Harnessing the immune system in the fight against cancer

- Introducing CareFront
- Reimbursement Watch
One goal: discovering breakthrough medicines to combat cancer.

We are excited to announce the launch of TAKEDA ONCOLOGY formerly known as MILLENNIUM: THE TAKEDA ONCOLOGY COMPANY. Our mission is unchanged as we endeavor to deliver extraordinary medicines to patients with cancer worldwide through our commitment to science, breakthrough innovation and passion for improving the lives of patients.

This singular focus drives our aspiration to discover breakthrough oncology therapies. By concentrating the power of leading scientific minds and the vast resources of a global pharmaceutical company, we are finding innovative ways to improve the treatment of cancer. We’ve built a portfolio of paradigm-changing therapies and a leading oncology pipeline. While we’ve made great strides in our fight against cancer, we are determined to do more—to work harder, to achieve greater—and to do it with the same passion, agility and entrepreneurial spirit that has always been at the heart of our culture and made us the leaders in oncology that we are today.

We know that our mission is not a quick or easy one but we are up to the task: we aspire to cure cancer.

Takeda Oncology is Proud to Partner with ION Solutions.

To learn more, visit us at takedaoncology.com.

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Challenge your expertise with Challenging Cases®

If you’re a physician interested in providing insight to impact patient treatment, then you’ll like Challenging Cases.

Hosted by Xcenda, a premier healthcare consulting firm, this series of live interactive events allows hematologists/oncologists to share their insights into the complex clinical decisions and patient challenges they face every day.

Check out our 2015 calendar of events:

March 21
Las Vegas

May 2
Chicago

March 28
NYC

May 16
SFO

HEMATOLOGY SERIES

August 8
NYC

October 17
SFO

August 22
New Orleans

November 7
Las Vegas

HEMATOLOGY SERIES

ONCOLOGY SERIES

New in 2015! Announcing Dr. John Marshall MD, chief of hematology/oncology at Georgetown Lombardi Comprehensive Cancer Center, as our acting Medical Director and Moderator for Challenging Cases.

Learn more about Challenging Cases at www.xcenda.com/challenging-cases.

To join our provider insights network and participate in a Challenging Cases event*:
Visit bit.ly/xcendaenroll or send an email to insights@xcenda.com

* Events are double-blinded market research events and therefore not reportable under the Sunshine Act. Transportation, hotel and meals are provided.
Table of Contents
spring 2015

6

Industry Insight
An interview with Dr. Joseph Leveque, Vice President, Oncology, Bristol-Myers Squibb Company

14

CareFront Helps Your Practice Connect with Patients
By Tricia Musslewhite

18

Reimbursement Watch
U.S. Clears Approval Pathway for Biosimilars: Considerations for Your Practice
By Sara Fernandez, Ph.D., MBA

22

Myelodysplastic Syndromes: What’s Next?
By Dr. Alan List, H. Lee Moffitt Cancer Center & Research Institute

26

What’s News at ION
Immuno-Oncology is a rapidly evolving field that focuses on harnessing the ability of the immune system in the fight against cancer. In this issue of Oncologistics, we learn how Bristol-Myers Squibb is finding new ways to stop cancer from evading the immune system, thereby restoring the body's natural ability to recognize and eliminate cancer. Read more on page six.

In March, the U.S. Food and Drug Administration approved Zarxio (filgrastim-sndz), the first biosimilar product ever approved in the U.S. A biosimilar product is highly similar to an already-approved biological product, known as a reference product. The biosimilar also must show it has no clinically meaningful differences in terms of safety and effectiveness from the reference product.

This issue's Reimbursement Watch addresses the implications biosimilars will have on the oncology and hematology communities. Learn more about biosimilars and how practices can prepare for their market entry on page 18.

I encourage you to continue to reach out to your congressional representatives to discuss the value of community-based oncology. ION Solutions is committed to community oncology and your mission to deliver quality patient care. Thank you for your continued support of ION Solutions.

Sincerely,
Mark Santos
President
ION Solutions GPO
Making a difference in the lives of patients

An Interview with Dr. Joseph Leveque, Vice President, Oncology, Bristol-Myers Squibb Company

As a global BioPharma leader, Bristol-Myers Squibb (BMS) uniquely combines the reach and resources of a major pharmaceutical company with the can-do spirit and agility of an innovative biotech. The guiding principles and values behind our business strategy are expressed in our company’s Mission “to discover, develop and deliver innovative medicines that help patients prevail over serious diseases.” Our focus these days in Oncology is on Immuno-Oncology (I-O). It’s an exciting time but ultimately, our success will be measured by one thing: the difference we can make in the lives of patients.

1. How does the immune system interact with cancer?

The immune system is complex, made up of multiple mechanisms that act to defend and protect the human body. The concept of Immuno-Oncology actually dates back to the 18th century, when the possibility of using the body’s immune system response to help fight disease began to be explored. It’s critical to understand the power of the body’s own immune system and how this response may be important to understanding the ability to fight cancer. Normally, the immune system is able to recognize internal and external threats through antigen recognition and mounts a response to eradicate abnormal cells, including tumor cells. However, when healthy cells mutate into malignant cells, they display abnormal tumor-associated antigens, that may prevent the immune system from mounting a normal response and prevents eradication of the cancer cell through evasion of recognition and elimination processes of the immune system. Immuno-Oncology research focuses on identifying pathways that can be manipulated to help restore the body’s own natural immune response to fight cancer.

2. Can you explain BMS’s research approach into checkpoint pathways?

Although many years have been dedicated to researching checkpoint pathways at BMS, every day we are still learning about how using this approach to modulate immune pathways may help fight cancer in different tumor types. Cancer cells may exploit “regulatory” pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack.

At BMS, we have a broad, global development program to study the potential of these checkpoint pathways with several potentially registrational trials in non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), head and neck cancer, glioblastoma and non-Hodgkin lymphoma.

3. What are you doing differently to develop your I-O agents?

What sets BMS apart from other companies is our clinical trial program collaboration through the Immuno-Oncology Integrated Community Oncology Network (IO-ICON). As part of our global oncology development program, we have taken a focus for the first time in our company’s history on conducting trials in the community setting. In the U.S., approximately 80 percent of cancer patients are diagnosed and treated in the community setting. For the past two decades, community-based oncologists have been joining together to form networks that conduct interventional and non-interventional research. The IO-ICON collaborative was formed with leading oncology networks to develop and execute applied and adaptive research, transfer knowledge...
and focus on policy centered on the imperative of improving cancer survivorship and the value of a longer, healthier life.

IO-ICON is conducting a series of specific programs focused on Immuno-Oncology. One is a non-interventional, longitudinal, observational study that will provide insights into the natural clinical, prognostic and molecular course of lung cancer. Another is a 1,000 patient study across lung cancer histologies, molecular subsets and lines of therapies intended to expand the safety knowledge base of I-O therapy. From these studies, IO-ICON will assemble a rapid learning system that can be used for the consideration of future research opportunities or to support applied clinical I-O decision making.

IO-ICON will also focus on educating community oncologists, their care teams and patients and caregivers on I-O and how to best care for patients receiving these medicines. Through health services research it will focus on quantifying the value to society of people living longer, the value of people being alive long enough to access additional therapies as they become available later in life, and dynamic cost-effectiveness, or the cumulative costs to society of drugs through their entire life cycle, from branded to generic.

4. Ten years from now, what do you hope to be able to say about BMS's contribution to Immuno-Oncology?

BMS has a rich history in Oncology research and development and specifically, Immuno-Oncology. We may be standing on the precipice of a major shift in cancer treatment. Our research goals hope to address the unmet need of improving survival rates. We hope our research may transform the outlook for patients and will provide more options. Over the next decade, we will remain dedicated to our Immuno-Oncology portfolio and continue to investigate the potential of different agents for both solid tumors and hematologic malignancies across multiple tumor types. Through collaborative efforts, our goal is to keep patients at the center of everything we do.

5. Where can healthcare professionals learn more about the role of the immune system in cancer?

We are committed to furthering the knowledge and understanding of Immuno-Oncology to healthcare practitioners, patients and caregivers. Engaging and informative educational videos I-O experts as well as downloadable slide decks, fact sheets, and other informational resources can be found at www.immunooncology.com.
We Support the Health of your Practice
With the Same Dedication that You Support Your Patients

Your number one priority is the health of your patients. With the changing healthcare landscape, our number one priority is the business health of your practice.

Dedicated exclusively to the viability of community oncology, ION Solutions provides contracting, technology, education and advocacy support that ensures you have the tools to run your practice both efficiently and effectively. With the practice support of ION Solutions, you can navigate this changing environment and focus on providing quality care for your patients.

To learn how ION Solutions enables community oncology practices to improve operational efficiency, financial performance and quality of care, contact your Strategic Account Manager or visit IONonline.com.

To experience ION Solutions advocacy support, visit ourcommunitycounts.org.
Results from the Phase III EMILIA trial KADCYLA vs lapatinib + capecitabine in patients with HER2+ metastatic breast cancer (MBC):

**Proven overall survival (OS) benefit**

KADCYLA contains the active antibody trastuzumab, the cytotoxic agent DM1, and a stable linker

---

**Indication**

KADCYLA (ado-trastuzumab emtansine), as a single agent, is indicated for the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.

**Important Safety Information**

Boxed WARNINGS: HEPATOTOXICITY, CARDIAC TOXICITY, EMBRYO-FETAL TOXICITY

- Do not substitute KADCYLA for or with trastuzumab
- Hepatotoxicity: Serious hepatotoxicity has been reported, including liver failure and death in patients treated with KADCYLA. Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases or total bilirubin
- Cardiac toxicity: KADCYLA administration may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate left ventricular function in all patients prior to and during treatment with KADCYLA. Withhold treatment for clinically significant decrease in left ventricular function
- Embryo-fetal toxicity: Exposure to KADCYLA can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception

**Additional Important Safety Information**

**Left Ventricular Dysfunction (LVD)**

- Patients treated with KADCYLA are at increased risk of developing LVD. In EMILIA, LVD occurred in 1.8% of patients in the KADCYLA-treated group and in 3.3% in the comparator group. Permanently discontinue KADCYLA if LVEF has not improved or has declined further

**Pregnancy Registry**

- Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. Encourage women who may be exposed to KADCYLA during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720

**Pulmonary Toxicity**

- Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome, have been reported in clinical trials with KADCYLA. In EMILIA, the overall frequency of pneumonitis was 1.2%
- Treatment with KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis

**Infusion-Related Reactions, Hypersensitivity Reactions**

- Treatment with KADCYLA has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) and/or hypersensitivity reactions; treatment with KADCYLA is not recommended for these patients. In EMILIA, the overall frequency of IRRs in patients treated with KADCYLA was 1.4%
- KADCYLA treatment should be interrupted in patients with severe IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be closely monitored for IRRs, especially during the first infusion

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Genentech
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Superior efficacy with a single agent\textsuperscript{1}

\textbf{NEARLY 6-MONTH IMPROVEMENT IN MEDIAN OS}

Results of the randomized, open-label, Phase III EMILIA trial of KADCYLA (3.6 mg/kg IV, Day 1) vs the combination of lapatinib (1250 mg/day oral, once daily) and capecitabine (1000 mg/m\textsuperscript{2}, oral, twice daily, Days 1-14) in 21-day cycles until disease progression in HER2+ MBC patients previously treated with trastuzumab and a taxane. Primary endpoints were OS, progression-free survival (PFS), and safety.\textsuperscript{2}

- 50% improvement in median PFS for KADCYLA vs lapatinib + capecitabine (9.6 months vs 6.4 months; HR=0.650; 95% CI: 0.548, 0.849; \textit{P}<0.0001)\textsuperscript{1}
- The most common adverse reactions Grades \textgeq3 (frequency >2\%) in the KADCYLA arm were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue, according to NCI-CTCAE (version 3)\textsuperscript{4}

\section*{Hemorrhage}

- Hemorrhagic events, sometimes fatal, have been reported in clinical trials. In EMILIA, the incidence of \textgeq Grade 3 hemorrhage was 1.8\% in the KADCYLA-treated group and 0.8\% in the comparator group (overall incidence 32.2\% and 16.4\%, respectively)
- In some of the observed cases the patients were also receiving antiagulation therapy or antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary

\section*{Thrombocytopenia}

- In EMILIA, the incidence of \textgeq Grade 3 thrombocytopenia was 14.5\% in the KADCYLA-treated group and 0.4\% in the comparator group (overall incidence 31.2\% and 3.3\%, respectively)
- Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose. Institute dose modifications as appropriate

\section*{Neurotoxicity}

- In EMILIA, the incidence of \textgeq Grade 3 peripheral neuropathy was 2.2\% in the KADCYLA-treated group and 0.2\% in the comparator group (overall incidence 21.2\% and 13.5\%, respectively)
- Monitor for signs or symptoms of neurotoxicity. KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to \textless Grade 2

\section*{HER2 Testing}

- Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA. Perform using FDA-approved tests by laboratories with demonstrated proficiency

\section*{Extravasation}

- In KADCYLA clinical studies, reactions secondary to extravasation have been observed and were generally mild. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration. Specific treatment for KADCYLA extravasation is unknown

\section*{Nursing Mothers}

- Discontinue nursing or discontinue KADCYLA, taking into consideration the importance of the drug to the mother

\section*{Adverse Reactions}

- The most common (frequency >25\%) adverse drug reactions (ADR) across clinical trials with KADCYLA were nausea, fatigue, musculoskeletal pain, hemorrhage, thrombocytopenia, increased transaminases, headache, constipation, and epistaxis. In EMILIA, the most common NCI-CTCAE (version 3) \textgeq Grade 3 ADRs (frequency >2\%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy, and fatigue

You are encouraged to report side effects to Genentech and the FDA. You may contact Genentech by calling 1-888-835-2565. You may contact the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

Please see the following pages for brief summary of full Prescribing Information, including Boxed WARNINGS.

For more information on KADCYLA, visit KADCYLA.com.

studies in human liver microsomes indicates that DM1 is not penetrated with trastuzumab, the antibody component of KADCYLA, during pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, and neonatal death. Oligohydramnios, DSM, the toxic cytokine component of KADCYLA, can be expected to cause embryo-fetal toxicity based on its mechanism of action.

In clinical trials of KADCYLA, a single patient treated with KADCYLA pregnant while receiving KADCYLA, apprise the patient of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

If pregnancy occurs during exposure to KADCYLA, immediately discontinue KADCYLA as appropriate in cases of increased serum hepatotoxic potential. Some of the observed cases may have been confounded by several factors, including sample handling, timing of sample collection, and other factors. Immunogenicity data are highly dependent on the sensitivity and specificity of the test method used. Clinical significance of anti-KADCYLA antibodies should be closely monitored for possible subclass mutations in fertility drug administration.

The following adverse reactions are discussed in greater detail in descriptions of the label:

- Neurotoxicity [see Warnings and Precautions (5.3), Use in Renal Impairment (8.7)]
- Embryo-Fetal Toxicity [see Warnings and Precautions (5.3)]
- Pulmonary Toxicity [see Warnings and Precautions (5.4)]
- Hyperglycemia and Reduced Glucose Tolerance [see Warnings and Precautions (5.6)]

6.7 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. In clinical trials, KADCYLA has been evaluated as single-agent therapy, combination therapy with trastuzumab and lapatinib, and in combination with lapatinib plus capecitabine. The most common (frequency ≥ 25%) adverse drug reactions (ADRs) seen in 884 patients treated with KADCYLA were fatigue, nausea, vomiting, anemia, leukopenia, neutropenia, decreased appetite, increased transaminases, constipation and epistaxis. The ADRs described in Table 6 were identified in patients with HER2-positive metastatic breast cancer treated in a randomized trial (see Clinical Studies (14.1)) and were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 3.6 months for patients in the KADCYLA-treated group and 5.5 months and 3.3 months for patients treated with lapatinib and capcitabine, respectively. Two hundred and ninety-three (64.1%) patients experienced ≥ 1 adverse event adverse reactions 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. In clinical trials, KADCYLA has been evaluated as single-agent therapy, combination therapy with trastuzumab and lapatinib, and in combination with lapatinib plus capecitabine. The most common (frequency ≥ 25%) adverse drug reactions (ADRs) seen in 884 patients treated with KADCYLA were fatigue, nausea, vomiting, anemia, leukopenia, neutropenia, decreased appetite, increased transaminases, constipation and epistaxis. The ADRs described in Table 6 were identified in patients with HER2-positive metastatic breast cancer treated in a randomized trial (see Clinical Studies (14.1)) and were randomized to receive KADCYLA or lapatinib plus capecitabine. The median duration of study treatment was 3.6 months for patients in the KADCYLA-treated group and 5.5 months and 3.3 months for patients treated with lapatinib and capcitabine, respectively. Two hundred and ninety-three (64.1%) patients experienced ≥ 1 adverse event

Table 6 reports the ADRs that occurred in patients in the KADCYLA-treated group (n=480) of the randomized trial (Study 1). Selected ADRs are shown in Table 6. The most frequent adverse events occurring in ≥ 1% of patients treated with KADCYLA were fatigue, muscle/cachexia, pain, nausea, diarrhea, and vomiting. The most frequent adverse event leading to dose delay of KADCYLA (in ≥ 1% of patients) included neutropenia, thrombocytopenia, leukopenia, and anemia. The most common ADRs (frequency ≥ 25%) were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue.
### Table 6: Summary of Adverse Drug Reactions Occurring in Patients on the KADCYLA Treatment Arm in the Randomized Trial (Study 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Grade (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Drug Reactions</strong>&lt;br&gt;<strong>Non-Hematologic Class</strong></td>
<td><strong>KADCYLA 30-mg</strong>&lt;br&gt;<strong>mEq/kg</strong>&lt;br&gt;<strong>N (n=396)</strong>&lt;br&gt;<strong>Frequency (%)</strong>&lt;br&gt;<strong>Frequency %</strong></td>
<td><strong>KADCYLA 30-mg</strong>&lt;br&gt;<strong>mEq/kg</strong>&lt;br&gt;<strong>N (n=396)</strong>&lt;br&gt;<strong>Frequency (%)</strong>&lt;br&gt;<strong>Frequency %</strong></td>
<td><strong>KADCYLA 30-mg</strong>&lt;br&gt;<strong>mEq/kg</strong>&lt;br&gt;<strong>N (n=396)</strong>&lt;br&gt;<strong>Frequency (%)</strong>&lt;br&gt;<strong>Frequency %</strong></td>
</tr>
<tr>
<td><strong>Bleeding and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6.7</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.2</td>
<td>4.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Thrombocyto- penia</td>
<td>31.2</td>
<td>14.5</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>1.8</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxation increased</td>
<td>3.3</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Dry eye</td>
<td>3.9</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>4.5</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3.8</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9.2</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.0</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18.6</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>19.2</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24.1</td>
<td>3.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>25.1</td>
<td>5.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.8</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Renal and Hypertension Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication-induced hypertension</td>
<td>0.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td><strong>Integumentary Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neuromuscular and Mental Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>0.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9.4</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>4.7</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased transaminase</td>
<td>28.8</td>
<td>8.0</td>
<td>14.3</td>
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<tr>
<td><strong>Metabolism and Nutritional Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10.2</td>
<td>2.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Hyperglycemia and Concomitant Tissue Disorders</td>
<td>14.1</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.8</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12.0</td>
<td>2.4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.1</td>
<td>1.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*NE = Not determined

### Table 7: Selected Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Grade (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
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<tr>
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<tr>
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<tr>
<td><strong>Cardiac Disorders</strong></td>
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<td>0.3</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxation increased</td>
<td>3.3</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Dry eye</td>
<td>3.9</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>4.5</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3.8</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9.2</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.0</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18.6</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>19.2</td>
<td>3.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24.1</td>
<td>3.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>25.1</td>
<td>5.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.8</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Renal and Hypertension Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication-induced hypertension</td>
<td>0.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td><strong>Integumentary Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neuromuscular and Mental Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>0.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9.4</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>4.7</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased transaminase</td>
<td>28.8</td>
<td>8.0</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Metabolism and Nutritional Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10.2</td>
<td>2.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Hyperglycemia and Concomitant Tissue Disorders</td>
<td>14.1</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.8</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12.0</td>
<td>2.4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.1</td>
<td>1.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*NE = Not determined

[Table 6: Summary of Adverse Drug Reactions Occurring in Patients on the KADCYLA Treatment Arm in the Randomized Trial (Study 1)]

[Table 7: Selected Laboratory Abnormalities]
CareFront Helps Your Practice Connect with Patients

By Tricia Musslewhite
CareFront helps better manage cancer care

When a health plan member or their relative is diagnosed with cancer, the first step is to access the CareFront directory either online or by calling CareFront’s toll-free number. The CareFront directory will highlight in-network community oncologists. This service is available to all employees, their dependents, parents and others for a low per member per month fee.

In addition to the list of oncologists, CareFront also provides invaluable information on how to choose a doctor, as well as what to expect during treatment, and information on numerous topics of interest to oncology patients and their caregivers. The Cancer Care Resource Guide is made available to all who access the directory service.
Who pays for CareFront?

Employers and health plans, called sponsors, pay for CareFront. Sponsors pay a small per member per month access fee so that all of their members can access the directory for their family members, whether covered by the health plan or not. The access fee also includes the Cancer Care Resource Guide and access to the CareFront Rewards program. When a covered member is diagnosed and elects to participate, the sponsor pays an administrative fee. As the participant completes actions, the sponsor funds up to the maximum contribution limit each year that the participant is in active treatment. ION practices pay nothing to be listed in the directory, including the enhanced listings.

CareFront will benefit your practice

CareFront highlights your practice as community based and helps increase referrals. Patients often use the Internet and health plan directories as sources of self-referrals. Through the directory and the Cancer Care Resource Guide, CareFront reinforces the value of community oncology and the quality you bring.

Through CareFront Rewards patients have more money available to pay for their copays and deductibles. With a recommended annual maximum benefit of $1,500 (determined by their health plan and benefits regulation) of which 100 percent must be spent on healthcare, they have more dollars available to pay any outstanding balance they may have with you.

For self-funded practices that sign up, you can expect to see lower cancer treatment costs for your covered plan members.

To learn more about how CareFront can help your practice, email CareFront at network@mycarefront.com.

Who pays for CareFront?

Employers and health plans, called sponsors, pay for CareFront. Sponsors pay a small per member per month access fee so that all of their members can access the directory for their family members, whether covered by the health plan or not. The access fee also includes the Cancer Care Resource Guide and access to the CareFront Rewards program. When a covered member is diagnosed and elects to participate, the sponsor pays an administrative fee. As the participant completes actions, the sponsor funds up to the maximum contribution limit each year that the participant is in active treatment. ION practices pay nothing to be listed in the directory, including the enhanced listings.

Tricia Musslewhite is manager, marketing and communications, at ION Solutions.

Health plans and employers are our customers. To maximize the benefit to your practice, we need to have as many health plan members and patients as possible enrolled in CareFront.

“Once your practice is signed up, we ask you to refer at least five large employers or local health plans to us (preferably 1,000 covered lives or more). AmerisourceBergen will follow up to sell the program to the employer or health plan. If you have a relationship (personal, professional, or because you have marketed directly to them in the past), we would appreciate a direct introduction and, if you feel it appropriate, have you join CareFront staff members on the sales call,” says Gordon Kuntz, Senior Director, Payer Solutions.

“We also encourage you to sign up for CareFront for your own employees,” continues Kuntz. In addition to the patient contribution, there is a small per member per month access fee and an administrative fee if a covered employee or dependent is diagnosed with cancer and enrolls in CareFront. For those who are self-funded, you can expect to see a significant return on your investment and greater peace of mind for your employees. Contact CareFront by emailing sales@mycarefront.com today for details.
Proteomic blood test for patients with advanced NSCLC
In standard of care guidelines
Medicare-covered
VeriStratSupport.com
U.S. Clears Approval Pathway for Biosimilars: Considerations for Your Practice

By Sara Fernandez, Ph.D., MBA
Patients will likely have questions about biosimilars. Be prepared to answer them.

The U.S. Food and Drug Administration (FDA)’s March 2015 approval of the biosimilar Zarxio® (filgrastim-sndz) promised to open a new era in the specialty therapy market: The product, manufactured by Sandoz as a biosimilar to Amgen’s Neupogen® (filgrastim), is the first drug approved through a groundbreaking biosimilar regulatory pathway. The implications for the oncology and hematology communities are sweeping and include the following:

- **Cost:** There is potential for lower drug prices in therapeutic categories with biosimilar entrants due to the increased competition.

- **Different safety/efficacy data:** Approval is based on similarity to reference product, not based on direct safety and efficacy data. Prescribers will need to feel comfortable with looking at a different type of data.

- **Coverage:** It will be important to watch how payers integrate the biosimilar product into formularies and/or coverage policies. Important questions include: How fast will payers review the new product? Will they simply add it to existing policies? Draft standalone policies? Mandate substitution over innovator products?

- **Coding:** The Centers for Medicare & Medicaid Services (CMS) will create a separate code for the first biosimilar to distinguish it from the innovator product, not based on direct safety and efficacy data. Prescribers will need to feel comfortable with looking at a different type of data.

- **Reimbursement:** Practices will need to understand Medicare’s reimbursement methodology for biosimilars and review private payers’ reimbursement and potential incentives for these new products.

### Background on Biosimilars

Since the introduction of the first for recombinant human insulin (HUMULIN-R) more than 30 years ago, biological products have revolutionized medicine by improving and extending patients’ lives. However, these products are costly to develop and produce. While many factors have contributed to rapid inflation in healthcare costs, the rise of biologicals and their increased utilization are ongoing concerns for payers. A biosimilar is a “biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and with no “clinically meaningful differences with [the] reference product in terms of the safety, purity and potency.” The complexity of these biological products in terms of their chemical structure and production processes make it impossible to duplicate branded originators perfectly. In fact, there is an inherent variability between different batches of a branded reference product, so when bringing a biosimilar to the market, a high level of similarity is the goal. Therefore, the rules that generally apply to generics of small molecule products need to be re-evaluated when thinking of biosimilars.

<table>
<thead>
<tr>
<th>Generics</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Types</strong></td>
<td>Small molecule entities</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td>No clinical trials required</td>
</tr>
<tr>
<td><strong>Production</strong></td>
<td>Chemical synthesis Low cost</td>
</tr>
<tr>
<td><strong>Development costs</strong></td>
<td>&lt;$10 Million</td>
</tr>
<tr>
<td><strong>Price differential</strong></td>
<td>Up to 90%</td>
</tr>
<tr>
<td><strong>Automatic substitution</strong></td>
<td>Available for all generics</td>
</tr>
</tbody>
</table>

Table 1: Comparing Generics vs. Biosimilars

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2. [http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/Selections-FromFDUUpdateSeriesonFDAHistory/ucm081964.htm](http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/Selections-FromFDUUpdateSeriesonFDAHistory/ucm081964.htm)
While the FDA will consider each biosimilar application differently, there are a few things to be learned from this first biosimilar approval:¹

<table>
<thead>
<tr>
<th>Naming</th>
<th>Zarxio provisional non-proprietary name or generic name is filgrastim-sndz. The suffix added to the existing non-proprietary name may help with pharmacovigilance efforts, although detractors claim it may create confusion and delay adoption of biosimilars in the market.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labeling</td>
<td>Zarxio label closely mirrors that of its reference product, Neupogen. All PK/PD and clinical data relies on that of the innovator; no data proving biosimilarity is included in the label.</td>
</tr>
<tr>
<td>Extrapolation of indications</td>
<td>Zarxio was approved for all five Neupogen indications, even though clinical studies were done only in one of them. However, filgrastim is a relatively simple, non-glycosilated protein with a well-known mechanism of action and good animal models.</td>
</tr>
</tbody>
</table>

Table 2: Details on the Zarxio Approval

Factors Influencing Biosimilar Adoption

Some factors expected to influence adoption of biosimilars include physician preference, patient confidence and payer incentives:

**Physician Preference**

Physicians will need to feel confident in the new biosimilar product after years of firsthand experience with the innovator. Approval by the new biosimilar review process (known as the 351.k pathway) requires the biosimilar manufacturer to prove that the biosimilar is highly similar to the reference product. It does not require biosimilar manufacturers to prove safety and efficacy directly. The biosimilar approval pathway relies heavily on analytical data, complemented by PK/PD data and fewer and smaller clinical studies than are ordinarily required for a full biologics license approval (BLA). Even so, the first wave of biosimilars expected to enter the U.S. market will be from manufacturers with years of experience in other highly regulated markets, which could help to ease physician concerns. Payer incentives to switch to a lower-cost product, such as differential reimbursement or more-favorable coverage, may accelerate adoption of biosimilars. Patient and provider support programs that are now the industry standard for branded biologics may also influence how quickly providers switch to biosimilars. Therefore, biosimilars are expected to enter the market offering these services at a level comparable to innovator products.

**Patient Confidence**

Patients will need education on biosimilars and their regulatory approval process. Given the amount of information available online, provider offices should be prepared to address concerns when a patient is prescribed one of these products (innovator or biosimilar). The amount and type of questions will likely vary depending on the type of product (lifesaving vs supportive therapy), site of care (administered at the office by the provider vs. at home by the patient), whether the patient is already on therapy or is a naïve patient and the reason for trying the biosimilar.

**Payer incentives**

Payers, already feeling pinched by continued increases in healthcare spending, ongoing cost-containment pressure from employers and heightened financial risk from formerly uninsured patients accessing coverage under the healthcare reform law, see biosimilars as a potential source of savings. How payers influence patient and provider choice of biosimilars can include the following:

**Mandates vs incentives:** More-aggressive payers may mandate use of the less-costly product by covering only one product in a therapeutic class on their formulary or

¹ [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm)
requiring step edits (trying and failing the biosimilar prior to covering the brand reference product). Other payers may try to influence patients and providers to select the less-costly product by offering higher reimbursement for the provider and lower out-of-pocket costs for the patient.

New patients vs. patients already on therapy: It is unlikely that payers will immediately require prescribers whose patients are responding favorably to the innovator therapy to switch to the biosimilar, especially before interchangeable biosimilars are approved. Instead, payers are likely to focus their influence on prescribing for new patients. However, some of the more-aggressive payers may explore switching existing patients in the future when patients and providers are more familiar and possibly more comfortable with biosimilars.

The Future for Biosimilars

With the imminent commercial launch of Zarxio following its FDA approval, other drug manufacturers have submitted applications to the FDA for biosimilar products. Among them:

- Celltrion announced filing an application for Remsima, its biosimilar version of Janssen’s Remicade (infliximab)\(^5\)
- Apotex announced its application for a biosimilar to Neulasta (filgrastim)\(^6\)
- Hospira announced it hoped to market a biosimilar for Procrit/Epogen (epoetin alfa)\(^7\)

More biosimilar applications are expected in the near and distant future, with significant impacts across multiple specialties and therapeutic areas.

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How Practices Can Prepare for the Market Entry of Biosimilars

| Clinical education | Physicians may want to learn about the approval process of biosimilars, and the data presented by different manufacturers. Biosimilar manufacturers will likely have resources available (brochures as well as sales and MSL teams) that can help with that education. Patients will likely have questions about biosimilars. Be prepared to answer them. |
| Resources | If you are considering using a biosimilar agent, reach out to the manufacturer for educational resources that may be useful for your patients and your practice. |
| EHR and billing systems | Based on the provisional generic name given to the first approved biosimilar, filgrastim-sndz, the generic name will be hyphenated. Make sure your billing and electronic health record (EHR) systems can accommodate it without any problems. |
| Reimbursement | Educate yourself on payer contracts and whether there are incentives to use specific products. Medicare will reimburse initially at 106 percent of the biosimilar’s Wholesale Acquisition Cost (WAC) until Average Sales Price (ASP) information is available. Once available, Medicare payment for the biosimilar will equal the ASP for the biosimilar product plus 6 percent of the ASP for the reference product.\(^8\) |
| Patient OOP | Research if the patient’s out of pocket will be more favorable when using one product over another. Leverage originator and biosimilar patient and provider support programs to gather this information. |

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\(^6\) http://www.apotex.com/global/about/press/20141217.asp
\(^7\) http://phx.corporate-ir.net/phoenix.zhtml?c=175550&p=irol-newsArticle&cleid=2006860

Sara Fernandez, Ph.D., MBA, is Director Reimbursement Strategy and Tactics (RST) at Xcenda.
Myelodysplastic Syndromes: What’s Next?

By Dr. Alan List, H. Lee Moffitt Cancer Center & Research Institute

We’ve learned much about myelodysplastic syndromes (MDS) over the last decade. Not only do we now have an intimate understanding of the biology of the deletion 5q (del5q) phenotype, but we have also recently characterized the vast majority of the gene mutations in MDS. Despite this knowledge, there are still many treatment challenges—including how to treat patients after the failure of a hypomethylating agent. Moreover, there is an urgent need for new disease altering treatment options for the majority of our patients who are not candidates for a potentially curative hematopoietic stem cell transplant. Where do we look next for the management of MDS patients? Some recent clinical trials help to shed some light.

Lower-Risk MDS

In transfusion-dependent MDS patients with lower risk disease who do not have del(5q), the response to erythropoiesis stimulating agents (ESAs) is typically low—roughly 20 percent to 30 percent—and alternate treatment options are limited. Although azacitidine (Vidaza®) offers hematologic benefit for approximately 30 percent of patients, agents that are more specific for the biology of the underlying disease would be a much needed treatment advance.

Lenalidomide (Revlimid®) is a very active agent in transfusion-dependent patients with del(5q) MDS, with approximately two-thirds of patients achieving red blood cell transfusion independence (RBC-TI) that lasts a median of 2.5 to 3 years. This agent also is being investigated for its activity in non-del(5q) patients. In a recent Phase III study, 239 lower-risk non-del(5q) MDS patients who were transfusion dependent and unresponsive or refractory to ESAs were randomized in a 2:1 fashion to treatment with lenalidomide (10 mg oral daily for 21 days every 3 weeks) or placebo (Santini et al., Proc ASH 2014, Abstract 409). In addition to seeking to validate a Phase II study of lenalidomide with an RBC-TI rate of approximately 26 percent lasting about 40 weeks in this population, the investigators also sought to evaluate a gene expression profile potentially predictive for lenalidomide response. The primary endpoint of this Phase III trial was the fraction of patients with RBC-TI ≥8 weeks. Consistent with the earlier Phase II study, the rate of RBC-TI lasting 8 weeks or longer was 26.9 percent, which was significantly higher than the 2.5 percent RBC-TI response rate in the placebo arm (P<0.001; Table 1). The median duration of TI in the lenalidomide arm was 8.2 months. Durable TI (~ 6 months or longer) was achieved in 17.5 percent of patients who received lenalidomide compared to 0 percent of patients in the placebo arm. In the subset of patients evaluated for the gene signature (n = 203), there was no relationship to response.

Table 1. Response to Lenalidomide vs. Placebo in ESA-Resistant Lower-Risk-MDS

<table>
<thead>
<tr>
<th>Response</th>
<th>Lenalidomide (n=160)</th>
<th>Placebo (n=79)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-TI ≥ 8 weeks, n (%)</td>
<td>43 (26.9)</td>
<td>2 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Media duration of TI, weeks</td>
<td>32.9</td>
<td>NE</td>
<td>—</td>
</tr>
<tr>
<td>RBC-TI ≥ 24 weeks, n (%)</td>
<td>28 (17.5)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: RBC, red blood cell; TI, transfusion independence; NE, not estimable.

Lenalidomide treatment was associated with significantly more myelosuppression compared to placebo, specifically grade ≥ 3 neutropenia (62 percent vs. 13 percent, respectively) and...
thrombocytopenia (36 percent vs. 4 percent, respectively). Overall, this study confirmed previous studies showing that approximately 1 in 4 patients with non-del(5q) MDS can achieve TI for a moderate duration.

Sotatercept (ACE-011), a new investigational agent, is a recombinant activin receptor-IIA fusion protein that neutralizes activin A and GDF11, proteins in the TGF-beta family. Activin A and GDF11 contribute to suppression of both erythropoiesis and osteoblast proliferation, making it a relevant target in MDS. In a recent open-label, dose-finding study, sotatercept given by subcutaneous (SC) injection every 3 weeks was active and well tolerated up to 1.0 mg/kg in 54 lower-risk, transfusion-dependent MDS patients who were anemic and previously treated with ESAs, lenalidomide, hypomethylating agents, and/or other MDS therapies (Komrokji et al. Proc ASH 2014, Abstract 3251). Overall, 45 percent of patients achieved an erythroid hematologic improvement (HI-E), defined by the International Working Group as a reduction in RBC transfusion needs by at least 4 units over 8 weeks, and responses were seen both in patients with a high transfusion burden (HTB; ≥2 units per month) and low transfusion burden (LTB; < 2 units per month). The response rate among HTB patients was 43 percent. Among LTB patients, 8/9 achieved a hematologic response and 6 had a sustained rise in hemoglobin ≥ 1.5 g/dL and achieved RBC-TI for at least 8 weeks. This study is now advancing into the highest dose level (2.0 mg/kg) and will be exciting to watch.

Luspatercept (ACE-536) is another recombinant fusion protein that involves activin receptor IIB, which also binds to ligands in the TGF-β superfamily. Its effects on anemia were evaluated in an open-label dose-finding study in patients with lower-risk MDS (Platzbecker et al. Proc ASH 2014, Abstract 411). Luspatercept administered SC every 3 weeks for up to 5 doses increased hemoglobin levels and decreased transfusion requirement, with a favorable safety profile. Erythroid response was achieved in 41 percent of patients treated at ≥0.75 mg/kg and in 67 percent of ring sideroblast-positive patients with SF3B1 gene mutations. These results are remarkable given the short duration of treatment (12 weeks), and support further evaluation of luspatercept in patients with lower-risk MDS.

**Higher-Risk MDS**

Among higher-risk patients, initial treatment with a hypomethylating agent such as azacitidine is considered standard of care. Can novel combinations with azacitidine improve outcomes, and how are next-generation hypomethylating agents performing in high-risk patients?

The North American Intergroup conducted a Phase II study to evaluate whether the addition of vorinostat (Zolinza®) or lenalidomide to azacitidine monotherapy could improve the overall response rate (ORR) in 276 patients with higher-risk MDS or chronic myelomonocytic leukemia (CMML) (Sekeres et al., Proc ASH 2014, LBA 5). Patients were randomized 1:1:1 to receive azacitidine (75 mg/m²/day on days 1-7 of a 28 day cycle; n=92), azacitidine plus lenalidomide (10 mg/day on days 1-21; n=93), or azacitidine plus vorinostat (300 mg twice a day on days 3-9; n=91). The ORR was similar across study arms, as were the rates of CR, PR and hematologic improvement (HI). There was a non-significant trend for improved relapse-free survival (RFS) in the combination therapy arms, but longer-term follow up is needed. The vorinostat combination arm was associated with significantly more gastrointestinal toxicity than azacitidine monotherapy, and both combination arms had a significantly higher percentage of patients who discontinued treatment due to toxicities compared to azacitidine alone.

**Table 2. S1117 Response to Treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>AZA</th>
<th>AZA+LEN</th>
<th>AZA+VOR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>33</td>
<td>34 (39)</td>
<td>20 (24)</td>
<td>87 (33%)</td>
</tr>
<tr>
<td>CR/PR/HI</td>
<td>24/0/13</td>
<td>18/1/19</td>
<td>15/1/7</td>
<td>19/1/13</td>
</tr>
<tr>
<td>Median RFS</td>
<td>7 mos</td>
<td>8 mos (P=0.45)</td>
<td>11 mos (P=0.29)</td>
<td>7 mos</td>
</tr>
</tbody>
</table>

Lenalidomide dose 10mg/d x 21d; vorinostat 300mg BID D3-9
Sekeres M, et al. ASH 2014; LBA 5

SGI-110 is an investigational DNA-hypomethylating agent formulated as a dinucleotide of decitabine (DAC) and deoxyguanosine that increases in vivo exposure to
decitabine by protecting it from deamination. It is delivered via SC injection. In a recent Phase II study in higher-risk MDS/CMML patients who were either treatment-naïve or failed previous hypomethylating agent treatment, SGI-110 was well-tolerated and showed similar safety and clinical activity at the two doses that were evaluated (60 mg/m² or 90 mg/m² daily x5 every 28 days), with an ORR of 26.4 percent (lower dose) and 34.7 percent (higher dose), respectively (Garcia-Manero et al. Proc ASH 2014, Abstract 529).

The benefits of azacitidine and other hypomethylating agents in higher-risk MDS patients are well known, but what do we do when a higher-risk patient has failed treatment with a hypomethylating agent? The prognosis after azanucleoside failure is poor, with a median survival of only 4 to 6 months. Achieving better outcomes in this population remains a major, unmet need.

Rigosertib is a multikinase inhibitor that is administered as a 72-hour continuous infusion every 2 weeks for the first 16 weeks, then every 4 weeks thereafter. The ONTIME trial was a recent open label Phase III, randomized, controlled study comparing rigosertib to best supportive care (BSC) in 299 patients with high-risk MDS who had either progressed on (37 percent), failed to respond to (25 percent) or relapsed after (38 percent) treatment with a hypomethylating agent (Garcia-Manero et al. Proc ASH 2014, Abstract 163). Patients were randomized in a 2:1 fashion and had been prospectively stratified according to bone marrow blast percentage. The primary endpoint was overall survival (OS).

There was no statistically significant difference in OS between treatment with rigosertib and BSC on an intent-to-treat (ITT) basis (8.2 months vs 5.9 months, respectively; P=0.33). However, in a post-hoc subset analysis, a statistically significant difference in OS was observed between rigosertib and BSC in patients who had primary resistance (n=184) to hypomethylating agents (8.6 months vs. 5.2 months, respectively; P=0.04). No survival benefit was found in the subset of patients who relapsed after responding to previous treatment with a hypomethylating agent (n=84).

The promising survival benefit of more than 3 months in patients with primary resistance to hypomethylating agents suggests that there may be an opportunity to take rigosertib forward in this population. A second randomized phase III study is needed to validate the findings.

Clofarabine (Clolar®) has also been investigated recently in this setting. In a Phase II trial, Jabbour et al. (Proc ASH 2014,
Abstract 534) investigated clofarabine, a second-generation nucleoside analog, plus low-dose cytarabine in 56 high-risk MDS patients who had failed prior hypomethylating agent therapy. Induction therapy consisted of clofarabine 15 mg/m² intravenous (IV) daily for 5 days (days 1-5) and cytarabine 20 mg SC twice daily for 7 days (days 1-7). Responding patients proceeded with consolidation therapy with clofarabine 15 mg/m² IV daily for 3 days (days 1-3) and cytarabine 20 mg SC twice daily for 5 days (days 1-5) every 4 weeks for a maximum of 12 cycles. The overall response rate (ORR) was 44 percent (n=27), with 10 patients achieving a complete remission (CR), 9 a marrow CR, 3 a CR with incomplete platelet recovery (CRp), 1 with a partial response (PR) and 4 with stable disease accompanied by hematological improvement. Most toxicities were grade 2 or lower. The median OS by response to treatment was 21.9 months among responders and 3.8 months among those who did not respond (P<0.001).

References


Dr. Alan List is the President and CEO of Moffitt Cancer Center, Tampa, Fla.
ACCC Appoints ION Solutions Members to 2015-2016 Board of Trustees

Congratulations to two ION Solutions members who recently were named to the Association of Community Cancer Centers (ACCC) Board of Trustees.

Steven L. D’Amato, BSPharm, BCOP, became President of the ACCC at its 41st Annual Meeting, CANCERSCAPE on March 18, 2015. He is Executive Director of New England Cancer Specialists in Scarborough, Maine, and a Clinical Associate Professor at the University of Tufts College of Medicine. He serves as a member of the Maine Medical Center Institutional Review Board in Portland, Maine, and has had experience in clinical oncology for 30 years in both the hospital and private practice settings.

Mr. D’Amato has been active in ACCC for many years, serving on the Program Committee and as an advisory board member for ACCC’s Oncology Pharmacy Education Network (OPEN). Most recently, he served on ACCC’s Board of Trustees as Secretary for two years.

Thomas A. Gallo, MS, is the 2015-2016 ACCC Treasurer. He is Executive Director of the Virginia Cancer Institute in Richmond, Va. In this role, he manages all aspects of a 24-provider medical oncology practice with seven medical offices, ambulatory infusion centers, laboratories, and more than 200 employees. Among his responsibilities are strategic planning, operations, financial management, personnel management, and purchasing.

Mr. Gallo has been an active member of the ACCC for more than 10 years. He currently serves on ACCC’s Investment Committee and Governmental Affairs Committee, which he previously chaired. He has presented at a number of ACCC Annual Meetings, and has previously served on the ACCC Board of Trustees (2004-2005).

The ACCC serves as the leading advocacy and education organization for the multidisciplinary cancer care team. Approximately 20,000 cancer care professionals from 1,900 hospitals and practices nationwide are affiliated with ACCC.

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CONQUER: The Patient Voice™ magazine in partnership with the Academy of Oncology Nurse & Patient Navigators® (AONN+) has announced the 2015 Hero of Hope Award™.

You can nominate a person with cancer who you believe should be recognized for:

- Outstanding contributions to his/her community through fundraising and association/organization leadership
- Serving as a role model to other cancer patients and survivors
- Exuding extraordinary spirit, grace and optimism in the face of adversity

The deadline to nominate someone is June 15, 2015. The four leading nominees will be profiled in the August 2015 issue of CONQUER: The Patient Voice™ Magazine. For more information, visit www.conquer-magazine.com.
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* Formerly known as Network for Oncology Communication and Research (NOCR)