

Some practices in the OCM have struggled to achieve savings, but CBCCA isn't one of them. Patel presented data showing that the relatively small oncology/hematology practice of 5 oncologists and 1 mid-level practitioner has seen success under the model. After up front investments of $715,000 including capital costs on technology, the practice is on track to achieve annualized savings of $550,000, while the savings for Medicare are $1.08 million.

> **"It's about instructing the patient to come to the office when they need to. Improving access is probably the lowest hanging fruit that our system has not emphasized."**
>
> —Kashyap Patel, MD,
> President and CEO,
> Carolina Blood and Cancer Care Associates

Patel insists there's no hidden formula. "The one thing that helped us the most was expanded access," he said. By keeping 2 appointment slots open each day for walk-ins or same-day patients, and by encouraging them to simply come in or use an urgent care center instead of the emergency department (ED), the practice has not only saved money but improved quality of life—for both patients and the doctors.

"We've reduced calls from 10 every night to 1 to 2 every night," Patel said. "It's not rocket science. See the patients when they need to be seen."

The practice saves money another way: Patel and his fellow oncologists evaluate the OCM feedback reports themselves, making adjustments instead of using consultants, as larger practices do.

Patel even makes some home visits, especially for patients who live in remote areas. It's all part of embracing what's required in the OCM, which calls for reducing the burden on the patient.

At the start, CBCCA leaders asked the staff for ideas on how to fully engage patients.

"They asked, 'Can we have a holistic approach?'" Patel said that besides things like upgraded computerized axial tomography scan technology, employees developed an education booklet with staff photos so patients know everyone's name and created a calming garden and fountain within the facility. One physician serves as a voluntary chaplain, and there is great attention to spirituality and end-of-life care.

Physicians also have embraced the use of biosimilars, especially filgrastim-sndz (Zarxio), to promote growth of neutrophils and prevent infection. Patel said the practices has not experienced resistance from patients to using biosimilars.

Their success has not gone unnoticed. The Center for Medicare and Medicaid Innovation is working with CBCCA to help it become one of the first oncology practices to take on 2-sided risk, and Patel is exploring innovative reinsurance ventures with other practices around the country that would make this financially feasible.

In Patel's view, it all comes back to the basics. "It's about instructing the patient to come to the office when they need to," he said. "Improving access is probably the lowest hanging fruit that our system has not emphasized."


Ana Marie Lopez, MD, MPH, and Valerie Csik, MPH, CPPS, both with Philadelphia-based Sidney Kimmel Cancer Center at Thomas Jefferson University, discussed efforts to implement value-based initiatives at the institution.

PHOTO © SKCC/THOMAS JEFFERSON UNIVERSITY

## The Value of Partnerships

RCCA operates in 4 states and treats 33% of all cancer cases in New Jersey. Ruiz de Somocurcio said this means dealing with a variety of payers and value-based care initiatives, from the OCM to bundled-payment programs with commercial payers, the largest being Horizon Blue Cross Blue Shield of New Jersey.

"When you're in these programs, it's absolutely critical that you work with community physicians outside of your walls," he said. These are all total-cost-of-care programs, so the oncologist is responsible whether the patient also has diabetes "or even if they get hit by a car." Figuring out how to find value by working with the independent physician is key, "based on site of service alone," Ruiz de Somocurcio said. And health plans have been receptive.

As he explained, value-based care in oncology isn't happening in a vacuum. Mergers between Cigna and Express Scripts, Aetna and CVS, and collaborations among Amazon, JP Morgan Chase, and Berkshire Hathaway are just some examples of healthcare realignment. "That's going to impact choices," Ruiz de Somocurcio said.

While the market shifts toward downside risk, he said RCCA is determined to get there ahead of the curve, and things seem to be moving toward an oncology medical home model, with quality metrics that focus on advanced care planning, pain, and management of depression, alongside cost metrics that target ED and inpatient admissions, as well as end-of-life care.

Data sharing is key. To get data, an entity must give it as well. But without data, taking on additional risk makes little sense. Doing so has revealed that the highest-cost patient isn't just the patient with cancer; rather, it's the patient with existing comorbidities, like congestive heart failure, who develops cancer. Scrutinizing data has also shown:

- Post acute care costs are 2 times higher than national averages compared with other OCM practices.
- New Jersey admits too many patients with cancer who appear at the ED, and this is consistent across all hospitals.
- End-of-life care needs improvement, particularly with physician buy-in.

Meanwhile, providers who are not in the OCM are adapting the impact of the Merit-based Improvement Payment System. CMS, Ruiz de Somocurcio said, "is creating winners and losers," which will further drive consolidation.

## What Do Stakeholders Value?

Csik gave an overview of the many initiatives attempted over the past decade to move reimbursement away from fee-for-service to outcomes-based models. Although the Trump administration initially balked at continuing some value-based models that started under its predecessors, that seems to be shifting, with HHS Secretary Alex Azar announcing November 8, 2018, that a radiation oncology model would be coming shortly.[1]

It's important to understand how different stakeholders define value. Patients want to know that the doctor they are seeing is in network. Physicians want a streamlined referral process. Payers want cost control.

Csik described an approach to practice transformation that included many of the same elements that Patel and Ruiz de Somocurcio included: having clearly defined goals, investing in technology, minimizing clinical variation, using data to promote accountability, reducing trips to the ED and unnecessary hospitalization, and improving end-of-life care.

The key to it all, she said, "is the commitment—staying the course. I think all of us that have participated in the Oncology Care Model have recognized the many shifts and changes that CMS has made in the last 2-and-a-half plus years in that program and they will continue to make in the remaining few years of the program. That agility is something that's really critical in terms of our ability to sustain progress."

Early efforts at value-based care, "heightened our awareness but didn't really give us a framework," Csik said. The OCM did just that and required Jefferson to learn and adapt to the data it was receiving.

Accelerating the process will happen through several strategies:

- Data optimization, which calls for "digging in" on performance and cost, and sharing both
- Incorporating a pharmacy strategy that includes an evaluation process for making therapy switches
- Improving navigation strategy and building a team of nurse and lay personnel, across disease states
- Instituting end-of-life strategies that include supportive medicine and social workers

Csik credited the rise of the OCM with driving conversations about improving care that would not otherwise happen. The key now is not just focusing on what payers need, but what patients want as well. "We need to understand what the stakeholders value," she said. ◆

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*Coverage by Mary Caffrey; Allison Inserro; Laura Joszt; David Bai, PharmD; and Samantha DiGrande*

# Azar Announces Mandatory Oncology Payment Model Is Coming

**A MANDATORY PAYMENT MODEL** is coming in oncology care, HHS Secretary Alex Azar said November 8, 2018, during an appearance at a value-based care summit.

Azar said that the administration would "revisit" mandatory models that it had previously scrapped in cardiac care and, in prepared remarks emailed to *Evidence-Based Oncology*™, the time had come for "exploring new and improved episode-based models in other areas, including radiation oncology."

Right now, the Center for Medicare and Medicaid Innovation is working with practices on care transformation through the Oncology Care Model (OCM), but that that 5-year pilot is voluntary.

The Trump administration did not move forward with a mandatory cardiac care model that was developed under the Obama administration and pulled back on bundled payments that were set to be made mandatory in several markets for hip and knee replacements. Those decisions were made by Azar's predecessor, Tom Price, MD, an orthopedic surgeon who was a known critic of bundled payments.

However, Azar, who previously worked in the pharmaceutical industry, said in prepared remarks to the Patient-Centered Primary Care Collaborative that bundled payments are back, and not just through voluntary programs like the Bundled Payments for Care Improvement initiative, which he said has shown significant savings.

Azar had a different message about mandatory bundles: "We have now re-examined the role that models like these could play in value-based transformation," he said. "We're also actively looking at ways to build on the lessons and successes of the Comprehensive Care for Joint Replacement Model." He cited the agency's ambitions as complementing the coming mandate to peg Medicare drug prices to what other countries pay based on an international index.

In a statement, the chief executive officer of the American Society for Radiation Oncology (ASTRO) said the organization is pleased that a radiation oncology alternative payment model (RO-APM) is moving forward, but also expressed concern that it would be mandatory from the start. "ASTRO has worked for many years to craft a viable payment model that would stabilize payments, drive adherence to nationally recognized clinical guidelines, and improve patient care. ASTRO believes its proposed RO-APM will allow radiation oncologists to participate fully in the transition to value-based care that both improves cancer outcomes and reduces costs," said Laura Thevenot. "Care must be taken to protect access to treatments for all radiation oncology patients and not disadvantage certain types of practices, particularly given the very high fixed costs of running a radiation oncology clinic."[1]

Steven J. Libutti, MD, FACS, director of the Rutgers Cancer Institute of New Jersey and Robert Wood Johnson Medical School and vice chancellor for Cancer Programs for Rutgers Biomedical and Health Sciences at Rutgers University, also said in an interview that implementation of what HHS is planning will be key in determining how it is received. "It depends on what we're defining as the bundle and how we define bundled care versus episodes of care," he said. "The concepts are similar, but how they are implemented are different."

Bundling a payment is not the same thing as an episode of care, and the cancer institute and some payers, most notably Horizon Blue Cross Blue Shield of New Jersey, are exploring the idea of care episodes with some test cases. "Episodes of care are really looking at the payment and the specific illness that they're dealing with and defining what we consider the start of their engagement with that episode and what would be the end of the acute care of that episode," Libutti said.

Providing all the episodes of that care, defining the cost, and setting the stages for how payments are received, such as up front or during milestones, is complicated by several varying factors, he said. Those factors include "where the care is being delivered, what stage of disease the patient has, the requirements of what components of care are in that bundle, or episode."


HHS Secretary Alex Azar announced November 8, 2018, that the CMS will pursue a new mandatory payment bundle in radiation oncology.

Although Libutti agreed with the idea of looking at episodes of care, because it will lead to better quality and value, bundling payments alone, without including quality and keeping the patient in mind, may not be the best way to either deliver value or lower costs, he said.

"We just have to be careful as we formulate these episodes that we're keeping value as the primary goal of what we're trying to do," said Libutti. ◆

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# ACOs Had No Significant Impact on Spending for Patients With Cancer

**ALTHOUGH ACCOUNTABLE CARE ORGANIZATIONS** (ACOs) have been shown generally to reduce costs for patients compared with similar patients who didn't receive care in an ACO, the same cannot be said for cancer care in ACOs.[1] ACO practices did reduce costs for cancer care, but not at a more significant rate than non-ACO practices during the same time.

A study in the *Journal of Clinical Oncology*, the journal of the American Society of Clinical Oncology, compared patients with cancer who were treated at ACO practices with those treated at non-ACO practices in the same geographic region.[2]

With the high cost of cancer care and the incidence of cancer expected to increase as the population ages, "it is critically important to understand how broad policy efforts to control healthcare spending are impacting the care of patients with cancer," the authors wrote.

The researchers analyzed a 20% sample of Medicare fee-for-service beneficiaries using 2011 to 2015 Medicare Research Identifiable files. They matched practices that became part of an ACO to non-ACO practices in the same region and calculated costs and utilization for beneficiaries.

The analysis showed that total mean spending per beneficiary was significantly different between ACO and non-ACO patients in the pre-ACO period ($18,909 vs $18,458, respectively), but that decrease in spending for ACO

patients (–$308) was not significantly different from the decrease in spending for non-ACO patients (–$319).

The data showed a significant increase in outpatient spending from the pre- to post-ACO periods, but the increases were not significantly different between ACO and non-ACO patients. In comparison, radiation therapy and chemotherapy spending decreased between the pre- and post-ACO eras, but there were no differences in the decreases between the 2 groups.

The authors postulated a few reasons why ACO practices didn't reduce spending or utilization much more than non-ACO practices. For instance, cancer care is complex and requires coordination across a variety of providers and settings, and it can be difficult to implement strategies to reduce utilization across settings. Second, technological advances and novel devices and drugs have contributed to the increasing cost of cancer care. Third, ACOs may have been targeting other chronic diseases.

Lastly, oncology providers have been engaged in multiple initiatives to promote value and alternative ways to deliver and pay for care, such as the Oncology Care Model and oncology medical homes, which could have resulted in widespread improvements that simultaneously affect both ACO and non-ACO patients.

**The authors speculated why accountable care organization practices did not reduce spending or use of medical services much more than other practices. Cancer care is complex and demands coordination across a variety of providers and settings, which can make it difficult to reduce healthcare utilization. Technological advances and new treatments are driving up costs, too.**

"Although it may be too early to see an impact of ACOs on patients with cancer, it is also possible that ACOs may need to explicitly focus on patients with cancer to improve their care and reduce unnecessary spending," the authors concluded. ◆

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## Tisagenlecleucel's High Price Aligns With Its Benefit in Pediatric B-ALL, Study Results Find

**DESPITE THE HIGH COST** of tisagenlecleucel (Kymriah), the chimeric antigen receptor (CAR) T-cell therapy to treat pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL), the benefits of the treatment support the price, according to research in *JAMA Pediatrics*.

A group of researchers that included individuals from the Institute for Clinical and Economic Review compared life-years gained, quality-adjusted life-years (QALYs) gained, and incremental costs per life-year and QALY gained of tisagenlecleucel with the chemoimmunotherapeutic agent clofarabine (Clolar).

Although research has shown that tisagenlecleucel has higher rates of response, event-free survival, and overall survival compared with other therapies used to treat this population, the "follow-up for patients receiving tisagenlecleucel is limited, with a maximum duration of less than 4 years; therefore, uncertainty remains around its long-term benefit," the authors explained.

They used a decision analytic model to extrapolate trial evidence from 3 studies and collected all costs and outcomes expected from the CAR T-cell therapy. They analyzed the therapy from a payer perspective and estimated outcomes over a patient's life.

They found that more than 40% of patients who initiated tisagenlecleucel would become long-term survivors or would be alive and responding to treatment after 5 years. In comparison, only 10% of patients who receive clofarabine would be long-term survivors.

The total discounted cost of tisagenlecleucel was $667,000, with 10.34 discounted life-years gained and 9.28 QALYs gained. Clofarabine had a total discounted cost of $337,000, with 2.43 discounted life-years gained and 2.10 QALYs gained. The approximate incremental cost-effectiveness ratio of tisagenlecleucel versus clofarabine was $42,000 per life-year gained and $46,000 per QALY gained.

The researchers ran multiple scenarios to account for long-term relapse and survival, and the cost-effectiveness estimates ranged from $37,000 to $77,500 per QALY gained. They concluded that tisagenlecleucel is priced in alignment with its benefits over a patient's life.

"Financing cures in the United States is challenging owing to the high up-front price, rapid uptake, and uncertainty in long-term outcomes; however, innovative payment models are an opportunity to address some of these challenges and to promote patient access to novel and promising therapies," the authors wrote. ◆

**REFERENCE**

Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term survival and value of chimeric antigen receptor T-cell therapy for pediatric patients with relapsed or refractory leukemia [published online October 8, 2018]. *JAMA Pediatr.* doi: 10.1001/jamapediatrics.2018.2530.

## Three Genetic Types Drive Higher Prevalence of Multiple Myeloma in African Americans

**MULTIPLE MYELOMA (MM) OCCURS** 2 to 3 times more frequently in Americans of African descent than in Americans of European descent, and a new study[1] has identified 3 gene types that account for this disparity.

The paper, published in *Blood Cancer Journal*, demonstrated that the disparity is largely driven by disparities in the occurrence of the t(11;14), t(14;16), and t(14;20) subtypes of MM.[1]

"We sought to identify the mechanisms of this health disparity to help us better understand why myeloma occurs in the first place and provide insight into the best forms of therapy," Vincent Rajkumar, MD, a hematologist at Mayo Clinic and senior author of the study, said in a statement.[2]

The researchers studied 881 patients with monoclonal gammopathies. Whereas previous research into disparities in prevalence of disease has relied on self-reported race, this study identified the ancestry of patients through DNA sequencing. Self-reported race can result in bias, but the DNA sequencing allowed researchers to determine ancestry more accurately, Rajkumar said.

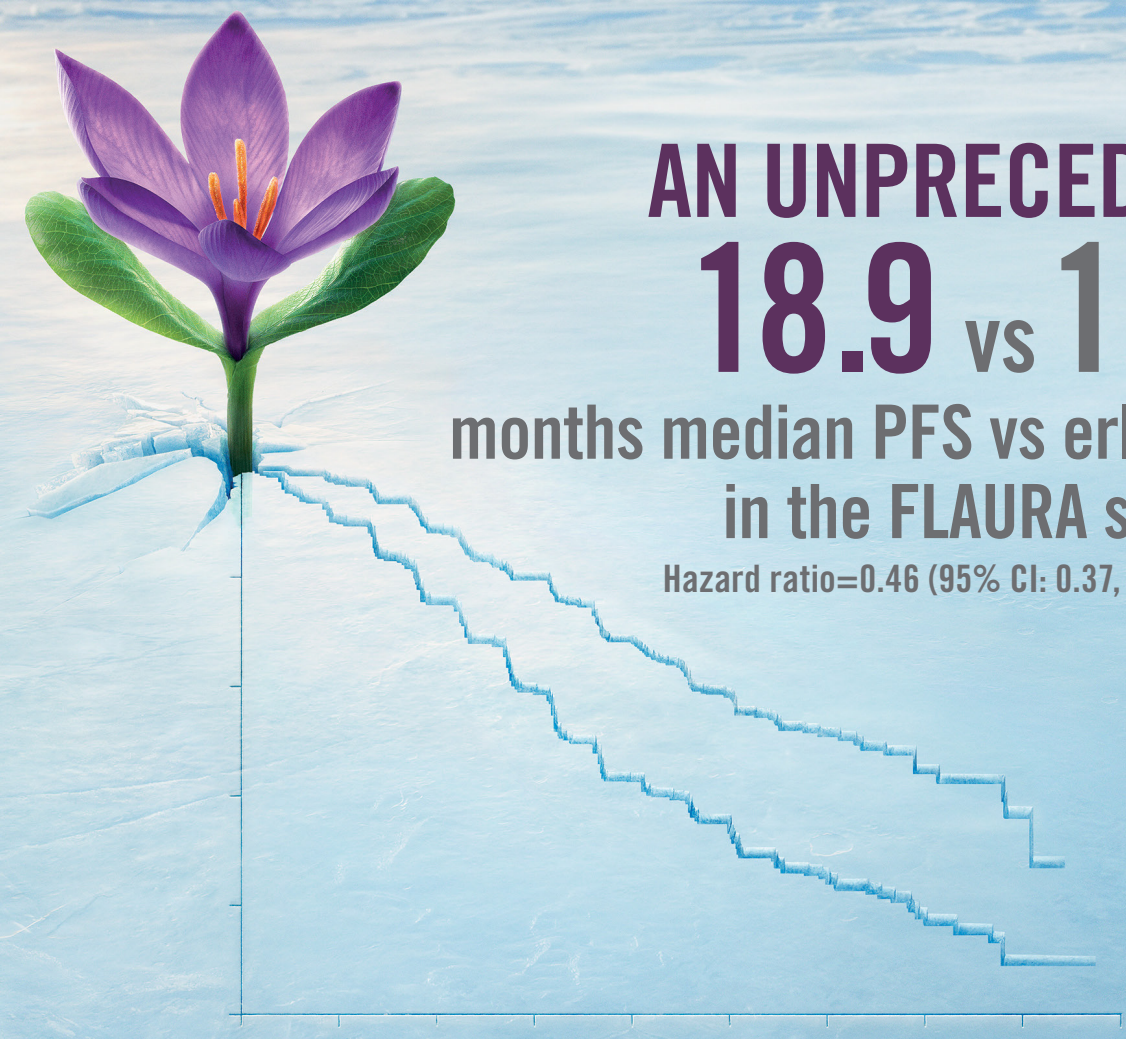
In the entire cohort, the median African ancestry was 2.3%, the median European ancestry was 64.7%, and the median Northern European ancestry was 26.6%. To better observe differences in the prevalence of MM subtypes, the authors separated the cohort into the most extreme populations with regard to African ancestry.

"Although many individuals in the US are of mixed ancestry, ancestral characterization of patient cohorts is required to fully understand how the role of human genetic variation associated with ancestry impacts health disparities," the authors wrote.

CONTINUED ON SP578 »

FOR THE TREATMENT OF METASTATIC EGFRm NSCLC

# FIRST-LINE TAGRISSO® DELIVERED



## AN UNPRECEDENTED

## 18.9 vs 10.2

**months median PFS vs erlotinib/gefitinib in the FLAURA study**

Hazard ratio=0.46 (95% CI: 0.37, 0.57), *P*<0.0001

Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg, once daily). Crossover was allowed for patients in the EGFR TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v.1.1). Secondary endpoints included OS, ORR, and DOR.[1,2]

## INDICATION

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

## SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported.

AstraZeneca

# GROUNDBREAKING EFFICACY

**DOSING**

**First-line TAGRISSO offers convenient, once-daily dosing, with or without food**[1]

**ALL SUBGROUPS**

**Delivered consistent PFS results across all subgroups, including patients with or without CNS metastases**[2]

NCCN CATEGORY 1 RECOMMENDED

**First-line osimertinib (TAGRISSO) is a National Comprehensive Cancer Network® (NCCN®) Category 1* option**[3]

*Category 1 means NCCN has uniform consensus based upon high-level evidence.[3]

## SELECT SAFETY INFORMATION

Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia

- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CNS, central nervous system; DOR, duration of response; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; ORR, overall response rates; OS, Overall Survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor.

**REFERENCES: 1.** TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.5.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 29, 2018. 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. To view the most recent and complete version of the guideline, go online to NCCN.org.

**Please see Brief Summary of Prescribing Information on adjacent pages.**

**LEARN MORE AT TagrissoHCP.com**

TAGRISSO®
osimertinib

## TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

### INDICATIONS AND USAGE

**First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)**

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

### DOSAGE AND ADMINISTRATION

**Patient Selection**

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens *[see Clinical Studies (14) in the full Prescribing Information]*. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

**Recommended Dosage Regimen**

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

**Administration to Patients Who Have Difficulty Swallowing Solids**

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

**Dosage Modifications**

Adverse Reactions

**Table 1. Recommended Dosage Modifications for TAGRISSO**

| Target Organ | Adverse Reaction[a] | Dosage Modification |
|---|---|---|
| *Pulmonary* | Interstitial lung disease (ILD)/Pneumonitis | Permanently discontinue TAGRISSO. |
| *Cardiac* | QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b] | Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose. |
| | QTc interval prolongation with signs/symptoms of life-threatening arrhythmia | Permanently discontinue TAGRISSO. |
| | Symptomatic congestive heart failure | Permanently discontinue TAGRISSO. |
| *Other* | Adverse reaction of Grade 3 or greater severity | Withhold TAGRISSO for up to 3 weeks. |
| | If improvement to Grade 0-2 within 3 weeks | Resume at 80 mg or 40 mg daily. |
| | If no improvement within 3 weeks | Permanently discontinue TAGRISSO. |

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

*Strong CYP3A4 Inducers*

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

**Interstitial Lung Disease/Pneumonitis**

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

**QTc Interval Prolongation**

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

**Cardiomyopathy**

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

**Keratitis**

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

**Embryo-Fetal Toxicity**

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

### ADVERSE REACTIONS

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

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Cardiomyopathy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Keratitis *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

**Clinical Trials Experience**

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

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) *[see Warnings and Precautions (5) in the full Prescribing Information]*.

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA***

| Adverse Reaction | TAGRISSO (N=279) | | EGFR TKI comparator (gefitinib or erlotinib) (N=277) | |
|---|---|---|---|---|
| | Any Grade (%) | Grade 3 or higher (%) | Any Grade (%) | Grade 3 or higher (%) |
| **Gastrointestinal Disorders** | | | | |
| Diarrhea[a] | 58 | 2.2 | 57 | 2.5 |
| Stomatitis | 29 | 0.7 | 20 | 0.4 |
| Nausea | 14 | 0 | 19 | 0 |
| Constipation | 15 | 0 | 13 | 0 |
| Vomiting | 11 | 0 | 11 | 1.4 |
| **Skin Disorders** | | | | |
| Rash[b] | 58 | 1.1 | 78 | 6.9 |
| Dry skin[c] | 36 | 0.4 | 36 | 1.1 |
| Nail toxicity[d] | 35 | 0.4 | 33 | 0.7 |
| Pruritus[e] | 17 | 0.4 | 17 | 0 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 20 | 2.5 | 19 | 1.8 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Cough | 17 | 0 | 15 | 0.4 |
| Dyspnea | 13 | 0.4 | 7 | 1.4 |
| **Neurologic Disorders** | | | | |
| Headache | 12 | 0.4 | 7 | 0 |
| **Cardiac Disorders** | | | | |
| Prolonged QT Interval[f] | 10 | 2.2 | 4 | 0.7 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue[g] | 21 | 1.4 | 15 | 1.4 |
| Pyrexia | 10 | 0 | 4 | 0.4 |
| **Infection and Infestation Disorders** | | | | |
| Upper Respiratory Tract Infection | 10 | 0 | 7 | 0 |

* NCI CTCAE v4.0
[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator
[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.
[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.
[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.
[e] Includes pruritus, pruritus generalized, eyelid pruritus.
[f] The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.
[g] Includes fatigue, asthenia.

**Table 3. Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients in FLAURA**

| Laboratory Abnormality[a,b] | TAGRISSO (N=279) | | EGFR TKI comparator (gefitinib or erlotinib) (N=277) | |
|---|---|---|---|---|
| | Change from Baseline All Grades (%) | Change from Baseline to Grade 3 or Grade 4 (%) | Change from Baseline All Grades (%) | Change from Baseline to Grade 3 or Grade 4 (%) |
| **Hematology** | | | | |
| Lymphopenia | 63 | 5.6 | 36 | 4.2 |
| Anemia | 59 | 0.7 | 47 | 0.4 |
| Thrombocytopenia | 51 | 0.7 | 12 | 0.4 |
| Neutropenia | 41 | 3.0 | 10 | 0 |
| **Chemistry** | | | | |
| Hyperglycemia[c] | 37 | 0 | 31 | 0.5 |
| Hypermagnesemia | 30 | 0.7 | 11 | 0.4 |
| Hyponatremia | 26 | 1.1 | 27 | 1.5 |
| Increased AST | 22 | 1.1 | 43 | 4.1 |
| Increased ALT | 21 | 0.7 | 52 | 8 |
| Hypokalemia | 16 | 0.4 | 22 | 1.1 |
| Hyperbilirubinemia | 14 | 0 | 29 | 1.1 |

[a] NCI CTCAE v4.0
[b] Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)
[c] Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

## DRUG INTERACTIONS

### Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in the full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

### Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

### Drugs That Prolong the QTc Interval

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

*Risk Summary*

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

### Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

### Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TAGRISSO.

Contraception

TAGRISSO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

*Females*

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

*Males*

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

### Pediatric Use

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

### Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

### Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CLcr) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr < 15 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

### Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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Rev. 08/18 US-23593 9/18

*Coverage by Mary Caffrey; Allison Inserro; Laura Joszt; David Bai, PharmD, and Samantha DiGrande*

CONTINUED FROM SP573

They found that the probability of having 1 of the 3 subtypes associated with higher risk of MM was significantly greater in the 120 individuals who had at least 80% African ancestry compared with the 235 individuals who had less than 0.1% African ancestry.

Previous research[3] has shown that despite being more likely to be given a diagnosis of MM, African Americans are underrepresented in MM disease research. As a result, improved overall survival for MM has largely been observed in Caucasian patients.

"There are efforts to enroll more minorities in clinical studies, and this is important," Rajkumar said. "However, it is equally, if not more important, to determine the mechanisms of racial disparities in terms of why cancers occur more often in certain racial groups. Our findings provide important information that will help us determine the mechanism by which myeloma is more common in African Americans, as well as help us in our quest to find out what causes myeloma in the first place." ◆

**REFERENCES**

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3. 3. Manoklovic A, Christofferson A, Liang WS, et al. Comprehensive molecular profiling of 718 multiple myelomas reveals significant differences in mutation frequencies between African and European descent cases. *PLoS Genet* 2017;13(11):e1007087. doi: 10.1371/journal.pgen.1007087.

## FDA Approves Cemiplimab-rwlc to Treat Second Most Common Skin Cancer

**THE FDA HAS APPROVED** the immune checkpoint inhibitor cemiplimab-rwlc, to be sold as Libtayo, for the treatment of metastatic cutaneous squamous cell carcinoma (CSCC) or in patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation.

CSCC is the second most common form of skin cancer and is responsible for nearly 7000 deaths each year in the United States. To date, the cancer accounts for an estimated 20% of all skin cancers in the United States, with the number of patients with the disease expected to rise on an annual basis.

Developed in conjunction by Regeneron Pharmaceuticals and Sanofi, cemiplimab-rwlc is a monoclonal antibody that targets the immune checkpoint receptor PD-1. According to Regeneron, this is the first and only treatment specifically approved and available for advanced CSCC in the United States.

The "FDA decision is great news for patients with advanced CSCC who previously had no approved treatment options.…Libtayo is an important new immunotherapy option for US physicians to help address a significant unmet need in this patient group," said Michael R. Migden, MD, lead investigator in the CSCC clinical program and professor in the departments of Dermatology and Head and Neck Surgery at The University of Texas MD Anderson Cancer Center.

Cemiplimab-rwlc was evaluated under the FDA's priority review pathway and was granted breakthrough therapy designation status for advanced CSCC in 2017. The recommended dosage of cemiplimab-rwlc is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until disease progression or unacceptable toxicity.

In the United States, the wholesale acquisition cost of the treatment is $9100 per 3-week treatment cycle; however, Regeneron and Sanofi noted that "the actual costs to patients are generally anticipated to be lower, as the list price does not reflect insurance coverage, copay support, or financial assistance from patient support programs."

"In the United States, CSCC accounts for 1 in 5 skin cancers, and the number of new diagnoses is increasing. We believe Libtayo has the potential to make a difference for US patients with advanced CSCC, as it helps to fill a critical gap in treatment options," said Olivier Brandicourt, MD, CEO of Sanofi. ◆

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## FDA Gives Speedy Approval to Brentuximab Vedotin for Peripheral T-cell Lymphoma

**THE FDA ANNOUNCED FRIDAY** that it expanded the approved use of brentuximab vedotin (Adcetris) in combination with chemotherapy for adult patients with certain types of peripheral T-cell lymphoma (PTCL), using a new review process designed to increase efficiency.

It is also the first FDA approval for the treatment of newly diagnosed PTCL. PTCLs are rare, fast-growing non-Hodgkin lymphomas that develop from T-cells, which spread quickly and are hard to treat. T-cell lymphomas account for between 10% and 15% of all non-Hodgkin lymphomas, according to the Leukemia and Lymphoma Society.

The pilot program under which the drug was approved, Real-Time Oncology Review (RTOR), allows the FDA to review much of the data after the clinical trial results become available and before the information is formally submitted to the FDA. The pilot focuses on early submission of data that are most relevant to assessing the safety and efficacy of a product.

The approval of brentuximab vedotin for PTCL is the fourth time the RTOR has been used, according to an FDA spokesperson.

"When the sponsor submits the completed application, the review team will already be familiar with the data and be able to conduct a more efficient, timely, and thorough review," said Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products, in a statement.[1]

Brentuximab vedotin is an antibody drug conjugate. Earlier this month, an analysis found that it was cost-effective[2] when combined with chemotherapy as frontline treatment for stage III or IV classical Hodgkin lymphoma.

The new approval was based on a clinical trial of 452 patients with certain PTCLs who received either brentuximab plus chemotherapy or a standard chemotherapy (CHOP) as first-line treatment. Progression-free survival was significantly longer (hazard ratio, 0.71; $P = .01$) in the brentuximab arm (median = 48 months vs 21 months with CHOP). Overall survival and overall response rates were also significantly better in the brentuximab arm.

The drug, sold by Seattle Genetics, had also received priority review and breakthrough therapy designation.

"By participating in the FDA's Real-Time Oncology Review process and working closely with the FDA, we are now able to make the Adcetris regimen available to previously untreated patients with CD30-expressing PTCL in an unprecedented less than 2 weeks after submission of our supplemental BLA," said Clay Siegall, PhD, the firm's president and chief executive officer of Seattle Genetics, in a statement.[3]

The most common adverse effects of brentuximab plus chemotherapy included peripheral neuropathy, nausea and vomiting, diarrhea, low white blood cell counts, fatigue, mouth sores, constipation, hair loss, fever, and anemia. ◆

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# New Melanoma Guidelines Identify Recommended Treatments, Weigh In on Genetic Testing

**NEW GUIDELINES RELEASED** by the American Academy of Dermatology (AAD) will help physicians provide the best treatment for more than 1 million Americans living with melanoma, the deadliest form of skin cancer. The guidelines were published[1] on Thursday, November 1, in the *Journal of the American Academy of Dermatology*.

"Guidelines of care for the management of primary cutaneous melanoma" outlines best practices for treating the disease and was developed by a work group of dermatologists, oncologists, and other experts.

"Melanoma is the deadliest form of skin cancer, and we hope these guidelines will help dermatologists and other physicians enhance their delivery of life-saving treatment to patients," board-certified dermatologist Susan M. Swetter, MD, FAAD, co-chair of the work group that developed the guidelines, said in a statement.[2] "In order to provide the best possible resource for practitioners, we reviewed the latest scientific data and addressed certain topics that weren't covered in the AAD's previous melanoma guidelines."

**According to the guidelines, patients with a family history of melanoma should receive education and counseling regarding their genetic risk, but formal genetic testing may not always be appropriate. The guidelines recommend that genetic testing be considered on an individual basis after counseling.**

Although melanoma is the deadliest skin cancer, current treatments are curative if the disease is detected early enough. The 5-year survival rate is 99% if melanoma is detected early and treated before it spreads to the lymph nodes.

The guidelines review biopsy techniques for lesions suggestive of melanoma; histopathologic interpretation of cutaneous melanoma; use of laboratory, molecular, and imaging tests, as well as follow-up for asymptomatic patients; treatment recommendations, including surgical and nonsurgical options; and the latest data regarding pregnancy and melanoma, genetic testing, and management of toxicities related to novel targeted agents and immunotherapies.

According to the guidelines, patients with a family history of melanoma should receive education and counseling regarding their genetic risk, but formal genetic testing may not always be appropriate. The guidelines recommend that genetic testing be considered on an individual basis after counseling.

Surgical excision is identified as the gold standard of treatment, but it is noted that Mohs surgery or other forms of staged excision may be considered for certain subtypes. Topical therapy or traditional radiation may be considered as second-line therapy in cases in which surgery is not possible. However, because of a lack of evidence, the guidelines do not recommend electronic brachytherapy.

"The guidelines development process included patient advocate and community dermatologist input, and the resulting document emphasizes the importance of the doctor–patient dialogue in all aspects of melanoma management," said board-certified dermatologist Hensin Tsao, MD, PhD, FAAD, co-chair of the guidelines work group. "Every case is unique, so physicians should work with their patients, and other specialists if necessary, to explain the available options and determine the best possible treatment plan for each patient." ◆

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# Pembrolizumab Plus Chemotherapy Approved to Treat Metastatic Squamous NSCLC

**ON OCTOBER 30, 2018,** the FDA approved[1] pembrolizumab (Keytruda) in combination with carboplatin and paclitaxel or nab-paclitaxel for the first-line treatment of patients with metastatic squamous non–small cell lung cancer (NSCLC).

The approval was based on findings from the KEYNOTE-407 trial, a randomized, double-blind, multicenter, placebo-controlled study that investigated the efficacy of the combination treatment in patients with metastatic squamous NSCLC regardless of tumor PD-L1 expression. Patients were randomized to receive pembrolizumab 200 mg and carboplatin every 3 weeks for 4 cycles, plus paclitaxel every 3 weeks for 4 cycles or nab-paclitaxel on days 1, 8, and 15 of every 3-week cycle for 4 cycles, followed by placebo every 3 weeks.

The trial found that pembrolizumab in combination with chemotherapy significantly improved overall survival and reduced the risk of death by 36% compared with chemotherapy alone (hazard ratio = 0.64 [95% CI, 0.49, 0.85]; $P = .0017$).

"Today's approval expands our current lung cancer indications to include combination treatment in patients with squamous cell carcinoma, a type of lung cancer that is particularly difficult to treat," said Roger M. Perlmutter, MD, president of Merck Research Laboratories.

The safety of the combination treatment was investigated in 101 patients at the first interim analysis of the trial. The most frequent (≥2%) serious adverse effects were febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

"With this important approval, more patients will have the opportunity to benefit from immunotherapy," said Balazs Halmos, MD, director of the multidisciplinary Thoracic Oncology Program at the Montefiore Einstein Center for Cancer Care.

This approval is the first time an anti-PD-1 treatment regimen was approved as a first-line treatment of squamous NSCLC regardless of tumor PD-L1 expression. Due to this newly approved treatment option, all appropriate patients with metastatic squamous NSCLC, as well as appropriate patients with metastatic nonsquamous NSCLC and no *EGFR* or *ALK* genomic tumor mutations, are now eligible for the pembrolizumab combination treatment as their first-line treatment option. ◆

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*Coverage by Kelly Davio and Samantha DiGrande*

# Community Oncologists Divided on the Value of Biosimilars

**DURING THE COMMUNITY ONCOLOGY ALLIANCE** (COA) Payer Summit, held October 29-30, 2018, The Center for Biosimilars® had the opportunity to sit down with several oncologists to discuss their opinions on and experiences with biosimilars.

When asked how he feels about the upcoming availability of anticancer biosimilars as treatment options, Lalan Wilfong, MD, executive vice president of Quality Programs at Texas Oncology, was hopeful. "I think most practices are looking forward to the development of biosimilars, similar to the generic market[1] when generics were introduced, that's when prices actually started falling for cancer therapy," Wilfong said at the event.

Kashyap Patel[2], MD, CEO of Carolina Blood and Cancer Care echoed Wilfong's statement, but also explained that he believes biosimilars have a central role to play in the US healthcare system as a whole, not just in cancer care. Patel speaks from personal experience; he presented data at ASCO's Quality Care symposium that found that "7% of total savings of the Oncology Care Model came from switching to biosimilar [granulocyte colony-stimulating factor] G-CSF, [filgrastim]" in his own health system.

However, not all oncologists were in agreement about the value of biosimilars. When asked if she believes biosimilars have a role in bringing down drug costs, Kavita Patel, MD, nonresident senior fellow at the Brookings Institution, said, "No. I think that there are limited numbers of biosimilars, and I don't think that the biosimilars are priced at such a degree that—when you have drugs that cost hundreds of thousands of dollars to millions of dollars—having a biosimilar even for something with a large clinical indication, it's like a fraction of the overall drug spend."

Although biosimilars have the potential to bring down costs, she conceded, some factors in the marketplace need to be addressed first before they begin generating significant savings.

"I think we need more biosimilars, which the FDA has signaled, and we need more biosimilars that are priced at such a delta to make an appreciable difference," she said. "There are some pretty 'hot' oncology drugs that have a biosimilar available, but then the way the practice might have already set up their pharmacy or their network, they've already kind of locked in to certain manufacturers, making the biosimilar less attractive."

One specific need reiterated by each oncologist was that, in order for physicians to feel more comfortable prescribing biosimilars in their own practice, education on the safety and efficacy data associated with the products is key going forward. ◆

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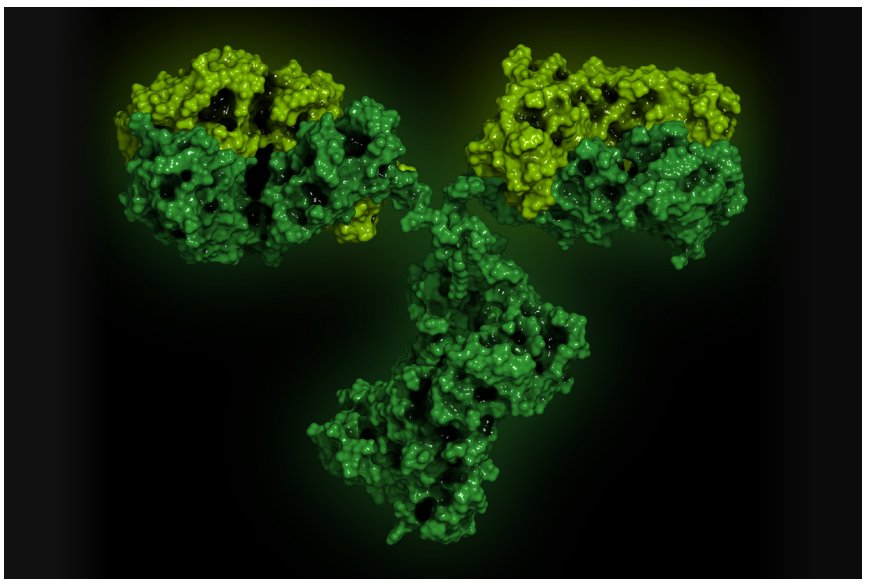
# Biosimilars Can Play a Key Role in Value-Based Care, Review Says

**GIVEN THE HIGH BURDEN** associated with cancer in the senior population, and given the increasingly high cost of cancer care, there is a growing interest in value-based oncology care payment models, particularly within CMS.

A recent review[1], authored by The Center for Biosimilars® advisory board member Kashyap Patel, MD[2], and colleagues, provides an overview of value-based care models and discusses the role of biosimilars in meeting these models' objectives.

The review, appearing in *Cancer Management and Research,* notes that US spending on cancer care grew from $27 billion in 1990 to $124 billion in 2010, with spending levels expected to reach $157 billion by 2020. Globally, spending on oncology and supportive care reached $100 billion in 2014. Among the fastest-growing drug classes in oncology are monoclonal antibodies—many of which are targeted by biosimilar developers—which account for 35% of US oncology spending.



Rituximab. FDA approved Celltrion's rituximab biosimilar, Truxima, on November 28, 2018.

To help address skyrocketing costs, CMS has developed value-based care programs that reward providers with incentives for improving the quality of care they provide to Medicare beneficiaries. These programs seek to move away from the fee-for-service (FFS) model that incentivizes high-quantity (although not necessarily high-quality) care.

In 2016, CMS implemented the Quality Payment Program, which offers payment to providers either through the Merit-based Incentive Payment System or through Advanced Alternative Payment Models, one of which is the Oncology Care Model (OCM).

The OCM is a voluntary program that seeks to provide higher-quality care at the same or lower cost to Medicare than traditional FFS payments. The OCM links payments to provider performance based on meeting quality metrics and making practice reforms.

Biosimilar therapies offer increased affordability and access—as well as improved outcomes and improved health-related quality of life—to patients treated in the OCM model; using lower-cost biosimilar granulocyte colony-stimulating factor therapies,[3] for example, can reduce the incidence of neutropenia, allowing for increased dose administration of patients' primary treatments and improved survival.

Not only may biosimilars, themselves, be offered at more affordable prices than biologics—as has been demonstrated in experience with biosimilar filgrastim—but they also may drive down overall prices in a given class as a result of market competition, producing substantial US cost savings. These savings, which have the potential to grow with upcoming availability of biosimilar epoetin alfa and biosimilars of targeted therapies, could help physicians to meet the OCM objective of improving patient care while reducing costs.

However, write Patel and colleagues, "Realization of cost savings possible from biosimilars…will require that biosimilars are utilized." Current gaps in physician education[4] on biosimilars have limited the use of these agents, making the need for provider education all the more pressing. ◆

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# As Reassuring Data on Anticancer Biosimilars Grow, ESMO Ups Its Biosimilar Education

**THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY** (ESMO) 2018 Congress, held October 19-23, 2018, in Munich, Germany, featured multiple presentations on biosimilars in oncology, all of which are contributing to the body of evidence that points to the safety and efficacy of these products.

Specifically, one study[1] closely investigated the efficacy of the trastuzumab biosimilar SB3, approved in the European Union and sold as Ontruzant, with the reference product in patients with early breast cancer (EBC).

The study enrolled 800 total patients, with 402 given the biosimilar and 398 given the reference trastuzumab. Patients were treated for 8 cycles concurrently with chemotherapy. Patients underwent surgery, and then 10 more cycles of SB3 or the reference.

The primary endpoint was breast pathologic complete response (bpCR) rate, which was measured at 51.7% for SB3, and at 42.0% for the reference, with an adjusted difference of 10.7% (95% CI, 4.13-17.26).

**The European Society for Medical Oncology published a paper on the integration of biosimilars into routine practice. When questioned about their knowledge and comfort with biosimilars, many oncologists exhibited only "moderate confidence" in their understanding of key concepts related to biosimilar drug development and use.**

Overall, the researchers found that the analysis results of bpCR, total pathologic response rate, and overall response rate leaned toward greater efficacy in patients treated with SB3 compared with the reference product.

In another study,[2] researchers conducted a systematic literature review to examine whether demonstrating bioequivalence in terms of efficacy is different in EBC versus metastatic breast cancer (MBC) when patients are treated with a biosimilar trastuzumab, Ogivri (trastuzumab-dkst), versus the reference product.

In total, researchers identified 8 phase 3 clinical trials for 6 proposed biosimilars. Of these, 4 were conducted in EBC, and 4 were in MBC. In all trials, the proposed biosimilar was found to be equivalent to the reference in terms of efficacy. Two biosimilars showed equivalent efficacy in both the EBC and MBC settings.

Regardless of clinical setting, all biosimilars analyzed demonstrated equivalent efficacy to reference trastuzumab.

Despite such reassuring data for biosimilars, however, many stakeholders have noted that lack of provider education on biosimilars is holding back progress with uptake of these products.

Concurrently with the meeting, ESMO published a new paper[3] on the integration of biosimilars into routine oncology practice. The paper reports that, when questioned about their knowledge of and comfort with biosimilars, many oncologists exhibited only "moderate confidence" in their understanding of key concepts related to biosimilar drug development and use. Nearly 87% of respondents said that they need more educational activities on the subject.

The paper also found that extrapolating the use of a biosimilar to all indications approved for the reference product seemed to be the most common misunderstanding among physicians, nurses, and patients alike.

"It is a very difficult concept to explain outside of the regulatory setting," said Elena Wolff-Holz, MD, of the European Medicines Agency. "This is what educational activities should focus on–not just for oncologists, but for all healthcare professionals and for patients," said Josep Tabernero, MD, PhD, MSc, president of ESMO.

Among ESMO's attempts to provide such education are its position paper on using biosimilars and its multistakeholder discussion forums held both at this year's congress and previously at the 2017 meeting. ◆

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# FDA Approves Celltrion's Rituximab Biosimilar, Truxima

**THE FDA HAS APPROVED** Celltrion and Teva's rituximab biosimilar, Truxima (rituximab-abbs). The biosimilar, referencing Rituxan, has been approved to treat adults with CD20-positive, B-cell non-Hodgkin lymphoma (NHL) either as monotherapy or in combination with chemotherapy.[1]

Like its reference product, Truxima has a label that carries a boxed warning alerting providers and patients to the risk of fatal infusion reactions, skin and mouth reactions, hepatitis B reactivation, and a rare but serious brain infection.

In a statement, FDA Commissioner Scott Gottlieb, MD, hailed approval of the drug as an example of the success of the agency's Biosimilar Action Plan. "The Truxima approval is our third biosimilar approval in the past month. The growing pipeline of biosimilars is encouraging," he said. "We're seeing more biosimilar drugs gain market share as this industry matures. We'll continue to make sure biosimilar medications are evaluated efficiently through a process that makes certain that these new medicines meet the FDA's rigorous standards for approval."[1]

Truxima's approval follows a unanimous recommendation of approval by the FDA's Oncologic Drug Advisory Committee (ODAC) in October 2018. In a vote on whether the totality of the evidence supported the licensure of the biosimilar, all 16 committee members voted yes, for reasons some voters enumerated as "overwhelming biosimilarity and clinical trial evidence" that "really sealed the deal."[2]

The committee heard a review of data presented from various speakers, including advisory officials for the FDA who analyzed the drug's data prior to the presentation. According to the FDA, although there were minor differences in clinically inactive compounds, the totality of the evidence suggested Truxima is highly similar to the reference product with no clinically meaningful differences.

Notably, while the reference rituximab also carries indications for inflammatory diseases including rheumatoid arthritis, Celltrion sought approval only for indications in oncology; when ODAC members asked about the reasoning behind only seeking an indication in NHL, a Celltrion representative stated that "We are only seeking approval in 3 [NHL] indications given the patent and exclusivity landscape at this time."

Truxima, which is also approved and widely used in the European Union, is the 15th biosimilar, and the first rituximab biosimilar, approved by the FDA. ◆

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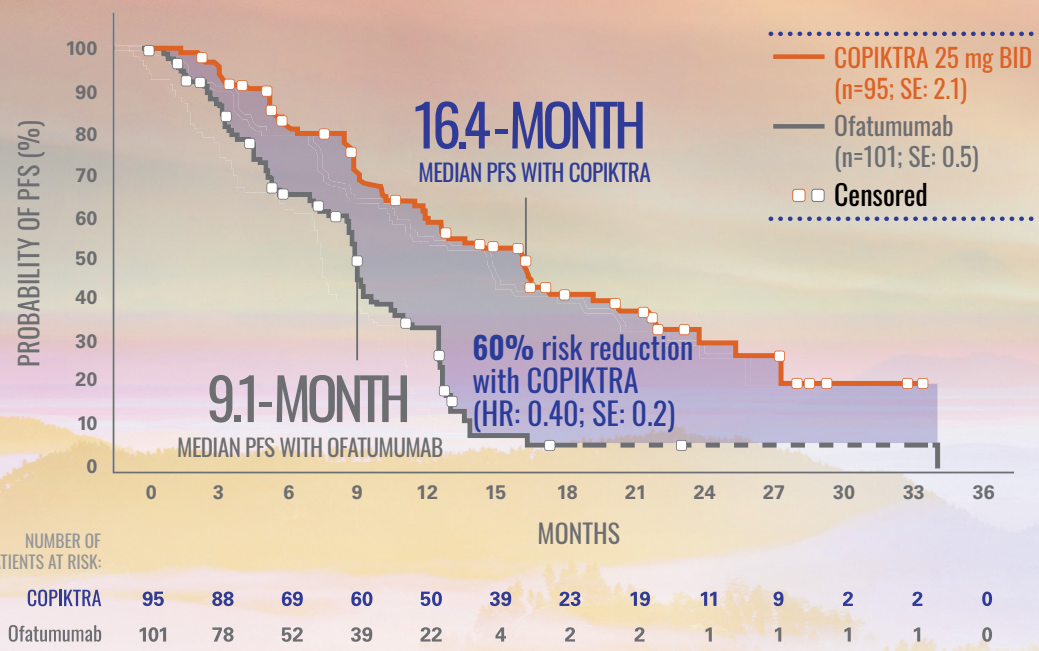


| NUMBER OF PATIENTS AT RISK: | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| COPIKTRA | 95 | 88 | 69 | 60 | 50 | 39 | 23 | 19 | 11 | 9 | 2 | 2 | 0 |
| Ofatumumab | 101 | 78 | 52 | 39 | 22 | 4 | 2 | 2 | 1 | 1 | 1 | 1 | 0 |

- Efficacy was based on a subanalysis of patients with at least 2 prior lines of therapy, where the risk:benefit ratio appeared greater in this more heavily pretreated population (n=196)[1]
- Safety was based on the comprehensive overall study population (N=319)[1]

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*Kaplan-Meier estimate.
CLL, chronic lymphocytic leukemia; δ, delta; γ, gamma; HR, hazard ratio; IV, intravenous; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival; SE, standard error; SLL, small lymphocytic lymphoma.

## IMPORTANT SAFETY INFORMATION

**WARNING: FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, and PNEUMONITIS**

- **Fatal and/or serious infections occurred in 31% of COPIKTRA-treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected.**
- **Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA.**
- **Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA.**
- **Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA.**

## WARNINGS AND PRECAUTIONS

**Infections:** Serious, including fatal (18/442; 4%), infections occurred in 31% of patients receiving COPIKTRA 25 mg BID (N=442). The most common serious infections were pneumonia, sepsis, and lower respiratory infections. Median time to onset of any grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Treat infections prior to initiation of COPIKTRA. Advise patients to report new or worsening signs and symptoms of infection. For grade 3 or higher infection, withhold COPIKTRA until infection is resolved. Resume COPIKTRA at the same or reduced dose. Serious, including fatal, *Pneumocystis jirovecii* pneumonia (PJP) occurred in 1% of patients taking COPIKTRA. Provide prophylaxis for PJP during treatment with COPIKTRA and following completion of treatment with COPIKTRA until the absolute CD4+ T cell count is greater than 200 cells/μL. Withhold COPIKTRA in patients with suspected PJP of any grade, and permanently discontinue if PJP is confirmed. Cytomegalovirus (CMV) reactivation/infection occurred in 1% of patients taking COPIKTRA. Consider prophylactic antivirals during COPIKTRA treatment to prevent CMV infection including CMV reactivation. For clinical CMV infection or viremia, withhold COPIKTRA until infection or viremia resolves. If COPIKTRA is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

**Diarrhea or Colitis:** Serious, including fatal (1/442; <1%), diarrhea or colitis occurred in 18% of patients receiving COPIKTRA 25 mg BID (N=442). Median time to onset of any grade diarrhea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring by 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75th percentile: 1 month). Advise patients to report any new or worsening diarrhea. For patients presenting with mild or moderate diarrhea (Grade 1-2) (i.e., up to 6 stools per day over

## IMPORTANT SAFETY INFORMATION (cont'd)

baseline) or asymptomatic (Grade 1) colitis, initiate supportive care with antidiarrheal agents, continue COPIKTRA at the current dose, and monitor the patient at least weekly until the event resolves. If the diarrhea is unresponsive to antidiarrheal therapy, withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g., budesonide). Monitor the patient at least weekly. Upon resolution of the diarrhea, consider restarting COPIKTRA at a reduced dose. For patients presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, or with severe diarrhea (Grade 3) (i.e., > 6 stools per day over baseline), withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart COPIKTRA at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue COPIKTRA. Discontinue COPIKTRA for life-threatening diarrhea or colitis.

**Cutaneous Reactions:** Serious, including fatal (2/442; <1%), cutaneous reactions occurred in 5% of patients receiving COPIKTRA 25 mg BID (N=442). Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). Median time to onset of any grade cutaneous reaction was 3 months (range: 1 day to 29 months, 75$^{th}$ percentile: 6 months) with a median event duration of 1 month (range: 1 day to 37 months, 75$^{th}$ percentile: 2 months). Presenting features for the serious events were primarily described as pruritic, erythematous, or maculo-papular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash. Advise patients to report new or worsening cutaneous reactions. Review all concomitant medications and discontinue any medications potentially contributing to the event. For patients presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue COPIKTRA at the current dose, initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids, and monitor the patient closely. Withhold COPIKTRA for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or antihistamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart COPIKTRA at a reduced dose. Discontinue COPIKTRA if severe cutaneous reaction does not improve, worsens, or recurs. For life-threatening cutaneous reactions, discontinue COPIKTRA. In patients with SJS, TEN, or DRESS of any grade, discontinue COPIKTRA.

**Pneumonitis:** Serious, including fatal (1/442; <1%), pneumonitis without an apparent infectious cause occurred in 5% of patients receiving COPIKTRA 25 mg BID (N=442). Median time to onset of any grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months. The median event duration was 1 month, with 75% of cases resolving by 2 months. Withhold COPIKTRA in patients with new or progressive pulmonary signs and symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation, and evaluate for etiology. If the pneumonitis is infectious, patients may be restarted on COPIKTRA at the previous dose once the infection, pulmonary signs and symptoms resolve. For moderate non-infectious pneumonitis (Grade 2), treat with systemic corticosteroids and resume COPIKTRA at a reduced dose upon resolution. If non-infectious pneumonitis recurs or does not respond to steroid therapy, discontinue COPIKTRA. For severe or life-threatening non-infectious pneumonitis, discontinue COPIKTRA and treat with systemic steroids.

**Hepatotoxicity:** Grade 3 and 4 ALT and/or AST elevation developed in 8% and 2%, respectively, of patients receiving COPIKTRA 25 mg BID (N=442). Two percent of patients had both an ALT or AST > 3 X ULN and total bilirubin > 2 X ULN. Median time to onset of any grade transaminase elevation was 2 months (range: 3 days to 26 months), with a median event duration of 1 month (range: 1 day to 16 months). Monitor hepatic function during treatment with COPIKTRA. For Grade 2 ALT/AST elevation (> 3 to 5 X ULN), maintain COPIKTRA dose and monitor at least weekly until return to < 3 X ULN. For Grade 3 ALT/AST elevation (> 5 to 20 X ULN), withhold COPIKTRA and monitor at least weekly until return to < 3 X ULN. Resume COPIKTRA at the same dose (first occurrence) or at a reduced dose for subsequent occurrences. For grade 4 ALT/AST elevation (> 20 X ULN), discontinue COPIKTRA.

**Neutropenia:** Grade 3 or 4 neutropenia occurred in 42% of patients receiving COPIKTRA 25 mg BID (N=442), with Grade 4 neutropenia occurring in 24% of all patients. Median time to onset of grade ≥3 neutropenia was 2 months. Monitor neutrophil counts at least every 2 weeks for the first 2 months of COPIKTRA therapy, and at least weekly in patients with neutrophil counts <1.0 Gi/L (Grade 3-4). Withhold COPIKTRA in patients presenting with neutrophil counts < 0.5 Gi/L (Grade 4). Monitor until ANC is > 0.5 Gi/L, then resume COPIKTRA at same dose for the first occurrence or at a reduced dose for subsequent occurrences.

**Embryo-Fetal Toxicity:** Based on findings in animals and its mechanism of action, COPIKTRA can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Conduct pregnancy testing before initiating COPIKTRA treatment. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose.

## ADVERSE REACTIONS

### B-cell Malignancies Summary

Fatal adverse reactions within 30 days of the last dose occurred in 8% (36/442) of patients treated with COPIKTRA 25 mg BID. Serious adverse reactions were reported in 289 patients (65%). The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%) most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The most common adverse reactions (reported in ≥20% of patients) were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain and anemia.

### CLL/SLL

Fatal adverse reactions within 30 days of the last dose occurred in 12% (19/158) of patients treated with COPIKTRA and in 4% (7/155) of patients treated with ofatumumab. Serious adverse reactions were reported in 73% (115/158) of patients treated with COPIKTRA and most often involved infection (38%; 60/158) and diarrhea or colitis (23%; 36/158). COPIKTRA was discontinued in 57 patients (36%), most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 46 patients (29%), most often due to diarrhea or colitis and rash. The most common adverse reactions with COPIKTRA (≥20% of patients) were diarrhea or colitis, neutropenia, pyrexia, upper respiratory tract infection, pneumonia, rash, fatigue, nausea, anemia and cough.

## DRUG INTERACTIONS

**CYP3A Inducers:** Coadministration with a strong CYP3A inducer may reduce COPIKTRA efficacy. Avoid coadministration with strong CYP3A4 inducers.

**CYP3A Inhibitors:** Coadministration with a strong CYP3A inhibitor may increase the risk of COPIKTRA toxicities. Reduce COPIKTRA dose to 15 mg BID when coadministered with a strong CYP3A4 inhibitor.

**CYP3A Substrates:** Coadministration of COPIKTRA with sensitive CYP3A4 substrates may increase the risk of toxicities of these drugs. Consider reducing the dose of the sensitive CYP3A4 substrate and monitor for signs of toxicities of the coadministered sensitive CYP3A substrate.

## INDICATIONS AND USAGE

COPIKTRA™ (duvelisib) is indicated for: The treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

Please see brief summary of full Prescribing Information on the following pages.

**REFERENCES: 1.** COPIKTRA Prescribing Information, Verastem, Inc. **2.** Data on file, Verastem Oncology.

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Verastem Oncology

**COPIKTRA (duvelisib) Capsules, for oral use**
**BRIEF SUMMARY OF PRESCRIBING INFORMATION - CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

WARNING: FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, and PNEUMONITIS

- Fatal and/or serious infections occurred in 31% of COPIKTRA-treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected *[see Warnings and Precautions (5.1)]*.
- Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA *[see Warnings and Precautions (5.2)]*.
- Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA *[see Warnings and Precautions (5.3)]*.
- Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA *[see Warnings and Precautions (5.4)]*.

## 1. INDICATIONS AND USAGE

### 1.1 Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

COPIKTRA is indicated for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

## 3 DOSAGE FORMS AND STRENGTHS

| Strength | Description |
|---|---|
| 25 mg | White to off-white opaque and Swedish orange opaque capsule printed in black ink with "duv 25 mg" |
| 15 mg | Pink opaque capsule printed in black ink with "duv 15 mg" |

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Infections

Serious, including fatal (18/442; 4%), infections occurred in 31% of patients receiving COPIKTRA 25 mg BID (N = 442). The most common serious infections were pneumonia, sepsis, and lower respiratory infections. Median time to onset of any grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Treat infections prior to initiation of COPIKTRA. Advise patients to report any new or worsening signs and symptoms of infection. For grade 3 or higher infection, withhold COPIKTRA until infection has resolved. Resume COPIKTRA at the same or reduced dose *[see Dosage and Administration (2.3)]*. Serious, including fatal, *Pneumocystis jirovecii* pneumonia (PJP) occurred in 1% of patients taking COPIKTRA. Provide prophylaxis for PJP during treatment with COPIKTRA. Following completion of COPIKTRA treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/μL. Withhold COPIKTRA in patients with suspected PJP of any grade, and permanently discontinue if PJP is confirmed. CMV reactivation/ infection occurred in 1% of patients taking COPIKTRA. Consider prophylactic antivirals during COPIKTRA treatment to prevent CMV infection including CMV reactivation. For clinical CMV infection or viremia, withhold COPIKTRA until infection or viremia resolves. If COPIKTRA is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly *[see Dosage and Administration (2.3)]*.

### 5.2 Diarrhea or Colitis

Serious, including fatal (1/442; <1%), diarrhea or colitis occurred in 18% of patients receiving COPIKTRA 25 mg BID (N = 442). The median time to onset of any grade diarrhea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring by 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75$^{th}$ percentile: 1 month). Advise patients to report any new or worsening diarrhea. For non-infectious diarrhea or colitis, follow the guidelines. For patients presenting with mild or moderate diarrhea (Grade 1-2) (i.e. up to 6 stools per day over baseline) or asymptomatic (Grade 1) colitis, initiate supportive care with antidiarrheal agents as appropriate, continue COPIKTRA at the current dose, and monitor the patient at least weekly until the event resolves. If the diarrhea is unresponsive to antidiarrheal therapy, withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g. budesonide). Monitor the patient at least weekly. Upon resolution of the diarrhea, consider restarting COPIKTRA at a reduced dose. For patients presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs or with severe diarrhea (Grade 3) (i.e. > 6 stools per day over baseline) withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g. budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart COPIKTRA at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue COPIKTRA. Discontinue COPIKTRA for life-threatening diarrhea or colitis *[see Dosage and Administration (2.3)]*.

### 5.3 Cutaneous Reactions

Serious, including fatal (2/442; <1%), cutaneous reactions occurred in 5% of patients receiving COPIKTRA 25 mg BID (N = 442). Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). Median time to onset of any grade cutaneous reaction was 3 months (range: 1 day to 29 months, 75$^{th}$ percentile: 6 months), with a median event duration of 1 month (range: 1 day to 37 months, 75$^{th}$ percentile: 2 months). Presenting features for the serious events were primarily described as pruritic, erythematous, or maculo-papular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash. Advise patients to report any new or worsening cutaneous reactions. Review all concomitant medications and discontinue any medications potentially contributing to the event. For patients presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue COPIKTRA at the current dose, initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids, and monitor the patient closely. Withhold COPIKTRA for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or anti-histamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart COPIKTRA at a reduced dose. Discontinue COPIKTRA if severe cutaneous reaction does not improve, worsens, or recurs. For life-threatening cutaneous reactions, discontinue COPIKTRA. In patients with SJS, TEN, or DRESS of any grade, discontinue COPIKTRA *[see Dosage and Administration (2.3)]*.

### 5.4 Pneumonitis

Serious, including fatal (1/442; <1%), pneumonitis without an apparent infectious cause occurred in 5% of patients receiving COPIKTRA 25 mg BID (N = 442). Median time to onset of any grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months. The median event duration was 1 month, with 75% of cases resolving by 2 months. Withhold COPIKTRA in patients who present with new or progressive pulmonary signs and symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation and evaluate for etiology. If the pneumonitis is infectious, patients may be restarted on COPIKTRA at the previous dose once the infection, pulmonary signs and symptoms resolve. For moderate non-infectious pneumonitis (Grade 2), treat with systemic corticosteroids, and resume COPIKTRA at a reduced dose upon resolution. If non-infectious pneumonitis recurs or does not respond to steroid therapy, discontinue COPIKTRA. For severe or life-threatening non-infectious pneumonitis, discontinue COPIKTRA and treat with systemic steroids *[see Dosage and Administration (2.3)]*.

### 5.5 Hepatotoxicity

Grade 3 and 4 ALT and/or AST elevation developed in 8% and 2%, respectively, in patients receiving COPIKTRA 25 mg BID (N=442). Two percent of patients had both an ALT or AST greater than 3 x ULN and total bilirubin greater than 2 x ULN. Median time to onset of any grade transaminase elevation was 2 months (range: 3 days to 26 months), with a median event duration of 1 month (range: 1 day to 16 months). Monitor hepatic function during treatment with COPIKTRA. For Grade 2 ALT/AST elevation (greater than 3 to 5 × ULN), maintain COPIKTRA dose and monitor at least weekly until return to less than 3 × ULN. For Grade 3 ALT/AST elevation (greater than 5 to 20 × ULN), withhold COPIKTRA and monitor at least weekly until return to less than 3 × ULN. Resume COPIKTRA at the same dose (first occurrence) or at a reduced dose for subsequent occurrence. For grade 4 ALT/AST elevation (greater than 20 × ULN) discontinue COPIKTRA *[see Dosage and Administration (2.3)]*.

### 5.6 Neutropenia

Grade 3 or 4 neutropenia occurred in 42% of patients receiving COPIKTRA 25 mg BID (N = 442), with Grade 4 neutropenia occurring in 24% of all patients. The median time to onset of Grade ≥ 3 neutropenia was 2 months (range: 3 days to 31 months), with 75% of cases occurring within 4 months. Monitor neutrophil counts at least every 2 weeks for the first 2 months of COPIKTRA therapy, and at least weekly in patients with neutrophil counts < 1.0 Gi/L (Grade 3-4). Withhold COPIKTRA in patients presenting with neutrophil counts < 0.5 Gi/L (Grade 4). Monitor until ANC is > 0.5 Gi/L, resume COPIKTRA at same dose for the first occurrence or a reduced dose for subsequent occurrence *[see Dosage and Administration (2.3)]*.

### 5.7 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, COPIKTRA 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 and males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1, 12.3)]*.

### 6.1 Clinical Trial Experience

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

***Summary of Clinical Trial Experience in B-cell Malignancies***

The data described below reflect exposure to COPIKTRA in two single-arm, open-label clinical trials, one open-label extension clinical trial, and one randomized, open-label, actively controlled clinical trial totaling 442 patients with previously treated hematologic malignancies primarily including CLL/SLL (69%) and FL (22%). Patients were treated with COPIKTRA 25mg BID until unacceptable toxicity or progressive disease. The median duration of exposure was 9 months (range 0.1 to 53 months), with 36% (160/442) of patients having at least 12 months of exposure. For the 442 patients, the median age was 67 years (range 30 to 90 years), 65% were male, 92% were White, and 93% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients had a median of 2 prior therapies. The trials required hepatic transaminases at least ≤ 3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤ 1.5 times ULN. Patients were excluded for prior exposure to a PI3K inhibitor within 4 weeks. Fatal adverse reactions within 30 days of the last dose occurred in 36 patients (8%) treated with COPIKTRA 25mg BID. Serious adverse reactions were reported in 289 (65%) patients. The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%), most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The median time to first dose modification or discontinuation was 4 months (range 0.1 to 27 months), with 75% of patients having their first dose modification or discontinuation within 7 months.

***Common Adverse Reactions***

Table 1 summarizes common adverse reactions in patients receiving COPIKTRA 25mg BID, and Table 2 summarizes the treatment-emergent laboratory abnormalities. The most common adverse reactions (reported in ≥ 20% of patients) were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia.

**Table 1 Common Adverse Reactions (≥ 10% Incidence) in Patients with B-cell Malignancies Receiving COPIKTRA**

| Adverse Reactions | COPIKTRA 25 mg BID (N = 442) | |
|---|---|---|
| | Any Grade n (%) | Grade ≥ 3 n (%) |
| **Blood and lymphatic system disorders** | | |
| Neutropenia[†] | 151 (34) | 132 (30) |
| Anemia[†] | 90 (20) | 48 (11) |
| Thrombocytopenia[†] | 74 (17) | 46 (10) |
| **Gastrointestinal disorders** | | |
| Diarrhea or colitis[†a] | 222 (50) | 101 (23) |
| Nausea[†] | 104 (24) | 4 (< 1) |
| Abdominal pain | 78 (18) | 9 (2) |
| Vomiting | 69 (16) | 6 (1) |
| Mucositis | 61 (14) | 6 (1) |
| Constipation | 57 (13) | 1 (< 1) |
| **General disorders and administration site conditions** | | |
| Fatigue[†] | 126 (29) | 22 (5) |
| Pyrexia | 115 (26) | 7 (2) |
| **Hepatobiliary disorders** | | |
| Transaminase elevation[†b] | 67 (15) | 34 (8) |
| **Infections and infestations** | | |
| Upper respiratory tract infection[†] | 94 (21) | 2 (< 1) |
| Pneumonia[†c] | 91 (21) | 67 (15) |
| Lower respiratory tract infection[†] | 46 (10) | 11 (3) |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 63 (14) | 2 (< 1) |
| Edema[†] | 60 (14) | 6 (1) |
| Hypokalemia[†] | 45 (10) | 17 (4) |
| **Musculoskeletal and connective tissue disorders** | | |
| Musculoskeletal pain[†] | 90 (20) | 6 (1) |
| Arthralgia | 46 (10) | 1 (< 1) |
| **Nervous system disorders** | | |
| Headache[†] | 55 (12) | 1 (< 1) |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Cough[†] | 111 (25) | 2 (< 1) |
| Dyspnea[†] | 52 (12) | 8 (2) |
| **Skin and subcutaneous tissue disorders** | | |
| Rash[†d] | 136 (31) | 41 (9) |

[†]Grouped term for reactions with multiple preferred terms
[a]Diarrhea or colitis includes the preferred terms: colitis, enterocolitis, colitis microscopic, colitis ulcerative, diarrhea, diarrhea hemorrhagic
[b]Transaminase elevation includes the preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hypertransaminasemia, hepatocellular injury, hepatotoxicity
[c]Pneumonia includes the preferred terms: All preferred terms containing "pneumonia" except for "pneumonia aspiration"; bronchopneumonia, bronchopulmonary aspergillosis
[d]Rash includes the preferred terms: dermatitis (including allergic, exfoliative, perivascular), erythema (including multiforme), rash (including exfoliative, erythematous, follicular, generalized, macular & papular, pruritic, pustular), toxic epidermal necrolysis and toxic skin eruption, drug reaction with eosinophilia and systemic symptoms, drug eruption, Stevens-Johnson syndrome

Grade 4 adverse reactions occurring in ≥ 2% of recipients of COPIKTRA included neutropenia (18%), thrombocytopenia (6%), sepsis (3%), hypokalemia and increased lipase (2% each), and pneumonia and pneumonitis (2% each).

**Table 2 Most Common New or Worsening Laboratory Abnormalities (≥ 20% Any Grade) in Patients with B-cell Malignancies Receiving COPIKTRA**

| Laboratory Parameter[a] | COPIKTRA 25 mg BID (N = 442) | |
|---|---|---|
| | Any Grade n (%)[b] | Grade ≥ 3 n (%)[b] |
| **Hematology abnormalities** | | |
| Neutropenia | 276 (63) | 184 (42) |
| Anemia | 198 (45) | 66 (15) |
| Thrombocytopenia | 170 (39) | 65 (15) |
| Lymphocytosis | 132 (30) | 92 (21) |
| Leukopenia | 129 (29) | 34 (8) |
| Lymphopenia | 90 (21) | 39 (9) |
| **Chemistry abnormalities** | | |
| ALT increased | 177 (40) | 34 (8) |
| AST increased | 163 (37) | 24 (6) |
| Lipase increased | 133 (36) | 58 (16) |
| Hypophosphatemia | 136 (31) | 23 (5) |
| ALP increased | 128 (29) | 7 (2) |
| Serum amylase increased | 101 (28) | 16 (4) |
| Hyponatremia | 116 (27) | 30 (7) |
| Hyperkalemia | 114 (26) | 14 (3) |
| Hypoalbuminemia | 111 (25) | 7 (2) |
| Creatinine increased | 106 (24) | 7 (2) |
| Hypocalcemia | 100 (23) | 12 (3) |

[a]Includes laboratory abnormalities that are new or worsening in grade or with worsening from baseline unknown.
[b]Percentages are based on number of patients with at least one post-baseline assessment; not all patients were evaluable.

Grade 4 laboratory abnormalities developing in ≥ 2% of patients included neutropenia (24%), thrombocytopenia (7%), lipase increase (4%), lymphocytopenia (3%), and leukopenia (2%).

***Summary of Clinical Trial Experience in CLL/SLL***

***Study 1***

The safety data below reflects exposure in a randomized, open-label, actively controlled clinical trial for adult patients with CLL or SLL who received at least one prior therapy. Of 313 patients treated, 158 received COPIKTRA monotherapy and 155 received ofatumumab. The 442-patient safety analysis above includes patients from Study 1. COPIKTRA was administered at 25 mg BID in 28-day treatment cycles until unacceptable toxicity or progressive disease. The comparator group received 12 doses of ofatumumab with an initial dose of 300 mg intravenous (IV) on Day 1 followed a week later by 7 weekly doses of 2000 mg IV, followed 4 weeks later by 2000 mg IV every 4 weeks for 4 doses. In the total study population, the median age was 69 years (range: 39 to 90 years), 60% were male, 92% were White, and 91% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior therapies, with 61% of patients having received 2 or more prior therapies. The trial required a hemoglobin ≥ 8 g/dL and platelets ≥ 10,000 µL with or without transfusion support, hepatic transaminases ≤ 3 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and serum creatinine ≤ 2 times ULN. The trial excluded patients with prior autologous transplant within 6 months or allogeneic transplant, prior exposure to a PI3K inhibitor or a Bruton's tyrosine kinase (BTK) inhibitor, and uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. During randomized treatment, the median duration of exposure to COPIKTRA was 11.6 months with 72% (114/158) exposed for ≥ 6 months and 49% (77/158) exposed for ≥ 1 year. The median duration of exposure to ofatumumab was 5.3 months, with 77% (120/155) receiving at least 10 of 12 doses. Fatal adverse reactions within 30 days of the last dose occurred in 12% (19/158) of patients treated with COPIKTRA and in 4% (7/155) of patients treated with ofatumumab. Serious adverse reactions were reported in 73% (115/158) of patients treated with COPIKTRA and most often involved infection (38% of patients; 60/158) and diarrhea or colitis (23% of patients; 36/158). COPIKTRA was discontinued in 57 patients (36%), most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 46 patients (29%) due to adverse reactions, most often due to diarrhea or colitis and rash.

***Common Adverse Reactions***

Table 3 summarizes selected adverse reactions in Study 1, and Table 4 summarizes treatment-emergent laboratory abnormalities. The most common adverse reactions with COPIKTRA (reported in ≥ 20% of patients) were diarrhea or colitis, neutropenia, pyrexia, upper respiratory tract infection, pneumonia, rash, fatigue, nausea, anemia and cough.

**Table 3. Common Nonhematologic Adverse Reactions (≥ 10% Incidence) in Patients with CLL/SLL Receiving COPIKTRA (Study 1)**

| Adverse Reactions | COPIKTRA N = 158 | | Ofatumumab N = 155 | |
|---|---|---|---|---|
| | Any Grade (%) | Grade ≥ 3 (%) | Any Grade (%) | Grade ≥ 3 (%) |
| **Gastrointestinal disorders** | | | | |
| Diarrhea or colitis†[a] | 57 | 25 | 14 | 2 |
| Nausea† | 23 | 0 | 11 | 0 |
| Constipation | 17 | <1 | 8 | 0 |
| Abdominal pain | 16 | 3 | 7 | 0 |
| Vomiting | 15 | 0 | 7 | 0 |
| **General disorders and administration site conditions** | | | | |
| Pyrexia | 29 | 3 | 10 | <1 |
| Fatigue† | 25 | 4 | 23 | 4 |
| **Hepatobiliary disorders** | | | | |
| Transaminase elevation†[d] | 11 | 6 | 4 | <1 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection† | 28 | 0 | 16 | <1 |
| Pneumonia†[b] | 27 | 22 | 8 | 3 |
| Lower respiratory tract infection† | 18 | 4 | 10 | 1 |
| **Investigations** | | | | |
| Weight decreased | 11 | 0 | 2 | 0 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 13 | 0 | 3 | <1 |
| Edema† | 11 | 1 | 5 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Musculoskeletal pain† | 17 | 1 | 12 | <1 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough† | 23 | 1 | 16 | 0 |
| Dyspnea | 12 | 3 | 7 | 0 |

**Table 3 (cont'd). Common Nonhematologic Adverse Reactions (≥ 10% Incidence) in Patients with CLL/SLL Receiving COPIKTRA (Study 1)**

| Adverse Reactions | COPIKTRA N = 158 | | Ofatumumab N = 155 | |
|---|---|---|---|---|
| | Any Grade (%) | Grade ≥ 3 (%) | Any Grade (%) | Grade ≥ 3 (%) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash†[c] | 27 | 11 | 15 | <1 |

Grades were obtained per CTCAE version 4.03.
†Grouped term for reactions with multiple preferred terms
[a]Diarrhea or colitis includes the preferred terms: colitis, enterocolitis, colitis microscopic, colitis ulcerative, diarrhea
[b]Pneumonia includes the preferred terms: All preferred term containing "pneumonia" except for "pneumonia aspiration"; bronchopneumonia, bronchopulmonary aspergillosis
[c]Rash includes the preferred terms: dermatitis (including allergic, exfoliative, perivascular), erythema (including multiforme), rash (including exfoliative, erythematous, follicular, generalized, macular & papular, pruritic, pustular), toxic skin eruption, drug eruption
[d]Transaminase elevation includes the preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatotoxicity

**Table 4. Most Common New or Worsening Laboratory Abnormalities (≥ 20% Any Grade) in Patients with CLL/SLL Receiving COPIKTRA (Study 1)**

| Laboratory Parameter | COPIKTRA N = 158 | | Ofatumumab N = 155 | |
|---|---|---|---|---|
| | Any Grade (%) | Grade ≥ 3 (%) | Any Grade (%) | Grade ≥ 3 (%) |
| **Hematology abnormalities** | | | | |
| Neutropenia | 67 | 49 | 52 | 37 |
| Anemia | 55 | 20 | 36 | 7 |
| Thrombocytopenia | 43 | 16 | 34 | 8 |
| Lymphocytosis | 30 | 22 | 11 | 6 |
| **Chemistry abnormalities** | | | | |
| ALT increased | 42 | 7 | 12 | 0 |
| Lipase increased | 37 | 12 | 15 | 3 |
| AST increased | 36 | 3 | 14 | 1 |
| Phosphate decreased | 34 | 3 | 20 | 3 |
| Hyperkalemia | 31 | 4 | 24 | 1 |
| Hyponatremia | 31 | 7 | 18 | 3 |
| Amylase increased | 31 | 5 | 10 | 1 |
| Hypoalbuminemia | 31 | 2 | 15 | 1 |
| Creatinine increased | 29 | 1 | 31 | 0 |
| Alkaline phosphatase increased | 27 | 0 | 14 | 0 |
| Hypocalcemia | 25 | 1 | 17 | 1 |
| Hypokalemia | 20 | 8 | 8 | 0 |

Grades were obtained per CTCAE version 4.03.

Grade 4 laboratory abnormalities that developed in ≥ 2% of COPIKTRA treated patients included neutropenia (32%), thrombocytopenia (6%), lymphopenia (3%), and hypokalemia (2%).

The data above are not an adequate basis for comparison of rates between the study drug and the active control.

## 7 DRUG INTERACTIONS

### 7.1 Effects of Other Drugs on COPIKTRA

*CYP3A Inducers:* Co-administration with a strong CYP3A inducer decreases duvelisib area under the curve (AUC) *[see Clinical Pharmacology (12.3)]*, which may reduce COPIKTRA efficacy. Avoid co-administration of COPIKTRA with strong CYP3A4 inducers.

*CYP3A Inhibitors:* Co-administration with a strong CYP3A inhibitor increases duvelisib AUC *[see Clinical Pharmacology (12.3)]*, which may increase the risk of COPIKTRA toxicities. Reduce COPIKTRA dose to 15 mg BID when co-administered with a strong CYP3A4 inhibitor *[see Dosage and Administration (2.4)]*.

### 7.2 Effects of COPIKTRA on Other Drugs

*CYP3A Substrates:* Co-administration with COPIKTRA increases AUC of a sensitive CYP3A4 substrate *[see Clinical Pharmacology (12.3)]* which may increase the risk of toxicities of these drugs. Consider reducing the dose of the sensitive CYP3A4 substrate and monitor for signs of toxicities of the co-administered sensitive CYP3A substrate.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary:* Based on findings from animal studies and the mechanism of action, COPIKTRA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### 8.2 Lactation

*Risk Summary:* There are no data on the presence of duvelisib and/or its metabolites in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from duvelisib in a breastfed child, advise lactating women not to breastfeed while taking COPIKTRA and for at least 1 month after the last dose.

### 8.3 Females and Males of Reproductive Potential

*Pregnancy Testing:* COPIKTRA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Conduct pregnancy testing before initiation of COPIKTRA treatment.

*Contraception*

Females Based on animal studies, COPIKTRA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with COPIKTRA and for at least 1 month after the last dose.

Males Advise male patients with female partners of reproductive potential to use effective contraception during treatment with COPIKTRA and for at least 1 month after the last dose.

*Infertility* Based on testicular findings in animals, male fertility may be impaired by treatment with COPIKTRA *[see Nonclinical Toxicology (13.1)]*. There are no data on the effect of COPIKTRA on human fertility.

### 8.4 Pediatric Use

Safety and effectiveness of COPIKTRA have not been established in pediatric patients. Pediatric studies have not been conducted.

### 8.5 Geriatric Use

Clinical trials of COPIKTRA included 270 (61%) patients that were 65 years of age and older and 104 (24%) that were 75 years of age and older. No major differences in efficacy or safety were observed between patients less than 65 years of age and patients 65 years of age and older.

PM-US-DUV-18-0056

An Exact Sciences employee checks in samples for screening. Offering consumers a less invasive alternative to colonoscopy could move screening rates for colorectal cancer closer to the goal of 80% of the population.

# Increasing Rates of Cancer Screening

*John B. Kisiel, MD, and Philip Parks, MD, MPH*

CONTINUED FROM COVER

## Colorectal Cancer Screening

As we look optimistically to a future state with more than 80% of the population screened for colorectal cancer (CRC),[8] we are also faced with 2 primary challenges. First, although CRC screening rates are modestly improving,[9] they have not yet reached stated goals, despite national campaigns led by influential organizations including the American Cancer Society (ACS), National Colorectal Cancer Roundtable (NCCRT), and large integrated delivery systems and advocacy groups. The barriers to screening include factors related to patients, healthcare providers, health systems, and communities. These barriers are difficult to overcome even though CRC screening reduces the incidence of CRC by one-half and mortality by one-third.[2,10] Second, evolving epidemiologic evidence demonstrates that there is a disturbing "birth cohort" effect that highlights a 51% increase in the incidence of CRC from 1994 to 2014 and an 11% increase in mortality from 2005 to 2015 among individuals 55 years and younger.[11,12] Based on these incidence and mortality data, the ACS has recommended that screening begin earlier, at age 45, for average-risk individuals.

With a goal of 80% of the average-risk population screened according to guidelines, clinicians, population health specialists, payers, employers, and large integrated health networks must fundamentally change and improve CRC screening programs. Improvements in CRC and other cancer screening programs aligns with the Triple Aim of healthcare: (1) better, higher quality of care; (2) healthier populations and communities; and (3) more affordable care.[13] One positive pivotal change that occurred in health policy was for the US Preventive Services Task Force (USPSTF) to provide an "A" rating for CRC screening for individuals aged 50 to 75 at average risk for CRC.[14] With their recommendation for any 1 of 7 screening strategies in the 2016 USPSTF update, patients and providers are encouraged to "choose the best test that gets [it] done." The NCCRT, established in 1997 by the Centers for Disease Control and Prevention and ACS, developed webinars, handbooks, and other resources for hospitals and health systems to support implementation of best practices in CRC.[15]

A high-quality screening test must have 3 characteristics: (1) high sensitivity, (2) compliance and adherence, and (3) access via insurance and shared decision making. Patient values and preferences play a significant role in compliance and adherence.[16,17] The majority of patients in the United States continue to be screened with colonoscopy,[9] which requires bowel preparation, time away from work, sedation/anesthesia, and risk of complications from preparation, sedation, or the procedure.[18-20] Many patients are apprehensive, if not fearful, about screening[21] and may prefer a noninvasive stool-based screening test.[16] According to the 2018 ACS guideline update, "Although prevention is highly valued by patients, test preparation, invasiveness, potential costs, and other considerations will lead some patients to prefer a noncolonoscopy test for screening."[16]

Currently there are several noninvasive tests, including the fecal immunochemical test (FIT), the guaiac fecal occult blood test, and the multitarget stool DNA, which are all included in the USPSTF recommendations.[14] Stool-based tests vary in sensitivity, with the multitarget stool DNA having the highest sensitivity for CRC (92% vs the FIT test's 74% sensitivity in a head-to-head trial),[22] and the highest sensitivity for adenomatous and sessile serrated precursors.[22] In addition to test performance and considerations of patient preference, another evidence-based component of successful screening programs is patient navigation.[23-25] Patient navigation programs vary in scope and effectiveness by hospital and health systems; however, 1 screening strategy, the multitarget stool DNA test, includes an embedded nationwide patient navigation program.[26]

There is also now 1 blood-based screening test for CRC that is available by FDA label to patients who are unwilling or unable to screen with other recommended CRC screening choices in the 2016 USPSTF guidelines. The Epi

proColon test detects methylated Septin-9 and has a sensitivity of 68% and specificity of 80%.[27-29] Although liquid biopsy for CRC screening is desired, current scientific and engineering limitations delay the availability of a blood-based screening test for precancer and cancer with sensitivity and specificity as high as stool-based testing. There are numerous research and development efforts underway to improve the molecular technology necessary to commercialize an effective blood-based screening test for CRC. The future of CRC is one where patients and providers make choices based on patient values and preferences, clinical performance, and awareness of risks, benefits, and alternatives, with the inclusion of patient navigation systems to optimize compliance and adherence.

## Lung Cancer Screening

Because molecular testing for early detection of CRC has made such inroads into the clinical space, we and others anticipate that similar chemistry could be applied to screening for the leading cancer killers. Of these, lung cancer alone accounts for 25% of all cancer deaths, with a loss of 154,000 lives annually.[30] To date, the only effective screening option for lung cancer is a low-dose computed tomography (LDCT) scan. The National Lung Screening Trial (NLST) involved over 53,000 current or former smokers, who were randomized between screening with LDCT versus chest x-ray. After 3 screens, there was a 20.0% reduction in lung cancer deaths.[31] Based on these results, the USPSTF recommends LDCT screening for those aged 55 to 80 with a 30 pack-year history of smoking and who either still smoke or have quit within 15 years.[32] Endorsement of a screening strategy represents a major leap forward; however, this approach is currently applied to too few at risk. A study based on the findings of the NLST found that if computed tomography (CT) screening was implemented among screening-eligible US populations, only 12,250 deaths, fewer than 10% of the current annual lung cancer mortality, would be averted each year.[33] Too few of those who are at high risk for lung cancer do not fit the recommended criteria; especially those who quit smoking more than 15 years ago. Additionally, lung cancer screening by CT may result in unnecessary intervention due to a false-positive rate that exceeds 96%.[31]

A blood-based screening test may offer superior clinical performance and improve access for patients. One promising approach entailed examining DNA methylation patterns using next-generation DNA sequencing in primary lung tumors and high-risk control tissues to identify highly sensitive and specific methylated DNA markers (MDMs) of lung cancer. These MDMs were validated in DNA extracted from independent tissue samples and clinically validated in archival (EDTA)-buffered plasma specimens from 23 cases and 80 controls. Early results showed that a 4-MDM panel achieved an overall sensitivity of 96% and specificity of 94%.[34] The MDM panel is currently being optimized for improved sensitivity of early stage lung cancers, and prospective enrollment of a phase 2 validation study is currently in progress. The future of lung cancer screening is promising as molecular techniques pave the way for a more accurate and convenient blood-based test.

## Liver Cancer Screening

Lung cancer screening by blood-based assays is biologically rational due to circulatory anatomy that gives tumor-specific DNA access to the plasma compartment; 100% of cardiac blood output passes through the lung. Another organ that receives high cardiac output is the liver, which outflows directly into systemic venous circulation. Although substantially less common than lung cancer in the general US population, primary cancers of the liver (hepatocellular carcinomas [HCCs]) are the second leading cause of cancer deaths worldwide and are projected to be the fourth leading cause of cancer death in the United States by 2030.[35] HCC primarily arises in patients with chronic liver disease. The most common of these are hepatitis B and C infections, alcoholic hepatitis, and non-alcoholic fatty iver disease (NAFLD). Because of the obesity epidemic, NAFLD is the most rapidly increasing risk factor for HCC.

Surveillance for HCC is supported by the results of a randomized controlled trial in patients with hepatitis B in China, which demonstrated a near 40% reduction in mortality among those surveilled by ultrasound and serum assay of alpha-fetoprotein (AFP).[36] While this trial has not been replicated in the West or by using patients with other liver diseases, there is ample observational data that patients under surveillance are more likely to be diagnosed with HCC at earlier stages, which may improve survival. The main drawback to this approach is low sensitivity for curable-stage disease. A recent meta-analysis estimates that ultrasound and AFP in combination are only 63% sensitive for early-stage HCC.[37] Moreover, adherence to surveillance testing is quite poor.[38]

In a similar approach to the discovery of lung cancer markers described earlier, DNA from primary HCC tumors and control liver tissues was sequenced to identify MDMs associated with HCC. The candidate MDMs were validated in independent samples before pilot testing in archival plasmas of 21 patients with HCC and 30 patients in the cirrhosis control group. A 2-marker MDM panel was found to be 89% sensitive and 87% specific in the pilot phase of clinical testing.[39] A larger phase 2 study assayed MDMs from archival plasma samples of 95 HCC cases, 51 cirrhotic controls, and 98 healthy controls, and a 6-marker MDM panel was found to be 95% sensitive for HCC at 92% specificity.[40] Most importantly, 93% of HCC tumors that were of curable stage were detected at the same specificity threshold. Larger phase 2 and phase 3 studies are in progress to set strict cut-offs for MDM markers in a clinical assay and determine if MDMs can detect HCC prior to other surveillance modalities. As with lung cancer screening test development, advances in liver cancer screening using a blood-based test show promise.

**For lung and liver cancer, surveillance is targeted to high-risk patient subsets where the prevalence of cancers is enriched by a predisposing chronic illness. Yet most cancer deaths occur in persons without a known predisposition. Unfortunately, population screening has not been justified for most other cancers due primarily to individual prevalence rates that are insufficient to allow cost-effective interventions.**

## Multicancer Screening: The Path Forward

For lung and liver cancer, surveillance is targeted to high-risk patient subsets where the prevalence of cancers is enriched by a predisposing chronic illness. Yet most cancer deaths occur in persons without a known predisposition. Unfortunately, population screening has not been justified for most other cancers due primarily to individual prevalence rates that are insufficient to allow cost-effective interventions. At a population-wide level, benefits of single-organ screening have been demonstrated most robustly for breast, cervix, colorectum, and, to some extent, prostate cancer. The relatively high prevalence of these cancers directly affects the positive predictive value of screen testing and the number of patients needed to screen to identify a specific cancer. For instance, roughly 1 CRC will be found among 170 persons screened. However, 500 to 1000 persons would need »

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to be screened to identify pancreatic or esophageal adenocarcinomas, respectively, due to lower prevalence of these very fatal diseases. As a result of screening so many persons, even a very specific test is anticipated to generate an unacceptable number of false-positive results, resulting in expensive downstream testing and unnecessary patient anxiety.

A screening test capable of detecting multiple cancer types is an attractive option to fill this gap. If lower and higher prevalence cancers could be screened simultaneously, the combined prevalence in the screened population would dramatically lower the number needed to screen.[41]

Next-generation DNA sequencing and other emerging technology platforms are being leveraged to identify markers that appear to have high sensitivity and specificity for cancers and appear to identify patterns predictive of the anatomic origin of the primary tumor. Our group has demonstrated proof-of-concept data that multiple cancer types can be detected from the same biological media, including blood and stool, using MDM assays directed towards markers of both pancreatic cancer and CRC.[42] Other investigative teams have combined DNA mutation and protein markers to detect multiple cancer types and have developed data models that associate biomarker patterns with each primary cancer type.[43] These observations herald an exciting and potentially transformative new direction in the fundamental approach to cancer screening. Noninvasive multicancer screening is expected to be a near-term reality and will fuel rapidly increasing competition in research and commercialization efforts to bring this concept to clinical practice. ◆

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**DISCLOSURE.** Mayo Clinic and Exact Sciences jointly own intellectual property on which Dr Kisiel is listed as an inventor and may receive royalties.

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# Renting Health vs Buying Cures: How New Financing Tools Can Boost Cancer Therapy Development

*Andrew Smith*

CONTINUED FROM COVER

His proposals seek to increase investment in medical innovation and utilization by giving investors many more ways to support both research organizations and individual patients. For example, Lo sees opportunities for attracting new investment via securitization, the practice of combining individually risky assets into large pools that provide more predictable returns. The resulting cash flows are then divided into tiers based on levels of risk and reward favored by different investors.

Lo's proposals typically rely solely on investors, drug developers, and patients acting in their own self-interest to produce the desired outcomes. However, he does see some opportunities for relatively small investments by philanthropies or the public sector to produce outsized returns in areas like pediatric cancer, where traditional finance tools would not be enough to attract socially optimal levels of investment. Indeed, by simply protecting private investors against loss during the riskiest phases of pediatric drug development, charities or governments may secure far more investment than they could fund on their own.[2] This concept was presented in June at the American Society of Clinical Oncology annual meeting,[3] with full results published in September in *JAMA Oncology*.[2]

*Evidence-Based Oncology*™ (*EBO*) spoke with Lo about his ideas, including those in his recent paper.

***EBO:* How did you get interested in how we finance drug development and usage?**

**LO:** It was really for personal reasons. A few years ago, a number of friends and a family member were dealing with different types of cancer, and it was through the process of trying to understand what they were dealing with that I realized that finance actually plays a pretty significant role in drug development.

For example, even though we seem to be on the verge of a number of breakthroughs in how we deal with these diseases, funding for early-stage drug discovery is actually getting scarcer. Why do we see this so-called "Valley of Death" for preclinical [research and development] and phase 1 clinical trials? In trying to make sense of this conundrum, I began doing research on the economics of the biopharma industry and realized that we could actually make a difference for patients if we used better methods for financing drug development.

***EBO:* How does that work?**

**LO:** My conjecture, which now has substantial supporting evidence, is risk. Drug development is really at its riskiest between the preclinical stage and phase 2 clinical trials. As financial pressures have increased on drug companies and venture capitalists [VCs] to improve performance, the response has been to focus on better bets, bets that are more of a sure thing. This means waiting until drug development projects reach certain milestones before investing.

Another risk that drug companies face is the risk that—thanks to all the recent biomedical innovation that's been going on—a better drug gets developed, destroying the valuable franchise that these companies have invested billions in. We see this happening now with gene therapies that are on the verge of curing certain diseases that used to be chronic manageable conditions. It's going to be a very interesting market dynamic as we see patients choosing between one kind of therapy and another and what kinds of pricing policies will emerge.

Despite those risks, overall returns on drug development are high enough to suggest we're not investing nearly enough in it.

***EBO:* Why is that?**

**LO:** Drug development has 3 unique characteristics that, taken together, make it very challenging for investors. First, it takes a long time: typically 3 to 5 years before you hit the first major milestone and 10 to 15 years until you get an approved therapy. Second, it takes a large amount of capital to bring a single product to market, typically 1 or 2 orders of magnitude more than you need for start-ups in other industries. Third, the success rate is very low, about 5% in oncology for example, based on historical data.

There's a small group of traditional biotech investors that are very sophisticated and understand how to manage these risks, but the larger pools of capital from ordinary investors that have been rushing into other areas like technology, social media, or cryptocurrencies simply aren't there for this market. This is where the opportunity lies for better financing. If you structure the investments differently, you can make biotech attractive to more people and draw more money into drug development.

**LO**

*Andrew W. Lo, PhD, the Charles E. and Susan T. Harris Professor at the MIT Sloan School of Management.*

***EBO:* How?**

**LO:** There are actually 2 ideas that have been used for decades in other industries and demonstrated the ability to reduce risk and improve average returns for investors. The first idea is "multiple shots on goal," to use a hockey or soccer analogy. If you put together series of investments into a single financial vehicle, you are, in most cases, going to be able to reduce the risk and increase the likelihood that you have at least 1 or 2 successes. And in biomedicine, you only need 1 or 2 approved drugs to pay for all the other tries and still earn significant profits for investors.

But to create a large enough portfolio of multiple shots on goal, you need [a] much larger scale than the typical VC would have—on the order of billions of dollars in the case of cancer therapeutics, rather than a few hundred million dollars. This is counter to the traditional VC view that "small is beautiful."

Which brings us to the second idea: using different kinds of financial instruments to fund these multiple shots on goal. Traditionally, biotech VCs use convertible preferred debt and then eventually equity to finance these start-ups. That's certainly the tried-and-true approach. But to create a large enough portfolio of multiple shots on goal for drug development, you need to attract more capital, and the way to do that is to offer different kinds of securities. You can divide the underlying portfolio of assets—claims on future drug sales of multiple drug targets—in ways that let you sell low-risk, low-return bonds to investors who want safety, higher-risk equity to investors who want to gamble for big returns and every other type of security for investors who fall somewhere in between.

***EBO:* You also believe that finance can increase utilization of expensive short-term treatments that either cure diseases or provide lifelong benefits. The idea is to find pools of capital that would be used to lend patients money that could be paid back over time.**

**LO:** Yes, but that's not the new idea. It's being done right now for all sorts of elective surgeries. Dental reconstruction is a good »

example. The typical cost of full-mouth reconstruction can range from $20,000 to $50,000, and candidates for these kinds of procedures can get consumer loans to pay for them right now.

What's new in our proposal is to do this on a much larger scale, greatly increasing patient access to costly therapies, and to be able to securitize and package these "healthcare loans" and sell them to investors who are perfectly happy to take on large pools of diversified kinds of risks. Again, the investors get multiple shots on goal, but in this case, you're talking about multiple consumer loans or loans to health insurers.

**"There are a number of ideas for solving this patient-migration problem through regulation or legislation to protect insurers. This is critical because insurers are going to be very reluctant to finance expensive cures until they're protected against this scenario. And currently, they're the only ones who have the resources to finance the most expensive cures."**

—Andrew W. Lo, PhD

The idea really came about because of the possibility of curative gene therapies as well as other shorter-duration treatments like Sovaldi and Harvoni, 12 weeks of pills that can cure hepatitis C. Taking traditional medications is like renting an apartment: You pay for your benefit a month at a time and keep on paying as long as you want to live in that apartment. New medications like gene therapies are more akin to buying a house. You pay the whole cost up front and the benefit lasts for many years. But most people can't afford to pay for the entire house in cash, so they get a mortgage, and that's what we're talking about here: drug mortgages. It's the difference between "renting health," one pill at a time, versus "buying a cure" and paying for it in installments.

The reason that this is an interesting approach is not just because it makes expensive one-time therapies more affordable for patients and payers. It can also serve as a way of dealing with cures that don't really cure. We don't yet know how permanent the effects of gene therapies really are; they're supposed to be permanent, but we don't have any real experience to rely on. What if it turns out that, after 2 or 3 years, the "cure" stops working and the patient relapses? Well, if you've paid for the therapy through a drug mortgage, you can simply stop making payments. That aligns the interest of the drug companies with the patients and the payers.

Based upon some very simple simulations that we've run by paralleling this submarket with the student loan market, we think there are tremendous amounts of resources that could be devoted to increasing patient access to these kinds of therapies. And with the 300-plus gene therapies currently in clinical trials, this is only the beginning of a huge wave of cures coming to patients over the next few years.

***EBO:* You have also explored the idea that insurance companies, rather than patients, would take out these loans.**

Yes, the idea of stretching out payments over a period of time is pretty straightforward, but the big question is who's going to be paying that mortgage, and the natural response is insurers. That's why we have health insurance.

The problem is that insurers expose themselves to potentially huge losses when they make large up-front payments for treatments that provide their policyholders with decades of benefits. This wouldn't be true if policyholders always stayed with the same company. If you pay for a cure for one of your policyholders and that policyholder now lives for the next 30 years instead of dying in 1 or 2 years, you've got 28 more years of premiums that you can use to offset the cost of this cure.

But in practice, that policyholder can leave her health plan at any time. Suppose she moves to another state after only 5 years. So now, instead of having 28 years of premiums, you've only collected 5 years' worth; the remaining 23 years of premiums go to an insurer in another state. That insurer will benefit from a healthy policyholder who's now cured of this disease, thanks to the previous insurer. She may have other problems, but that's one really serious disease that the new insurer doesn't have to pay for.

There are a number of ideas for solving this patient-migration problem through regulation or legislation to protect insurers. This is critical because insurers are going to be very reluctant to finance expensive cures until they're protected against this scenario. And currently, they're the only ones who have the resources to finance the most expensive cures.

***EBO:* Because the idea of lending money directly to patients doesn't work when the loans get much bigger than $40,000?**

Exactly. There are very few patients that can afford million-dollar therapies. And we're now on the verge of developing a gene therapy for hemophilia. The best guess today for that price tag is about $1.5 million. There are few enough people who can afford $1.5-million homes, never mind $1.5-million drugs. And in the case of a home, at least there's some pretty substantial collateral. In the case of your health, it's very difficult to repossess a lung, so that's why we used student loans as a model for this market: You purchased a college education, but they can't really repossess your math courses. That's why, ultimately, insurance companies are the ones that will be taking out these loans, and we need to deal with the patient-migration issue that they face.

***EBO:* Talk about the research on how you could use these financial tools on pediatric disease, particularly cancer. Why doesn't the market work now, and how can finance improve it?**

Ironically, I think part of it is because we care so much about our children. Traditionally, pharma companies have not developed drugs for children exclusively. They start with adults for the simple reason that drug testing is a very dangerous business that often involves toxic side effects. Patients do die in clinical trials, so it's a matter of ethical consideration to have adults take on these risks first before we expose children to them. But the consequence of that kind of ethical perspective is that pediatric oncology drugs are harder to come by. Drug developers will focus first on adults and unless, and until, they develop a successful therapy, they won't try it on children. Now that's changing, particularly with recent legislation requiring drug companies to develop therapies for adults and children simultaneously. But historically it's been a challenge.

It's also harder to develop pediatric oncology drugs because children have far fewer mutations than adults, implying fewer genetic biomarkers and druggable targets. Also, the biology of a 5-year-old can be quite different from that of a 12-year-old, and both are different from the biology of an adult, so it can be more complex to develop therapies for pediatric indications. Finally, the smaller patient populations make the economics of pediatric cancer drugs less attractive than those of adult counterparts, even with incentives like priority review vouchers and orphan drug designation. We ran the numbers and were shocked to discover that the simulated rates of return for pediatric oncology drug-development programs typically yielded double-digit negative returns on capital. Companies still do develop pediatric cancer drugs, but it's probably more for ethical than financial reasons. And while it's laudable that companies and investors still do invest in pediatric cancer drug development, they don't invest nearly enough because the financial risk/reward profile isn't very compelling.

Our proposal to get more investment into this field is a public–private partnership where the government and/or philanthropic organizations get involved in funding some of the riskiest parts of the development chain, preclinical R&D and phase 1 trials, and then hand it off to the private sector for completion after phase 1. We found that relatively reasonable amounts of public-sector funding, certainly much less than what goes into other areas of the drug development, could actually go a long way toward making the private sector interested in these kinds of health issues. Now that our paper is published (including our simulation software), our hope is that it'll attract the attention of industry participants as well as philanthropic organizations and government agencies and that might spur them to collaborate with private-sector investors and biopharma companies.

***EBO:* If you were the Trump administration's health policy czar, what's the first thing you would do?**

The first thing that I would do is to use the convening power of the White House to bring together various stakeholders to work together collaboratively to develop solutions to some of the biggest medical challenges facing our country. The 3 areas I would prioritize are Alzheimer's, infectious

diseases, and antibiotics. These 3 areas present huge challenges, both current and pending, not only for our country but for the world, and they've gotten far too little resources and attention to date. As we saw with the Biden Cancer Moonshot, the White House can be extremely effective in coordinating the efforts of various groups to deal with the biggest issues facing humankind.

### *EBO:* How could things improve on the regulatory side?

Having now spent some time interacting with the FDA, I have to say that I'm incredibly impressed by the quality of their staff, their dedication, and how effective they've been. One of the most surprising things about them is their openness to new ideas and constant focus on improving "regulatory science." To that end, I've been collaborating with several of their researchers to incorporate patient preferences into drug approval decisions. The standard approach for weighing the evidence from a clinical trial is to use a fixed statistical threshold of significance, also known as a *P* value or false positive rate, of 5% to determine whether a treatment is meaningful. Clinical trials with treatment effects that have a *P* value lower than 5% have traditionally been interpreted as statistically significant and those with higher *P* values are interpreted as insignificant. This 5% threshold is almost always applied across all diseases, but there's reason to think that patients would be better served if the threshold were disease-specific.

For example, if we're dealing with a disease that's not particularly life-threatening, say acne medication, using a threshold of 5% for screening out false positives may be perfectly reasonable. But if we're dealing with a potential therapy for a deadly disease like glioblastoma or pancreatic cancer where there's currently no existing effective therapy and patients are likely to die anyway, patients might prefer to take more of a risk of a false positive so as not to miss a potentially effective therapy. We've developed a method for calculating the optimal threshold of false positives, given the severity of a disease and patient preferences regarding the costs and benefits of false positives versus false negatives. The FDA has been collaborating with us to construct a practical version of this framework.

### *EBO:* What are you doing to get your ideas for financing healthcare put into practice?

I've advised a number of companies pro bono on how to apply these ideas and have been more directly involved in 2 start-ups, BridgeBio and Roivant, as a seed investor and a director. I'm now in the process of talking with a number of stakeholders about possible financing structures that can make gene therapies more widely accessible. The hope is that we can get something in place in time to be used as a template for the many other gene therapies that are coming online.

### *EBO:* How enthusiastic are people about working with you and putting these ideas into practice?

I'm seeing tremendous enthusiasm from investors, drug manufacturers, and patients. There's definitely money out there, waiting to be deployed and clearly a need for these new financing structures. Where we're getting some hesitation—not so much pushback, but cautiousness—is among payers. State Medicaid plans don't have an ability to amortize expenses; their budgets are set year to year and it's not trivial for them to borrow funds or move expenses across budget years. As a result, they're interested but more hesitant because they don't really know what's involved and they've got enough challenges to deal with currently. But given how many gene therapies are likely to be approved over the next few years, I suspect they'll figure out a way to use these creative financing methods when the time comes. ◆

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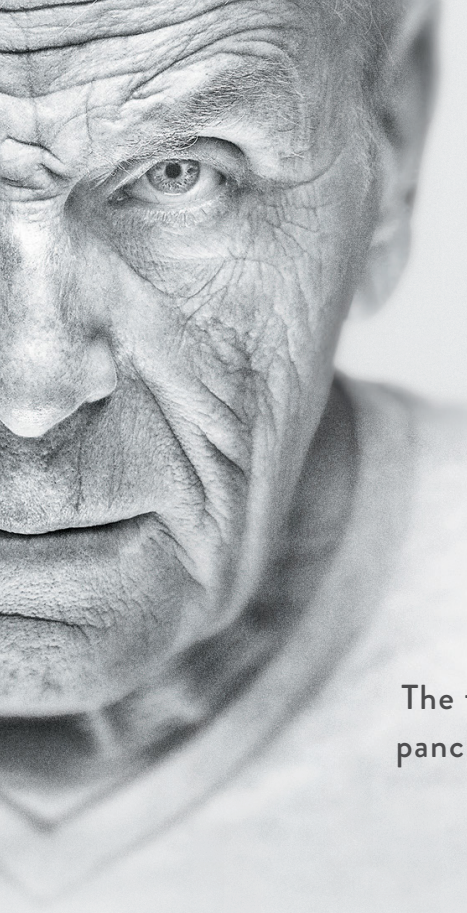

IN POST-GEMCITABINE
METASTATIC PANCREATIC CANCER

onivyde®
(irinotecan liposome injection)

THE EVIDENCE TO

# FIGHT ON

with ONIVYDE®

**The first and only FDA-approved treatment, in combination with 5-FU/LV, for metastatic pancreatic cancer after gemcitabine-based therapy, proven to extend overall survival (OS)[1]**

## INDICATION

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

## IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

**Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm$^3$ or neutropenic fever. Monitor blood cell counts periodically during treatment.**

**Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.**

## CONTRAINDICATION

- ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl

## WARNINGS AND PRECAUTIONS

- **Severe Neutropenia: See Boxed WARNING.** In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients
- **Severe Diarrhea: See Boxed WARNING.** Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed
- **Interstitial Lung Disease (ILD):** Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD
- **Severe Hypersensitivity Reactions:** Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction
- **Embryo-Fetal Toxicity:** ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment

**Please see additional Important Safety Information throughout and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.**

# ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

## THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST-GEMCITABINE METASTATIC PANCREATIC CANCER[2]*

## FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE[1]

- Proven in combination with 5-FU/LV in NAPOLI-1—the largest phase 3 trial† in patients with metastatic pancreatic cancer with disease progression after gemcitabine-based therapy[3,4]

**Liposomal irinotecan + 5-FU/LV is the only Category 1 National Comprehensive Cancer Network® (NCCN®) chemotherapy recommendation for patients with post-gemcitabine metastatic pancreatic cancer with good performance status and disease progression.[2] 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.*

*†NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m$^2$ every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m$^2$ every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were progression-free survival and objective response rate.[1,4]*

## IMPORTANT SAFETY INFORMATION (cont.)

### ADVERSE REACTIONS

- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)
- Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; The most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis
- Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia
- ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

### DRUG INTERACTIONS

- Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

### USE IN SPECIFIC POPULATIONS

- **Pregnancy and Reproductive Potential:** See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after ONIVYDE treatment
- **Lactation:** Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment

**Please see full Prescribing Information, including Boxed WARNINGS.**

**References: 1.** ONIVYDE® [package insert]. Basking Ridge, NJ. Ipsen Biopharmaceuticals, Inc.; 2017. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V.3.2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed November 2, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **3.** Data on file #1. Basking Ridge, NJ. Ipsen Biopharmaceuticals, Inc.; 2015. **4.** Wang-Gillam A, Li C-P, Bodoky G, et al. *Lancet*. 2016;387:545-557.

**For more information, visit ONIVYDEinfo.com**

onivyde® (irinotecan liposome injection)

**ONIVYDE® (irinotecan liposome injection) for intravenous use**
**Initial U.S. Approval: 1996**

## BRIEF SUMMARY: refer to full Prescribing Information for complete product information.

### 1. INDICATIONS AND USAGE

ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas *(see Clinical Studies, 14)*.

**WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA**

**Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE®. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. (*see Dosing and Administration* 2.2, 5.1)**

**Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity. (*see Dosing and Administration* 2.2, *see Warnings and Precautions* 5.2)**

### 4 CONTRAINDICATIONS

ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

### 5 WARNINGS AND PRECAUTIONS

**5.1 Severe Neutropenia:** ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients *(see Clinical Pharmacology, 12.3)*.

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles *(see Dosage and Administration, 2.2)*.

**5.2 Severe Diarrhea:** ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) *(see Cholinergic Reactions, 6.1)*. An individual patient may experience both early- and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose *(see Dosage and Administration, 2.2)*.

**5.3 Interstitial Lung Disease (ILD):** Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

**5.4 Severe Hypersensitivity Reaction:** Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

**5.5 Embryo-Fetal Toxicity:** Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose *(see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1)*.

### 6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia *(see Warnings and Precautions, 5.1; Boxed Warning)*
- Severe Diarrhea *(see Warnings and Precautions, 5.2; Boxed Warning)*
- Interstitial Lung Disease *(see Warnings and Precautions, 5.3)*
- Severe Hypersensitivity Reactions *(see Warnings and Precautions, 5.4)*

**6.1 Clinical Trials Experience**

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; n=134) *(see Clinical Studies, 14)*. Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/5-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

**Table 2: Adverse Reactions with Higher Incidence (≥5% Difference for Grades 1–4* or ≥2% Difference for Grades 3 and 4) in the ONIVYDE®/5-FU/LV Arm**

| Adverse Reaction | ONIVYDE®/5-FU/LV n=117 | | 5-FU/LV n=134 | |
|---|---|---|---|---|
| | Grades 1–4 (%) | Grades 3–4 (%) | Grades 1–4 (%) | Grades 3–4 (%) |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 59 | 13 | 26 | 4 |
| Early diarrhea† | 30 | 3 | 15 | 0 |
| Late diarrhea‡ | 43 | 9 | 17 | 4 |
| Vomiting | 52 | 11 | 26 | 3 |
| Nausea | 51 | 8 | 34 | 4 |
| Stomatitis§ | 32 | 4 | 12 | 1 |
| **Infections and infestations** | 38 | 17 | 15 | 10 |
| Sepsis | 4 | 3 | 2 | 1 |
| Neutropenic fever/neutropenic sepsis♠ | 3 | 3 | 1 | 0 |
| Gastroenteritis | 3 | 3 | 0 | 0 |
| Intravenous catheter-related infection | 3 | 3 | 0 | 0 |
| **General disorders and administration site conditions** | | | | |
| Fatigue/asthenia | 56 | 21 | 43 | 10 |
| Pyrexia | 23 | 2 | 11 | 1 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 44 | 4 | 32 | 2 |
| Weight loss | 17 | 2 | 7 | 0 |
| Dehydration | 8 | 4 | 7 | 2 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | 14 | 1 | 5 | 0 |

*NCI CTCAE v4.0.
†Early diarrhea: onset ≤24 hours of ONIVYDE® administration.
‡Late diarrhea: onset >1 day after ONIVYDE® administration.
§Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
♠Includes febrile neutropenia.

*Cholinergic Reactions:* ONIVYDE® can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE®-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

*Infusion Reactions:* Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE® administration, were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV.

**The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥5% difference Grades 3–4 [severe] according to NCI CTCAE v4.0) for patients receiving ONIVYDE/5-FU/LV (n=117) vs 5-FU/LV (n=134).** Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. **Hematology:** anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). **Hepatic:** increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%). **Metabolic:** hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%). **Renal:** increased creatinine (any 18%, 13%; severe 0%, 0%).

## 7 DRUG INTERACTIONS

**7.1 Strong CYP3A4 Inducers:** Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort) if possible. Substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy *(see Clinical Pharmacology, 12.3)*.

**7.2 Strong CYP3A4 or UGT1A1 Inhibitors:** Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE® with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE® therapy *(see Clinical Pharmacology, 12.3)*.

## 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy,** Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman *(see Clinical Pharmacology, 12.1)*. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m$^2$ in humans, administered to pregnant rats and rabbits during organogenesis *(see Data in the full Prescribing Information)*. Advise pregnant women of the potential risk to a fetus.

**8.2 Lactation,** Risk Summary: There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk *(see Data in the full Prescribing Information)*.

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE®, advise a nursing woman not to breastfeed during treatment with ONIVYDE® and for 1 month after the final dose.

**8.3 Females and Males of Reproductive Potential,** Contraception, *Females*: ONIVYDE® can cause fetal harm when administered to a pregnant woman *(see Use in Specific Populations, 8.1)*. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month after the final dose. *Males*: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE® and for 4 months after the final dose *(see Nonclinical Toxicology, 13.1)*.

**8.4 Pediatric Use:** Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

**8.5 Geriatric Use:** Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/5-FU/LV in Study 1, 49% were ≥65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

## 10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE®.

COMMENTARY

# The Future of Cancer Care

*Joseph Alvarnas, MD*

**ALVARNAS**

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CONTINUED FROM COVER

In the early 1970s and 1980s, stories in the popular media embraced the idea of anticancer "magic bullets" that would prove the key to providing cures for all types of cancer. In the end, there was no magic, just a growing appreciation for the fact that curing cancer is not based upon some underlying simplicity in cancer biology or fortune in identifying a universal cure. Instead, there was a growing realization that conquering cancer would require a deep level of scientific inquiry into the genetic and molecular underpinnings of each type of cancer, so that individual cures could potentially be crafted to manipulate the underlying biology of the disease. The requisite quantum intellectual leap from a belief in magic bullets toward a mindset that embraced the inherent complexity of cancer biology led to the "precision medicine" mindset. The future of cancer care lies in this continuing, dynamic journey of discovery while ensuring that our systems of delivering care can match this clinical promise, so that patients can benefit equitably from these advances in care.

The promise of targeted anticancer therapeutics was first demonstrated through the extraordinary success of imatinib (Gleevec) and the tyrosine kinase inhibitors (TKIs) in the treatment of patients with chronic myelogenous leukemia (CML). By exploiting the mechanism of action of the unique fusion protein created by gene fusion specific to CML, daily dosing of the TKIs could produce a significant percentage of molecular complete remissions for a population of patients whose prognosis prior to the advent of these innovative therapeutics was poor, with a median survival of less than 3 years.[11]

Although the information derived from convention cytogenetic studies on cancer have had some impact upon the development of targeted anticancer therapeutics, the Human Genome Project has produced a veritable Rosetta Stone for identifying unique tumor-related mutations in the cancer cell genome and leveraging this information in the pursuit of innovative targeted therapeutics.[12] This process has been accelerated by increasing numbers of patients with cancer whose tumors have undergone genomic testing, including whole exome sequencing, as well as the availability of supercomputer analysis of these data. The availability of supercomputer-based analytics allows for very high throughput of immense amounts of unstructured genomic data that can help identify potentially relevant cancer-related mutations.[13] These advances in our understanding of tumor genomics and the identification of new tumor neo-antigens as marks for targeted therapeutics and immune-oncologic therapeutics have accelerated the pace of development for these therapeutics.

In a relatively short period of time, these data and other data obtained from basic science research directed at identifying tumor genomics and potential targets for innovative immuno-oncological treatments have produced significant, tangible results for patients with previously unmet cancer care needs. Earlier this year, in a randomized phase III trials of checkpoint inhibitors added to the standard treatment of non–small cell lung cancer (NSCLC) for patients without mutations of *EGFR* or *ALK* produced a significant prolongation of survival and improvements in progression-free survival.[14] The standard of care for patients with NSCLC has evolved dramatically during this period, with inclusion of genomic testing as part of the assessment of patients with advanced disease prior to treatment. Moreover, these treatment guidelines also reflect increasing therapeutic options, including targeted therapeutics for patients with selected mutations of *EGFR, ALK, BRAF, MET, ROS1*.[15] Many types of cancer that have proven historically refractory to standard chemotherapeutic approaches may respond dramatically to targeted immune-oncological agents, often producing an excellent quality of life for patients affected by these diseases.[16] This pace of innovation continues to increase at a previously unprecedented pace. Between 2014 and 2017, there were more than 50 FDA approvals for targeted anticancer therapeutics.[17] Although some of these reflect approval of a single agent for multiple indications, most reflect a breadth of therapeutics that include bispecific molecules, checkpoint inhibitors, small molecules, and monoclonal antibodies that demonstrated effectiveness in a broad array of tumors, including many cancers that have been refractory to standard chemotherapeutic approaches. Moreover, the future pipeline for new, targeted anticancer therapeutics looks robust.[18] As more potential therapeutic targets are identified through genomic, molecular, proteomic, and metabolomic investigation and data analysis, there is enormous hope that the promise of precision medicine will translate into greater opportunities for patients with historically refractory and poor-prognosis cancers.[19] These advances portend a future in which cancer survival rates will continue to rise and the number of cancer survivors in the United States will continue to grow.

Yet, inasmuch as the future is likely to bring enormous progress and innovative treatments for patients with unmet care needs, it is also likely to bring a series of increasingly complex challenges to our healthcare system. The first of these relates to concerns about the financial sustainability of delivering these innovations, given their rapidly escalating price tags. In a recent study, the average cost of an anticancer drug approved between 2006 and 2015 rose more that 5-fold to an average of $13,176 per month.[20] Although the challenge of paying for new therapeutics with an average annual cost of $160,000 sounds daunting, the example of chimeric antigen receptor (CAR) T-cell therapeutics stands as a bellwether for some of the expected cost challenges to come. Thus far, 2 CAR T-cell products have been approved, with the possibility of a third in the near term. These genetically modified agents are manufactured on a per-patient basis for the treatment of young patients with relapsed, refractory B-cell acute lymphoblastic leukemia (ALL) and patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), respectively. Both products have demonstrated clinical activity that is superior to historical approaches, and the Institute for Clinical and Economic Review report on CAR T-cell therapies found that these products met the threshold for cost-effectiveness for both treatment indications.[21] Yet the line-item procurement costs of the 2 commercially available therapeutics ($373,000 for DLBCL and $475,000 for B-cell ALL) has been met with significant concern.[22] These represent some of the most expensive therapeutics released to date in the United States. This has led policymakers to wrestle publically with the question of how to deal with therapeutics whose cost is seen as a challenge to the sustainability of our government-based payment systems. In the 2019 Inpatient Prospective Payment System (IPPS) rule, a large part of the cost of delivering these treatments was left unreimbursed, thus leaving the hospitals and healthcare systems that offered these therapeutics to cover half or more of the cost of product procurement alone.[23] This issue seems to have had a

chilling effect upon the availability of these therapeutics to patients who may need them. Recently, FDA Commissioner Scott Gottlieb, MD, said the failure to resolve the issue of CAR T-cell reimbursement could stifle future therapeutic innovations for patients with cancer.[24]

Although the rising costs of pharmaceuticals and engineered therapeutics pose a challenge, it is inappropriate to consider the issue of therapeutic cost in isolation. In one study, a review of the cost of care for third- and fourth-line treatments for patients with relapsed or refractory DLBCL ranged from $600,000 to $750,000.[25] This is a sum that may actually exceed the cost of much more effective care for this population of patients. The difference is that the transactions costs associated with CAR T-cell procurement have created a perception of greater overall costs where that may not, in fact, be true.

The idea of shifting toward payment for value, rather than volume, is a concept that is routinely cited as an essential principle in gaining control over care-related costs. Experts and national leaders—from Michael E. Porter, PhD, MBA, and Thomas H. Lee, MD, both of Harvard, to former HHS Secretary Sylvia Mathews Burwell—have all embraced this as an essential principle of creating a high-quality, financially sustainable system of care delivery.[26,27] Yet we have made amazingly little global progress in this regard in creating a national value-based care model in the oncology domain. There are some important pilot projects, including the Oncology Care Model (OCM) from the Center for Medicare and Medicaid Innovation, but we have yet to see the creation of a national ecosystem that consistently fosters and rewards high-value oncology care, especially a system that can support and reward the appropriate and effective use of high-cost therapeutics.

Whereas it is easy to become enthralled with the unprecedented pace of innovation around genomic diagnostic technologies and advances in targeted therapeutics, these things risk becoming intellectual curiosities unless we can create an ecosystem that aligns financial incentives with providing patients with the most effective suite of services throughout their cancer journey. For some this might entail treatments with a recently approved therapeutic, while for others this might be a system that ensures that compassion and palliation are equally valued when they represent the most patient-centered options for a particular patient. One of the benefits of the OCM is that it has brought the idea that cancer care is delivered throughout a series of episodes that should align around the needs of patients and their families. As knowledge is gleaned from this pilot project, the hope is that the concept of value-based care may grow from an aspirational platitude to a fully realized ecosystem that provides patient-centered care and sustainable reimbursement for physicians and healthcare systems across the breadth of a patient's entire cancer journey. Creating this system will require that big data science and information technology can be fully leveraged to carefully define clinical risk through rigorous patient segmentation (based upon demographic, diagnostic, genomic, and goals of care data) in order to reimburse a system of care that is focused upon the patient's needs throughout the continuum of care. Key elements of this ecosystem, including the creation of big data analytic models and care delivery frameworks, are in progress.[28-32] Data gleaned from this set of experiences can help to create the scaffolding upon which a better, more effective, sustainable system can be created.

It will be impossible to deliver the transformational level of care that genomics and innovative therapeutics equitably, effectively, or sustainably unless we create a transparent, data-rich system of care that can sustain and deliver these consistently. This linkage between the needs and voice of the patient, genomic testing data, and the creation of a care ecosystem that aligns clinical risk, goals of care, the patient experience, and meaningful outcomes with reimbursement, is perhaps the best finish line for the end of the beginning of our road toward sustainable, patient-centered oncology care. ◆

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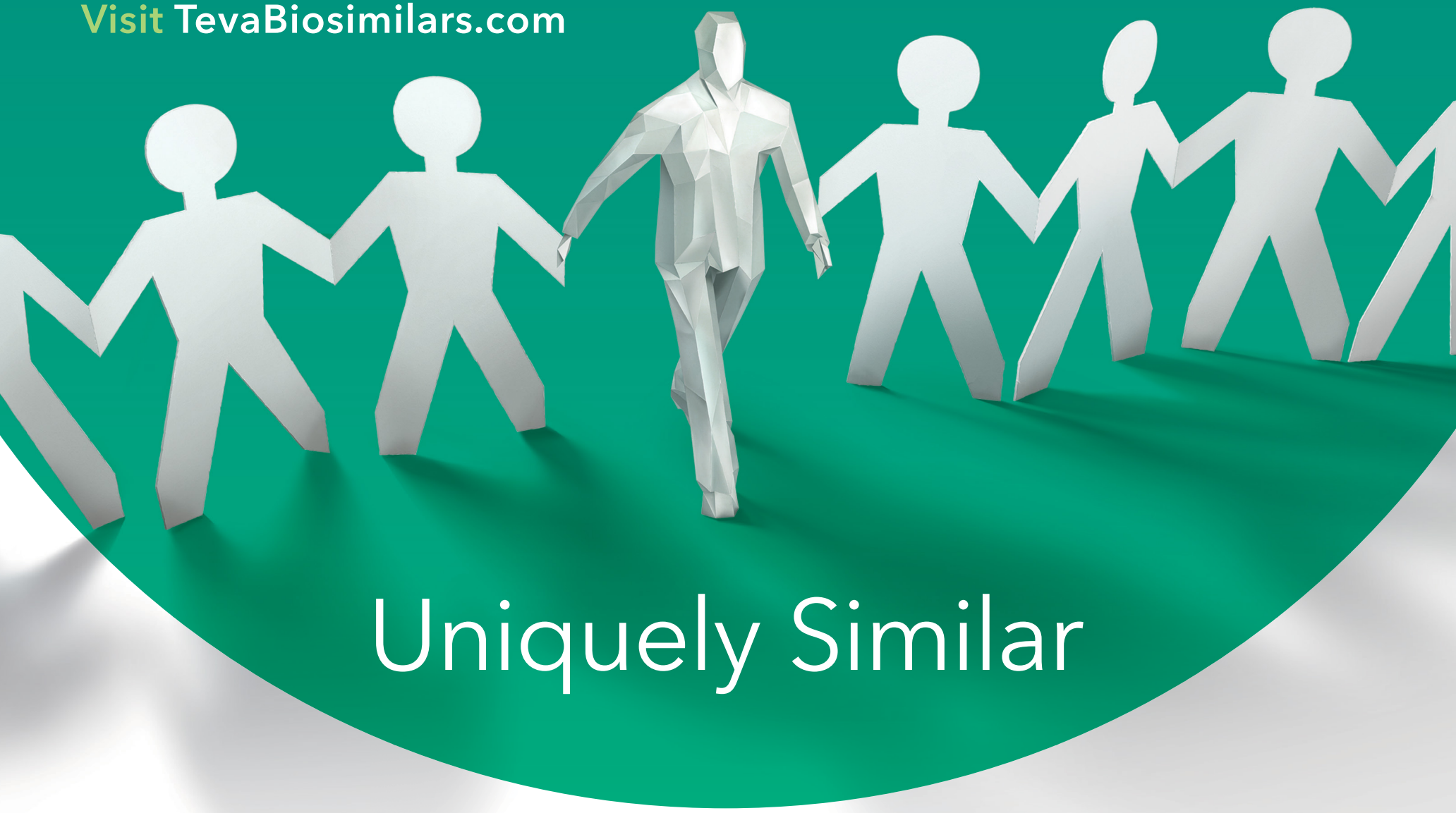

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