Understanding Precision Medicine in Cancer
As true leaders in industry, true innovators in care and true partners in service, ION Solutions has been dedicated to fighting for community oncology for 20 years.

One of the ways we demonstrate our commitment to independent community oncology is through our advocacy efforts on Capitol Hill.

Since 2015, Community Counts has raised awareness on the impact of sequestration, the Part B Demo Project, and other issues paramount to the viability of the community setting. Just last year, more than 500 individuals contacted 280 legislators through this outreach program.

True leaders.
True innovators.
True partners.

ION Solutions
AmerisourceBergen

2019 Meeting Schedule

<table>
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<th>Meeting Date</th>
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<td>January 25</td>
<td>Multiple Myeloma</td>
<td>Orlando, FL</td>
<td>Renaissance Sea World</td>
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<td>January 25-26</td>
<td>ASH Review</td>
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<td>Renaissance Sea World</td>
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<td>March 8-9</td>
<td>Oral Therapies</td>
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<td>May 16-17</td>
<td>Smart ID</td>
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<td>May 17-18</td>
<td>National Healthcare Practitioners</td>
<td>Charlotte, NC</td>
<td>Westin Charlotte</td>
</tr>
</tbody>
</table>

*Meeting Dates Subject to Change*
Registration will be available approximately 60 days prior to each event. To register, visit www.iononline.com.

ION Solutions
AmerisourceBergen

CommunityCountsAdvocacy.org
In September, ION Solutions held our inaugural Precision Medicine Summit and launched our new testing recommendations for various tumor types. These recommendations were developed by your peers — fellow oncologists, pharmacists, nurses and administrative staff — to give you guidance for genetic and genomic testing. Learn more beginning on page six and then visit the Precision Medicine Center, which is now available for all ION members at www.iononline.com.

The Centers for Medicare & Medicaid Services (CMS) recently issued its Proposed Rule for 2019 under the Quality Payment Program (QPP). We expect the Final Rule to be released in November and will have resources available to answer your questions and help your practice report. In the meantime, become familiar with what CMS is proposing to change on page 23.

The QPP is just one example of how we operate in an ever-evolving market. Priorities change. Regulations shift. The path forward is not always easily traced. But I stand behind the work we’ve done in three areas – contracting, dispensing and distribution – and I firmly believe that we’ve proven to be an essential partner in this space. I also know that the work is never complete, we can never be satisfied with resting on past accomplishments. We’re committed to evolving and expanding our offerings to you so that we can continue to serve as your partner in enhancing patient care.

Thank you for your partnership,
Brian Ansay
President, ION Solutions
Understanding Precision Medicine in Cancer

Cancer can typically start in the body based on three almost equal factors: heredity, environment and chance. Despite all efforts to create a healthy lifestyle by avoiding tobacco, eating healthy and exercising, your heredity and even chance continue to play a part.

Every person also has potential cancer cells in their body. There may be even the slightest misalignment in the DNA. You are born with cells that will mutate, but your immune system has been designed to fight them off in the early stages. When your immune system does not kill off those cells, that is when they become their own type of organism and it can turn into cancer.

“As a body lives and grows, its cells are constantly dividing, copying their DNA—this vast genetic library—and bequeathing it to the daughter cells. They in turn pass it to their own progeny: copies of copies of copies. Along the way, errors inevitably occur. Some are caused by carcinogens but most are random misprints.”

As you age and your cells replicate, your risk for a diagnosis of cancer increases.

Precision Medicine vs. Personalized Medicine

The phrases precision medicine and personalized medicine are often used interchangeably when discussing a patient’s health. In a report from the National Research Council in 2011, scientists defined precision medicine as an exploration of how treatment or prevention approaches can be developed based on the combination of genetic, environmental and social factors targeted to individuals or populations.

“To be sure, precision medicine and personalized medicine are highly related and genomics plays a big role in both. However, even highly personalized information may or may not lead to improved health outcomes. Moreover, precision medicine approaches may lead to non-personalized interventions that can be used population-wide.”

Precision medicine is an approach to care that allows doctors to select treatments that are most likely to help patients based on a genetic understanding of their disease. Personalized medicine is the tailored treatment approach for a specific individual—and many agree that the treatment of any patient is considered personalized. Personalized medicine continues to evolve as doctors understand more about how certain patients respond to treatment and how mutations of cancer might happen in one patient, yet not in another.

Genomic Testing or Genetic Testing

Patients often confuse the terms genomic testing with genetic testing. Genomic testing refers to the examination of unique abnormalities or mutations that occur in the cancer cells. Some or all of these abnormalities may be driving the cancer cells to grow. Genetic testing will provide information on an inherited predisposition to a specific cancer.

With a cancer diagnosis, you can have two individuals diagnosed at the same stage, yet the same chemotherapy treatment can produce completely different outcomes. That can often be attributed to the molecular make-up of their tumors. Depending on the test or panel ordered, healthcare providers can use results for either diagnostic purposes or for use the results for additional monitoring.

As an example in understanding genetic versus genomic testing, breast cancer is considered. Patients with breast cancer can potentially have the BRCA1 or BRCA2 gene mutations, which are associated with a genetic predisposition to the cancer and can be passed down through generations. Those individuals who have the mutation have more frequent screenings like earlier mammograms, and sometimes undergo prophylactic mastectomies. Finding the BRCA1 and BRCA2 mutations can be done through genetic testing. But that genetic testing will not tell how a particular tumor will respond to therapy.
There are limitations to targeted therapies. Cancer cells can either resist the planned action of therapy or mutate so they find another pathway to continued growth. You can liken the change to the change seen in viruses, for example what has happened with HIV. Over time, immune systems can learn how to stop cells from replicating, but viruses and certain cancer cells can adapt or evolve, making them resistant to the initial drug treatment. The cells survive because they have found a new pathway or mechanism to reproduce by mutation. In Canada, the mutation of the HIV virus has led to faster developing AIDS-related illnesses.4

Tumor cells can show mutations in a single cell, in an entire tumor or in mutations per megabase (or an area of the genome equal to the length of 1 million bases—the chemicals that serve as the building blocks of DNA).5 The number of mutations is being considered as to whether or not it is an indicator of a response to treatments.

One of the biggest challenges facing researchers and providers is identifying who will respond to therapy, and if they can see any indications that specific patients (based on biomarkers) will show a resistance or even genetic mutations after therapy. As therapies result in changes to a person’s immune system, longitudinal studies or real-world data will be needed to show that these changes don’t increase the possibility of other, possibly deadlier, cancer cells to grow. Increased education on the understanding of these biomarkers is necessary to make decisions on a single or combination of treatment therapies for cancer.

The Impact of Therapies on the Genomics of a Tumor

As genomic panels are completed, and genetic mutations are identified, providers can decide on a treatment plan which would target the specific tumor or cancer cell mutations. Those targeted therapies can be one of several approved cancer treatments—horizon therapies, therapies which block a blood supply to a tumor, therapies which try to kill or destroy specific cancer cells or even immunotherapies which try to trigger the patient’s immune system to destroy those cancer cells.

In non-small cell lung cancer—often associated with a history of smoking, which accounts for 85 percent of all lung cancers—genomic testing looks for EGFR mutations (a gene that produces a protein—epidermal growth factor receptor which can indicate a positive response to treatment). Often the EGFR mutation is observed in patients with no prior history of smoking. According to the National Institutes of Health (NIH), at least eight mutations in the EGFR gene have been associated with lung cancer.6 “Lung cancers with EGFR gene mutations tend to respond to treatments that specifically target the overactive epidermal growth factor receptor protein that allows cancer cells to constantly grow and divide.”

While genomic testing can be critical to deciding on treatment plans, without the knowledge of the full panel of tests (which can take two weeks to complete) providers could be making decisions based on partial information. Gene panels are designed to include certain genomic regions of interest and often screen for mutations in more than 300 genes at one time.6

ION Solutions Launches Precision Medicine Testing Recommendations

At its inaugural Precision Medicine Summit, ION Solutions launched its new Precision Medicine Testing Recommendations. These recommendations include physician-developed guidelines for genetic and genomic testing.

The Precision Medicine Testing Recommendations provide ION Solutions’ network of more than 5,300 community oncologists and researchers with the critical guidance and tools needed to navigate the evolving landscape of genetic testing. Practices will now be able to better determine when and how to test appropriately, manage the challenges of payer reimbursement for testing and, ultimately, connect patients with the most effective personalized treatments. ION Solutions members can access these resources in the new Precision Medicine Center, a web-based access point for real-time industry updates, on the homepage of www.ionline.com.

“Researchers anticipate that more than 50 percent of oncology therapies on the market will require testing by 2025. Having access to top operational and educational resources on when and how to offer genetic and genomic tests is imperative for community oncology practices,” said Barry Fortner, Ph.D., Senior Vice President and President of Specialty Physician Services at AmerisourceBergen.

“Bringing our network together to discuss precision medicine advancements and these recommendations further demonstrates our dedication to ensuring our providers have all the necessary resources for providing the most effective and optimal care.”

To develop the recommendations, ION Solutions convened an expert Precision Medicine Advisory Panel—made up of oncologists, pharmacists, nurses and administrative staff—to bring forth their years of experience, perspective and industry knowledge to better inform members of genomic and genetic testing. Panel members walked attendees through the recommendations and Precision Medicine Center during the Precision Medicine Summit. Throughout the two-day conference, providers and patient support staff attended sessions on the clinical advancements of cancer treatments, evolving payer considerations and helping patients understand the impact of testing in relation to treatment.

“These recommendations are vital in helping community oncologists stay abreast of the latest updates in precision medicine and the growing number of genomic and genetic tests that can impact care,” said Dr. William N. Harwin, Founder and President of Florida Cancer Specialists & Research Institute and Chairman of ION Solutions’ Precision Medicine Advisory Panel. “Providers across the country have requested this information and now, with the support of ION Solutions, they will have access to clinical and operational recommendations for six disease states—a game changer for practices looking to provide personalized care to patients.”
The Financial Impact of the Sequester Cut to Medicare Part B Drug Reimbursement in Community Oncology

In a recent article for the American Journal of Managed Care (AJMC), Dr. Lucio Gordon, head of Quality and Medical Informatics for Florida Cancer Specialists; Casia Schaedig, vice president, InfoDive, ION Solutions; and Susan Weidner, MBA, MS, senior vice president of IntrinsiQ Specialty Solutions; discuss the financial impact of the sequester cuts to Medicare Part B drug reimbursements to community oncology practices. They report a correlation between sequester cuts and community practice closures. To read the study visit https://www.ajmc.com/contributor/coa/2018/08/the-financial-impact-of-the-sequester-cut-to-medicare-part-b-drug-reimbursement-in-community-oncology.

AmerisourceBergen Comments on Trump Administration Blueprint for Lowering Drug Pricing

ION Solutions and Oncology Supply leadership submitted comments on behalf of AmerisourceBergen on more than 150 concepts laid out by the U.S. Department of Health and Human Services (HHS) Secretary Alex Azar to reduce prescription drug prices and improve affordability for patients. The comments focused on protecting the future of community oncology:

- Support for eliminating prohibition on pharmacists alerting consumers to lower cost prescription options (gag clauses)
- Support for greater access and availability to biosimilars and generic products
- Oppose moving Medicare Part B drugs to Part D and reinstitution of Medicare Competitive Acquisition Program (CAP)
- Support patient copayment assistance programs
- Support for value-based purchasing arrangements

To read the letter visit www.iononline.com.

Senate Passes Comprehensive Opioid Legislation

On Sept. 17, the Senate passed The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act (H.R. 6), comprehensive legislation intended to help mitigate the opioid epidemic. AmerisourceBergen supports many provisions in the bill, specifically Sec. 3202, sponsored by Sens. Feinstein (D-CA), Grassley (R-IA), Capito (R. WV) and Durbin (D-IL); and Sec. 3602, sponsored by Sens. Hassan (D-NH) and Grassley—which will enhance critical data sharing between distributors and the DEA, as well as state regulatory agencies and local law enforcement. Consistent with AmerisourceBergen’s repeated calls for increased data transparency between DEA and industry, these provisions also provide greater visibility around the overall number of controlled substances shipped, as well as establish a more streamlined approach to reporting suspicious orders through the creation of a centralized database.

AmerisourceBergen provided technical expertise to the bill sponsors throughout this process and we remain committed to advancing additional policies we believe can help detect potentially suspicious orders before they are shipped. There are significant differences between the Senate and previously passed House opioid legislation.

Along the MBC journey* – explore Verzenio1

Verzenio®
abemaciclib
150 mg tablets
500 mg tablets
5 mg tablets
oral daily

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.** 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 characteristics1,141

Select Important Safety Information

Diarrhea: Diarrhea occurred in 8% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 1, 18% of patients receiving Verzenio plus fulvestrant in MONARCH 2, and 100% of patients receiving Verzenio alone in MONARCH 3. 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 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, with the median duration of diarrhea for Grades 2 and 3 diarrhea was 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 5 days, and the median duration of diarrhea for Grades 2 and 3 diarrhea was 9 and 6 days, respectively. In MONARCH 1, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 78% patients with diarrhea required a dose omission and 15% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 1, MONARCH 2, and MONARCH 3.

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 if further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio with toxicity resolution (10% favorable, 1) and then resume Verzenio at the next lower dose.

Select Important Safety Information and Brief Summary of full Prescribing Information for Verzenio on the following pages.
For women with HR+, HER2- MBC
Verzenio + AI as first-line endocrine-based therapy

-28-month median PFS as initial endocrine-based therapy

>28 months median PFS with AI alone (95% CI: 23.5-14.8 months) vs 14.8 months with Verzenio (HR=0.54) (95% CI: 0.34-0.84) 

- The percentage of events at the time of analysis was 43% (n=178) and 65.5% (n=148) in the Verzenio + AI and AI alone arms, respectively.

- At the time of the PFS analysis, 19% of patients had died, and overall survival data were immature.

ITT

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

- ORR in patients with measurable disease

- ORR in patients with measurable disease

PFS results in women with concerning clinical characteristics were consistent with the ITT population

Liver metastases

- 150 months median PFS with AI alone (95% CI: 74.2-237.7) vs 7.2 months median PFS with Verzenio + AI (95% CI: 21.4-10.3) (HR=0.54) (95% CI: 0.27-0.83) 

- 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 Cs 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.

Treatment-free interval <36 months

- 295 months median PFS with Verzenio + AI (95% CI: 11.6-19.4 months) vs 9.0 months median PFS with AI alone (95% CI: 37.1-14.2) (HR=0.44) (95% CI: 0.24-0.80) 

- 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 Cs 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.

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 endocrine therapy, 79% 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 OS and DoR.

Select Important Safety Information (cont’d)

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant compared to 2.8% of patients treated with fulvestrant plus placebo. Verzenio thromboembolic events included deep vein thrombosis, pulmonary embolism, puerperal 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.
Abemaciclib (Verzenio®): recommended by the National Comprehensive Cancer Network® (NCCN®)

**Abemaciclib (Verzenio) as a single agent**
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.

**Abemaciclib (Verzenio) + an AI**
Recommended option for the treatment of postmenopausal women with HR+, HER2- MBC as initial endocrine-based therapy

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**Select Important Safety Information (cont’d)**

**MONARCH 1** was a single-arm, open-label, multicenter study in 132 women with metastatic HR+, HER2- whose disease progressed during or after ET and who received ≥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 ≥2 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.

**MONARCH 2** was a single-arm, open-label, multicenter, randomized study of 177 women with metastatic HR+, HER2- whose disease progressed during or after ET, had received a taxane in any setting, and who were ≥70% in the Verzenio arm vs ≥5% in the Placebo arm (independent review) of patients received a prior endocrine therapy in combination with a taxane.

**MONARCH 3** was a single-arm, open-label, multicenter study in 132 women with metastatic HR+, HER2- whose disease progressed during or after ET, had received a taxane in any setting, and who were ≥70% in the Verzenio arm vs ≥5% in the Placebo arm (independent review) of patients received a prior endocrine therapy in combination with a taxane.

**Select Important Safety Information (cont’d)**

**Abemaciclib** (Verzenio) as a single agent
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.

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For heavily pretreated women with HR+, HER2- MBC: The only CDK4 & 6 inhibitor approved as a single agent

**ORR**

(95% CI: 13.3-27.5) per investigator assessment

ORR was defined as the proportion of patients with ≥PR + PI, and does not include stable disease

≥19.7% ORR

- 17.6% ORR (95% CI: 11.4-25.0), per independent review

**Median duration of response (mDoR)**

- 3.7-month median time to response (range: 1-14.2 months)

- 7.2-month median mDoR (95% CI: 5.6-NR), per independent review

- *ORR defined as ≥10% reduction in target lesion size per RECIST 1.1. Among 26 patients (investigator assessed) and 23 patients (independent review) who had a PR.

**Category 1**

Based on high-level evidence, there is a sufficient NCCN consensus that the intervention is appropriate.

**Category 2A**

Based on lower-level evidence, there is a sufficient NCCN consensus that the intervention is appropriate.

NCCN makes no warranties of any kind whatsoever regarding their content, use, or applicability and disclaims any responsibility for their application or use in any way.

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**Oral administration of abemaciclib increases the exposure of abemaciclib via its active metabolites and may lead to increased toxicity. Avoid concomitant use of ketoconazole.**

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**Abemaciclib (Verzenio): the only CDK4 & 6 inhibitor recommended by NCCN in combination with fulvestrant or an AI and as a single agent**
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 (96% of patients receiving VERZENIO plus fulvestrant in MONARCH 2) and 80% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 15% of patients receiving VERZENIO plus fulvestrant in MONARCH 3, 15% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 40% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and hypotension.

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 6 days, and the median duration of diarrhea of 2 days and 3 or 4 days, respectively, in MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea of 3 and 2 days, respectively. In MONARCH 3, 10% of patients with diarrhea required a dose omission and 15% required a dose reduction. In MONARCH 2, 10% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and duration of diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start anti-diarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 2 or 3 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to Grade 1, and then resume VERZENIO at the next lower dose.

Neuropathy
Neuropathy occurred in 44% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 40% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 decrease in multiple motor/sensory clinical endpoints occurred in 22% of patients receiving VERZENIO plus aromatase inhibitor as monotherapy in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 2% of patients receiving VERZENIO in MONARCH 1.

In MONARCH 3, the median time to first episode of Grade 3 neuropathy was 33 days, and in MONARCH 2 and MONARCH 1, median duration of Grade 3 neuropathy was 11 days, and in MONARCH 2 and MONARCH 1 it 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. Discontinue, dose reduction, or withholding of treatment is recommended for patients who develop Grade 3 neuropathy.

Fatigue neuropathy has been reported in 5% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neuropathy were observed in MONARCH 1. MONARCH 2 patients who rapidly report any episodes of fewer than 2 miles of walking.

Hepatotoxicity
In MONARCH 3, Grade 3 increases in ALT 40% versus 24% 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 5% versus 3% were reported in the VERZENIO and placebo arms, respectively.

VERZENIO™ (abemaciclib) tablets, for oral use

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

References:
Additional adverse reactions in MONARCH 1 include venous thromboembolic events and hematologic disorders (Table 2). The most common adverse reactions reported (≥20% in the VERZENIO arm) were anemia, neutropenia, neutrophil count decreased, lymphocyte count decreased, and platelet count decreased. The most frequent serious adverse reaction was neutropenia, observed in 13% of patients in the VERZENIO arm. Anemia, neutropenia, lymphopenia, and thrombocytopenia were the most common grade 3/4 hematologic disorders.

**Table 2: Laboratory Abnormalities in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 3 or 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3 or 4</th>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>12%</td>
<td>0%</td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9%</td>
<td>1%</td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>2%</td>
<td>2%</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>6%</td>
<td>3%</td>
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<td>3%</td>
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</table>

**Table 3: Laboratory Abnormalities in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1%</td>
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**Table 4: Adverse Reactions in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3 by Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3%</td>
<td>0%</td>
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**Table 5: Grade 4 Adverse Reactions in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td>Neutropenia</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Table 7: Grade 3 Adverse Reactions in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 8: Grade 2 Adverse Reactions in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 9: Adverse Reactions in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3 by Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 10: Grade 4 Adverse Reactions in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo in MONARCH 3**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0%</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>0%</td>
</tr>
</tbody>
</table>
Table 10: Adverse Reactions (≥10% of Patients) in MONARCH 1 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VERZENO®</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>15%</td>
<td>10%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>65%</td>
<td>13%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Interactions**

**Effect of Other Drugs on VERZENO**

**Strong CYP3A4 Inhibitors**

**Strong CYP3A4 inhibitors** increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

**Creatinine Increased**

Liver toxicity was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

In patients treated with abemaciclib, there was a trend toward a higher frequency of elevated serum creatinine levels compared to patients treated with placebo.

**Creatinine Increased**

In patients treated with abemaciclib, there was a trend toward a higher frequency of elevated serum creatinine levels compared to patients treated with placebo.

**Other Strong CYP3A4 Inhibitors**

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, the effect of abemaciclib was significantly reduced in patients treated with strong CYP3A4 inhibitors compared to patients treated with placebo.

**Infections and Infestations**

**Blood and Lymphatic System Disorders**

**Neutropenia**

Neutropenia was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Neutropenia**

Neutropenia was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Metabolism and Nutrition Disorders**

**Weight Decreased**

Weight decreased was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Metabolism and Nutrition Disorders**

**Weight Decreased**

Weight decreased was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Musculoskeletal and Connective Tissue Disorders**

**Ankle Swell**

Ankle swell was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

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**Respiratory, Thoracic and Mediastinal Disorders**

**Gag**

Gag was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Gag**

Gag was observed in patients treated with abemaciclib. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Musculoskeletal and Connective Tissue Disorders**

**Ankle Swell**

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**Data**

Abnormal Date

In an embryofetal development study, preclinical rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Tissues and major organs were developed. Increased serum creatinine (≥2-fold) occurred in approximately 13% of patients treated with abemaciclib compared with patients treated with placebo.

**Data**

Abnormal Date

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Medicare Changes Rules for Local Coverage Determinations

By Aileen Soper

The Centers for Medicare & Medicaid Services (CMS) is overhauling the process its contractors follow to develop local coverage policies. The policies, known as local coverage determinations (LCD), determine how many things—from injectable oncolytics to evaluation and management services for cancer patients—are covered under the Medicare Part A and B benefits. Medicare Administrative Contractors (MAC) can issue LCDs when national coverage determinations (NCD) do not exist or when MACs need to further define covered services. In cases where a MAC does not have an LCD or there is no applicable NCD, services are reviewed for coverage on a case-by-case basis.

The updated instructions, policies and procedures will be added to chapter 13 of the Medicare Program Integrity Manual. The move is how the Medicare program is addressing Congress’ requirement in section 4009 of the 21st Century Cures Act for a more transparent LCD process. The reforms are intended to increase transparency and patient engagement to ensure that Medicare beneficiaries have access to the latest therapies and devices, CMS said in a news release.

According to a CMS fact sheet, the changes to the LCD process include:

1. Publishing a step-by-step description of the LCD process in language intended to be accessible to all stakeholders
2. Standardizing presentation of clinical evidence that supports LCD decisions and rationale for MAC coverage determinations
3. Providing an option to request an informal meeting with the MAC to discuss potential LCD requests
4. Implementing a new process by which interested parties in a MAC jurisdiction can request a new LCD
5. Restructuring Contractor Advisory Committee (CAC) meetings. CAC members serve in an advisory capacity to review the quality of the evidence used in the development of an LCD. MACs can host CAC meetings in various ways (eg, in-person, telephone, video, webinar). MAC’s determine how frequently these meetings occur based on the appropriateness and volume of LCDs requiring CAC input. CAC meetings will be open to the public.
6. Opening CAC membership to include patients and non-physician healthcare professionals such as nurses and social workers
7. Opening meetings in the MAC jurisdiction to present proposed coverage, including evidence and rationale of decisions
8. Retiring proposed policies if they are not finalized within one year of the original posting date
9. Removing codes such as International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) and Current Procedure Terminology (CPT®) diagnosis and procedure codes from LCDs. The codes will instead be listed in coverage articles that can be linked to the LCD.
10. Linking MAC responses to public comments to the final LCD and maintaining them in the Medicare Coverage Database indefinitely
11. Creating a reconsideration process for LCDs that is consistent with the NCD reconsideration process

Stakeholders can submit feedback to CMS on their experiences with the revised LCD process to LCDmanual@cms.hhs.gov. The agency says it will consider future revisions to the LCD process requirements based on the feedback.


Aileen Soper is assistant director, Reimbursement Strategy and Tactics, with Xcenda, a part of AmerisourceBergen.
Performance Threshold Points: The minimum number of points needed to avoid a downward adjustment in reimbursement moves from 15 points to 30 points in 2019. Category Reweighting: Categories are reweighted in 2019 to include Quality at 45 percent, Promoting Interoperability at 25 percent, Cost at 15 percent and Improvement Activities at 15 percent.

Payment Adjustments: Payment adjustment for the performance year of 2017 (payment year of 2019) are +/-4 percent; in the 2018 performance year (payment year of 2020) it is +/- 5 percent; in the 2019 performance year (payment year of 2021) the payment adjustment increases to +/-7 percent.

Quality Category

CMS will apply the general rules as the agency has done before in the proposed Quality category. Practices or providers will report six measures with one being an outcome measure. The category continues to be 45 percent of the final score and data completeness is at 60 percent. Eligible clinicians and groups can report Quality measures across multiple collection types, including registry, EHRs and claims.

One of their most significant proposed changes is to the measures that can be selected for reporting. CMS plans to implement 10 new measures, but also to eliminate 33 other measures. Some practices may currently be using those measures in reporting, so CMS encouraged practices to review both sets of measures—those new and those scheduled for removal. The change in measures may impact some practices, especially those measuring Hypertension: Improvement in Blood Pressure Control. As an example, to earn the full 25 points for the category in 2018, practices or eligible clinicians need to earn 100 out of 165 points available. In 2019, only 110 total points are available in the category, and that includes a 10-point bonus if you are able to report on a new measure and EPCS (Electronic Prescriptions for Controlled Substances) is available in your state. The following year, 2020, practices will have to earn the entire 100 total points in the category to gain those 25 composite points.

The measures proposed for removal in this category include:
- Patient-specific Education
- Secure Messaging
- View, Download and Transmit
- Patient-generated Health Data
- Clinical Information Reconciliation*
- Request/Accept Summary of Care*

(*These last two measures will be combined into a new category called Support Electronic Referral Loops Receiving and Incorporating Health Information.)

More emphasis will be placed on the issue of prescription drug abuse. New measures to address those include Query of Prescription Drug Monitoring (PDMP) and Verify Opioid Treatment Agreement. Practices will be excluded from reporting on these measures if the practice or provider cannot e-prescribe Schedule II opioids.

In addition, a Security Risk Analysis is not a scored measure, but it will still be required to achieve any points in this category.

Improvement Activities

CMS does not plan to change the weighting to the final score from 15 percent (as it was in the 2018 performance year). They also maintain that activities are to be performed for at least a continuous 90 days during the performance period.

CMS is proposing to remove the previous bonus points to align with the new Promoting Interoperability scoring requirements. For the number of activities, clinicians will still need to reach a total of 40 points but will have six new Improvement Activities (IA), five activities will be modified and one existing activity will be removed from the IA inventory. The number of activities for small practices or clinicians involved in rural or HPSAs has not changed. They will continue to report on no more than two medium or one high-weighted activity to reach the highest score.

Cost

CMS continues to place increasing emphasis on cost and quality for MIPS Reporting. In the Cost category, CMS will continue to look at claims data, but the performance measure will be weighted more heavily each year. The percentage increases five percent each year, topping off at 30 percent of the total. In 2019, the proposed weighting will be 15 percent, up from 10 percent in the 2018 performance year.

Promoting Interoperability

CMS has proposed several changes to the Promoting Interoperability category (formerly Meaningful Use and Advancing Care Information) for 2019, including significantly reducing the number of measures that are available. It is expected that the proposed changes will make it more difficult for practices to achieve the full 25 points in this category.

The measures proposed for removal in this category include:
- Improvement Activities
- Request/Accept Summary of Care*

(These last two measures will be combined into a new category called Support Electronic Referral Loops Receiving and Incorporating Health Information.)

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In addition, a Security Risk Analysis is not a scored measure, but it will still be required to achieve any points in this category.

Practices will have to report a minimum of 90 days up to the full calendar year for 2019 measures and will be required to use the 2015 Edition CEHRT. The 2014 Edition will not be an option.

Keep in Mind:
- The reporting period is a minimum of 90 days.
- Claiming exclusions does not always help you. If you can meet the measure, that will help your score.
- Be prepared to use secure transmission methods to send and receive referrals. Check with other providers involved in your patient’s care to understand their methods so you are prepared to accept and send.
- Check with your EHR vendor on available transmission methods; PDMP and Opioid Agreement verification for those bonus points; and EPCS, if allowed in your state.

The Total Per Capita Cost (TPCC) and Medicare Spending per Beneficiary (MSPB) measures will work similar to past years. Benchmarks will be made based on comparisons to your peers in your specialty but will not look at historical data.

If your practice does not meet the minimums (applicable to your practice or provider), your cost category moves to additional weighting on your Quality performance measure. You will be scored on as many measures that meet the case minimum. If only one measure can be scored, that score will be the total Cost category score.

CMS is proposing to add eight new episode-based measures that were field tested in 2017. The measures include:
- Elective Outpatient Percutaneous Coronary Intervention (PCI)
- Knee Arthroplasty
- Revascularization for Lower Extremity Chronic Critical Limb Ischemia
- Routine Cataract Removal with Intracocular Lens (IOL) Implantation
- Intracranial Hemorrhage or Cerebral Infarction
- Simple Pneumonia with Hospitalization
- ST-Elevation Myocardial Infarction (STEMI) with Percutaneous Coronary Intervention (PCI)

The comment period for the 2019 Proposed Rule closed in September. We expect the Final Rule on the proposals to be released in November.
The ION Solutions Precision Medicine Center is your gateway to a single, centralized library of precision medicine testing recommendations and resources. Access all of the testing recommendations created by our physician- and pharmacist-based advisory panel as well as resources curated by ION Solutions and our precision medicine partners to help you make informed decisions for your patients.

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- NSCLC
- Colorectal
- Genitourinary
- Lymphoma
- Rare Disease

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