ABSENT A LATE CHANGE OF HEART from CMS, the Oncology Care Model (OCM) will end June 30, 2022, without a replacement—ending one of Medicare’s most ambitious efforts to shift the mindset and the results of cancer care delivery. However, the end of the model does not mean the lessons of value-based care will cease. The challenge, many providers say, will be figuring out how to keep what worked in the OCM without the support of the model’s Monthly Enhanced Oncology Services (MEOS) payments, which helped practices afford navigation and nutrition services and social workers. This team-based approach is credited with bringing savings while keeping patients out of the hospital and improving their quality of life.

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- Rhonda Henschel, senior director of payer solutions,
- Ben Jones, vice president of government relations and public policy, McKesson Specialty Provider Organization, supporting The US Oncology Network, and
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PAYMENT MODELS
Value-Based Care Will “Continue to Evolve” Even if OCM Expires
Mary Caffrey

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CONTINUED ON SP208 »

CLINICAL PATHWAYS
Adding Drug Costs to the Clinical Support Equation
Skylar Jeremias

IN AN INTERVIEW WITH Evidence-Based Oncology™ (EBO), Amy Valley, PharmD, vice president of clinical strategy and technology solutions, Cardinal Health Specialty Solutions, discusses the Decision Path, a clinical support tool designed to inform oncology providers about drug costs along with clinical information, all embedded into the electronic health record workflow. This transcript has been lightly edited for clarity.

EBO: Can you describe Cardinal Health’s Decision Path and explain how the technology works?

VALLEY: Decision Path is the latest addition to our Navista TS platform, which is designed to help oncology practices be successful at value-based care. I think everyone is acutely aware that the oncology care model is ending, which has been the CMS’ demonstration model over the past 6 years. We don’t know exactly what’s coming next, but we’re certain that there will be successor programs.

CONTINUED ON SP209 »

POLICY
Crowdfunding for Cancer: What Financial Toxicity Among Young Adults Says About the US Health Care System
Skylar Jeremias

GOFUNDME, KICKSTARTER, Indiegogo, even Facebook: Crowdfunding websites have proven to be effective fundraising platforms for important causes. However, the staggering rise in crowdfunding campaigns among young adults to cover medical bills and basic essentials is very alarming.

CONTINUED ON SP212 »
Indication
PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

IMPORTANT SAFETY INFORMATION
Risk From Radiation Exposure
PLUVICTO contributes to a patient’s long-term cumulative radiation exposure, which is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection.
In the phase 3 VISION trial, PLUVICTO + BSOC vs BSOC alone demonstrated\textsuperscript{1-3,a}:

**Alternate Primary End Points**

- **Significantly improved survival**
  - Median OS
    - 15.3 months (n=551) vs 11.3 months (n=280)
    - HR=0.62 (95% CI, 0.52-0.74); \( P<.001 \)

- **Significantly improved rPFS**
  - Median rPFS
    - 8.7 months (n=385) vs 3.4 months (n=196)
    - HR=0.40 (95% CI, 0.31-0.52); \( P<.001 \)

**Key Secondary End Point**

- **Improved overall response rate**
  - Overall response rate\textsuperscript{b}
    - 30% (n=319) vs 2% (n=120)\textsuperscript{c}
    - \( P<.001 \)

Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early dropout in the control arm.

Ensure patients with PSMA-positive mCRPC have access to PLUVICTO. To learn more, visit hcp.novartis.com/products/pluvicto.

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**Indication**

PLUVICTO \textsuperscript{TM} (lutetium Lu 177 vipivotide tetraxetan) is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

**IMPORTANT SAFETY INFORMATION**

**Risk From Radiation Exposure**

PLUVICTO contributes to a patient’s long-term cumulative radiation exposure, which is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection.

Ensure patients increase oral fluid intake and advise them to void as often as possible to reduce bladder radiation.

To minimize radiation exposure to others, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days, to refrain from sexual activity for 7 days, and to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

**ORR** is reported as a measure of response in soft tissue disease, lymph node, or visceral lesions.

\textsuperscript{1} Patients with evaluable disease at baseline.

\textsuperscript{2} Stratified Wald’s Chi-square test 2-sided \( P \) value.

VISION was an international, prospective, open-label, randomized, multicenter phase 3 clinical trial evaluating PLUVICTO in 831 adult patients with progressive PSMA-positive mCRPC previously treated with at least 1 AR pathway inhibitor and 1 or 2 taxane regimens. Participants were randomized in a 2:1 ratio to receive PLUVICTO (7.4 GBq every 6 weeks for up to 6 cycles) plus BSOC or BSOC alone.\textsuperscript{1,2}

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**AR**, androgen receptor; **BSOC**, best standard of care; **mCRPC**, metastatic castration-resistant prostate cancer; **OS**, overall survival; **PSMA**, prostate-specific membrane antigen; **RLT**, radioligand therapy; **rPFS**, radiographic progression-free survival.

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Please see additional Important Safety Information and Brief Summary on the following pages.
**IMPORTANT SAFETY INFORMATION (continued)**

**Myelosuppression**

PLUVICTO can cause severe and life-threatening myelosuppression. In the VISION study, grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥3 pancytopenia occurred in 1.1% of patients (including 2 fatal events). Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed. One death due to sepsis and concurrent neutropenia was observed. Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO and clinically treat patients based on severity of myelosuppression.

**Renal Toxicity**

PLUVICTO can cause severe renal toxicity. In the VISION study, grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with PLUVICTO.

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated creatinine clearance (CrCl), before and during treatment. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity of renal toxicity.

**Embryo-Fetal Toxicity**

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose.

**Infertility**

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation-absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

**Adverse Reactions**

The most common adverse reactions (≥20%) occurring at a higher incidence in patients who received PLUVICTO plus best standard of care (BSoC) were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. Clinically relevant adverse reactions in <5% of patients included dry eye, vertigo, and pancytopenia (including bicytopenia).

**Laboratory Abnormalities**

The most common laboratory abnormalities that worsened from baseline in ≥30% of patients who received PLUVICTO plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

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

2. References

1. PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use

Initial U.S. Approval: 2022

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

1 INDICATIONS AND USAGE

PLUVICTO is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk From Radiation Exposure

PLUVICTO contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional good radiation safety practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.

Before the patient is released, the healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure to others [see Patient Counseling Information (17) in the full prescribing information]. Following administration of PLUVICTO, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days. Following administration of PLUVICTO, advise patients to refrain from sexual activity for 7 days. Following administration of PLUVICTO, advise patients to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

5.2 Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression, including anemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, Grade 3 or 4 and neutropenia (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade 3 or 4 pancytopenia occurred in 1.1% (which includes two fatal events) in patients treated with PLUVICTO. Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropenia was observed in patients who received PLUVICTO.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO and clinically treat patients based on the severity of myelosuppression [see Dosage and Administration (2.4) in the full prescribing information].

5.3 Renal Toxicity

PLUVICTO can cause severe renal toxicity. In the VISION study, Grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.8%) occurred in patients treated with PLUVICTO.

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated CrCl, before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on the severity of renal toxicity [see Dosage and Administration (2.4) in the full prescribing information].

5.4 Embryo-Fetal Toxicity

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [see Clinical Pharmacology (12.1) in the full prescribing information]. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see Use in Specific Populations (8.1, 8.3)].

5.5 Infertility

PLUVICTO may cause infertility in males. The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility [see Use in Specific Populations (8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

• Myelosuppression [see Warnings and Precautions (5.2)]
• Renal Toxicity [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The safety of PLUVICTO was evaluated in the VISION study in patients with progressive, PSMA-positive mCRPC [see Clinical Studies (14) in the full prescribing information]. Of the 831 patients randomized, 734 patients received at least one dose of randomized treatment. Patients received at least one dose of either PLUVICTO 7.4 GBq (200 mCi) administered every 6 to 10 weeks plus BSoC (N = 529) or BSoC alone (N = 205). The median duration of exposure to randomized treatment was 7.8 months (range, 0.3 to 24.9) for patients who received PLUVICTO plus BSoC. Among patients who received PLUVICTO plus BSoC, the median number of doses of PLUVICTO received was 5 (range, 1 to 6). The median cumulative dose of PLUVICTO was 37.5 GBq, range, 7.0 to 48.3). The median duration of follow-up was 14.8 months for patients receiving PLUVICTO plus BSoC.

Serious adverse reactions occurred in 36% of patients who received PLUVICTO plus BSoC. Serious adverse reactions in > 1% of patients who received PLUVICTO plus BSoC included hemorrhage (4%), musculoskeletal pain (3.8%), sepsis (3.2%), anemia (2.8%), urinary tract infection (2.6%), acute kidney injury (1.7%), pneumonia (1.7%), pancytopenia (1.3%), pyrexia (1.3%), spinal cord compression (1.1%), and pulmonary embolism (1.1%).

Fetal adverse reactions occurred in 2.8% of patients who received PLUVICTO plus BSoC, including sepsis (0.9%), pancytopenia (0.6%), hepatic failure (0.4%), intracranial hemorrhage (0.2%), subdural hematoma (0.2%), ischemic stroke (0.2%), COVID-19 (0.2%), and aspiration pneumonia (0.2%).

PLUVICTO was permanently discontinued due to adverse reactions in 12% of patients. Adverse reactions leading to permanent discontinuation of PLUVICTO in ≥1% of patients who received PLUVICTO plus BSoC were anemia (2.8%), thrombocytopenia (2.8%), and leukopenia (including neutropenia) (1.7%).

Adverse reactions leading to a dose interruption of PLUVICTO occurred in 16% of patients. The most frequent (>3%) adverse reactions leading to a dose interruption of PLUVICTO in patients who received PLUVICTO plus BSoC was anemia (5%) and thrombocytopenia (3.6%).

Adverse reactions leading to a dose reduction of PLUVICTO occurred in 6% of patients. The most frequent (>1%) adverse reactions leading to a dose reduction of PLUVICTO in patients who received PLUVICTO plus BSoC were thrombocytopenia (1%) and anemia (1%).

The most common laboratory abnormalities that worsened from baseline in ≥30% of patients who received PLUVICTO plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

Table 3 and Table 4 summarize the incidence of adverse reactions and laboratory abnormalities, respectively.

Table 3: Adverse Reactions (≥5%) in Patients with PSMA-positive mCRPC Who Received PLUVICTO plus BSoC in VISION

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PLUVICTO Plus BSoC (N = 529)</th>
<th>BSoC (N = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 to 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>11</td>
<td>4.9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>1.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>1.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>0.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>0.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3.8</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>9</td>
<td>3.2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>0.9</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>Dyseusia</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: BSoC, best standard of care.

6.2 Preclinical Studies

Sartor O, de Bono J, Ci KN, et al; for the VISION Investigators.

[See full prescribing information for details.]

[Continued]
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on PLUVICTO use in pregnant females. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm.

8.2 Lactation

Risk Summary

The safety and efficacy of PLUVICTO have not been established in females. There are no data on the presence of lutetium Lu 177 vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on its mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information].

Infertility

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility. 

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 529 patients who received at least one dose of PLUVICTO plus BSoC in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older. No overall differences in effectiveness were observed between patients ≥ 75 years of age and younger patients. Serious adverse reactions occurred in 11% of patients ≥ 75 years of age and in 11% of younger patients. Grade ≥ 3 adverse reactions occurred in 40% of patients ≥ 75 years of age and in 31% of younger patients.

8.6 Renal Impairment

Exposure of lutetium Lu 177 vipivotide tetraxetan is expected to increase with the degree of renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]. No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Frequently monitor renal function and adverse reactions in patients with mild to moderate renal impairment [see Dosage and Administration (2.4) in the full prescribing information]. The pharmacokinetics and safety of PLUVICTO have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

10 OVERDOSAGE

In the event of administration of a radiation overdose with PLUVICTO, reduce the radiation absorbed dose to the patient by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. Estimate the effective radiation dose that was applied and treat with additional supportive care measures as clinically indicated.

Distributed by:
Advanced Accelerator Applications USA, Inc.
Millburn, NJ 07041

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PLUVICTO is a trademark of Novartis AG and/or its affiliates
U.S. Patents 10398791; 10406240
T2022-17
On the Road Again With IVBM

AFTER A BREAK of more than 2 years, The American Journal of Managed Care® (AJMC®) was back on the road April 21 with a highly successful gathering of our Institute for Value-Based Medicine® (IVBM). With our partner Tennessee Oncology, AJMC® and cochairs Stephen M. Schleicher, MD, MBA, and Leah Owens, DNP RN, we hosted more than 100 attendees at the Hutton Hotel in Nashville. By all accounts, the evening was a huge success—presenters covered new health care delivery concepts in oncology care and an update on lessons from the Oncology Care Model (OCM). Then, Schleicher led one of the most interesting panel discussions we’ve had in the IVBM series—a peek into the world of venture capital, which has provided funding for a wave of new ideas to make oncology care more effective for patients and more efficient for payers.

The new buzzword from this session is “tech-enabled.” Apps and software solutions won’t replace the human touch in health care and especially not in cancer care. But digital assistance can help match patients with resources to reduce wait times and bring help to practices that cannot afford full-time staff to make care more consumer friendly. In the example of Thyme Care (see SP176), the cofounders are drawing on decades of combined experience in oncology practice and technology to offer better navigation at scale. Their goal: bring the best cancer care to everyone, regardless of where they live or who they know.

As we move forward in 2022 and beyond, our IVBM series will bring more of these ideas to you through the pages of Evidence-Based Oncology™. We encourage you to attend an IVBM session if there is one taking place near you. IVBM evenings are conceived and driven by our faculty partners, who develop the meeting themes and invite the speakers. So every meeting has its own local flavor. Among other locations, we will bring the IVBM Oncology series to Austin, Atlanta, and Minneapolis. An IVBM Population Health series also will be traveling to New Orleans. (For a full list of upcoming events, use the QR code below.)

We saw in Nashville that oncology providers are just like everyone else: after only seeing colleagues online during the pandemic, they are now eager to engage in person. For some, however, massive international meetings may not feel quite right. That’s why white bagging is a symptom of where they live or who they know.

As we move forward in 2022 and beyond, our IVBM series will bring more of these ideas to you through the pages of Evidence-Based Oncology™. We encourage you to attend an IVBM session if there is one taking place near you. IVBM evenings are conceived and driven by our faculty partners, who develop the meeting themes and invite the speakers. So every meeting has its own local flavor. Among other locations, we will bring the IVBM Oncology series to Austin, Atlanta, and Minneapolis. An IVBM Population Health series also will be traveling to New Orleans. (For a full list of upcoming events, use the QR code below.)

We saw in Nashville that oncology providers are just like everyone else: after only seeing colleagues online during the pandemic, they are now eager to engage in person. For some, however, massive international meetings may not feel quite right. That’s what makes our IVBM meetings the perfect way to learn right now: our gatherings are just big enough to feel the energy of reconnecting but not so large that attendees are overwhelmed. We were honored to host our guests from Tennessee Oncology, who came together from practices across the state. Many connected with colleagues they had not seen in person for more than 2 years. We hope to bring that experience to many more partners in the months ahead.

Sincerely,
Mike Hennessy Jr
President & CEO

For our full list of events, scan the code or visit:
https://www.ajmc.com/ivbmevents?display=listofevents
FDA Approves Enhertu for Use in Metastatic Breast Cancer
FDA Approves Amneal Pharmaceuticals’ Avastin Biosimilar, Bevacizumab-maly

MANAGED CARE UPDATES
Spotlighting Health-, Cost-Related Benefits of Genomic Testing and How Employers Can Drive Adoption
Clinical, Economic Benefits of Pegfilgrastim Biosimilars as Prophylactic Against Febrile Neutropenia
Nearly One-Fourth of DLBCL Cases May Be Attributable to Obesity in Young Adulthood, Study Finds
Primary Care Screening for Skin Cancer Appears to Boost Early Detection

CLINICAL UPDATES
Neurocognitive Changes After CAR T-Cell Therapy for NHL Similar to Other Cancers
Review Highlights Progress and Potential in Immunotherapy/Radiotherapy Combinations for Cancer Treatment

FDA ACTIONS
Nivolumab-based Combos Approved in First-line Advanced ESCC

CONTINUING EDUCATION
Focused Updates and Evidence-Based Approaches to Anemia in Cancer

From left, Bobby Green, MD; Stephen M. Schleicher, MD, MBA; Ravi Parikh, MD, MPP; Chris Booker, and Brenton Fargnoli, MD, MBA, gather after the Institute for Value-Based Medicine® meeting in Nashville, Tennessee.
INDICATION
SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

SARCLISA is indicated, in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.
Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 29% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H1 antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 3 or grade 4 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management.

Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

Neutropenia
SARCLISA may cause neutropenia.

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 15% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antifungal prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil counts recover to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Secondary Primary Malignancies
The incidence of secondary primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of secondary primary malignancies in all the SARCLISA-exposed patients was 3.6%.

In ICARIA-MM, secondary primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

In IKEMA, secondary primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

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The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone, as shown in Table 1 (see Clinical Studies [14] in the full prescribing information).

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carfilzomib and Dexamethasone

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Days 1, 8, 15, and 22 (weekly)</td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
</tr>
</tbody>
</table>

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. SARCLISA is used in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone. For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information and manufacturer’s prescribing information.

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, as shown in Table 1 (see Warnings and Precautions [5.1]). More than one SARCLISA vial may be necessary to obtain the required dose for the patient.

Patient-related drug products should be inspected visually for particulate matter and discoloration prior to administration. The infusion solution should be administered as a single intravenous infusion injection into an antecubital vein using a 22-gauge or larger needle and through an in-line Y-site. The infusion solution should be filtered through a 165-μm filter prior to administration.

The infusion solution should be administered as a single intravenous infusion injection into an antecubital vein using a 20-gauge or larger needle and through an in-line Y-site. The infusion solution should be filtered through a 0.22-μm filter prior to administration.

Patients who have received prior treatment with SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of multiple myeloma. For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.
The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma. Patients received SARCLISA 10 mg/kg intravenously weekly in the first cycle, and every two weeks thereafter, in combination with carfilzomib and dexamethasone ( Isa-Kd ) ( N=177 ) or carboplatin and dexamethasone ( N=169 ) ( see Clinical Studies ( 14 ) in the full prescribing information ). Among patients receiving Isa-Kd, 68% were exposed to SARCLISA for 12 months or longer and 51% were exposed for greater than 18 months.

Data on SARCLISA safety were obtained in 509 patients across 9 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM and KIA ( N=1818 ), the incidence of treatment emergent ADAs was 1.9%. No clinically significant differences in the hematokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

In IKEMA, infusion-related reactions were reported in 81 patients (48%) treated with Isa-Kd. Grade 1 infusion-related reactions were reported in 14%, grade 2 in 30%, and grade 3 in 42% of the patients treated with Isa-Kd. Signs and symptoms of grade 3 infusion-related reactions included dyspnea and hypoxemia. SARCLISA was discontinued in 6.5% of patients due to infusion-related reactions ( see Warnings and Precautions ( 5.1 ) ).

In a separate study ( OC01997 Part B ) with SARCLISA, 43% of patients who received SARCLISA administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions ( all grade 2 ) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the incidence of infusion-related reactions of SARCLISA 40 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

In IKEMA, the incidence of grade 3 or higher infections was 43% in the Isa-Pd group. Pneumonia was the most common severe infection with grade 3 reported in 22% of patients in the Isa-Pd group compared to 16% in the Pd group, and grade 4 in 8% of patients in the Isa-Pd group compared to 2.3% in the Pd group. Depletions from treatment due to infection in treatment in 63% of patients in the Isa-Pd group compared to 4.9% in the Kd group. Treatment was discontinued due to infection in 4.8% of patients in the Isa-Pd group compared to 0.8% in the Kd group.

Focal failure in IKEMA: Cardiac failure ( including cardiac failure, cardiac failure congestive, cardiac failure acute, ventricular failure, and pulmonary edema ) was reported in 7% of patients with the Isa-Kd group ( grade 4 in 4% and in 6.6% of patients with the Kd group ( grade 4 in 4.1% ). Serious cardiac failure was observed in 4% in patients in the Isa-Kd group, and in 3.3% in patients of the Kd group. See the current prescribing information for carboplatin for more information.

With all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody ( including neutralizing antibody ) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other isatuximab-irfc products may be misleading.

In ICARIA-MM and KIA, no patients tested positive for anti-idiotype antibodies ( ADA ). Therefore, the neutralizing ADA status was not determined. Overall, across 9 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM and KIA ( N=1818 ), the incidence of treatment emergent ADAs was 1.9%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

2.1 Recommended Dosage

2.2 DOSAGE AND ADMINISTRATION

2.4 WARNINGS AND PRECAUTIONS

3.1 ADVERSE REACTIONS

3.5 PATIENT FOCUSED INFORMATION

3.7 LABORATORY TEST INTERACTIONS

3.10 ADVERSE REACTIONS

Table 4 summarizes the laboratory abnormalities in ICARIA-MM.

Table 5: Adverse Reactions (% ) in Patients Receiving SARCLISA, Carfilzomib, and Dexamethasone with a Difference Between Arms of < 5% Compared to Control Arm in IKEMA

Table 6 summarizes the laboratory abnormalities in IKEMA.

Table 7: Laboratory Test Interactions

Table 8 summarizes the hematology laboratory abnormalities in IKEMA.

Table 9: Laboratory Test Interactions

+10.475" T:10.875" B:11.125" ßFatigue includes fatigue and asthenia.

#Dyspnea includes dyspnea and dyspnea exertional.

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Job Description: Sarclisa NCCN

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Safety: 10.375" x 13.375"
Pulling a Rabbit Out of the Hat

THE EXPRESSION, to “pull a rabbit out of a hat,” can mean different things, from doing something unexpected or surprising, to solving a problem through unorthodox but effective means, to surprising others with a sudden act of skill. Of course, the expression comes from the act of the magician bringing a furry friend seemingly from nowhere.

I recently had the chance to visit The Magic Castle at the invitation of a patient. For those of you who have never been there, The Magic Castle is a grand chateau located in Hollywood, California, that is the performance center and clubhouse for the Academy of Magic Arts. Expert magicians come to perform everything from close-up magic to grand illusions, and their extraordinary skill and mastery is breathtaking.

I visited The Magic Castle the same week that I spent most of my time reviewing the most recent proposed CMS Inpatient Prospective Payment System (IPPS) rule. To say that these 1700 pages made for less than magical reading would be a profound understatement. While the skill and knowledge of those preparing this document is indisputable, a page turner it is not. Yet, something beyond the absurdist level of contrast between the “castle” and “the rule” began to gnaw at me as I reread portions of “the rule.” It eventually came to me: in a time when innovations in cancer care can produce breathtakingly better outcomes for patients and their families, nothing in the draft rule speaks to the future of oncology. Much of the IPPS rule remains grounded in care and payment models beholden to the past; little of what is here speaks toward a future when innovations in cancer care can produce with humility, kindness, and compassion. It is the knowledge, insights, skills, and experiences of cancer care leaders like you that will help bring us to a deeper understanding of how to build the future of oncology. We invite you to share your knowledge and experience with us by submitting an article for publication. Become a part of these conversations that can help drive innovative and unexpected solutions to the question of how to deliver the best, most innovative care possible for our patients and their families.

Joseph Alvarnas, MD
EDITOR-IN-CHIEF

REFERENCES

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COTA’s Miruna Sasu on Real-world Evidence: “The Ecosystem Has Changed”

MARY CAFFREY

MIRUNA SASU, PHD, MBA, became president and CEO of COTA Healthcare in March 2022.1 not quite a year after joining the company as its chief strategy officer. COTA, founded in 2011 by physicians and data scientists who believed they could find ways to organize real-world data (RWD) to gather meaningful clinical insights, was well known to Sasu when she left her research and development position in the pharmaceutical industry—she was already a believer in COTA’s data. Now, as the importance of RWD grows, Sasu is ready to take its use in precision oncology to new levels. She spoke with Evidence-Based Oncology2 (EBO) about her new role. This interview has been edited lightly for clarity.

EBO: How has the field of RWD and real-world evidence changed over the past year, since you joined COTA?

SASU: A lot has changed over the past year. In fact, a lot has changed since the pandemic hit. For doctors who are treating patients, just introducing the virtual components of care has made a big difference in how we treat data and the importance of data. On the COTA side, we breathe and live data every day. The idea for us is to be able to understand patients and the patient population to figure out what works and what doesn’t work and what can extend lives and make quality of life better.

Over the past year, I think that the environment, the ecosystem, has changed. The FDA has issued some guidance around how to handle electronic medical records [EMRs], data, and evidence.2 And here at COTA, a lot has changed as well. We have a new strategy in place. We are working very closely with life science companies to perform external control arms on clinical trials using data, and we’ve seen a big uptake of that in the past 12 to 18 months. We also have large growing data sets that companies can license. Those data sets can either be used for evidence generation or they can be used for training algorithms. For example, we’ve seen a lot of companies come up with predictive algorithms that look at predictability of care or predictability of outcomes. Especially in oncology patients, [this involves] mobility: How will patients be moving from place to place in the post-COVID era? Are patients willing to continue to travel to a clinical trial site? In some cases, the answer is increasingly “no,” because now they have video options and care options that are administered right at home. We are also making a big push on diversity, by being sure that our data sets are representative of a diverse population and the epidemiologically relevant population in the United States.

EBO: You spent a lot of years in the pharmaceutical industry before joining COTA. Could you discuss how the use of RWD can shake up the traditional approach to research and development?

SASU: Yes, I could talk about this for hours! In fact, I did spend a lot of time in life science. I started as the head of digital health and innovation at Bristol Myers Squibb, where we incubated companies like COTA. They came to us with a glimmer of an idea, and we essentially productized [these ideas]; we helped them to develop and perform the strategy where these companies would be producing things for life science companies. The first thing we did was to attempt to bring data—both raw data and data science—into every aspect of product development and the product launch at a pharmaceutical company. That starts in discovery.

So, discovering medicines with data: What does that mean? First of all, it can’t be just with data; it must be done in a lab, but it can be augmented with data sets. What are they looking for in discovery? They’re looking for signals to figure out if a particular person’s tumor responds better or worse, given that they are positive for a particular biomarker or biomarker set. So, you can do that work on tumor tissue in a wet lab. You can also do that work as a data science project in a database. You can take data from different genetic screens on tumor types in real people. So, someone who has a genetic panel that’s been done on their particular tumor, you can take those data—and take many, many of those—and run your analysis on what happened. How does it work? Do they respond to, [say], a PD-L1 inhibitor? That’s discovery; next, you move on to the development organization. A compound that has been discovered gets pushed into a sort of machine that is clinical trial evidence generation. Lots of teams will take that compound, productize it, send it out to sites, and then perform clinical trials [that] put it in humans. And there are ways to do this in an actual database as well. Before the trial even starts, you can look for patients who match particular criteria. You can say I want patients with X, Y, and Z, this type of tumor—show me where those patients might be. You look on a map [for the answer], and you choose the sites to work with based on where those patients are, instead of making those patients come to your sites. That’s a big deal, because before this was ever thought about, it wasn’t done that way. It was always that you selected your sites and then you took in patients, and that’s what makes the patient travel 150 miles to the site.

“You choose the sites to work with based on where those patients are, instead of making those patients come to your sites. ... before it wasn’t done this way: It was always that you selected the sites and then you took in patients, and that’s what makes the patient travel 150 miles to the site.”

—Miruna Sasu, PhD, MBA, president and CEO, COTA Healthcare

EBO: You spent a lot of years in the pharmaceutical industry before joining COTA. Could you discuss how the use of RWD can shake up the traditional approach to research and development?

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Doing it this way makes the development of a clinical trial much easier, less burdensome on the patient, and just better for the trial altogether. Also, you can look for whatever population of interest there might be. For example, in multiple myeloma, do you want to enroll Black patients? Well, of course you do. So, you can go to them by looking in the database first.

Once the drug has launched, the FDA always asks for post-marketing trials. The clinical trial [included just] a very small population that was meant to get the drug to market, and the FDA wants to know how it’s working in the real world. Previously, we would have had to open a trial and say, “OK, let’s see how these patients are doing. Let’s bring them into the clinic.” Now, you don’t have to do that anymore—because you can just take a database from COTA and see how those patients are doing based on their medical records. You can literally see all the patients who are,
for example, on pembrolizumab. How are they doing after the drug has launched? What sort of events are they having? Are there any quality-of-life issues? We can garner this type of information directly from the EMR.

I told you I could speak for hours on this topic! There’s just so much potential for what you can do in a database for drug development.

**EBO:** At this point, the RWD space has multiple players. What sets COTA apart?

**SASU:** I came to COTA because it is a gem. It is the differentiator. [When I worked in the pharmaceutical sector], I was the buyer of all these data sets. I’d perform an analysis on a big data set, and then I would validate it in the COTA data, because at the time COTA had smaller data sets than [others] that were on the market. But the reason they had smaller data sets is because they’re deeper and of higher quality. So that was always my source of truth: I would always go to COTA data to validate my findings. Now, we don’t have to do that—COTA is actually expanding and we are making bigger data sets.

Part of the reason that the COTA data are so good is that there’s medical oversight over how the elements from the EMR are abstracted. That matters, especially in hemato logic oncology where patients tend to live for a longer period of time. So, you have thousands—tens of thousands—of pages of documentation, and you can imagine an abstractor trying to figure out what happened to this patient over their lifetime from many doctors’ notes, perhaps 25 notes. If no medical professional is checking this, it [will most likely be] laden with errors. What’s great about COTA is that within our abstraction system, we actually make the patient’s story. We go through and curate the data, and someone actually does that patient’s story, and for that reason, it’s always accurate. The dates match up. If there is a potential error, we know where and what it is. And we can tell the user, “Hey, there’s a probability that this might not be the right thing.”... If a lab [result] comes in 10 times larger or 1000 times larger than [would be expected in] a potential sequence, then we know there might be something wrong or that the lab might be an outlier. That’s something we can figure out because of how the data are curated.

Second, COTA is a mission-driven company. I’ve never seen such hard workers [as my colleagues are]: They put in the hours, they put in the time, and the answer for why they do it is always the same—“Because I would want someone to do this for my family member.”

**EBO:** As you know, many of our readers are payers. What does COTA have to offer to the payer community?

**SASU:** I’m glad you asked, because we have a lot to offer. COTA was born for the payer and provider community. We have a proprietary patented technology, called the COTA Nodal Address. You’re familiar with an ICD-9 [International Classification of Diseases, Ninth Revision] or ICD-10 code that is based on the diagnosis? Well, this [COTA Nodal Address] is based on the totality of the data set for a patient. It’s very, very granular; it’s very specific, and [we’re going to use it to advance] precision medicine. Each patient has a particular digital code, and that digital code changes over time as the patient progresses through the disease—hopefully into remission [and other positive outcomes]. You can group similar patients—if you think about the endeavor, called Patients Like Me—this is a digital, data-driven way of doing that. [It] can prove that your [actions], like putting a patient on a particular regimen, impacts the outcome of the patient. For instance, if you took patients with a certain digital code and showed that they were taken through a particular type of treatment regimen, and that always resulted in a 6-month addition to their life, you, as a payer, would pay for that outcome. And not necessarily just the intervention.

We are doing this actively in pilot form with 2 health systems: They’re utilizing COTA Nodal Address and our platforms to make cases to payers. I would want payers to come to us and ask us to do this for them as well, because that is a win-win situation. In fact, we can connect the different elements here—providers, payers, health care companies, and life science [drug development] companies—all pushing to give patients the best care [possible] for the longest and best outcomes.

**EBO:** Can you provide more detail on what else the FDA needs to do to facilitate the use of RWD?

**SASU:** I used to work for the federal government, and I’m a big believer that they need to see industry innovate and then respond to that. [The FDA has actually] done a lot so far. One thing they did that I really respect was ensuring the enablement of EMRs in general; that was a big deal. A second thing was the guidance on how RWD should be used for clinical trials and regulatory approvals; that was a big deal as well. That guidance being issued said, “We’re doing this work, and we are open to receiving external controls and databases, and so on.” The third thing they can do, and should do, goes along with the EMR piece, now that we’re going into using EMRs for clinical trials and augmenting clinical trials. To ease the burden on both patients and providers, one area of expansion would be to capture the data at the provider level in such a way that it looks more like a clinical trial. Statisticians have a saying, “Garbage in, garbage out.” So, if the input into the EMR is really, really messy, you can only do so much to clean it up and place it in a database for use. But if the data entry at the source was very, very clean—and if it were processed in an almost clinical-trial-like way—then [the information] you can segment out of those data is a lot cleaner and better. So, I would argue that the FDA should help us, and providers, figure out a way to work on [providers’] EMR data capture, so that the data look a little more like clinical trial data.

**EBO:** Does CMS have a role? If they’re reimbursing the provider, do they have the ability to compel providers to enter data into the EMR in a certain way? A lot of discussion at [the 2021 American Society of Hematology annual meeting] was about the need for RWD to have common standards internationally, so that they can be shared. And in this area, CMS has the biggest hammer on the block.

**SASU:** Exactly! I wasn’t going to say it, but I’m glad you did. That’s exactly what we need. We need incentives—it could be a carrot, or it could be a stick, right?—for providers to be able to do this. As we all know, and [we at COTA know], providers are always strapped for cash; they’re always trying to make things better for their patients. And some of the providers are nonprofits [who really] need as much cash as they possibly can get. If we can incentivize them from that angle—for them to have the money to be able to enter the data with extra staff, or extra time for the current staff to be able to enter the data in [the right] way—then that is exactly where we need to go. And I think the data sets [element] is a good point. Clinical trial data standards [in the form of] CDISC [Clinical Data Interchange Standards Consortium] have been around for a long time. These are the types of data standard that the FDA looks for. In fact, when you send [the FDA] data sets, they will analyze the data sets using your own code in CDISC format. If we were to slightly augment CDISC, or another data standard called [Observational Medical Outcomes Partnership], we could capture just a bit more information, and the data that are really important about what happened to the patient would not be in paragraph form. That would be enough to get us a long way. So, yes, if we could reimburse or incentivize providers to do this, that would be a tremendous step forward.

**EBO:** Would you like to add anything else?

**SASU:** Just that this entire ecosystem is constantly moving, and at COTA, our whole team is just excited to be a part of it. Most importantly, I think what’s near and dear to my heart is that every day we feel very embedded with patients and their interests and in really making their journey easier.

**REFERENCES**


3. Tallman MS. The role of real-world data collection in hematologic malignancy research (ASH Research Collaborative). Presented at: 63rd American Society of Hematology Annual Meeting & Exposition; December 12, 2021; Atlanta, GA. Special interest session.
NATHAN H. WALCKER, MBA, HAS BEEN CEO of Florida Cancer Specialists & Research Institute (FCS) since August 2020, after joining the practice as chief financial officer in 2019. As CEO, Walcker describes his priorities in leading FCS’ 4200 employees as ensuring clinical care of the highest quality, with attention to innovative treatments; convenient access to clinical trials, including early-phase drug trials; and “delivering a relentless focus on operational, clinical, and financial excellence.”

FCS was an early adopter of value-based care initiatives. For nearly a decade, its physician, pharmacy, and business leaders have been active participants in the Oncology Care Model (OCM), and equally active in policy discussions at the state and national levels about the future of payment reform. Today, as the practice readiness its transition from the OCM, Walcker spoke with Evidence-Based Oncology (EBO) on what’s next for value-based care.

This interview has been edited for clarity.

EBO: We’ve heard the term “value-based care” for some time, but patients might not understand what it means. How would you explain the concept of value-based care to a new patient?

WALCKER: Value-based care at its core is rooted in a simplistic mathematical equation of value equating benefit, or outcomes, over cost. But from this simplistic equation, many other questions follow: Value to whom? How is value measured? Cost to whom, and over what time period? So, breaking that down further, I think value-based care is really about alignment. It’s making sure that the health care delivery system has the right incentives in place. That way, regardless of where your provider is practicing—whether it’s in the acute care setting, community setting and across modalities / specialties — we are taking the time to actually get to know you [the patient] as a person and coordinating care across the entire value chain, [creating] the best experience and results possible so people can be healthier.

At the same time, value-based care means taking an opportunity to identify areas of improvement, reduction of waste, and making sure that it’s all about the patient.

EBO: At FCS, what do you consider the most important elements of value-based care?

WALCKER: We at Florida Cancer Specialists have the privilege to serve patients and communities across the state. Our holistic approach to value-based care goes back to the proverbial Triple Aim in health care: that is, improving patient experience, improving population health, and reducing cost. Coming out of the COVID-19 pandemic, we’ve now recognized that it’s also about our caretakers and our care teams—and making sure that we’re providing the opportunity to appreciate that patient experience is about the person, [but would not be possible without also prioritizing] everyone that’s taking care of that patient.

Ultimately, we care how all these things interact with one another in a holistic, coordinated fashion. Here’s an example: If the 100% of the focus is on the reduction of costs, you have to believe that the patient experience probably won’t be great. Think about the last time that you were at a primary care clinic. I was at one with my 4-year-old daughter recently, and our primary care physician [PCP] spent about 8 minutes with us: I know because we counted. That’s because of the clinic burden; the schedule is incentivized to see as many patients as possible and is a real pain point in the fee for service (volume) model we live in today. Now, that’s for a regular wellness check-up—think about how the patient experience would be if that same 8 minutes was with a patient battling cancer. You can see the point I’m trying to make.

So here at FCS, we’re making sure that these factors of value-based care are working together in a balanced fashion. We are bringing Best-in-Breed therapeutics into the marketplace, and we are harnessing the ability of tools, technology, and data to best inform the right treatment pathways in a cost-efficient manner at the right time. Something I’m very, very proud of at FCS is that we’ve taken a deliberate and intentional approach to bringing precision diagnostics in-house. To me, the ability at diagnosis—or candidly, prior to diagnosis as the suspicion of disease—to learn the genetic, molecular makeup of a person, [to help] ensure that we are getting in front of disease progression, will bend the cost curve, and hopefully stave off the higher-acuity setting downstream. Ultimately, the result will be better patient care.

At FCS, that’s what it’s all about—making sure that the Triple Aim, and now the Quadruple Aim, and other facets in health care act in unison with one another.

EBO: You mention the Triple Aim and balancing the various factors. What are your priority metrics? Should we be giving more priority to survival outcomes? To patient satisfaction scores? Savings? Reduced time in the hospital? What metrics do you value the most?

WALCKER: First, I’ll answer by listing the dimensions that we don’t value. In this world of information overload, “analysis paralysis” is the surest path to failure in anything—but especially in health care. We need to be in a situation in which no matter what program is being implemented—whether it’s the OCM, an alternative payment model [APM] with a commercial payer, even fee-for-service—[that we know] the metric that leads to the best outcome for the patient, and also for the health care ecosystem at large. What delivers this from a cost-to-delivery perspective, and from a quality perspective, ultimately comes down to making sure that we are measuring at a macro level.

Second, how do we ensure that we are measuring and monitoring and also incentivizing the most cost-effective, clinically appropriate therapeutic for that particular patient? And ultimately, how do we measure that over time, and follow that patient with a survivorship program? That’s why I’m excited about the advances that we’ve seen in precision diagnostics.

Today, we’re at a unique inflection point—not only in oncology, but in health care delivery [generally]. So much advancement in science and experiments coming out of CMS has changed the way that health care is delivered; we’re holding folks accountable to make sure that we’re not overutilizing care and we’re not overutilizing therapeutics. Nobody wants to be stuck with a needle one more time than they need to be, right? We’re making sure that we’re aligning all those things.

We take the vantage point at FCS that we need to be flexible, because the metric that matters today isn’t going to be the metric that matters tomorrow. But having a design infrastructure in
which you trust the data that you have, you utilize them in an appropriate way, and they also drive meaningful change—not only for patients, but for the broader ecosystem of the company as well—is essential.

**EBO**: You mentioned the OCM. As we speak with oncologists and practice managers about the upcoming end of the OCM, we hear consistently that the model cannot be turned off overnight. Do you agree? What will it mean for your practice when the OCM ends?

**WALCKER**: I wholeheartedly agree with that statement. This is like trying to try to turn a cruise ship on a dime—to go in the other direction at the snap of a finger is just not going to happen. We can all appreciate that behavior change, that transformation of anything that requires a long period of time, is a journey. It’s almost like a butterfly effect, where small incremental changes (occur) over time, and you create meaningful change over a sustained period.

The analogy that I would use is to go back to everybody’s favorite technology system, the electronic medical record [EMR]. If you think about 10, 15, 20 years ago, the notion of using an electronically delivered system to monitor patient records and to use it to look at care packages was a foreign concept. But how did we get there? It took the HITECH Act in 2009, with which the government essentially incentivized providers to adopt the EMR. Now, we can agree or disagree and have a really heated discussion on the merits of that government-sponsored initiative. But ultimately, I don’t think anybody can argue with the fact that over the past 10-plus years, there has been widespread adoption of technology and the office EMR—and certainly, some unintended consequences [have occurred].

Please don’t misunderstand me: [I do believe in part] that providers and expanded care teams are being data entry clerks. That is something that must change in health care, and it’s necessary most of all in oncology. At the same time, that evolution of getting off paper systems has been transformative. It’s allowed us to have data and analytics and better monetary records, which again, from a macro perspective, have been really helpful. However, we certainly still need to do things.

Again, I go back to my PCP visit with my 4-year-old. We had to fax our records to the office. In 2022, the fact that this still happening is crazy. I mention this to shine a bright light on the fact that, absolutely, the OCM and our commitment to APMs are not things that happen overnight. It’s not a flip of a switch. But we will say that CMS and the Center for Medicare and Medicaid Innovation deserve a lot of credit for having the courage to try something.

Nothing in life is ever perfect, but we must continue to challenge the status quo of health care in America. The only way we can continue to improve is by taking some risks. I think the OCM from a very high level was very much a success. Depending on who you talk to, and what literature you read, there’s various schools of thought on this. But certainly, at FCS, we’ve seen tremendous benefits, not only for the practice, but also for our physicians, and ultimately for patients. My hope and expectation is that it sets a foundation for many, many successful programs to come.

**EBO**: Practice leaders tell us, and studies also show, that the shift to value-based care requires buy-in—it requires champions at the top. What has been your experience of champions for value-based care at FCS?

**WALCKER**: At FCS, we’ve been very proud the model that we’ve adopted and scaled across our 100 clinical sites across Florida. We haven’t trademarked it, but we’ve coined the term “regional accountability.” What that means is recognizing and appreciating that there’s both a global approach and a local approach, and it asks, “What is the change management that we will need to go from a macro perspective across FCS, but at the same time, give due credit to the fact that health care is local?” It recognizes that treating your patient in Tallahassee may be different than treating your patient in Naples, which could be a byproduct of different demographics in these markets, or different physicians, or other factors. We’ve adopted this regional accountability model, and we’re pinpointing champions in each specific market. Then, we’re aligning that to the broader company, by making sure that if we’re looking at something like the adoption of biosimilar [agents], we are asking, “How do we best effectuate and communicate the opportunity, but also still give credence and autonomy to the local position in that market, with respect to the disease mix, etc., that the physicians may be treating on a day-to-day basis?”

At the end of the day, physicians are competitive beings by nature. So, we have found that recognizing that regional accountability, being intentional, and coupling that with benchmarking and reporting has been very successful throughout our time in the OCM. It’s an approach—the physician scorecard—that we’ve adopted in many of our other alternate payment models with commercial partners as well. We are removing the ambiguity around someone’s performance and then showing them, based on a benchmark, how they are doing vs their peers. How are they doing vs the broader OCM program?

And importantly, where are their opportunities to improve? The issue could be communicating [information about] biosimilar adoption, offering care that is clinically appropriate, or even doing something as simple as engaging with our care management professionals in a different way, to make sure that our patients appreciate that they have the opportunity to pick up the phone and talk to an oncology-certified nurse 24/7/365. That’s really been among the silver linings with OCM—that we’ve taken the opportunity to be really intentional with investing in that regional accountability model. It has paid off for patients and for our physicians as well.

**EBO**: Going forward, what would you like to see a future CMS model look like?

**WALCKER**: The best model starts with recognizing that no 2 practices are alike, just like no 2 people are alike. No 2 patients are alike—certainly not in oncology. So, I’d like to see a model that is flexible, one that allows practices to opt in and opt out of risk where they deem appropriate. Given the onslaught of risks and threats, candidly, that community oncology faces—whether from pharmacy benefit managers, drug pricing reform, or challenges to the traditional buy-and-bill model—many variables are at play that certainly call into question the ability for community oncology practices across the country to survive. Whatever model comes to fruition, the next evolution really needs to be meeting practices where they are and make sure that folks feel comfortable as they walk toward risk. If they’ll be moving to a model where they are not only providing opportunities for upside savings but electing to take downside risk, [they have to know that] they’re able to do so without finding themselves in a very precarious position.

At the end of the day, given the sticker prices and the inflation we’ve seen in drug prices [of late, we know] it can take only 1 or 2 bad events to potentially bankrupt the practice. Cancer care is too important for that to be a risk factor. The next evolution of the model needs to provide, again, the visibility and transparency for somebody to perform in an APM and know what the metrics are. How are they being reported? Are we making sure that whatever benchmark somebody is being managed to, or being asked to manage to, has been done in a transparent, fair way? An interesting thing we’ve seen at FCS—not only with OCM, but with other APMs that have been incubated with commercial payer—is that everyone has a different rubric or a different scorecard or quality metric. This makes it challenging for a community of like-minded stakeholders—payers, providers, and patients—aligned around the notion that we want to be delivering the care and the experience and outcomes consistently. You or someone you love receiving care would want to make sure that we’re balancing the financial incentives with the right clinical protocols and doing so in a fair and transparent manner. •

**REFERENCES**


5. HITECH Act of 2009. 42 USC sec. 13401–4212 (February 2009), part 2, subtitle-C, sec 13301, subtitle B, sec 1014. Comparative grants to States and Indian tribes for the development of loan programs to facilitate the widespread adoption of certified EHR technology.
REDEFINE THEIR STORYLINE

60% REDUCTION IN RISK OF EFS* EVENTS WITH YESCARTA® vs STANDARD THERAPY**

HR: 0.398 (95% CI, 0.31-0.51) (P<0.0001)

ZUMA-7 is a phase 3, randomized open-label, multicenter study of YESCARTA single-infusion therapy vs salvage chemotherapy +/- HDT+ASCT, a current standard therapy, in 359 adult patients with relapsed or refractory large B-cell lymphoma (R/R LBCL). Patients were randomized 1:1 to YESCARTA (N=180) and standard therapy (N=179) and stratified by response to 1L therapy and 2L age-adjusted IPI. Two recipients of nonconformal product are included in the YESCARTA arm for the efficacy analysis.

The primary endpoint was event-free survival (EFS). The median follow-up time for the primary analysis was 19.2 months.

In the ZUMA-7 trial, safety was evaluated in 168 patients with primary refractory or first relapse of LBCL treated with YESCARTA.

ZUMA-7 safety data were consistent with previous YESCARTA ≥3L LBCL clinical trial data and real-world experience:

- No new safety signals were identified
- 7% of patients receiving YESCARTA experienced Grade ≥3 CRS, and 25% experienced Grade ≥3 NTs

INDICATION

YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

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

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving Yescarta. Do not administer Yescarta to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Yescarta, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with Yescarta. Provide supportive care and/or corticosteroids as needed.

- Yescarta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta and Tecartus REMS Program.

CYTOKINE RELEASE SYNDROME (CRS)

CRS, including fatal or life-threatening reactions, occurred. CRS occurred in 90% (379/422) of patients with non-Hodgkin lymphoma (NHL), including ≥ Grade 3 in 9%. CRS occurred in 93% (256/276) of patients with large B-cell lymphoma (LBCL), including ≥ Grade 3 in 9%. Among patients with LBCL who died after receiving Yescarta, 4 had ongoing CRS events at the time of death. For patients with LBCL in ZUMA-1, the median time to onset of CRS was 2 days following infusion (range: 1-12 days) and the median duration was 7 days (range: 2-58 days). For patients with LBCL in ZUMA-7, the median time to onset of CRS was 3 days following infusion (range: 1-10 days) and the median duration was 7 days (range: 2-43 days). CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including ≥ Grade 3 in 8%. Among patients with iNHL who died after receiving Yescarta, 1 patient had an ongoing CRS event at the time of death. The median time to onset of CRS was 4 days (range: 1-20 days) and median duration was 6 days (range: 1-27 days) for patients with iNHL.
IMPORTANT SAFETY INFORMATION

CYTOKINE RELEASE SYNDROME (continued)

Key manifestations of CRS (≥10%) in all patients combined included fever (85%), hypotension (40%), tachycardia (32%), chills (22%), hypoxia (20%), headache (15%), and fatigue (12%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome.

The impact of tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in 2 subsequent cohorts of LBCL patients in ZUMA-1. Among patients who received tocilizumab and/or corticosteroids for ongoing Grade 1 events, CRS occurred in 93% (38/41), including ≥ Grade 3 (2/141) with Grade 3 CRS; no patients experienced a Grade 4 or 5 event. The median time to onset of CRS was 2 days (range: 1-8 days) and the median duration of CRS was 7 days (range: 2-16 days). Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA. Thirty-one of the 39 patients (79%) developed CRS and were managed with tocilizumab and/or therapeutic doses of corticosteroids with no patients developing ≥ Grade 3 CRS. The median time to onset of CRS was 5 days (range: 1-15 days) and the median duration of CRS was 4 days (range: 1-10 days). Although there is no known mechanistic explanation, consider the risk and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities.

Ensure that 2 doses of tocilizumab are available prior to YESCARTA infusion. Monitor patients for signs and symptoms of CRS at least daily for 7 days at the certified healthcare facility, and for 4 weeks thereafter. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES

Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome) that were fatal or life-threatening occurred. Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving YESCARTA, including ≥ Grade 3 in 25%. Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 in 31% and in 74% (124/168) of patients in ZUMA-7 including ≥ Grade 3 in 25%. The median time to onset was 4 days (range: 1-43 days) and the median duration was 17 days for patients with LBCL in ZUMA-1. The median time to onset for neurologic toxicity was 5 days (range: 1-133 days) and median duration was 15 days in patients with LBCL in ZUMA-7. Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including ≥ Grade 3 in 21%. The median time to onset was 6 days (range: 1-79 days) and the median duration was 16 days. Ninety-eight percent of all neurologic toxicities in patients with LBCL and 99% of all neurologic toxicities in patients with iNHL occurred within the first 8 weeks of YESCARTA infusion. Neurologic toxicities occurred within the first 7 days of infusion for 87% of affected patients with LBCL and 74% of affected patients with iNHL.
IMPORTANT SAFETY INFORMATION
NEUROLOGIC TOXICITIES (continued)

The most common neurologic toxicities (≥ 10%) in all patients combined included encephalopathy (50%), headache (43%), tremor (29%), dizziness (21%), aphasia (17%), delirium (15%), and insomnia (10%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events, including aphasia, leukoencephalopathy, dysarthria, lethargy, and seizures occurred. Fatal and serious cases of cerebral edema and encephalopathy, including late-onset encephalopathy, have occurred.

The impact of tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in 2 subsequent cohorts of LBCL patients in ZUMA-1. Among patients who received corticosteroids at the onset of Grade 1 toxicities, neurologic toxicities occurred in 78% (32/41) and 20% (8/41) had Grade 3 neurologic toxicities; no patients experienced a Grade 4 neurologic event. The median time to onset of neurologic toxicities was 6 days (range: 1-93 days) with a median duration of 8 days (range: 1-144 days). Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA. Of those patients, 85% (33/39) developed neurologic toxicities. Further toxicities 8% (3/39) developed Grade 3, and 5% (2/39) developed Grade 4 neurologic toxicities. The median time to onset of neurologic toxicities was 6 days (range: 1-274 days) with a median duration of 12 days (range: 1-107 days). Prophylactic corticosteroids for management of CRS and neurologic toxicities may result in higher grade of neurologic toxicities or prolongation of neurologic toxicities, delay the onset and decrease the duration of CRS.

Monitor patients for signs and symptoms of neurologic toxicities at least daily for 7 days at the certified healthcare facility, and for 4 weeks thereafter, and treat promptly.

REMS

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

HYPERSENSITIVITY REACTIONS

Allergic reactions, including serious hypersensitivity reactions or anaphylaxis, may occur with the infusion of YESCARTA.

SERIOUS INFECTIONS

Severe or life-threatening infections occurred. Infections (all grades) occurred in 45% of patients with NHL. ≥ Grade 3 infections occurred in 17% of patients, including ≥ Grade 3 infections with an unspecified pathogen in 12%, bacterial infections in 5%, viral infections in 3%, and fungal infections in 1%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines.

Febrile neutropenia was observed in 36% of patients with NHL and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, including those who have received YESCARTA, life-threatening and fatal opportunistic infections including disseminated fungal infections (e.g., candida sepsis and aspergillus infections) and viral reactivation (e.g., human herpes virus-6 [HHV-6] encephalitis and JC virus progressive multifocal leukoencephalopathy [PML]) have been reported. The possibility of HHV-6 encephalitis and PML should be considered in immunosuppressed patients with neurologic events and appropriate diagnostic evaluations should be performed.

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminating hepatitis, hepatic failure, and death, has occurred in patients treated with drugs directed against B cells, including YESCARTA. Perform screening for HBV, HCV, and HIV and management in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. ≥ Grade 3 cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 39% of all patients with NHL and included neutropenia (33%), thrombocytopenia (13%), and anemia (8%). Monitor blood counts after infusion.

HYPOGAMMAGLOBULINEMIA

B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia was reported as an adverse reaction in 14% of all patients with NHL. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement. The safety of live immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

ADVERSE REACTIONS

The most common non-laboratory adverse reactions (incidence ≥ 20%) in patients with LBCL in ZUMA-7 included fever, CRS, fatigue, hypotension, encephalopathy, tachycardia, diarrhea, headache, musculoskeletal pain, nausea, febrile neutropenia, chills, cough, infection with unspecified pathogen, dizziness, tremor, decreased appetite, edema, hypoxia, abdominal pain, aphasia, constipation, and vomiting.

Please see additional Important Safety Information on previous page and Brief Summary of full Prescribing Information on following pages, including BOXED WARNING.

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. Do not infuse YESCARTA until the patient identification is confirmed, remove the YESCARTA product bag from the cassette if necessary, and confirm patient identity:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemotherapy or that relapses within 12 months of first-line chemotherapy.
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy; including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL, arising from follicular lymphoma.

Indications and Usage

YESCARTA is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:

- Adult patients with large B-cell lymphoma that is refractory to first-line chemotherapy or that relapses within 12 months of first-line chemotherapy.
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy; including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL, arising from follicular lymphoma.

Dose and Administration

For autologous use only. For intravenous use only. 

- Adult patients with large B-cell lymphoma that is refractory to first-line chemotherapy or that relapses within 12 months of first-line chemotherapy.
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy; including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL, arising from follicular lymphoma.

Preparation of YESCARTA for infusion: Confirm the information on the patient-specific label does not match the intended patient.

- Preparing YESCARTA infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. Perform treatment with a lymphodepleting chemotherapeutic regimen of cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA. Premedicate: Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Consider the use of prophylactic corticosteroids in patients after weighing the potential benefits and risks.

Management of Severe Adverse Reactions

Cytokine Release Syndrome: Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypertension. If CRS is suspected, manage according to the recommendations in CRS Grading and Management Guidance. Patients who experience Grade 2 or higher CRS (e.g., hypoxia not responsive to tents; or hypoxia requiring supplemental oxygen) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intravenous corticosteroids as supportive therapy.

CRS Grading and Management Guidance

Grade 1: Symptoms require symptomatic treatment only (i.e., fever, nausea, fatigue, headache, myalgia, malaise).

- Tocilizumab: If symptoms in (g), fever not improving after 24 hours, consider managing as Grade 2.
- Carfilzomib: If not improving after 3 days, administer one dose of dexamethasone (10 mg intravenously).

Grade 2: Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% O2, or hypoxia responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity.

- Tocilizumab: Administer tocilizumab: 8 mg/kg intravenously over 1 hour (to exceed 800 mg). If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 6-8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. If improving, discontinue tocilizumab.

- Carfilzomib: Administer dexamethasone 10 mg intravenously once daily. If not improving after 3 days, administer one dose of dexamethasone (10 mg intravenously).

- Tocilizumab: Per CRS Grade 2 if improving, manage as appropriate grade above.

- Carfilzomib: Dexamethasone 10 mg intravenously three times a day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as appropriate grade above.

Grade 3: Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% O2, or hypoxia requiring high-flow or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transient/c.

- Tocilizumab: Per CRS Grade 2 if improving, manage as appropriate grade above.
- Carfilzomib: Dexamethasone 10 mg intravenously once daily. If not improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as appropriate grade above.

Grade 4: Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemolysis (CVVH) or other organ support (such as renal support) and/or organ toxicity (excluding mild transferrable syndrome and mild neurologic toxicity).

- Tocilizumab: Per CRS Grade 2 if improving, manage as appropriate grade above.

- Carfilzomib: Administer methylprednisolone 1000 mg intravenouslyonce daily for 3 days. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider methylprednisolone 1000 mg-2-3 times a day or alternate therapy.

- No concurrent CRS: Dexamethasone 10 mg intravenously four times a day. If improving, discontinue corticosteroids as appropriate grade.

- Concurrent and No Concurrent CRS: Considerlevetiracetam for seizure prophylaxis for any grade of neurologic toxicities.

Management of Neurologic Toxicities

Neurologic Toxicity/ICANS Grading and Management Guidance

- Grade 1: Seizures requiring oral anticonvulsants.

- Grade 2: Seizures not requiring anticonvulsants.

- Grade 3: Other neurologic toxicities requiring hospitalization.

- Grade 4: Other neurologic toxicities requiring ICU admission.

- No Concurrent CRS: Dexamethasone 10 mg intravenously daily for 3 days. If improving, discontinue corticosteroids as appropriate grade.

- Concurrent and No Concurrent CRS: Consider levetiracetam for seizure prophylaxis.

- Concurrent CRS: Consider levetiracetam for seizure prophylaxis.
Cytokine Release Syndrome:
• No Concurrent CRS: Administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.
• Concurrent and No Concurrent CRS: Consider live vaccinations for severe prophylaxis.

Grade 4
• Concurrent CRS: Administer tocilizumab per CRS Grading and Management Guidance for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy (but is not limited to) analgesics, ibrutinib, cyclophosphamide, 6-mercaptopurine.

• No Concurrent CRS: Administer methylprednisolone 1000 mg intravenously twice per day. If improving, redose as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy (but is not limited to) analgesics, ibrutinib, cyclophosphamide, 6-mercaptopurine.

• Concurrent and No Concurrent CRS: Consider live vaccinations for severe prophylaxis.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS
Cytokine Release Syndrome: CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. CRS occurred in 80% (379/475) of patients with non-Hodgkin lymphoma (NHL) receiving YESCARTA, including ≥ Grade 3 (32% grading system) CRS in ≥ 9% (93/1056) of patients with large B-cell lymphoma (LBCL), including ≥ Grade 3 CRS in 9%. Among patients with LBCL, who died after receiving YESCARTA, four had ongoing CRS events at the time of death. For patients with LBCL, in ZUMA-1, the median time to onset of CRS was 2 days following infusion (range: 1 to 12) days and the median duration of CRS was 7 days (range: 2 to 56) days. For patients with LBCL, in ZUMA-7, the median time to onset of CRS was 3 days following infusion (range: 1 to 7) days and the median duration of CRS was 7 days (range: 2 to 43) days.

Key manifestations of CRS (≥ 10%) in all patients included fever (69%), hypotension (40%), tachycardia (39%), chills (22%), hypoglycemia (19%), headache (18%), and fatigue (12%). Serious events that may be associated with CRS include: cardiac arrhythmias including atrial fibrillation and ventricular tachycardia, renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

The impact of tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in two subsequent cohorts of LBCL patients in ZUMA-1. Among patients who received tocilizumab and/or corticosteroids for ongoing Grade 1 events (per CRS Grading and Management Guidance), CRS occurred in 8% (93/1056), including 2% (14/31) with Grade 3 CRS or higher. The median time to onset of CRS was 2 days (range: 1 to 8) and the median duration of CRS was 7 days (range: 2 to 16) days.

Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA. Thirty-one of the 39 patients (79%) developed CRS at which point the patients were managed with tocilizumab and/or therapeutic doses of corticosteroids with no patients developing Grade 3 or higher CRS. The median time to onset of CRS was 5 days (range: 1 to 15) days and the median duration of CRS was 4 days (range: 1 to 15) days. Although there is no known mechanistic explanation, consider the risk and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities.

Ensure that 3 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs of symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, instate treatment with supportive care, tocilizumab, or corticosteroids as indicated.

Neurologic Toxicities: Neurologic toxicities including (CANS) that were fatal or life-threatening occurred following treatment with YESCARTA. Neurologic toxicities occurred in 78% (334/427) of patients with NHL, receiving YESCARTA, including ≥ Grade 3 cases in 25%.

Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 cases in 31% and in 74% (124/168) of patients in ZUMA-7 including ≥ Grade 3 cases in 25%. The median time to onset was 4 days (range: 1 to 41) days and the median duration was 17 days in patients with LBCL, in ZUMA-1. The median time to onset for neurologic toxicity was 5 days (range: 1 to 133) days and median duration was 15 days in patients with LBCL, in ZUMA-7. Ninety-eight percent of all neurologic toxicities in patients with LBCL occurred within the first 8 weeks of YESCARTA infusion. Neurologic toxicities occurred within the first 7 days of YESCARTA infusion in 87% of affected patients with LBCL.

The most common neurologic toxicities (≥ 10%) in all patients combined included encephalopathy (50%), headache (47%), tremor (29%), dizziness (21%), aphasia (17%), delirium (15%), and insomnia (10%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including aphasia, leukoencephalopathy, dysarthria, lethargy, and encephalopathy occurred with YESCARTA. Fatality and serious cases of cerebellar edema and encephalopathy, including late-onset encephalopathy, have occurred in patients treated with YESCARTA.

The impact of tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in two subsequent cohorts of LBCL patients in ZUMA-1. Among patients who received corticosteroids at the onset of Grade 1 toxicities (see Neurologic Toxicity/ICANS Grading and Management Guidance), neurologic toxicities occurred in 9% (81/900) patients who experienced Grade 2 or 3 events. The median time to onset of neurologic toxicities was 6 days (range: 1 to 90) days with a median duration of 8 days (range: 1 to 144) days. Prophylactic treatment with tocilizumab and/or corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA. Of these 39 patients, 90% (35/39) developed Grade 3 and 5% (2/39) developed Grade 4 neurologic toxicities. The median time to onset of neurologic toxicities was 6 days (range: 1 to 274) days with a median duration of 12 days (range: 1 to 107) days. Prophylactic corticosteroids for management of CRS and neurologic toxicities could be considered in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities. Delay the onset and decrease the duration of CRS.

Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA and TECARTUS REMS Program: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program. The required components of the YESCARTA and TECARTUS REMS Program are:

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

• Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Additional Information
Hepatitis B virus Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with drugs directed against cells, including YESCARTA. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

Prolonged Cytophenias: Patients may exhibit cytophenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher cytophenias not resolved by Day 30 following YESCARTA infusion occurred in 39% of all patients with NHL and included neutropenia (3%), thrombocytopenia (17%), and anemia (8%). Monitor blood counts after YESCARTA infusion.

Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinemia was considered an adverse reaction in 14% of all patients with NHL. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended at any time during 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and for immunocompetent recovery following treatment with YESCARTA.

Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-404-KITE (5483) to obtain instructions on patient samples to collect for testing.
Adverse Reactions in ≥ 10% of Patients Treated with YESCARTA in ZUMA-7 (CONT'D)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>YESCARTA N = 168</th>
<th>Any Grade (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (≥ 10%)</td>
<td>31 of 168</td>
<td>19</td>
<td>0</td>
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<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tachycardia</td>
<td>94 of 168</td>
<td>56</td>
<td>4 (%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>43 of 168</td>
<td>26</td>
<td>3 (%)</td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>42 of 168</td>
<td>25</td>
<td>2 (%)</td>
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<tr>
<td>Nausea</td>
<td>40 of 168</td>
<td>24</td>
<td>1 (%)</td>
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<tr>
<td>Abdominal pain</td>
<td>20 of 168</td>
<td>12</td>
<td>0 (%)</td>
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<tr>
<td>Constipation</td>
<td>20 of 168</td>
<td>12</td>
<td>0 (%)</td>
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<tr>
<td>Vomiting</td>
<td>20 of 168</td>
<td>12</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 of 168</td>
<td>12</td>
<td>0 (%)</td>
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<tr>
<td>Rectal bleeding</td>
<td>10 of 168</td>
<td>6</td>
<td>0 (%)</td>
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<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fever (≥ 10%)</td>
<td>93 of 168</td>
<td>56</td>
<td>4 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52 of 168</td>
<td>31</td>
<td>2 (%)</td>
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<tr>
<td>Chills</td>
<td>28 of 168</td>
<td>17</td>
<td>1 (%)</td>
</tr>
<tr>
<td>Edema (≥ 10%)</td>
<td>23 of 168</td>
<td>14</td>
<td>0 (%)</td>
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<tr>
<td>Immune System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>92 of 168</td>
<td>55</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>91 of 168</td>
<td>54</td>
<td>2 (%)</td>
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<tr>
<td>Infections and infestations</td>
<td></td>
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<tr>
<td>Infections with pathogens, unspecified</td>
<td>25 of 168</td>
<td>15</td>
<td>1 (%)</td>
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<tr>
<td>Viral infections</td>
<td>15 of 168</td>
<td>9</td>
<td>0 (%)</td>
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<tr>
<td>Bacterial infections</td>
<td>15 of 168</td>
<td>9</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>10 of 168</td>
<td>6</td>
<td>0 (%)</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>24 of 168</td>
<td>14</td>
<td>0 (%)</td>
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<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Musculoskeletal pain</td>
<td>41 of 168</td>
<td>25</td>
<td>1 (%)</td>
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<tr>
<td>Motor dysfunction</td>
<td>15 of 168</td>
<td>9</td>
<td>0 (%)</td>
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<tr>
<td>Nervous System Disorders</td>
<td></td>
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<tr>
<td>Encephalopathy</td>
<td>46 of 168</td>
<td>28</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 of 168</td>
<td>25</td>
<td>1 (%)</td>
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<tr>
<td>Tremor</td>
<td>25 of 168</td>
<td>15</td>
<td>1 (%)</td>
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<tr>
<td>Dizziness</td>
<td>25 of 168</td>
<td>15</td>
<td>1 (%)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>20 of 168</td>
<td>12</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>11 of 168</td>
<td>7</td>
<td>0 (%)</td>
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</tbody>
</table>
| Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-7 Following Treatment with YESCARTA (N = 168) Leukocytosis decrease: 95%, Neutropenia decrease: 94%, Lymphocyte decrease: 94%, Hemoglobin decrease: 43%, Platelet decrease: 26%, Sodium decrease: 12%, Glucose increase: 11%. Baseline lab values were acquired prior to lymphodepleting chemotherapy.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (9%), cardiac disorders: cardiac failure (5%), eye disorders: visual impairment (5%), infections and infestations: pneumocystis jiroveci (3%), nervous system disorders: ataxia (7%), seizure (1%), myoclonus (2%), facial palsy (2%), respiratory and mediastinal disorders: dyspnea (8%), pleural effusion (6%), respiratory failure (2%), vascular disorders: hypertension (9%), thrombosis (7%). Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-7 Following Treatment with YESCARTA (N = 168) Leukocytosis decrease: 95%, Neutropenia decrease: 94%, Lymphocyte decrease: 94%, Hemoglobin decrease: 43%, Platelet decrease: 26%, Sodium decrease: 12%, Glucose increase: 11%. Baseline lab values were acquired prior to lymphodepleting chemotherapy.

ZUMA-1: The safety of YESCARTA was evaluated in ZUMA-1, a study in which 108 patients with relapsed or refractory LBCL received CD19-positive CAR T cells based on a recommended dose which was weight-based. Patients with a history of CNS disorders (such as seizures or crenotrocalic sclerosis) or autoimmune disease requiring systemic immunosuppression were ineligible. The median age of the study population was 58 years (range: 23 to 76 years); 68% were male. The baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 43% of patients and 1 in 46%.

The most common non-laboratory adverse reactions to YESCARTA (incidence ≥ 20%) included fever, CRS, fatigue, hypotension, encephalopathy, tachycardia, diarrhea, headache, musculoskeletal pain, nausea, febrile neutropenia, chill, cough, infection with unspecified pathogens, dizziness, tremor, decreased appetite, edema, hypotension, abnormal blood pressure, paresthesia, and vomiting. Serious adverse reactions occurred in 50% of patients. The most common serious adverse reactions (> 2%) included CRS, fever, encephalopathy, hypotension, infection with unspecified pathogens, and pneumonia. Fatal adverse reactions occurred in 2 of 287 patients (1 of 286 patients treated with YESCARTA after infusion of YESCARTA).

The following events were also counted in the incidence of CRS: coagulopathy, tachycardia, encephalopathy, arrhythmia, cardiac failure, diarrhea, nausea, vomiting, fever, fatigue, chill, edema, decreased appetite, musculoskeletal pain, head, tremor, dizziness, renal insufficiency, cough, hypotension, dyspnea, pleural effusion, respiratory failure, rash, hypoxia, and hypereosinophilia.

The most common serious adverse reactions (> 5%) included CRS, fever, encephalopathy, constipation, and vomiting. Serious adverse reactions occurred in 50% of patients. The most common serious adverse reactions (> 2%) included CRS, fever, encephalopathy, infections and infestations: pneumocystis jiroveci (3%), nervous system disorders: ataxia (7%), seizure (1%), myoclonus (2%), facial palsy (2%), respiratory and mediastinal disorders: dyspnea (8%), pleural effusion (6%), respiratory failure (2%), vascular disorders: hypertension (9%), thrombosis (7%).
Cardiovascular Disorders | Rash (9%), capillary leak syndrome (3%)
Thrombosis includes deep vein thrombosis, embolism, embolism venous, pulmonary embolism, splenic
Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.
Cough includes cough, productive cough, upper-airway cough syndrome.
Hypoxia includes hypoxia, oxygen saturation decreased.
Aphasia includes aphasia, dysphasia.
Dizziness includes dizziness, presyncope, syncope.
Heart failure includes heart failure.
Hypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin D decreased.
Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper.
Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, bundle branch
Tachycardia includes tachycardia, sinus tachycardia.
The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, hypotension,
The safety and efficacy of YESCARTA were evaluated in two subsequent cohorts of BCL patients. The first subsequent, open label, safety management cohort in ZUMA-1 evaluated the safety and efficacy of YESCARTA with the use of tocilizumab and/or corticosteroids (750 mg PO or IV daily) for Grade 1 CRS or neurotoxic event. A total of 46 patients with grade 1 or 2 CRS were enrolled in 41 patients were treated with YESCARTA. Of the remaining 5 patients who were not treated, 2 patients died prior to receiving YESCARTA. Six patients were withdrawn due to disease progression. Twenty-eight patients (86%) treated with YESCARTA received bridging therapy between lymphodemand and lymphodepleting chemotherapy. Thirty-two patients (10%) treated with YESCARTA received lymphodepleting chemotherapy.

### Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
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<tbody>
<tr>
<td>Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in ZUMA-1</td>
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NCCN Recommends Pacritinib for Treatment of Myeloproliferative Neoplasms

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) Clinical Practice Guidelines have been updated to include pacritinib, a novel oral kinase inhibitor with specificity JAK2 and interleukin receptor associated kinase 1 (IRAkB), as a recommended treatment for myeloproliferative neoplasms.

“We are grateful that NCCN acted quickly to include pacritinib” with a Category 2A designation in its Clinical Practice Guidelines on Oncology as a first-line treatment for high-risk patients with myelofibrosis with platelet counts of less than 50 x 10^9/L who are not candidates for transplant…There is no other FDA-approved first-line treatment for these patients with a 2A designation within the NCCN guidelines,” Adam R. Craig, MD, PhD, president and CEO of CTI BioPharma, said in a statement.1

In addition, pacritinib was included as a Category 2A designation as second-line treatment for lower-risk and higher-risk patients with myelofibrosis with platelet counts equal to or greater than 50 x 10^9/L who are not candidates for transplant.

Pacritinib is an oral kinase inhibitor with activity against JAK2, mutant Jak2 form, and FMS-like tyrosine kinase 3, which contributes to signaling for cytokines and growth factors that are important to hematopoiesis and immune function. Pacritinib does not inhibit JAK1. Myelofibrosis is associated with dysregulated JAK2 signaling.

A phase 2 trial conducted in 2020 determined that pacritinib was best prescribed in twice-daily doses of 200 mg each. No adverse effects (AEs) above grade 3 or higher hemorrhages or cardiac events occurred in the highest dose group during this trial.

Gastrointestinal difficulties, thrombocytopenia, and anemia were the most common AEs.2

Grade 3 bleeding events occurred in 15% of patients in the experimental arm of the 2020 phase 2 trial, compared with 7% in the control arm.

Of the patients taking pacritinib in that trial, 48% experienced diarrhea, compared with 15% of patients in the control group. The incidence of reported diarrhea decreased over time, from 41% in the first 8 weeks to 8% in the final 8 weeks.

Pacritinib can also cause worsening thrombocytopenia and prolonged QTc intervals. Other JAK inhibitors have been associated with increased risks of major cardiac events, thrombosis, lymphoma and other malignancies, and infection. Coadministration of pacritinib and CYP3A4 inhibitors or inducers is contraindicated. •

Final Response Analysis of ALPINE Finds Zanubrutinib Superior to Ibrutinib in R/R CLL

ACCORDING TO THE RESULTS of the phase 3 ALPINE trial, zanubrutinib demonstrated superiority compared with ibrutinib in adult patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma. This information was released in an April 11 statement from manufacturer BeiGene.3

Zanubrutinib had achieved superiority in the primary end point of investigator-assessed overall response rate (ORR) in the interim analysis. Zanubrutinib had an ORR of 80.4% compared with 72.9% for ibrutinib. The 652 patients who were enrolled in the trial across Europe, the United States, China, New Zealand, and Australia were followed for a median of 24.2 months.

Patients were randomized to receive either zanubrutinib 160 mg orally twice a day or ibrutinib 420 mg orally once a day.

Results were consistent with those of previous studies on zanubrutinib. The rate of atrial fibrillation or flutter continued to be lower in the zanubrutinib arm. The rate of atrial fibrillation or flutter at 24.2 months of median follow-up was 4.6% in the zanubrutinib arm vs 12.0% in the ibrutinib arm.

Zanubrutinib is a second-generation Bruton tyrosine kinase inhibitor, which accounts for the lower rate of atrial fibrillation or flutter. Compared with ibrutinib, zanubrutinib minimizes off-target inhibition of TEC- and EGFR-family kinases.

In ALPINE, 13.0% of patients who received zanubrutinib discontinued treatment due to adverse events (AEs) compared with 17.6% of patients who received ibrutinib. The most common AEs for zanubrutinib vs ibrutinib respectively were neutropenia (14.2% vs 13.9%), hypertension (12.7% vs 10.2%), pneumonia...
(4.0% vs 7.4%), decreased neutrophil count (4.3% vs 4.0%), and COVID-19 pneumonia (4.3% vs 3.1%).

“We understand that for people living with CLL and their families, relapse and treatment resistance are especially devastating,” Lai Wang, PhD, global head of research and development at BeiGene, said in the statement. “That’s why we are encouraged by this final response analysis, which adds to the growing body of clinical evidence for [zanubrutinib] as a potential treatment for CLL.”

The interim results of ALPINE were presented at the European Hematology Association 2021 Virtual Congress last June. In those results, the ORR was 78.3% (95% CI, 72.0%-83.7%) for zanubrutinib vs 62.5% (95% CI, 55.5%-69.1%) for ibrutinib. The 12-month progression-free survival was 94.9% for zanubrutinib vs 92.07% for ibrutinib. In the interim results, 7.8% of patients receiving zanubrutinib discontinued treatment due to AEs compared with 13.0% of patients receiving ibrutinib. The zanubrutinib arm also reported a lower proportion of deaths due to AEs (3.9% vs 5.8%).

“We understand that for people living with CLL and their families, relapse and treatment resistance are especially devastating. That’s why we are encouraged by this final response analysis, which adds to the growing body of clinical evidence for [zanubrutinib] as a potential treatment for CLL.”

—Lai Wang, PhD, global head of research and development, BeiGene

BeiGene has submitted the results from ALPINE to support its applications for the approval of zanubrutinib in CLL in the United States, European Union, and other markets. The FDA and European Medicines Agency had previously accepted supplemental new drug applications in February 2022. The target action date under the Prescription Drug User Fee Act is October 22, 2022. Zanubrutinib is already approved in the United States to treat adults in 3 categories: those with R/R marginal zone lymphoma who have received at least 1 anti–CD20-based regimen, those with Waldenström macroglobulinemia, and those with mantle cell lymphoma who have received at least 1 prior therapy.

REFERENCES

We’re Heading Back to Nashville!

Join us for our annual Patient-Centered Oncology Care® (PCOC) conference, where you can:
• Learn how the focus on equity can improve care delivery;
• Listen to engaging discussions on key topics in oncology and beyond;
• Meet and network with other experts and key stakeholders.

November 9-10, 2022
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Presented by AJMC
**What's a Little Innovation among friends?**

After a 2-year break due to the pandemic, Institute of Value-Based Medicine (IVBM) brought health care leaders together on April 21 in Nashville, Tennessee, to discuss oncology care delivery—and to see colleagues in person, some for the first time since 2020.

The meeting, hosted by Tennessee Oncology's chief medical officer Stephen M. Schleicher, MD, MBA, and Leah Owens, DNP, RN, executive director of Care Transformation, was part salon, part family reunion, as oncology providers from practices across the state gathered at the Hutton Hotel. Schleicher welcomed presenters he described as friends, either from his residency at Brigham and Women's Hospital in Boston, or from Nashville, now one of the hottest hubs of health care innovation and investment. After talks on new delivery concepts and lessons from the Oncology Care Model (OCM), Schleicher led a conversation with experts from the world of venture capital, which is providing the fuel for technology-driven solutions.

In recent years, the focus of delivery reform has been the OCM—which Tennessee Oncology mastered better than most. But now, practices must shift to delivering the model's best elements without extra funding from Medicare, as the OCM is set to lapse on June 30, 2022.

"A lot has changed over the past 6 months," Schleicher said. As support from CMS ebbs, he explained, commercial payers are looking at value-based contracts as a way to keep the OCM pieces that worked best. For some, venture capital offers a bridge to growth until payers can learn where these new solutions fit. Emerging companies offer “tech-enabled” tools, with which people provide the care while technology helps maximize resources, predict behavior, or speed decision-making.

**Thyme Care: Navigation at Scale**

Bobby Green, MD, was in oncology practice for more than 20 years—and with Flatiron Health for 7 years—before he co-founded Thyme Care with fellow Flatiron executive Robin Shah, MBA. As Green explained to the audience, ample evidence shows that cancer care navigation works and that digital delivery can improve survival. Results of a 2017 study led by Ethan Basch, MD, MSc, indicated that patients with advanced cancer gained 5 months of survival using an electronic system to log patient-reported outcomes. If a drug offered that much benefit, Green said, its use would spread quickly. But the Basch study and others have not pointed out, by keeping patients out of the emergency department (ED) and saving money.

The new challenge is scaling that success, and that’s where Thyme Care comes in. As Green said, the first step is building “a patient-centered care navigation platform. And the second is to work as an intermediary with the health plan and with practices to enable value-based contracts.”

While health plans provide the revenue (see Sidebar), Green said, Thyme Care forms partnerships with oncology practices, to understand their workflows, access electronic health records, and fully understand each patient. Primary care practices are part of the picture, too. Thyme Care makes heavy use of data—from claims, from prior authorizations, and from practices—that help greatly in connecting patients with services and high-value care.

Green shared pictures of the different types of reports that Thyme Care can generate, ranging from acuity scoring to prioritization of needs, documenting interventions and outcomes, and tracking a patient’s individual journey. “We think it’s really necessary to connect the dots and put people with the technology,” he said. “We call it technology-enabled navigation.”

Thyme Care, Green said, can “sit between the health plans and the clinicians to help design value-based contracts—and to help understand where the opportunity is.”

**Using Nudges to Drive High-Value Care**

Ravi Parikh, MD, MPP, an assistant professor of medical ethics and health policy and of medicine at the University of Pennsylvania’s Perelman School of Medicine in Philadelphia, turned the discussion to a longstanding problem in cancer care: what to do about low-value care. By some estimates, low-value care represents 30% of all cancer care spending, Parikh said, but measuring it, pinpointing it, and eliminating it are tough to do. High-profile efforts, such as the Choosing Wisely campaign, and Medicare’s crackdown on low-value care have had mixed results.

In the months before COVID-19 vaccines were available, the scenario that arose from the pandemic was one in which many experts thought low-value cancer care would be revealed: Providers and patients would weigh the risk of being in medical facility—and halting cancer’s progression—against the chances of contracting COVID-19.

But, as Parikh explained, it’s not that simple. “We could just decrease utilization across the board,” he said. “That might decrease low-value care, but it also might decrease some high-value cancer care.”

What is clear is that cancer screenings—considered a high-value practice—dropped as much as 50%, and some screening rates have not recovered. Thus, deciding how much low-value care is still happening based on claims data is difficult, Parikh said, and he pays more attention to the trends that have emerged.

Instead, Parikh and his fellow researchers partnered with Anthem to study 5 specific metrics for non-guideline-directed care. He shared data showing that low-value cancer care was common before the pandemic, and with the exception of a specific radiation procedure, low-value care remained common after the pandemic began.

Low-value care tends to happen in certain practices; even when it declined, the numbers didn’t shrink much. What does
Thyme Care: A Human Touch in Cancer Care, Guided by Technology
Mary Caffrey

CANCER CARE NAVIGATION is not a new, unproven idea. The value of pairing a patient diagnosed with cancer with someone who knows the system—who can schedule appointments, warn about effects from medications, or connect a family with counseling—was first demonstrated in the 1990s when Harold P. Freeman, MD, created a program at Harlem Hospital in New York to help poor, mostly minority patients with follow-up care.²

Patients in the program had remarkably improved outcomes compared with similar patients at the same hospital who lacked assistance. For those receiving navigation, the 5-year survival rate nearly doubled, from 39% to 79%.

In multiple studies completed since that time, results have confirmed Freeman’s findings: Cancer care navigation can improve patient experience and outcomes, and even reduce costs.³,⁴ Unfortunately, despite the evidence, navigation is not universal. The founders of Thyme Care knew this. Over the past decade, as this group of oncologists and health technology leaders were busy with other successful startups—notably Flatiron Health—they heard from friends who were bewildered by the task of guiding a loved one through cancer treatment. The idea that not everyone knows a friend in the cancer field begged for a solution, and in 2020, the founders launched a company to close the navigation gap.⁵

Oncologist and health tech veteran Bobby Green, MD, who practiced for 17 years in West Palm Beach, Florida, and was previously with Flatiron, is now Thyme Care’s president and chief medical officer. He has relocated to Nashville, Tennessee, where Thyme Care is among the city’s health tech startups—and nestled among the investment funds that focus on these ventures. Nashville-based funds are among those that helped Thyme Care raise $22 million in October 2021.⁶

During an interview at the company’s office, Green explained that ‘Thyme Care doesn’t try to replace the one-on-one relationship a patient develops with a cancer care navigator. “Especially with cancer, there’s a human touch component, which you just can’t replace with...”
training, but especially in this moment, people are tired. And change is hard.”

**OCM Lessons and the Path Forward**

On paper, the OCM may not look like a financial winner, but it did spur practice transformation—and patients both inside and outside Medicare saw benefits, according to an official from the Center for Medicare & Medicaid Innovation (CMMI).

Hillary Cavanagh, MA, deputy director of the Division of Ambulatory Payment Models at CMMI, took part in the IVBM meeting remotely to give an overview of lessons learned from the OCM, which supporters say should not be judged solely on whether most practices saved Medicare money. Practices that became more proficient at operating under the OCM as time went on say that the decision to let it expire related too narrowly on financial results accrued through only the first half of the model (see Cover). In doing so, they say, CMMI has failed to appreciate how much savings were achieved in some practices during the past 2 years. "We need to appreciate how much savings can happen over time," Cavanagh said. "More important, we need to make those savings a reality for all patients." Cavanagh noted that the savings were achieved at the cost of risk being shifted to the commercial insurance system. In 2019 and the first half of 2020, 126 practices, 7000 practitioners, and 200,000 beneficiaries, and 260,000 episodes of care, covered 126 practices, 7000 practitioners, and 200,000 beneficiaries, and 260,000 episodes of care, which were released results that show $5 million in savings from the second half of 2019 and the first half of 2020.¹

In the OCM, practices are evaluated in 6-month blocks called performance periods; Cavanagh’s presentation included data produced by Abt Associates from the first 5 periods, although she noted the program will run for 11 periods.² The early data, Cavanagh said, show that while Medicare did not see savings in low-risk episodes, it did create savings in the care of higher-risk patients. Through period 5, the net loss to Medicare was $377 million. But CMMI evaluations have shown benefits, Cavanagh said. The scope of the OCM meant it reached a lot of patients: Almost 25% of the Medicare fee-for-service (FFS) chemotherapy-related cancer care fell under the model during the program’s life. This covered 126 practices, 7000 practitioners, and 260,000 episodes of care, according to the data presented. Five commercial payers took part alongside Medicare.

The CMMI evaluation team identified specific changes that led to higher-quality scores: (1) better and faster access to oncology staff, (2) patient navigation and coordination, (3) screening for pain, depression, and other needs, (4) patient education, and (5) expanding palliative care and culturally sensitive end-of-life care.

Most OCM practices extended delivery system reforms across all their patients, not just those in Medicare FFS; 40 of 47 practices evaluated by CMMI had done so. That meant commercial patients also experienced the benefit of navigation services, survivorship care, advanced care planning, and practice changes that kept patients out of the ED. Some large changes practiced centralized navigation services that reached patients by phone.

"Many oncologists, nurses, and administrators [felt] that the high-quality care should be the same for every patient," Cavanagh said. "We’ve heard different versions of this across the different practices that were visited: ‘If it’s good for Medicare patients, we should do it for everyone.’"

Although commercial payers did not like certain aspects of the OCM, care transformation has offered...
CONTINUED FROM PREVIOUS PAGE

In September 2021, Thyme Care formed a partnership with Clover Health to deliver services to underserved Clover Medicare Advantage members in New Jersey.8

“The revenue comes from health plans. We don’t charge patients; we don’t charge providers,” Green said. Nonetheless, the Thyme Care model calls for a full collaboration—and aligning incentives. He has viewed these relationships from both the business side and in oncology practice, and he knows that provider engagement can suffer when a third party provides navigation. “Provider focus is really important,” Green stressed.

Does the end of the OCM create a need for Thyme Care? Yes, health plans are interested, even though there’s plenty about the OCM they’re ready to leave behind. “We’ve taken the position that we want to help build models that are very clinician/oncologist-centric, and bring the tools and technology and the expertise to figure out what the right value-based care models are to align incentives between the health plan and the provider—and then bring the tech to enable them,” Green said.

People are very motivated to try to improve the patient experience, to drive higher-value care, to prevent acute care events, to make sure that the therapies that people are getting are the highest-value therapies,” said Green. “And I think that’s a space where health plans and oncologists are very much aligned.”

REFERENCES

Data-Driven Health Care Companies such as Thyme Care, Aspire Health, and Monogram Health don’t just magically grow: All required investment from those who understood the companies’ potential in their early stages. That piece of Nashville’s rise—as a place both home to and a magnet for health care venture capital (VC)—was the closing chapter of the April 21 meeting of the Institute of Value-Based Medicine8.

Tennessee Oncology chief medical officer Stephen M. Schleicher, MD, MBA, led the discussion with a group of VC investors:

- Brenton Fargnoli, MD, MBA, managing partner, AlleyCorp Healthcare Fund;
- Benjamin Robbins, MD, MBA, venture partner, GV (formerly Google Ventures); and
- Chris Booker, partner, Frist Cressey Ventures.

The panelists arrived in the VC arena via different paths, but they share an interest in the “tech-enabled” solutions that aim to squeeze inefficiencies from health care delivery. The focus today, unlike in prior waves of investment, is on better health care delivery, not just short-term savings.

Fargnoli, for example, described his interest in investing in Nashville-based Thyme Care with former colleagues from Flatiron Health. Thyme Care, which seeks to scale successful models of cancer care navigation, could address the experience of Fargnoli’s colleague, whose mother is being treated for cancer in Boston. The mother, who is a Harvard professor, “described the experience as being alone in a small boat being bounced around by stormy waves,” Fargnoli said. “If she’s flailing, then nearly everyone else in the country is going to be doing worse.”

As much money as venture capital investors have made in health care, Robbins said, “I feel like we are only starting to get

Health Care VC Leaders Talk Successes, Value-Based Care, and Nashville’s Rise

MARY CAFFREY

Data-Driven Health Care Companies such as Thyme Care, Aspire Health, and Monogram Health don’t just magically grow: All required investment from those who understood the companies’ potential in their early stages. That piece of Nashville’s rise—as a place both home to and a magnet for health care venture capital (VC)—was the closing chapter of the April 21 meeting of the Institute of Value-Based Medicine.

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into the core of health care delivery.” Only a few enterprises, he noted, are touching the parts of health care “that a large number of people are experiencing.”

Robbins pointed to a company called Headway, which helps connect people with mental health providers with open appointments—eliminating the need for each patient to call dozens of providers to find an opening. Some models call for technology or software to be given to providers for free; payers then create the revenue stream to tap into a built network of precredentialed clinicians.

Schleicher invited each panelist to share success stories—and stories of the ones that got away. In the world of VC, however, each fund must be selective, so there will always be tales of investments not made.

“Clearly, health care is expensive and cost reductions need to happen. But the thing that is exciting about value-based care is the other part, which is this quality piece.”

—Benjamin Robbins, MD, MBA, venture partner, GV

Booker noted that Frist Cressey provided investment in OneOncology, which was started by leaders of Tennessee Oncology and West Cancer Center to build a platform for oncology practices to share data, clinical pathways, clinical trial opportunities, and best practices while maintaining independence. “Today, it’s one of the largest groups in the country,” Booker said.

VALUE-BASED CARE. Although the models need work, the panelists agreed that the broad principles of value-based care are here to stay. Some panelists said the challenge with the term is that when each stakeholder—whether it’s a payer or provider—views the concept through a different lens, not everyone has the same expectation.

“Clearly, health care is expensive and cost reductions need to happen,” Robbins said. “But the thing that is exciting about value-based care is the other part, which is this quality piece.” He would rather see the focus on efficiency begin from the patient’s perspective, and if “we can align things to reduce cost, that’s great.”

NASHVILLE’S EMERGENCE. For Booker, Nashville’s rise as a center for health care innovation has a simple explanation: The talent is here. Early on, the city became home to Hospital Corporation of America, founded in 1968 by the Frist family. As Booker described it, the health care infrastructure in the city was built on “the legacy hospital model,” and when industry consolidation occurred, there was already a critical mass of people with knowledge and dedication to improving health care. Schleicher asked if other health care ventures relocating to Nashville had contributed to momentum.

“Absolutely,” Booker confirmed. “The biggest minds are saying, ‘Hey, this is where we want to be.’”

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Why White Bagging Is a Symptom of High Drug Costs, and What States Are Doing

**THE RISE OF WHITE BAGGING** is wreaking havoc for patients and has spurred legislation in several states, according to 2 experts who said their oncology practices refuse to take part in the practice. With white bagging, pharmacy benefit managers (PBMs) require certain high-cost drugs to be shipped from their own specialty pharmacies to practices, where clinicians then administer the drugs to patients—assuming the drugs arrive safely, and doctors do not need to change the dose.

But the real issue, according to a third panelist who discussed PBM practices during the National Comprehensive Cancer Network (NCCN) 2022 Annual Conference, is that payers are determined to do something about rising drug costs.

Michael Kolodziej, MD, who has had a long career as a medical oncologist and then an executive with Aetna/CVS before joining ADVI, noted that oncologists didn’t create the “buy-and-bill” reimbursement system, in which they receive 6% of the average sales price of the drugs they administer. The optics of this method are “problematic,” he said, especially with so many new expensive cancer drugs being approved through the FDA’s accelerated pathway. Payers, he said, are skeptical of the value of some treatments; indeed, in the past year, some drug companies withdrew indications after confirmatory trials failed.

“Payers don’t like this,” Kolodziej said. “And, oh, by the way—neither does the federal government.”

Kolodziej was joined on the panel by Kathy W. Oubre, MS, Pontchartrain Cancer Center; Kenneth M. Komorny, PharmD, BCPS, Moffitt Cancer Center; and Michael I. Rabin, MBA, MPA, City of Hope National Medical Center, who served as moderator.

Oubre explained the difference between white bagging and clear bagging: in the latter, a provider’s in-house specialty pharmacy prepares a medication and administers it during a patient visit—which oncologists prefer because doses can be adjusted based on lab reports taken that day. Brown bagging, another cost-cutting practice, involves shipping drugs directly to the patient. In some cases, the patient is expected to bring the drugs to the oncologist for administration. Documented cases include patients leaving drugs in their car instead of putting them in the refrigerator.

**PATIENT SAFETY.** Both Oubre and Komorny raised safety and chain-of-custody issues that have been reported to pharmacy boards and professional associations, such as the Community Oncology Alliance. These include drugs shipped to the wrong address, drugs left on loading docks not at a controlled temperature, or drug shipments that were interrupted due to weather events.

Komorny said delays in shipping a patient’s granulocyte colony-stimulating factor, for instance, are extremely dangerous. “In these cases, patients have missed this rescue medication when the medicine was due,” he said. “Not receiving this medication when due could lead to significant complications, including neutropenic fever, which of course has a higher mortality rate.”

“All of these issues negatively affect the patient, by resulting in delays in care,” Oubre said. “And if it’s a dose reduction, you’re talking about additional co-pays for that patient.”

**FRUSTRATION OVER COST.** Noting that the issue might be sensitive to some NCCN member institutions, Kolodziej explained that payers are frustrated by hospitals that inflate the cost of oncology drugs. He cited 2 reports: one, paid for by the pharmaceutical industry, found that hospitals mark up drug prices by an average of 500%; and another, from Drug Channels, included data showing that more than half of hospitals now take part in the 340B program, which allow them to participate in drug discount purchasing programs while charging payers full price.

The combination is not sustainable, Kolodziej said, and that’s why white bagging exists. Kolodziej noted that he wasn’t defending the practice and did not allow it when he was practicing. But the policy is a way for vertically integrated payers and PBMs to push down on costs: by controlling site of service. Step edits are another tactic. “The fact of the matter is that all of these policies can be executed now, because they can control the pharmacy benefit in house,” he said.

It might be in oncologists’ interest to embrace a phaseout of buy-and-bill for something similar to a plan advocated by former American Medical Association president Barbara McAneny, MD: It pays oncologists for the actual services they provide, with an administrative fee to cover the drugs they administer.

“I think most of us would agree that we’d like to be paid for the work that we’re doing,” Kolodziej said. “The question is, how do we get from Point A to Point B?”

**LEGISLATION.** In her home state of Louisiana, Oubre successfully advocated for a law that says payers cannot refuse to reimburse providers for approved physician-administered drugs and services “even if these services are obtained at out-of-network pharmacies,” according to the summary. Oubre has since pressed for similar laws in other states, and governors in such politically diverse states as Michigan, New York, and Texas have signed legislation.

At the federal level, she’s working with bipartisan sponsors on the TACT Act, which requires that patients be provided their orally administered cancer drugs within 72 hours, allowing for situations such as obtaining financial assistance, that are “understandable and acceptable.”

**HOSPITAL LIABILITY.** Komorny sought to help those NCCN members with connections to institutional pharmacies understand the laws and regulations that apply to white bagging. The real-world situations that community oncology has experienced—and the potential liability—will only grow as this practice becomes more widespread.

“As this practice is being expanded to hospitals, hospital pharmacies need to be aware of how this practice might affect hospital regulations—[regulations] that must be followed,” Komorny said. CMS accreditation by the Joint Commission requires multiple standards to which hospitals must adhere: These include 9 specific standards related to medication management, 10 standards adopted in March 2001 to prevent drugs from being diverted, and 5 standards developed in May 2007 that involve compounding under proper supervision and sterile conditions. Separately, the FDA has supply chain requirements that must be followed to prevent counterfeiting.

Komorny outlined the detailed steps that are taken to ensure temperature control in his home base of sunny Florida.

“Within the pharmacy, we store these medications in temperature-regulated storage units that are monitored 24/7, 365 days a year. Electronically, these units record the temperature every 5 minutes, average those 3 temperatures every 15 minutes, and document that 15-minute average continuously. If there’s any deviation from the recommended range, we’re alerted and take action,” Komorny described.

Hospitals, Komorny continued, must follow the same regulations—and are expected to maintain these standards with all the drugs coming in the door from unaffiliated pharmacies. Rules state that the hospital must remove any vials that are damaged or stored outside FDA-recommended temperature ranges.

An unaffiliated specialty pharmacy will receive, store, prepare, and ship medications via third-party shipping companies, which means the hospital will not know the chain of custody of the medication. “As we did not have possession of this medication until the very end, it’s impossible for us to assure proper storage or protection against contamination or counterfeiting. Cases of delayed shipments and receipt of boxes with room-temperature freezer packs,
along with medications that should have been refrigerated, are not uncommon,” Komorny said.

It’s for reasons like this that Moffitt and Pontchartrain will not allow white bagging, Komorny outlined some scenarios that spoke to serious patient safety issues around chain of custody and dosing—as some of which involve the transfer of data for the prescription itself—as well as legal questions of whether the hospital pharmacy would need to assume additional levels of responsibility to get a drug to a patient. Sometimes, insurers try to avoid this by brown bagging the drugs to the patient. But Komorny warned that if something went wrong, the hospital pharmacy and perhaps the individual pharmacist would risk violating state laws.

And yet, if a pill is missed, there is the chance that a state board of pharmacy will discipline the pharmacy or pharmacist. “Brown bagging into the hospital is becoming very popular with insurance companies,” Komorny said. “Regulatory and legal compliance with white bagging can be impossible to meet for health system pharmacies.”

“At the end of the day, it’s not the insurance company and the PBM, or even the specialty pharmacy, that is going to be accountable to the regulatory bodies, including the Board of Pharmacy. It’s going to be your hospital and your pharmacy that will be held accountable,” warned Komorny.

Cancer Care Closer to Home—or at Home—is Worth Extra Effort, NCCN Panelists Say

THE DAYS OF ORGANIZING CANCER CARE around what’s convenient for doctors and nurses instead of patients are over, according to panelists who took part in the session, “The Patient Journey: Access to Care,” during the National Comprehensive Cancer Network (NCCN) 2022 Annual Conference.

Moderated by Timothy Kubal, MD, MBA, of Moffitt Cancer Center, the panel featured:

- Diane K. Hammon, MHA, who is the chief strategy officer at Moffitt but discussed her experience advocating for her father during his treatment for bladder cancer;
- Elizabeth A. Souza, MHA, senior administrative director, Massachusetts General Hospital (MGH) Cancer Center;
- Anne Chiang, MD, PhD, chief integration officer, Yale Cancer Center/Smilow Cancer Hospital; and
- Lawrence N. Shulman, MD, MACP, deputy director for clinical services, Abramson Cancer Center at the University of Pennsylvania.

Hammon began the discussion with the story of her father’s decision to forgo aggressive treatment upon learning he had high-risk myelodysplastic syndrome, after living with bladder cancer for more than 5 years. Hammon’s father lived more than 2 hours away from her in Florida, but he came to Moffitt to see Kubal for the diagnosis. It was November 2019, and Hammon’s father was given a life expectancy of less than 3 years.

“His desire was for treatment with dignity, respect, honesty, partnership. He wanted little disruption to my mom. He wanted to be close to home. And he would trade a little bit of smarts for a lot of heart from his oncologist. And we didn’t have to trade anything because we got both,” Hammon said.

Her father wanted to stay active, caring for his trees and seeing family and friends for as long as he was able. “We talked about clinical trials; we talked about him coming to Moffitt and living with me and my family for a period of time. And he was clear that was not the option that he wanted,” recounted Hammon.

Instead, Hammon’s father found a local oncologist who consulted with Moffitt, and through virtual visits, local lab work, and oral chemotherapy, he stayed out of the emergency department and the hospital. His care was not typical, and there were “some bumps along the way,” Hammon said. “But for about 6 months there were no transfusions, no platelets, no blood, and he was able to live a very active, productive life—high quality, just enjoying the rest of the time that he had.”

Hammon’s example may represent one extreme of the patient journey, but Souza, Chiang, and Shulman described models of care and participation in clinical trials that offer new ways to receive care and participate in research on terms far different than would have been allowed in the past.

When the pandemic forced new ways of doing things, it showed that patients could safely take experimental oral drugs at home, get lab results taken outside academic centers, and even receive drug infusions at home. And for some, there’s no going back.

NETWORK EVOLUTION. Souza outlined the evolution of the MGH Cancer Center Network, which is centered in Boston and spreads north to southern New Hampshire and southern Maine, south to Nantucket, and west to Newton and Wellesley. The system is anchored by 4 key MGH facilities closer to Boston—known as the “quad”—with several non-MGH affiliates further offering some services closer to patients.

The pandemic was a key event for this network, Souza explained. “Having 4 national cancer center locations within 20 miles of each other allows the cancer center leadership team to leverage each site for maximum utilization, to provide the right care for the patient at the right site at the right time,” she said.

“The value of the integrated system is highlighted by our ability to seamlessly facilitate care for patients across our system,” said Souza. Because physicians can see patients at separate MGH locations, not everyone had to go to Boston for specialized care during the pandemic. In fact, the percentage of patients with cancer seen in Boston has been reduced since 2019.

Souza described the network as a work in progress. “We still have to do work to ensure that each network location is providing the same level of quality care,” she said. “We are focusing on pathways implementation, unified safety reporting, and further development of a guideline-driven care model as we move forward to the future state of the National Cancer Center Network.”

Souza highlighted ongoing challenges the network faces, which include patient willingness to accept care at the community level.

CLINICAL TRIALS ACROSS A NETWORK. Chiang then discussed the expansion of clinical trials across the Yale/Smilow network, which occur at 15 different centers across Connecticut and Rhode Island. “From the very beginning, the vision was to include clinical research as a quality way to provide cutting-edge technology and opportunities for patients where they live,” she said.

Patients with cancer are enrolled in a mix of investigator-initiated trials and those sponsored by industry and by National Cancer Institute grants, Chiang said. New grant monies are allowing patients to be screened remotely for their possible participation in clinical trials, with the hope of increasing diversity in studies. Unsurprisingly, the research sites with the highest number of accruals have the largest portfolio of trials—these are the half-dozen “research champions,” exclaimed Chiang.

“Physician engagement is, of course, key to everything that we do,” Chiang said.

A monthly clinical research working group reviews trials, decides which ones will be added to the portfolio, and invites disease teams to discuss trends. Community physicians may be invited to become principal investigators to help fill gaps. Disease-specific “retreats” are used review research portfolios. COVID-19 was disruptive to all of these collaborative efforts, Chiang said, but
the processes are getting back on track. Levels of patient accrual in trials track the disease types in the community—such as breast, lung, and gastrointestinal cancer—but some subspecialties, such as neurological oncology, are increasing because of individual physician champions.

“The bottom line here is that these relationships are really robust,” said Chiang. “Of course, this boosts our referrals. But it also boosts the meaningful relationships and helps with engagement.”

**CARE AT HOME.** Shulman presented Penn’s efforts to bring care into the home, an initiative that launched slowly in the months before the pandemic and then took off—from only 50 to about 450 referrals a month.

“Why move cancer care to the home?” Shulman asked rhetorically. Referring to Hammon’s discussion of her father’s wishes, he replied, “We want this to be a better patient experience. We want to improve the clinician experience [as well].”

Shulman said that care in the home can allow Penn to “improve our capacity to provide world-class care to a broader reach of patients in a broader geographic area.”

“Why move cancer care to the home? We want this to be a better patient experience. We want to improve the clinician experience [as well].”

—Lawrence N. Shulman, MD, MACP, deputy director for clinical services, Abramson Cancer Center, University of Pennsylvania

A Penn fellow’s research study found that in the last month of life, a patient typically spent 10% of their time in health care encounters, with each one lasting an average of 4.6 hours—and more than half of that was commuting or waiting. “That’s a lot,” Shulman said.

Almost every other industry has adjusted to allow consumers to spend just a few minutes obtaining a given service without long waits, but medicine has not—and this has profound impacts on patients and their lives, said Shulman. The pandemic demonstrated that things can be different, but the shift won’t necessarily be easy.

At least for now, the administrative part of care in the home is tougher, Shulman said. “There are a lot of issues with preauthorizations, which turned out—at least in our market—to be different for hospital and home infusions, so you’re doubling the preauthorization times. And the payers often don’t understand why some of the treatment is in one place, and some in another,” he pointed out.

For safety reasons, an initial round of chemotherapy is given in the hospital to see if the patient has a reaction, Shulman described. If things go well, future rounds could be infused at home. Scans and other tests would still need to be performed in the hospital. During a question-and-answer session, Shulman and Chiang discussed how, currently, physicians still need to see patients in person, but a hybrid model could represent the future. To be sure, huge staffing and education challenges exist at a time when nursing shortages are already acute. And one has to hope, and assume, that health systems can overcome the challenge of integrating all this into the electronic health record.

None of these problems are trivial, given that medical staff are already taxed from burdens of the pandemic. But the bottom line, Shulman said, is that patients like care at home. Satisfaction scores increased. One barrier, however, is that patients may be charged higher out-of-pocket costs, and that is a problem that must be resolved. Given the capacity at infusion centers, he said, it’s worth doing.

“Treatment can take place at home with high patient satisfaction levels. It’s time-saving for them, and it can also free up the clinic and the infusion capacity,” Shulman said.

**Early Treatment Matters More Than Ever in Multiple Myeloma, Kumar Says**

**THE MULTITUDE OF OPTIONS** to treat multiple myeloma (MM) doesn’t change some key facts: The duration of a patient’s response to the first treatment will define the disease biology going forward, and how well the disease is managed early on matters a great deal, according to Shaji K. Kumar, MD, of the Mayo Clinic Cancer Center. He gave an update on MM management during the National Comprehensive Cancer Center (NCCN) 2022 Annual Conference.

Fortunately, results from the GRiFFIN trial are showing what’s possible. Results presented at the December 2021 meeting of the American Society of Hematology (ASH) showed positive outcomes after 24 months for newly diagnosed patients who took quadruplet therapy after an autologous stem cell transplant (ASCT). The combination—which added daratumumab to the usual triplet of lenalidomide, bortezomib, and dexamethasone (RVd)—led to better stringent complete responses (sCRs; 66.0% vs 47.4%) and higher minimal residual disease (MRD) negativity rates.

“This clearly appears to be translating into an improvement in progression-free survival (PFS),” Kumar said. “It’s too soon to start treating every patient with newly diagnosed, transplant-eligible MM this way; he noted, but “given the high rates of MRD negativity that we see with Dara-Rvd, this regimen is definitely one to consider for patients with high-risk multiple myeloma.”

What about patients who are not transplant eligible, or need to wait? The IFM 2009 study compared giving ASCT right away with no transplant, but additional doses of therapy. Although ASCT clearly offered better PFS, there was no comparable improvement in overall survival (OS), Kumar noted. Thus, “it is very reasonable to delay stem cell transplant to the time of first relapse.”

For these patients, daratumumab with lenalidomide and dexamethasone should be considered the standard, based on the MAIA study, Kumar said.

**ONGOING TREATMENT.** After initial treatment and lenalidomide maintenance, treatment choices are driven by whether patients are refractory to lenalidomide. Kumar explained. He shared a slide with multiple doublet and triplet options and explained that dexamethasone-containing triplets are now preferred. Prior treatments, age, comorbidities, frailty, and any lingering toxicity should be considered.

“In general, the approach—especially in the earlier lines of therapy—is to treat patients to maximum response, and then maintain them on at least 1 of the drugs from the combination until disease progression,” Kumar said. This is easier in the early lines of therapy, he acknowledged. Whether a patient is refractory on their initial therapy is a “key differentiator” that guides treatment going forward.

Selinexor, an XPO1 inhibitor, was approved in December 2020 for use with bortezomib and dexamethasone in patients who have had at least 1 prior therapy. Belantamab mafodotin, an antibody-drug conjugate that targets B-cell maturation antigen (BCMA), could be used to treat patients who have been refractory to other major drug classes, including protease inhibitors. Long-term data from the DREAMM-2 study found that median duration of response, OS, and PFS were 11.0 months, 13.7 months, and 2.8 months in heavily pretreated patients with relapsed/refractory (R/R) multiple myeloma.

A recent advance is the FDA approval in April 2022 of a second chimeric antigen receptor T-cell therapy for MM, ciltacabtagene autoleucel (cilta-cell), which also targets BCMA. In the CARITITUDE trial, results at 2 years in patients with R/R multiple myeloma showed that median PFS and OS were not reached and the sCR rate was 82.5%.
Kumar also reported on several clinical trials involving investigational therapies and new uses of existing therapies:

- Tisleltamab is a bispecific antibody that binds to CD3 on T cells and to BCMA on plasma cells. The MajesTEC-1 study explored dosing and reported early data at the ASH meeting in December 2021.
- Iberdomide is a novel CRBN E3 ligase modulator, or CELMoD, that is under development as a next-generation immunomodulatory agent. One-third of patients with R/R MM responded in a first-in-human trial presented at ASH.
- Venetoclax, studied for several years in MM after success in other blood cancers, had previously shown improvement in PFS. More recently, Kumar said, his study group showed that this benefit is seen in t(11;14) translocation, which is linked to the BCL-2 protein that venetoclax inhibits.

**CDK4/6 Inhibitors, SERDs, and More in NCCN Talk on Breast Cancer Updates**

**DESCRIBING THE LATEST UPDATES** from the National Comprehensive Cancer Network (NCCN) as tales of “escalation and de-escalation,” William J. Gradishar, MD, of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, offered an overview of guidelines for treatment of HER2-negative breast cancer during the NCCN 2022 Annual Conference.

NCCN guidelines are no longer “a group of monotherapy choices,” but selections that feature partners for endocrine therapy, he said. Gradishar also offered some updates in triple-negative breast cancer (TNBC).

“What is dominant in this partnership is CDK4/6 inhibitors, at least at the outset,” said Gradishar, who discussed the importance of the MONALEESA trials for ribociclib, especially the overall survival (OS) benefit seen in the MONALEESA-7 trial. MONALEESA-7, he said, was unique because it included premenopausal patients.

He also reviewed results for PALOMA-3, which found that OS was favorable for palbociclib and fulvestrant compared with fulvestrant plus placebo, regardless of a patient’s mutational status.

Among the questions to be addressed at the 2022 annual meeting of the American Society of Clinical Oncology is how long patients should stay on CDK4/6 inhibitors. Gradishar said that the MAINTAIN trial, as well as the PACE and TRINITY trials, will ask the question, “Whether or not after disease progression, is there merit in continuing a CDK4/6 inhibitor, either the same one or a different one?”

**SERDS.** Gradishar reviewed trials involving oral selective estrogen receptor degraders (SERDs). While fulvestrant is approved, newer-generation therapies are in development to offer an option for treating patients after CDK4/6 inhibitors. He spent time reviewing results from the phase 3 EMERALD trial comparing elacestrant vs standard of care: Elacestrant demonstrated superior inhibitors. He spent time reviewing results from the phase 3 EMERALD study prior therapy—[that is], you haven’t received prior chemotherapy for metastatic disease—you’re more likely to benefit. That group clearly had about a 7-month advantage in terms of overall survival.”

**IMMUNOTHERAPY.** Gradishar covered the major development of the year: Genentech’s voluntary withdrawal of the indication for atezolizumab after the IMPassion131 trial did not meet its primary end point in TNBC. However, he said, a lot of knowledge was gained from these trials, including an understanding of adverse effects and the role of testing in determining who should have checkpoint inhibitors.

**ANTIBODY-DRUG CONJUGATES.** The mechanism of ADCs involves attaching a small-molecule agent to an antibody with a linker to target a specific antigen on the tumor. Gradishar discussed the phase 3 ASCENT study involving sacituzumab govitecan (SG), which is now a preferred regimen for metastatic TNBC. Patients in ASCENT had at least 2 prior lines of therapy. SG targets TROP2, a cell-surface protein that is associated with aggressive tumor behavior but is hardly seen in normal tissue.

Results from ASCENT presented at the San Antonio Breast Cancer Symposium in December 2021 showed significant OS improvement with SG vs physician’s choice of treatment, with a near-doubling among patients aged at least 65 years (6.7 vs 12.1 months). The trial was halted early due to these responses. Asked to summarize the latest NCCN updates, Gradishar said there are some recommendations to intensify therapy when patients are higher risk, and to ease it in other cases. “We may not be giving endocrine therapy to everybody forever,” he said. “I think it is an issue that is really summarized by saying, ‘We’re getting better at tailoring our therapy, enhancing it for high-risk patients, and perhaps de-escalating it for those with lower risk of recurrence.’”

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**Incremental Steps Helpful but Not Enough to End Underinsurance Issue, Panelists Say**

**IN AMERICA, ONE CAN CONCEIVABLY** have health coverage, yet be unable to afford care or treatment. Three policy experts recently gave an update on the underinsurance crisis in the United States, in which the proliferation and the growth in size of health insurance deductibles relative to income leaves many exposed to medical debt, as well as to delayed or averted care.

The Commonwealth Fund defines one measure of “underinsured” as having a deductible that is equivalent to 5% or more of income. For 2020, the most recent year for which statistics are available, 28% of Americans with health insurance were underinsured, up from 19% a decade earlier, according to the Commonwealth Fund’s Vice President for Health Care Coverage and Access, told moderator Clifford Goodman, PhD, senior vice president, Comparative Effectiveness Research, The Lewin Group.
One recent change is guidance around preventive care than can be paid for on a pre-deductible basis using health savings account (HSAs) or HDHPs. When these were created as part of the 2003 Medicare Modernization Act, the statute included a safe harbor that allowed for costs of preventive care, but in 2004, the IRS took a very limited view on what counted as preventive care, Spangler said. Both the Smarter Health Care Coalition and the V-BID Center advocated for a change in that guidance, and in 2019, the Department of the Treasury released a notice that allows HSAs and HDHPs the flexibility to cover specified medications and services used to treat chronic diseases prior to meeting the plan deductible.

Employers and health plans have responded positively to this guidance, Spangler said. Surveys show that between 75% and 80% of employers are offering more chronic disease prevention on this basis.

About 14 specific types of high-value, low-cost items and services that are now allowed under this new guidance include insulin, glucose monitoring, asthma drugs, statins, and blood pressure monitors, and the impact on premiums has been negligible, said Spangler.

With that success in hand, the Smarter Health Care Coalition and the V-BID Center are now asking the IRS to recognize that the list is meant to be used as an illustration of low-cost, high-value care, and not a finite one. The goal is for a plan or employer to have even more flexibility about what can be offered on pre-deductible basis.

In the end, the panel agreed that while incremental fixes alone won’t be enough to solve the entire problem of underinsurance. “Ideally, we all owe it to ourselves to work toward a system where we are thinking about the total cost of care but also integrating the concepts around social determinants of health and health equity. It’s vitally important, but we have no choice but to move toward incremental fixes,” said Niles.


CONTINUED ON SP186 »

340B, Biosimilars, and More in the Future of Specialty Pharmacy

A BATTLE IS GOING ON for control of the specialty patient, according to Adam J. Fein, PhD, CEO of Drug Channels Institute. During a general session on day 2 of Asembia’s Specialty Pharmacy Summit, held May 2-5 in Las Vegas, Nevada, Fein and Doug Long, MBA, vice president of industry relations at IQVIA, discussed trends in the specialty pharmacy market in the United States. Pharmacy benefit managers (PBMs) still dominate specialty dispensing, Of the top 5 specialty pharmacies by revenue in 2021, 4 are PBMs: CVS Health, Express Scripts, OptumRx, and AllianceRx Walgreens Prime. (However, as of late 2021, AllianceRx Walgreens Prime no longer had PBM ownership; starting in June 2022, it will be known as AllianceRx Walgreens Pharmacy.) These 4 specialty pharmacies had about two-thirds of specialty drug dispensing revenues in 2021. So few dominate the space as a result of strategies in the industry. “Manufacturers have limited the number of specialty pharmacies that they allow their products to go through,” Fein said. “For the most part, they have limited them to pharmacies that are owned by payers or PBMs.”

When manufacturers limit their products to independent pharmacies, those pharmacies get acquired by PBMs, he added.

In addition, payers limit where patients can go, often sending patients to the specialty pharmacy owned by their PBM. This has created “quite a lot of market-access challenges for the hospitals,” said Fein.

A big driver of specialty pharmacy profits has been the 340B program, but that has changed enormously, Fein said. As of April 2022, more than half of the pharmacy locations in the United States were 340B-contracted pharmacies.
Know cancer’s next move

Signatera is prognostic and predictive of treatment benefit in early-stage CRC

Data presented at ASCO Gastrointestinal Cancers Symposia in January 2022 included an interim analysis from the largest MRD-guided trial indicating that personalized MRD testing can guide adjuvant treatment decisions.

Key takeaways
- MRD-positive CRC patients at 4w post-op benefit significantly from chemo (HR 8.8-9.4)
- MRD-negative CRC patients at 4w post-op do NOT benefit significantly from chemo

Scan or visit www.natera.com/events/asco-gi-2022 to learn how a tumor informed approach optimizes patient management

References
1 Kotaka et al. Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan. ASCO GI 2022.
Between those pharmacies and the 340B hospitals and other entities, there are 160,000 relationships in 340B. “And you might think, ‘Well, that’s a lot of diversity,’” Fein said, but actually, 73% of those relationships are held by 5 companies: CVS Health, Walgreens, Walmart, Express Scripts, and OptumRx. And collectively, those 5 companies earn about $3.2 billion in gross profits from 340B, he said. However, 16 manufacturers recently pulled back from 340B pricing from contract pharmacy networks, with one of the most dramatic effects being a drop in the rate of growth of 340B. Over the last 4 years, the growth in value of 340B purchases for mail pharmacies had been averaging more than 50% annually. However, after the manufacturers made this change, the growth rate of new purchases decreased by 20%.

“We haven’t seen the full impact of this yet, but it will have a big impact on contracting,” Fein said.

Emerging profit drivers for specialty pharmacy include:

- co-pay maximizers;
- nonbiologic specialty generics;
- white bagging; and
- pharmacy benefit biosimilars, such as adalimumab (Humira) biosimilars coming to market in 2023.

Finally, Fein looked at the vertical integration happening in the market. Although consolidation has occurred in the last 3 to 5 years, so has some deconsolidation; some companies have found that vertical integration “is not a panacea and is a lot harder than it looks,” noted Fein. Centene and Prime Therapeutics have both pulled back from the pharmacy business and Humana has leaned away from some vertical integration efforts, Fein said. But what may have gone under the radar during the pandemic is that hospitals and health systems have been on a “massive vertical integration kick,” buying up a lot of doctors’ practices, he pointed out.

In the last 2 years, more than 50,000 physicians have moved from independent practices to practices owned by hospitals, occurring particularly frequently in areas with 340B pricing, Fein said.

Hospitals and health systems have also begun to steer patients to their own specialty pharmacies, especially in health systems with larger specialty pharmacies. Vertically aligned channels pose novel market-access risks for new products, companies, and pharmacies trying to enter the market, Fein said.

“We saw a little bit of a pause on some of these things during the pandemic,” he said. “But I think now...we’re gonna be bringing it all back. It’s going to be a very, very challenging and highly competitive world.”

In the session’s second half, Long gave a presentation that expanded on his keynote address at the Academy of Managed Care Pharmacy annual meeting. He reminded the audience that for years, specialty medicines have been closing in on traditional medicines for share of sales. In February 2022, the split was 49.9% specialty and 50.1% traditional, and he expected specialty to overtake traditional in a month or two. Specialty would have represented the split was 49.9% specialty and 50.1% traditional, and he expected specialty

Biden Administration May Make a Push for Health Care Priorities Ahead of Midterms

**Coverage, Equity, and Value-Based Payments** are critical areas of focus for the Biden administration’s health care agenda leading up to the midterm elections, according to 3 experts from Avalere who gave one of the final presentations at Asembia’s Specialty Pharmacy Summit, held May 2-5 in Las Vegas, Nevada.

During his 2022 State of the Union address, President Biden laid out his health care agenda and its priorities, explained Ryan Urgo, managing director of Avalere. Those priorities were:

- allowing HHS to negotiate drug prices, a goal that remains at the forefront;
- making permanent the enhanced Affordable Care Act (ACA) premium subsidies that are set to expire at the end of this year;
- securing funding for pandemic-related activities;
- focusing on cancer research through the reigned Cancer Moonshot initiative; and
- tackling health equity, which is a theme throughout the priorities.

Another area of focus is passing a so-called “skinny” version of the Build Back Better Act (BBBA), which the Senate failed to pass. “The tortured BBBA conversations are now emerging in a narrower context,” Urgo explained.

Part of the reason for a skinny BBBA is that the administration feels pressure to secure a big political win in the run up to the midterm elections, according to 3 experts from Avalere who gave one of the final presentations at Asembia’s Specialty Pharmacy Summit, held May 2-5 in Las Vegas, Nevada.

According to Urgo, Democrats want to avoid unwelcome Republican commercials about premium increases ahead of what is already going to be a difficult midterm election season. They may enact a temporary or permanent extension of enhanced subsidies.

Climate policy is also likely to be included in the skinny BBBA because there is broad consensus around it. In addition, changes that roll back the corporate and individual tax cuts of the Trump administration will probably be part of the bill.

Finally, drug pricing will be another part of the skinny BBBA. “The political popularity of drug pricing can’t be understated,” Urgo said. “So, that continues to be at the forefront of an emerging deal.”

The drug pricing priorities in a skinny version of the bill are likely to be Medicare negotiation, inflation-based rebates, and a Part D redesign. This deal will need to focus on the hold-out senators; specifically, Senator Joe Manchin, D-West Virginia, has said he sees a path for a deal, but he wants a focus on inflation with all revenue raised to be dedicated to a deficit reduction.

Whether or not this deal can get done remains to be seen, but Urgo and his colleagues think talks have begun in earnest, although they won’t be publicized much. However, time for negotiation is limited, according to Urgo. If nothing
The United States Is Entering Round 2 of Biosimilar Activity, Says Cardinal Health’s Oskouei

A KEY PROMISE OF BIOSIMILARS is to reduce costs, and right now the drugs that either have biosimilars approved or in the pipeline are some of the most expensive on the market, said Sonia Oskouei, PharmD, vice president of biosimilars for Cardinal Health, during a session at Asembia’s Specialty Pharmacy Summit, held May 2-5 in Las Vegas, Nevada.

Early in her presentation, Oskouei showed a slide with the top 20 drugs by overall expenditure in 2021. At the top was Humira, which will face competition from at least 7 adalimumab biosimilars in 2023. Also in the top 10 were Lantus (insulin glargine), which already has 2 approved biosimilars, and Enbrel (etanercept), which also has 2 approved biosimilars, although they won’t come to market until 2024.

Other drugs in the top 10 that don’t have approved biosimilars yet, but that have products in the pipeline, are Stelara (ustekinumab) and Keytruda (pembrolizumab).

The latest estimates show that aggregate savings for biosimilars could exceed $133 billion by 2025, Oskouei said. In 2020, biosimilars drove $8 billion in savings.

The oncology space has been hugely successful for biosimilars. Not only do 17 of 35 FDA-approved biosimilars have oncology indications, but adoption has been strongest among the oncology biosimilars. Biosimilars for filgrastim, bevacizumab, rituximab, and trastuzumab have 92%, 77%, 72%, and 61% market share, respectively. Despite those successes, “there are still barriers to adoption, broadly speaking,” Oskouei said.

Infliximab biosimilars, for instance, have reached only 37% market share despite the first product launching in 2016, and the sole eteopetin alfa biosimilar has reached only 55% market share despite launching in 2018.

Cardinal Health surveys that have gauged provider perceptions and experience with biosimilars have found oncologists to be the most comfortable. Two-thirds of oncologists said they feel comfortable both with starting new patients on biosimilars and switching existing patients from the originator product to a biosimilar.

The future pipeline for biosimilars includes agents for new therapeutic areas:

- Eylea, which treats age-related macular degeneration, macular edema, and diabetic retinopathy, may have 7 aflibercept biosimilars in 2023 and 2024.
- Stelara, which treats plaque psoriasis and psoriatic arthritis, may have 5 ustekinumab biosimilars in 2023 and 2024.
- Simponi, which treats rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, may have a golimumab biosimilar in 2024.
- Prolixa, which treats osteoporosis, hypercalcemia, and bone problems in patients with cancer, may have 5 denosumab biosimilars in 2022.

“IT’S LIKE WE’VE HAD ROUND 1 of biosimilar activity in the United States, and now we’re about to enter round 2, which is this whole expansion of therapeutic areas [and] product product types.”

—Sonia Oskouei, PharmD, vice president of biosimilars, Cardinal Health

Overall, the number of biologics facing biosimilar competition will more than double by 2026 based on what is in the pipeline.

“It’s like we’ve had round 1 of biosimilar activity in the United States, and now we’re about to enter round 2, which is this whole expansion of therapeutic areas [and] product types,” Oskouei said.

Part of round 2 is when the adalimumab biosimilars come market to in 2023, a “monumental year” in Oskouei’s opinion because Humira is the world’s top-selling drug. Amgen’s product, Amjevita, will launch first, in January 2023, and have a 6-month lead on the rest of the approved biosimilars. Still more adalimumab biosimilars are seeking approval.

Cyltezo is the only adalimumab biosimilar that was granted interchangeability status by the FDA, but others are seeking the designation.

Humira’s situation is unique among the products with biosimilars. When it originally launched, it was a low-concentration version, but AbbVie submitted a supplemental biologics license application for a high-concentration, citrate-free version. The approved biosimilars are all for the low-concentration version, but several manufacturers are seeking to develop high-concentration versions.

There is debate about the interchangeability for adalimumab biosimilars, Oskouei said. An interchangeable adalimumab biosimilar is based on the low-concentration version, is it also interchangeable with the high-concentration version?

In addition to the 7 adalimumab biosimilars that have been approved but kept off the market so far because of patent challenges and litigation, 2 etanercept biosimilars have been approved but are unable to launch in the
United States. Although biologics exclusivity is only supposed to last 12 years, Humira and Enbrel have both been able to extend this exclusivity. By the time the adalimumab biosimilars come to market in 2023, Humira will have had exclusivity for more than 20 years. If the etanercept biosimilars stay delayed until a 2029 launch, then Enbrel will have had exclusivity for more than 30 years, Oskouei noted.

“And so, the patent process and these exclusivity periods really can have a significant role on when these products come to market,” Oskouei said. “In fact, this is what’s driving quite a bit of policy discussions; of economists’ discussions on how can we bring lower-cost, high-quality alternatives to market quicker; and [of talks to] make sure that any exclusivity period granted to an innovator product is on the basis of true innovation vs seeking to delay competition.*

Of the FDA-approved therapies, there are 4 CD19-targeting therapies:

- Axicabtagene ciloleucel (axi-cel; Yescarta) to treat adults with R/R LBCL or adults with follicular lymphoma (FL), both after a 2 lines of systemic therapy
- Bruenabtagene autoleucel (brx-cel; Tecartus) to treat adults with R/R mantle cell lymphoma (MCL) or R/R ALL
- Lisocabtagene maraleucel (liso-cel; Breyanzi) to treat adults with R/R LBCL after a 2 lines of systemic therapy
- Tisagenlecleucel (tisa-cel; Kymriah) to treat patients ≥ 25 years with R/R B-cell precursor and adults with R/R LBCL after a 2 lines of systemic therapy

Of the FDA-approved therapies, there are 2 B-cell maturation antigen (BCMA)–targeted therapies. Both idecabtagene vicelucel (ide-cel; Abecma) and ciltacabtagene autoleucel (cilta-cel; Carvykti) are approved to treat adults with R/R MM after a 4 prior lines of therapy.

Looking specifically at the pivotal trials for the indolent lymphomas—brex-cel for MCL, axi-cel for FL, and tisa-cel for FL—Mahmoudjafari said that the responses were very durable in a patient population that is historically difficult to treat.

In the future, CAR T-cell therapy won’t only be a treatment for hematologic malignancies, she said. They’re being studied in solid tumors now and while the data is immature, it’s promising. The global CAR T-cell therapy market was $449.6 million in 2021, and it is expected to grow 35% to nearly $3.8 billion in 2028.

Another future development for CAR T-cell therapy is the study of allogeneic CAR T-cell treatments, which are considered “off the shelf.” The benefit of these therapies is that large quantities can be made from 1 donor and the treatment is on demand. The wait times with current CAR T-cell therapies will go away.

The finances remain a challenge. Is it possible to safely administer CAR T-cell therapy in the outpatient setting? Doing so would be in everyone’s financial interest, but it would require a strong outpatient infrastructure, said Mahmoudjafari. Moving to the outpatient setting would also require the patient and caregiver being up to speed on monitoring for toxicities and knowing a quick way to reach the care team. And members of the care team need to be available during off hours if a patient is experiencing toxicities in the middle of the night.

The cost of these therapies range from $373,000 to $465,000, but that is just for the CAR T. There are additional costs for leukapheresis and chemotherapy before infusion, plus hospitalization, intensive care admission, tocilizumab treatment, and long-term toxicity management, she pointed out. Overall, the actual cost of treatment ranges from $500,000 to $1 million per patient.

Initially, Medicare was reimbursing CAR T-cell therapies at a loss for the institution and commercial payers don’t have a common payment path, although single-case rate agreements have been established. However, this all remains unsustainable as volumes increase and more patients are treated with more CAR T-cell therapies.

Scientifically, CAR T-cell therapy remains an exciting opportunity. Mahmoudjafari pointed to Emily Whitehead and noted “she’s the reason and her cure’s the reason we have CAR T-cell therapies in their current state.” Whitehead was diagnosed with ALL at age 5 and was the first pediatric patient in the world to receive the treatment. Now, she’s 10 years cancer free. If Whitehead hadn’t made it, CAR T-cell therapies might not have made it either.

“So, CAR T-cell therapy remains an exciting therapeutic opportunity—when you’re not thinking about how much costs,” Mahmoudjafari said. ●

REFERENCES
BeiGene is committed to a thoughtful approach to drug pricing and is looking to partner with access stakeholders across the US healthcare ecosystem.

- We engage customers in meaningful partnerships that drive access and affordability
- We focus on bringing important new medicines to areas of high unmet need
- We believe in demonstrating and proving value through HEOR and real-world customer data

How can BeiGene help bring value to you? Learn more about BeiGene at BeiGene.com and the treatment areas we are focused on at BeiGeneVirtualExperience.com.
COA Creates Standing Committee on Humanitarian Aid

THE COMMUNITY ONCOLOGY ALLIANCE (COA) has launched a new standing Humanitarian Aid Committee, which will coordinate aid for those affected by war, natural disasters, and other crises. The group’s first effort will be supporting 4 medical charities that are assisting those affected by the war in Ukraine: Americares, Direct Relief, Doctors Without Borders, and International Medical Corps. COA has created a webpage for the committee. A statement from COA released April 18 says that although the group’s mission is based in the United States, “the greater oncology community has a responsibility to act and engage on a global scale during times of crisis.” COA has worked with other groups on hurricane relief efforts and on the global effort to keep patients safe during the COVID-19 pandemic.

“Cancer isn’t localized to one country or region of the world, and it certainly doesn’t become less important during times of crisis. As people are displaced and seek shelter, it’s our responsibility to help them continue treatment. Cancer doesn’t stop during an emergency. COA’s mission to fight cancer doesn’t either.”

—Mark Thompson, MD, medical director of public policy, Community Oncology Alliance

The frequency of such events makes a standing committee necessary, the group said. “Cancer isn’t localized to one country or region of the world, and it certainly doesn’t become less important during times of crisis,” said Mark Thompson, MD, COA’s medical director of public policy. “As people are displaced and seek shelter, it’s our responsibility to help them continue treatment. Cancer doesn’t stop during an emergency. COA’s mission to fight cancer doesn’t either.” The Humanitarian Aid Committee will include both volunteers and staff. In addition to Thompson, current members are:

- Stephen “Fred” Divers, MD; Genesis Cancer & Blood Institute; American Oncology Network
- Nicolas Ferreyros; COA
- Lucio Gordan, MD; Florida Cancer Specialists & Research Institute
- Rich Ingram, MD; Shenandoah Oncology
- Drew Lovejoy; COA
- Alti Rahman, MHA, MBA; Oncology Consultants
- Fred Schnell, MD; Cancer Center of Middle Georgia; COA chief medical officer
- Iuliana Shapira, MD; Regional Cancer Care Associates
- Emily Touloukian, DO; Coastal Cancer Center

AON’s Chang Studies Hospital vs Community Setting Care Costs for Patients With Pancreatic Cancer

PATIENTS WITH COMMERCIAL INSURANCE who have metastatic pancreatic cancer have a lower overall cost of care when treated in the community vs hospital setting. The data are from a recent study coauthored by Melody Chang, MBA, RPh, BCOP, vice president of pharmacy operations at American Oncology Network (AON).

The findings, presented at the Academy of Managed Care Pharmacy 2022 annual meeting in Chicago, showed that the total cost of care is 29% lower in the community setting than in the hospital. The study addressed a research gap by evaluating the cost of care for commercially insured patients who received National Comprehensive Cancer Network (NCCN) category 1 preferred regimens.

Differences in cost of care were most pronounced for patients who received first-line treatment with FOLFIRINOX (leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin). The smallest difference was seen for patients who received first-line gemcitabine monotherapy.

“OneOncology Forms Partnership With Employer Direct Healthcare

OneOncology, a national platform for independent community oncology practices, announced a partnership whose goal is to overhaul delivery and reimbursement for cancer care.

According to a joint statement from EDH and OneOncology on March 15, the partnership is explicitly aimed at improving community-based access to precision medicine, clinical trials, and new therapies such as chimeric antigen receptor T-cell therapy, while lowering costs for employers through episode-based payment models.

“OneOncology’s leading network of community oncology practices significantly expands our ability to provide patients access to expert cancer care close to home,” stated Carolina Escobar, MD, chief medical officer for EDH. “As a physician-led organization that has made extensive investments in clinical excellence, precision medicine, clinical research, and value-based care, OneOncology represents an ideal partner to advance our mission.”

Beyond expanding patient access to innovative therapies, the partnership will serve as a platform to bring more patient-centric, value-based care programs to patients.

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“Community oncology is the definition of value-based care,” said Jeff Patton, MD, CEO of OneOncology. “In addition to the benefits of improved patient access and experience, community oncology provides material cost savings compared with hospital-based care. This is further enhanced by the value-enabling tools and payment models we are developing at OneOncology to help combat rising health care costs.”

OneOncology, which now serves more than 700 cancer care providers across more than 260 sites of care, will complement EDH’s growing network of National Cancer Institute–designated cancer centers. In a statement, the partners said this will allow employees to gain access to high quality cancer care close to home.

“Employer Direct Healthcare’s solution is exactly what oncology care needs,” added Davey Daniel, MD, chief medical officer at OneOncology. “Their truly comprehensive offering, including longitudinal navigation and support, extensive center of excellence network, and expert second opinions, provides a differentiated patient-centered experience. We look forward to collaborating with EDH to advance care delivery, including development of optimal clinical pathways, patient experience measures, and access to clinical trials.”

Moffitt Team Finds Potential CAR-T Target for Solid Tumors

The most recent reconciliation of OCM data, the practice announced in April, the OCM, a value-based alternative payment model developed by the Center for Medicare and Medicaid Innovation (CMMI), was launched in 2016 to give cancer care practices a vehicle to move away from fee-for-service reimbursement. The agency offered practices monthly payments to care for each patient as well as performance-based payments based on exceeding benchmarks of quality and cost-effectiveness. In turn, practices had to provide extra services, such as care navigation, access to extended hours, advanced care planning, and 24/7 access to records.

In a statement, FCS Chief Executive Officer Nathan H. Walcker, MBA, said the ranking came as no surprise.

“Our value-based practice initiatives at FCS are programmatic, intentional, and thoughtfully designed to be organized squarely around the patient, yielding consistent results that outpace industry benchmarks and make good on our commitment to prioritize patient outcomes and quality,” he said.

FCS provides care for more than 22,000 OCM beneficiaries annually and has recorded more than $140 million in Medicare savings since 2016. In the last 6-month performance period of 2021, FCS saved Medicare $31.7 million. FCS Senior Director of Value-Based Care TR Strickland, MBA, said OCM participation has allowed FCS to make "substantial strides and investments in our strategic focus on value-based programs." FCS has worked with accountable care organizations, managed service organizations, and commercial/Medicare Advantage payers throughout Florida.

The practice reports on at least 50 quality-of-care metrics per performance period to help measure OCM effectiveness. Of those 50, FCS received exceptional scores in the areas of pain assessment, limiting emergency department visits/inpatient hospital stays, prevention/screenings, appropriate utilization of hospice and patient-reported experience, and patient satisfaction.

CMMI’s most recent report also shows that FCS hospital admissions were 8% lower than those of other OCM-enrolled practices. Further, in that same period, FCS had 21% fewer cases of emergency department visits not leading to admission.

FCS Chief Medical Officer of Therapeutics and Analytics Lucio N. Gordan, MD, attributes the organization’s success with OCM and other value-based programs to prioritizing a “well-built” infrastructure.

“At FCS, our guiding principle is to put the patient first in everything we do; we are laser-focused on providing world-class cancer care while reducing the overall cost of that care for our patients,” he said. “In the long run, quality care doesn’t increase costs, as quality delivered at the right time in the most appropriate venue often decreases overall costs and prevents adverse events.”

Moffitt Team Finds Potential CAR-T Target for Solid Tumors

INVESTIGATORS FROM MOFFITT CANCER CENTER in Tampa, Florida, have published results identifying a potential target for chimeric antigen receptor (CAR) T-cell therapies in solid tumors, which could be a step toward bringing this game-changing treatment beyond blood cancers.

In Molecular Cancer Therapeutics, a publication of the American Association of Cancer Research, the Moffitt team presents the identification of OR2H1, an olfactory receptor that they demonstrate inhibits growth in lung and ovarian tumors.

The creation of individualized CAR T-cell therapy involves genetic modification of a patient’s own T cells, which are collected through apheresis and then put through a manufacturing process; the cells are modified to include a gene for the T-cell receptor that allow them to hunt down the cancer in the body when the treatment is infused back into the patient.

Finding tumor markers that will make this process work in solid tumors has been a huge challenge. The Moffitt team, led by Jose Conejo-Garcia, MD, PhD, has zoomed in on proteins—the olfactory receptors—that are expressed in the nose but are also found in many solid tumors and very few normal cells.

The investigators created CAR T cells specific to the OR2H1 protein, which were able to kill lung and ovarian cells that expressed OR2H1 but did nothing to healthy cells. The same effect was seen in mice implanted with human tumors with varying levels of OR2H1.

“Our work demonstrates the applicability of this therapy to a wide variety of patients, given the expression of OR2H1 in a subset of solid tumors across multiple histologies, including high-grade serous ovarian cancers, lung carcinoma, cholangiocarcinoma, prostate cancer and ovarian cancers of multiple other histologies,” Conejo-Garcia, chair of Moffitt’s Department of Immunology, said in a statement. “Targeting a molecule that is not expressed in vital tissues would allow us to further engineer T cells to overcome immuno-suppression at tumor beds, if needed.”
Medical World News® is a first-of-its-kind 24-hour online program for health care professionals, by health care professionals. The site provides video editorial content on a variety of cutting-edge topics delivered through a livestream and on demand for all health care stakeholders, offering the latest news and information in an easily digestible, one-stop-shop format.

AFTER HOURS: Biosimilar Whiskey

As high-end whiskey can take decades to develop and cost thousands of dollars per bottle, a novel process created by Sarfaraz K. Niazi, PhD, adjunct professor of biopharmaceutical sciences and advisory board member for the Center for Biosimilars, seeks to circumvent the time-consuming, expensive process by developing whiskey with an approach similar to the biosimilar process used to make low-cost versions of popular therapies. Dr Niazi speaks with The American Journal of Managed Care® on the distillation process, how the “biobetter” whiskies compare with their reference products, and what the future considerations are for the alcohol industry.

AFTER HOURS: Dirt-Biking Physician

After moving to Las Vegas, Nevada, 30 years ago, Steve Evans, MD, chief medical officer of SilverSummit at Centene, became enamored with the sightseeing, nature, and adventure brought by dirt biking—a hobby he continues to enjoy safely with family and friends to this day. Dr Evans spoke with The American Journal of Managed Care® about the trails and mountains he’s seen and how the sport allows him to decompress from a demanding career. He does offer some advice: “Don’t do anything stupid.”

BEHIND THE SCIENCE: Equitable Care in Dermatology

Equitable care has been a long-standing issue in dermatology because of a lack of diversity in clinical trials and management criteria that fail to account for different skin types. Key opinion leaders at the 2022 American Academy of Dermatology Annual Meeting spoke with The American Journal of Managed Care® about factors that contribute to health disparities for minority populations and current efforts to address these concerns in the field.
FDA Approves Amneal Pharmaceuticals’ Avastin Biosimilar, Bevacizumab-maly

ON APRIL 13, AMNEAL PHARMACEUTICALS announced that the FDA had approved the company’s Biologics License Application for bevacizumab-maly, a biosimilar referencing the originator product (Avastin). Amneal said the product will be sold under the name Alymsys. It is the third bevacizumab biosimilar approved in the United States, and the second of 3 US biosimilars that Amneal expects to see approved this year.

Earlier this year, Amneal received approval of filgrastim-ayow (Releuko) which references Neupogen. The firm’s pegfilgrastim biosimilar referencing Neulasta is currently under FDA review.

Bevacizumab-maly was developed by mAbxience. The vascular endothelial growth factor inhibitor is indicated for the treatment of:

- metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment;
- metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line regimen containing a bevacizumab product;
- nonsquamous non–small cell lung cancer, for first-line treatment in combination with carboplatin and paclitaxel;
- recurrent glioblastoma in adults;
- metastatic renal cell carcinoma in combination with interferon alfa;
- persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and carboplatin;
- epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with paclitaxel.

Avastin, made by Roche, brought in $7 billion for the company in 2018, according to Forbes.

REFERENCES

Nivolumab-based Combs Approved in First-line Advanced ESCC

ON MAY 27, FDA APPROVED 2 combinations featuring nivolumab, including a dual immunotherapy combination, for first-line treatment for adult patients with unresectable, advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) regardless of PD-L1 status.

The approvals were announced by Bristol Myers Squibb (BMS), maker of the 2 immunotherapy treatments approved for 1 combination: nivolumab (Opdivo), the first approved PD-1 immune checkpoint inhibitor, and ipilimumab (Yervoy), which activates the immune system by targeting CTLA-4.

FDA’s decision covers the use of the dual immunotherapy as well as a combination of nivolumab with fluoropyrimidine- and platinum-containing chemotherapy in these ESCC patients. According to the American Cancer Society, an estimated 20,640 new cases of esophageal cancer will be diagnosed in the United States in 2022, and 16,410 deaths will result from the disease this year.

Treatments that include nivolumab are now approved for 5 indications in upper gastrointestinal cancers, according to BMS. “We recognize the need that exists for many patients facing upper gastrointestinal cancers, including advanced or metastatic esophageal squamous cell carcinoma, and we are focused on our goal to bring forward new treatment options with proven survival benefits regardless of PD-L1 status and histology.” Adam Lenkovsky, senior vice president and general manager, US Cardiovascular, Immunology, Oncology, Bristol Myers Squibb, said in the statement.

“Today’s approvals bring 2 first-line immunotherapy-based treatment options at once, (nivolumab) in combination with chemotherapy and (nivolumab plus ipilimumab) as the first dual immunotherapy option, to newly diagnosed patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, further building on the role of (nivolumab)-based regimens in upper gastrointestinal cancers.”

Approval is based on results of the phase 3 CheckMate-648 trial, presented a year ago during the 2021 annual meeting of the American Society of Clinical Oncology. The trial examined nivolumab in combination with chemotherapy (321 patients) and nivolumab plus ipilimumab (325 patients), each compared with chemotherapy alone (324 patients).

NIVOLUMAB PLUS CHEMO. Nivolumab with chemotherapy demonstrated superior overall survival (OS) compared with chemotherapy alone, both in all randomized patients, with a hazard ratio (HR) of 0.75 (95% CI: 0.61-0.90, P = .0021) and in patients whose tumors express PD-L1 (≥1%), HR 0.54 (95% CI: 0.41-0.71, P = .0011); the latter was a primary end point. In all randomized patients, the median OS was 13.2 months with nivolumab in combination with chemotherapy vs 10.7 months with chemotherapy alone; in patients whose tumors express PD-L1, median OS was 15.4 months for nivolumab with chemotherapy vs 9.1 months for chemotherapy alone.

DUAL IMMUNOTHERAPY. The nivolumab-ipilimumab combination also improved OS compared to chemotherapy in all-randomized patients, a secondary end point, with HR 0.78 (95% CI: 0.65 to 0.95, P = .0110) and in patients whose tumors express PD-L1 (≥1%), a primary end point, with HR 0.64 (95% CI: 0.49-0.84, P = .0010). Median OS was 12.8 months with the immunotherapy combination vs 10.7 months with chemotherapy alone in all randomized patients and 13.7 months for the combination vs 9.1 months for chemotherapy alone for those with tumors that express PD-L1.

ADVERSE EVENTS. During the study, nivolumab and/or chemotherapy were stopped in 39% of patients and delayed in 71% due to adverse events (AEs); serious AEs occurred in 62% of patients taking nivolumab with chemotherapy. Most common serious AEs for those taking nivolumab with chemotherapy were pneumonia, dysphagia, esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). Five patients died during the study while being treated with nivolumab in combination with chemotherapy.

In the dual immunotherapy arm, nivolumab and/or ipilimumab were discontinued in 23% of patients; they were delayed in 46% of patients due to AEs. Serious AEs were seen in 69% of patients receiving nivolumab plus ipilimumab. The most frequent serious AEs in these patients were pneumonia, pyrexia, pneumonitis, aspiration pneumonia, dysphagia, abnormal hepatic function, decreased appetite, adrenal insufficiency, and dehydration (2.5%). Five patients died during the study while being treated with dual immunotherapy.

REFERENCES

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FDA Approves Enhertu for Use in Metastatic Breast Cancer

ADULT PATIENTS LIVING WITH unresectable or metastatic HER2-positive breast cancer have a new treatment option in their armamentarium following the FDA’s May 5 approval of trastuzumab deruxtecan (Enhertu; AstraZeneca/Daiichi Sankyo) in several settings, including earlier in the course of disease, based on final data from the phase 3 DESTINY-Breast03 trial.1

In 2021, breast cancer was the most common cancer diagnosed in the United States, at an estimated 284,200 new cases.2 Now, Enhertu can be utilized as adjuvant or neoadjuvant therapy by individuals whose disease recurs within 6 months of finishing treatment with another anti-HER2 therapy, as well as in cases of metastatic disease. The chemotherapy is already approved for use in the setting of treatment failure on 2 or more anti-HER2–based regimens among those with disease metastasis.3

“Enhertu is already established in the later-line treatment of patients with HER2-positive metastatic breast cancer, and we are thrilled that with this approval, patients in the United States will now be able to access the transformative potential of Enhertu earlier in their treatment,” said Dave Fredrickson, executive vice president, Oncology Business Unit, AstraZeneca, in a news release announcing the approval. “We look forward to bringing this important, potentially paradigm-shifting medicine to even more patients across the globe in an earlier setting as quickly as possible.”

The approval follows the March 2022 release of interim data from DESTINY-Breast03, which evaluated progression-free survival (PFS), overall survival, objective response, and safety among patients with metastatic breast cancer (mBC); they were randomized 1:1 to trastuzumab deruxtecan or trastuzumab emtansine (T-DM1), the current standard of care in HER2-positive mBC. Those data demonstrated superior outcomes from trastuzumab deruxtecan, including PFS and an overall response rate that were more than twice as high, at 75.8% vs 34.1% and 79.7% vs 34.2%.4

Enhertu first received an accelerated approval from the FDA in December 2019, which was based on data on tumor response rate and response duration from the phase 2 DESTINY-Breast01 trial. That was followed by a Breakthrough Therapy Designation in October 2021 and a Priority Review in January 2022.

This newest approval comes via the FDA’s Real-Time Oncology Review program. The news release also noted the inclusion of Enhertu as a Category 1 recommendation in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for persons who have local or regional stage IV HER2-positive breast cancer.

Among the DESTINY-Breast03 findings upon which the FDA based its decision are the 72% (HR, 0.28; 95% CI, 0.22-0.37; P < .0001) reduced risk of disease progression or death vs trastuzumab emtansine, as well as the lack of grade 4/5 treatment-related interstitial lung disease events.

“Today’s FDA approval highlights the importance of the FDA’s accelerated pathway that allows for earlier approval of medicines to treat serious medical conditions such as breast cancer,” stated Ken Keller, global head, oncology business, and president and CEO, Daiichi Sankyo. “Data from DESTINY-Breast03 not only confirmed the results of DESTINY-Breast01, but also demonstrated the superiority of Enhertu in prolonging PFS compared [with] T-DM1 in an earlier setting of HER2-positive mBC.”

REFERENCES

FDA ACTIONS | MANAGED CARE UPDATES

Clinical, Economic Benefits of Pegfilgrastim Biosimilars as Prophylactic Against Febrile Neutropenia

USE OF BIOSIMILAR PEGFILGRASTIM as a prophylaxis in patients with cancer and a high risk of chemotherapy-induced neutropenia can save money, according to a study published in Future Oncology. The researchers used real-world data to assess the cost-effectiveness of using pegfilgrastim vs filgrastim using a Markov model with a lifetime horizon. Febrile neutropenia (FN) results in approximately 60,000 patients with cancer being hospitalized annually and costs an estimated $28,000 per admission in the United States.

While biologics are an important treatment for cancer, they are expensive. “Biosimilar versions of these drugs represent an opportunity to reassess the value of the treatment and consider a change in reimbursement practice and clinical management protocols,” the authors explained. “To date, the approval of biosimilar versions of G-CSFs [granulocyte colony-stimulating factors] has been the most striking example of this effect.”

The authors created an economic model to assess the cost-effectiveness of primary prophylaxis with pegfilgrastim vs filgrastim for patients at high (>20%) and intermediate (10%-20%) risk of FN. There were 5 strategies: pegfilgrastim biosimilars, pegfilgrastim reference in a prefilled syringe, pegfilgrastim reference in an on-body injector, filgrastim biosimilars, and filgrastim reference. In both the high-risk and intermediate-risk groups, biosimilars for pegfilgrastim and filgrastim outperformed the reference products in quality-adjusted life-years, (QALYs), life-years (LYs), and FN events.

Comparing the 2 biosimilars, the authors found:

- In the high-risk group, pegfilgrastim had 8.02 QALYs, 9.52 LYS, and 0.73 FN events vs 7.73 QALYs, 9.12 LYS, and 1.16 FN events for filgrastim per patient treated.
- In the high-risk group, the total cost of pegfilgrastim biosimilar resulted in $5703 savings over filgrastim biosimilar, with savings largely driven by reduced FN incidence and a lower cost of inpatient FN management.
- In the intermediate-risk group, pegfilgrastim had 8.61 QALYs, 10.21 LYS, and 3.02 FN events vs 8.49 QALYs, 10.07 LYS, and 1.21 FN events for filgrastim per patient treated.
- In the intermediate-risk group, the total cost of pegfilgrastim was $1752 more than filgrastim, primarily driven by the higher cost of pegfilgrastim despite the lower cost of FN management.

In most of the tested scenarios, pegfilgrastim biosimilar was cost-saving over filgrastim biosimilar for the high-risk group. Pegfilgrastim biosimilar remained dominant in most scenarios for the intermediate-risk group.

The benefits of pegfilgrastim biosimilars were substantial at a population level, the authors noted. They provided a scenario of 10,936 patients treated with short-acting G-CSF in a health plan of 1 million members, in which switching all patients from filgrastim biosimilar to pegfilgrastim biosimilar “could potentially lead to better clinical outcomes and a total cost saving of approximately USD $13 million.”

They suggested optimizing FN management through the use of a framework that integrates pegfilgrastim biosimilar into routine oncology practice. One of the limitations mentioned was that most of the real-world settings assessing use of pegfilgrastim vs filgrastim to prevent chemotherapy-induced FN have been in breast cancer, lung cancer, and non-Hodgkin lymphoma, which may limit the generalizability of the findings. In addition, they estimated the effectiveness of G-CSFs to prevent FN in the intermediate-risk group since there were no real-world comparative effectiveness studies of the use of G-CSFs to prevent FN in the intermediate-risk group.

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MANAGED CARE UPDATES
Spotlighting Health-, Cost-Related Benefits of Genomic Testing and How Employers Can Drive Adoption

CLOSING THE CARE GAP

In what is possible through genomic testing and current medical treatment warrants a collaborative approach beginning at the physician level and expanding to payers, delivery systems, and employers. Randy Scott, PhD, executive co-chairman of Genomic Life, notes that despite the rapid pace in which DNA sequencing technology has evolved in recent years, the use of genomic information remains underutilized to prevent, diagnose, or treat disease. He spoke during a recent panel discussion called “Let’s Get Personal: The Power of Genomics.” Issues such as a lack of physician training and cost/access barriers have been cited as impediments to use of genomic profiling. Scott mentioned that Genomic Life aims to work directly with employers to monitor all the available technologies on the market and pair the right test with employees.

“We can actually screen people for cardiovascular risk and cancer risk, which are the 2 leading causes of death,” he said. “And we now know that roughly 6% of the population—that’s 20 million people in the United States—have an inherited risk for cancer and cardiovascular disease that’s clinically actionable.”

From the point of care, genomic testing has the potential to minimize emergency department visits, hospitalizations, and even death—all major cost-related events for employers. Optimizing the health- and cost-related significance of these data is no simple feat, in which a major challenge to leveraging genomic testing is understanding the subsequent results.

But by taking the steps necessary to ensure that adequate interpretation of these data is provided, its ability to predict risk of developing diseases and response to certain therapies can have notable implications for employers; they can then form health plans that are preventive in design and lead to reduced health care spend. Cancer treatment costs currently account for 12% of employer health care spend, and they are expected to reach $240 billion overall by 2023.1

“The technologies of sequencing and variant interpretation are propelling [forward] so quickly, and so usefully, it’s actually hard for doctors to keep up,” said Robert Green, MD, MPH, medical and clinical advisor for Genomic Life. “And that’s why it’s really important to have specialized resources, specialized expertise, to bring this solution to people—through their health care systems, through their employers, through their own personal doctors.

“The important thing here is we’re not taking it out of the hands of your doctor. [Instead], we’re creating a resource that should make your doctor happy, because it will supplement what they know, and frankly, what they don’t know.”

Describing genomics as the tip of the spear for precision medicine and risk stratification, Green highlighted that the capabilities of pharmacogenomics have widespread implications for employers who manage the care of large, diverse populations.

“[Imagine] if someone could come in and say, Hey, you’ve got a tendency toward this, and you will do better on this drug than that drug,” Green said. “[While] it wouldn’t be perfect—because it’s a statistical thing—it would guide your clinicians to start you on smarter drugs that were better for you, faster…When you apply this across many, many people, you get statistically significant results, you get improvements, and you eventually will get cost savings.”

Speaking on next steps to better leverage genomic testing, Scott addressed the negative feedback loop present between physicians and health insurance: Physicians typically do not order tests that are not covered by health plans, and health plans do not cover services that doctors are not routinely using.

Working directly with employers to provide coverage for genomic testing was recommended to buck this trend. Ultimately, employers are at the forefront of cost burden risk when losing employees to disability or early death.

Referencing the BRCA mutations, which commonly present in patients with breast cancer and ovarian cancer, Scott said that 80% of people with the mutation have never had a genetic test or screening.

The health and cost benefits of such screenings are substantial, exclaimed Scott, who noted that the availability of targeted drugs and different types of chemotherapy can lead to better outcomes for these patient populations.

“We can dramatically save lives and save money…If you’re at 10,000 employees, you have half of 1% each year, [or 500 people, who, statistically, will] develop cancer. So, having this cancer population, have they ever been tested? Are they getting the right drugs? The impact is dramatic,” Scott said.

“I think that [employer involvement] is what will drive health equity, for poor communities who don’t have access, who can’t afford to drive 3 hours to me, who [maybe] can’t afford the cost of parking at most medical centers. Now with telemedicine and telegenetics, we could really wrap a package together that says we can bring this to everybody, and I think that’s a huge difference maker.”

Nearly One-Fourth of DLBCL Cases May Be Attributable to Obesity in Young Adulthood, Study Finds

NEARLY 1 IN 4 CASES of the most common subtype of non-Hodgkin lymphoma (NHL) may be prevented by tackling obesity in young adulthood, suggest findings from a recent study.

The 20-year study, which collected data from 6 different cohorts around the United States, revealed that across the collective group of tumors classified as NHL, both weight and height could have an impact on the risk of disease. The researchers underscored the relevance of their findings, noting that while more than 100,000 cases of NHL and more than 25,000 NHL deaths are expected in 2022, a clear understanding of risk factors is lacking.

“Young adult BMI [body mass index], in particular, was a strong risk factor for DLBCL [diffuse large B-cell lymphoma]. Individuals who had an obese young adult BMI, and remained obese throughout adulthood, had an almost threefold higher DLBCL risk compared with maintenance of a lean body mass throughout adulthood,” the researchers detailed, noting that further studies confirming their finding is needed. “Although adult weight loss is a rare occurrence, our results suggest that DLBCL risk is attenuated in participants who moved to a lower average BMI in middle/later adulthood.”

Across all measures included in the study, the researchers found that BMI in young adulthood had the strongest association with NHL risk, estimating...
that 23.3% of DLBCL cases and 11% of NHLs overall can be attributed to the measure. They did not observe differences based on gender, and they did not have adequate data on risk based on race.

The researchers also found that height played a role in NHL risk, with an overall association as well as an association with more common NHL subtypes, such as DLBCL, and with rarer subtypes like mantle cell lymphoma. The measure had the strongest association with B-cell NHLs among Black patients, with a hazard ratio (HR) of 2.06, and was also stronger for Asian/American Indian/Hawaiian patients (HR, 1.65) compared with White patients (HR, 1.13), who had the weakest association.

"Future studies are also needed to expand upon our findings among non-White participants, including the observed differences for height and NHL risk," highlighted the group.

"Although the present study included a substantial number of non-White participants overall, the sample sizes in key groups, such as overweight/obese [adults], Black, Hispanic, or Asian/American Indian/Hawaiian young adults, were too small to study. In part this was due to unavailable data for some of the body size measures or NHL subtypes."

The group did not find any other body measures significantly associated with NHL overall or subtypes of the disease. Waist circumference had a positive, albeit weak, association with NHL overall (HR, 1.05), although the authors noted that no clear patterns by waist circumference categories were observed.

DLBCL was the only subtype associated with predicted fat mass, and the amount of weight change between young and later adulthood showed no associations with NHL or any subtype.

**REFERENCE**

**CLINICAL UPDATES**

**Primary Care Screening for Skin Cancer Appears to Boost Early Detection**

**PATIENTS OLDER THAN 35 YEARS** who were screened for melanoma during primary care visits were more likely to receive an in situ or a thin invasive melanoma diagnosis compared with patients who were not offered a routine screening in a primary care setting, according to a new study published in JAMA Dermatology.

These findings suggest that implementation of primary care–based screening can help physicians catch skin cancer earlier, potentially leading to better outcomes.

The authors explained that skin cancer can be diagnosed with a simple naked-eye examination, and early diagnosis is among the best predictors of outcomes. However, they wrote that there have been no randomized clinical trials to gauge the impact of melanoma screening in a primary care setting.

Five-year data were examined from a quality improvement program at the University of Pittsburgh Medical Center that was launched in 2014 with the goal of boosting rates of screenings during primary care visits. Under the voluntary program, physicians were encouraged to offer full skin examinations annually to patients older than 35 years who visited the health system’s clinics for routine care. The program immediately yielded higher rates of melanoma detection and a decrease in the median thickness of invasive melanoma.

However, after 1 year, there was no significant difference in the incidence of melanoma thicker than 1 mm between screened and unscreened patients. Over 600,000 patients in the data set were eligible for screening, and about one-fourth (24.3%) received at least 1 screening. Patients who were screened tended to be older; women and White patients were also more likely to be screened.

In terms of outcomes, patients who were screened had a higher likelihood of receiving an in situ or thin invasive melanoma diagnosis vs those who did not receive the screenings. In situ incidence was 30.4 vs 14.4 cases per 100,000 person-years and thin invasive melanoma was 24.5 vs 16.1 cases per 100,000 person-years. Those findings were adjusted for age, sex, and race. Thin invasive melanomas were defined as having a thickness of less than 1 mm. Patients who were screened were also more likely to get an in situ or thin-invasive interval melanoma diagnosis.

"Longer follow-up is needed to fully determine the association of screening with outcomes such as the incidence of thick melanoma, treatment cost and morbidity, distant metastasis, and death."

—study authors

Rates of melanoma thicker than 4 mm were higher in unscreened patients, at 3.3 vs 2.7 cases per 100,000 person-years for all melanomas and 2.7 vs 1.5 cases per 100,000 person-years for interval melanomas. The authors said the overall difference in the incidence of thick melanomas did not reach statistical significance. However, they did add that the study design will allow them to follow these same patients over a longer period of time.

"Longer follow-up is needed to fully determine the association of screening with outcomes such as the incidence of thick melanoma, treatment cost and morbidity, distant metastasis, and death," they wrote.

In addition, they said longer follow-up will make it easier to understand the cost-benefit ratio of this type of proactive screening.

**REFERENCE**

**Neurocognitive Changes After CAR T-Cell Therapy for NHL Similar to Other Cancers**

A RECENT STUDY IN Transplantation and Cellular Therapy is the first to the authors’ knowledge to address neurocognitive performance changes in patients with non–Hodgkin lymphoma (NHL) after chimeric antigen receptor (CAR) T-cell therapy. Neurotoxicity and cytokine release syndrome (CRS) are common adverse effects (AEs) of CAR T-cell therapy, but neurocognitive performance in survivors after CAR T-cell treatment has not been well researched.

CAR T-cell therapy has emerged as a revolutionary treatment in certain cancers, including relapsed or refractory hematologic malignancies. With more patients having achieved and maintained durable responses, research on longer-term AEs of CAR T-cell therapy in survivors is warranted.

The current study examined neurocognitive performance in patients with NHL prior to CAR T-cell therapy conditioning treatment and at 30 days, 90 days, and 1 year post treatment. Patients were eligible regardless of disease response after treatment.

A total of 117 patients with a mean age of 61 years were eligible for the study; 87% of those patients received axicabtagene ciloleucel while the rest received tisagenlecleucel. Overall, 73% of patients responded to therapy by 90 days
after infusion. Of the 54 patients who underwent neurocognitive assessment at 1 year, 71% were still showing disease response.

Neurocognitive assessments were conducted either by trained research coordinators or by doctoral or postdoctoral trainees in clinical psychology, who were supervised by a licensed clinical psychologist and neuropsychologist with expertise in assessing patients with cancer.

The overall rate of neurocognitive impairment at baseline was 33%. By day 30, this had risen to 42%, and at day 90, the rate was 48%. However, by day 360, the overall rate had decreased to 35%. The most impaired measures of neurocognitive ability were verbal ability at baseline, immediate verbal memory at day 30, verbal ability at day 90, and delayed memory at 1 year post treatment (5%, 7%, 7%, and 4%, respectively). Total neurocognitive performance (TNP) and executive function generally decreased from baseline to day 90 before improving by day 360. There were small but significant linear visuospatial declines throughout the study period.

Overall, patients who had undergone fewer than 4 lines of therapy prior to CAR T-cell treatment had slightly better TNP throughout the time points in the study. Additionally, those who experienced grade 2 or higher neurotoxicity—but not CRS—performed slightly worse compared with patients with grade 0 or 1 neurotoxicity throughout the study, including at baseline. The study authors note the possibility that those patients with poorer neurocognition before CAR T-cell therapy may be at a greater risk of neurotoxicity.

The rates of cognitive impairment in patients with NHL undergoing CAR T-cell therapy in this study are similar to those in studies of other populations with cancer. Early screening may help identify patients who are at risk of longer-term cognitive impairment after CAR T-cell therapy, the authors concluded.

“Because neurocognitive performance after CAR-T cell therapy could change for a complex variety of reasons, we did not attempt to attribute changes to particular causal factors,” the study authors noted. “Instead, the study is intended to provide information to help educate patients and family members about what to expect after CAR-T cell therapy and identify potential supportive care needs.”

**REFERENCE**

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**Review Highlights Progress and Potential in Immunotherapy/Radiotherapy Combinations for Cancer Treatment**

**IMMUNOTHERAPY AND RADIOThERAPY** have both improved cancer survival rates, and combination therapies have the potential to be even more effective and reduce recurrence. A recent review published in *Frontiers in Oncology* examined the mechanisms of immunotherapy and radiotherapy and how they can be combined and administered for maximum efficacy.

Radiotherapy is standard for cancerous tumors, used to treat approximately 70% of patients with malignancies. It works by damaging the DNA of tumor cells within the irradiation field to control tumor growth. Data have increasingly shown that radiotherapy also leads to the release of myeloid-derived suppressor cells, M2-like tumor-associated macrophages, T-regulatory cells, N2 neutrophils, and immunosuppressive cytokines, promoting an immunosuppressive microenvironment.

Advances in technology have made radiotherapy more precise and effective, with proton heavy ion therapy being the most advanced option in the current treatment landscape. “With the advancement of heavy ion therapy equipment and technology, the decline of treatment costs, and the advancement of research, heavy ion therapy will gradually be popularized in various countries across the world,” wrote the study authors.

Recent research has also found an abscopal effect with radiotherapy, further suggesting that radiotherapy affects not just the tumor site of treatment, but also the immune system.

“Many preclinical studies have shown that irradiation triggers immunogenetic cell death (ICD), which promotes the release of tumor-associated antigens, changes the tumor microenvironment (TME), and activates the immune system to exert an antitumor immune response,” the authors wrote.

Radiotherapy alone does not eradicate all malignant cells, though. Tumors with hypoxic cells can be resistant to radiotherapy, compared with more oxygenated cells. Hypoxia can also lead to HIF signaling pathway activation, causing gene expression that can help tumors survive. A variety of other TME changes due to radiotherapy can also spur cell growth, and both short- and long-term adverse effects (AEs) can occur.

Radiotherapy has seen advances in recent years, but as immunotherapy has gained traction, it has emerged as the most likely route to find a cancer cure, the authors wrote. The use of immune checkpoint inhibitors (ICIs) tumor vaccines, adoptive cell therapies, cytokine therapies, and other immunotherapies has increased in recent years.

Immunotherapy alone, however, is only used on particular tumor types in clinical practice and does not benefit all patients. Just 10% to 30% of patients respond to single ICIs because of the complexity of cancer cell immune systems and TMEs. Single ICIs or combination therapies are most likely to be effective in “hot” tumors, which have tumor-infiltrating lymphocytes, vs “cold” tumors, which do not. Immunotherapy can also lead to immune-related AEs that can happen in any organ.

Given the resistance of hypoxic cells to radiotherapy and the generally low response to single-agent immunotherapy, the 2 methods can be complementary. The combinations that have been studied include ICIs/radiotherapy, tumor vaccine/radiotherapy, adoptive cell therapy/radiotherapy, and cytokine therapy/radiotherapy. Large-scale clinical data are still limited, although the work involving radiotherapy/immunotherapy combinations continues to grow.

Combining radiotherapy with ICIs that target programmed cell death receptor 1 and programmed cell death ligand 1 is a promising option, and one that has been approved in certain advanced lung cancers. It has been most effective in non-small cell lung cancer (NSCLC). However, many patients with NSCLC remain resistant to ICIs.

Currently available tumor vaccines do not, on their own, elicit tumor-eliminating immune responses, but adding radiotherapy may enhance immune response *in vivo* through several mechanisms. Various trials are underway investigating this combination.

Adaptive cell therapy—accomplished by isolating immunoreactive cells from patients and reintroducing them to target antigen-specific tumor cells—is another increasingly studied treatment option that includes chimeric antigen receptor (CAR) T-cell therapy. However, approximately 90% of patients experience relapse with CAR T-cell therapy, and early data show that radiotherapy may promote CAR-T cell effectiveness in solid tumors.

Cytokines, which regulate innate and adaptive immunity, have been shown to have significant antitumor activity, but their dose-limiting severe AEs inhibit their efficacy. Studies are ongoing, but there may be potential for increased effectiveness with radiotherapy with adjuvant cytokine treatment or cytokine treatment, followed by additional radiotherapy.

Overall, while some studies point to the effectiveness of combination radiotherapy and immunotherapy to improve treatment response, the optimal sequencing and timing of these strategies are still unclear. Toxicity and safety must also be clarified with further research, and it is still not clear which biomarkers are most useful to determine which patients may respond best to certain therapy combinations.

“If the results of more and more clinical trials are positive, it will determine how best to integrate these models and optimize synergy,” the study authors wrote.

**REFERENCE**

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CLINICAL UPDATES
Focused Updates and Evidence-Based Approaches to Anemia in Cancer

CHRISTOPHER T. ELDER, PHARMD, BCOP

Abstract

IT IS ESTIMATED THAT 30% to 90% of patients with cancer develop anemia at some point during their treatment. These patients may experience symptoms from anemia, including weakness, impaired physical function, in addition to experiencing poor performance status. Studies have shown reduced survival times in these patients when compared with patients without anemia. In addition, patients with cancer and anemia have shown significantly greater healthcare expenditure compared with patients with cancer without anemia. A limited number of treatment options include erythropoietin-stimulating agents (ESAs), oral and intravenous (IV) iron therapy, and red blood cell (RBC) transfusions. ESAs were popularly used in the past until a 2007 FDA warning brought to light substantial safety concerns including thrombotic events, which have limited their use in recent years. RBC transfusions rapidly improve anemia-related symptoms and immediately increase hemoglobin and hematocrit levels, but do have potentially serious adverse effects (AEs) such as iron overload and immunosuppression, which may lead to infections or cancer progression. Iron products can correct iron deficiency anemia, reduce the number of RBC transfusions needed, and increase response to ESAs. AEs are limited but can include infusion reactions and electrolyte abnormalities. Pharmacists can play a key role in educating providers of the missed opportunities of utilizing supplemental iron products and identifying which patients are most appropriate for therapy. The pharmacist’s role is also crucial to managing the safe use of anemia medications in patients with cancer.

Educational Objectives

At the completion of this activity, the participant will be able to:

• Examine the pathophysiology, impact on quality of life, and the clinical burden of anemia in patients with cancer.
• Analyze the evidence-based recommendations and clinical trial data for the use of iron replacement in managing cancer-related and chemotherapy-induced anemia.
• Illustrate the managed care strategies to facilitate evidence-based utilization management of iron replacement for the treatment of anemia in cancer.

INTENDED AUDIENCE: Health-system, managed care, and oncology pharmacists

RELEASE DATE: May 26, 2022
EXPIRATION DATE: May 26, 2023
ESTIMATED TIME TO COMPLETE ACTIVITY: 2 hours
TYPE OF ACTIVITY: Application
FEE: Free

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Focused Updates and Evidence-Based Approaches to Anemia in Cancer

Overview of Iron Deficiency Anemia and Cancer

ANEMIA IS FREQUENTLY EXPERIENCED BY patients with cancer and can have negative impacts on overall prognosis. Up to 30% to 90% of patients with cancer are estimated to have anemia. This complication is often detrimental and can compromise both quality of life (QOL) and life expectancy. The severity of anemia is often influenced by the type of malignancy and treatment regimen. A high incidence of anemia is reported across the major non-myeloid tumors treated with common chemotherapy agents and combinations.

Cancer-related anemia (CRA) is a common occurrence in patients with cancer regardless of whether they are undergoing chemotherapy or immunotherapy. It may result from a variety of processes, including decreased production, increased destruction, or increased loss of red blood cells (RBCs). Anemia may also be attributed to underlying comorbidities such as bleeding, hemolysis, nutritional deficiencies, endocrine disease, renal insufficiency, hormone dysfunction, or a combination of these factors. Changes in iron availability are the basis for anemia in many patients with CRA. A comprehensive systematic review of 60 studies evaluating survival found a 65% overall increase in mortality risk in patients with cancer and anemia compared with patients with cancer without anemia.

Iron deficiency anaemia is the most common cause of anemia in patients with cancer. These patients often present with functional iron deficiency, a condition with adequate iron storage but insufficient iron supply for erythroblasts and other iron-dependent tissues. Functional iron deficiency is caused by cancer-related cytokine release. In absolute iron deficiency, iron reserves are depleted, leading to similar and more severe symptoms of inadequate iron storage.

Alternatively, chemotherapy-induced anemia (CIA) is commonly encountered in patients undergoing active chemotherapy with or without radiation therapy. The pathogenesis is often complex and multifactorial. Disease-related blood loss can be encountered in gastrointestinal, genitourinary, and gynecologic cancers. Radiation and chemotherapy can both be immunosuppressive and inhibit erythropoiesis. A significant number of patients with cancer and anemia have no identifiable cause, in which this situation is called anemia of chronic illness. Underlying mechanisms responsible for this type of anemia are unclear but may involve cytokines such as interferon-γ, interleukin-1, and tissue necrosis factor (TNF). These cytokines may suppress endogenous erythropoietin (EPO) production, impairing iron utilization and reducing erythroid precursor proliferation. Iron homeostasis is maintained by a small peptide hormone produced by the liver called hepcidin. Hepcidin works in a negative feedback system to regulate systemic iron homeostasis but cancer-associated proinflammatory cytokines and chronic inflammation result in upregulation of hepcidin synthesis in the liver. Increases in hepcidin can lead to a reduction in iron absorption from the gastrointestinal (GI) tract.

Burden of Disease

Limited data are available regarding iron deficiency anemia and its correlations with clinical parameters in patients with cancer. Anemia may lead to several clinical symptoms such as impaired physical function, weakness, and fatigue. One study aiming to evaluate these clinical parameters included 1528 patients with cancer, assessing patients consecutively within a 4-month period. Iron deficiency was highest in pancreatic (63.2%), colorectal (51.9%), and lung cancers (59.7%) (Figure 1). In addition,

TAKING AWAY POINTS

Iron deficiency anemia is common among patients with cancer, is complex to manage, carries a significant disease burden, and has led to significant healthcare system costs.

- Optimizing treatment with the various therapies (IV and oral iron, ESAs, and blood transfusions) can help reduce healthcare costs.
- Ferric carboxymaltose is the first IV iron therapy with prospective randomized monotherapy clinical trial data in patients with cancer.
- Specific guideline recommendations are needed to improve access to effective treatments.
- Pharmacists play an important role providing patient education, recommending and monitoring therapies, and counseling on adherence to improve satisfaction and outcomes.

<table>
<thead>
<tr>
<th>FIGURE 1. Prevalence of Iron Deficiency and Anemia Across Tumor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
</tr>
<tr>
<td>% iron deficiency</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>Pancreatic</td>
</tr>
<tr>
<td>Colorectal</td>
</tr>
<tr>
<td>Lung</td>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Breast</td>
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<tr>
<td>Gynecological</td>
</tr>
<tr>
<td>Testicular</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Hematological malignancies | 50% | 70% |

| All | 40% | 70% |
| Pancreatic | 50% | 60% |
| Colorectal | 50% | 60% |
| Lung | 40% | 50% |
| Gastrointestinal | 40% | 50% |
| Breast | 30% | 40% |
| Gynecological | 30% | 40% |
| Testicular | 20% | 30% |
| Other | 10% | 20% |

Hematological malignancies | 50% | 70% |
both iron deficiency and anemia significantly correlated with poor Eastern Cooperative Oncology Group (ECOG) performance status (P = .005 and
P = .001, respectively). Patients with solid tumors with poor performance status (ECOG 2-4) presented with a greater frequency of iron deficiency (61.1%)
and anemia (60.2%) than patients with good performance status (ECOG 0-1; iron deficiency: 43.9%; anemia: 27.9%). This study sheds light on the prev-
ance of iron deficiency and anemia across tumor types and correlation to poor performance status.12
Several studies have shown a reduction in survival times in CRA compared with those without anemia in a variety of malignancies, including carcinoma of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma. A literature review carried out using the MEDLINE database found that, in patients with anemia, the relative risk of death increased by 19% (95% CI, 10%-29%) compared with those without anemia. This relationship and survival in an array of different cancer types.7
QOL improvements have been associated with increases in hemoglobin (Hb) levels in patients with CRA treated with epoetin alfa, but interventions are often reserved for symptomatic anemia found that, in patients with anemia, the relative risk of death increased by 19% (95% CI, 10%-29%) with lung carcinoma, 47% (21%-78%) with prostate carcinoma, 67% (30%-113%) with lymphoma, and by 75% (37%-123%) with head and neck carcinoma compared with patients without anemia. Overall, the estimated increase in risk was 65% (54%-77%). This demonstrates the association between anemia and survival in an array of different cancer types.7
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A strongly suggestive symptom is pagophagia (ice craving), which may lead to gingival disease. Other symptoms include brittle nails, hair loss, and restless legs syndrome.14 Signs of iron deficiency upon physical evaluation include pallor (with anemia), decreased papillation of the tongue, cheilitis (cracking of the corners of the mouth), and noticeable defects of the nail beds including Mees lines and kolonychia (spooning of the nails).14

Laboratory diagnosis includes several tests that require some degree of interpretation to be applied. A panel of tests, shown in Table 1,15-18 each give important information needed for diagnosis. Serum iron represents the iron bound to the transport protein, transferrin, available to be incorporated into Hb in development of erythroblasts in the bone marrow. Serum iron can be influenced by external factors and therefore no serum iron value alone is diagnostic of iron deficiency. Total iron binding capacity (TIBC) is a functional measurement of the amount of transferrin in circulation. The TIBC is generated by adding the serum iron to the unsaturated iron-binding capacity. The serum iron and TIBC are used to calculate percent transferrin saturation (TSAT) (serum iron/TIBC *100 = TSAT). A low-value TSAT (typically less than 15%) can be indicative of iron deficiency but is not diagnostic by itself. The serum ferritin (or apoferitin) is the protein in plasma that reflects the body’s iron stores under normal circumstances. However, ferritin level can fluctuate and can increase in the setting of inflammation or hepatocellular injury, so may be problematic when used for interpretation. A low TSAT combined with low ferritin (<15-25 ng/mL) confirms the diagnosis of iron deficiency.15
Red cell indices will also change with iron deficiency with the red cells gradually becoming microcytic and hypochromic. These changes are later when compared with changes in serum iron and storage iron. The reticulocyte count is expressed by modern cell analyzers as a percentage of all red cells or preferably in absolute numbers per micro-liter of whole blood. This number can be used to provide an estimate of the rate of effective marrow production compared with normal (production index of 1) rate. The soluble transferrin receptor (sTIR) level is often an underutilized laboratory measurement. Expression of this gene is regulated in part by intracellular iron. In the absence of iron, translation of TIR is upregulated, but in the setting of inflammation, TIR levels do not rise. TIR measurements can be useful in distinguishing between true iron deficiency and inflammatory conditions associated with low serum iron and low TSAT (anemia of inflammation).15 Reticulocyte Hb content (CHR) may provide a snapshot of recent iron availability for Hb synthesis. In iron deficiency, this value is low. However, because a low value can be associated with a variety of conditions including inflammation, CHR has not been widely adopted as a routine workup panel of suspected iron defi-
cency.15,16 Hepcidin is also another promising tool for evaluating iron status, but further validation is needed and it is unclear when hepcidin assays will be widely available.17
Once evaluation of iron deficiency has been completed through iron studies, iron status is determined. Absolute iron deficiency is defined as ferritin <30 ng/mL AND TSAT <20%. Classic functional iron deficiency anemia involves ferritin 30-100 ng/mL AND TSAT <20%. Possible functional iron deficiency is considered with lab values of ferritin 500-800 ng/mL AND TSAT <50%. Chronic inflammation and release of cancer-associated proinflammatory cytokines (eg, IL-6, IL-1, TNF-α, and interferon-γ) leading to increased hepcidin in the liver to shut down iron absorption through the GI tract is one of the key pathophysiological features of functional iron deficiency anemia.17

| Table 1. Laboratory Tests Used to Evaluate Iron Status | \[15,18\]| Text | Reference interval | Comment |
|---|---|---|---|
| Serum ferritin | Male: 30-500 ng/mL | Lab value for iron stores |
| | Female: 12-240 ng/mL | Absolute iron deficiency indicated with value lower than reference range |
| | | Acute phase reactant |
| Serum iron | Male: 50-170 mcg/dL | A normal or elevated value does not exclude iron deficiency in patients with inflammatory diseases such as cancer or liver disease |
| | Female: 30-160 mcg/dL | Used to calculate transferrin saturation |
| TIBC | 240-450 mcg/dL | Often elevated in iron deficiency, signaling lack of iron availability |
| TSAT % | 20%-50% | Indicates iron availability in the body for erythropoiesis |
| Haptoglobin | | Test not routinely available |
| | Optimal threshold for response not yet defined | Strong correlation between baseline haptoglobin level and response to IV iron in functional IDA |
| Reticulocyte hemoglobin content (CHR) | 30-38 pg | Reflects the amount of iron available for hemoglobin production in the bone marrow |
| Mean corpuscular volume (MCV) | Male: 83-98 fL | Average size of RBC |
| | Female: 85-97 fL | Low sensitivity and specificity for iron deficiency since value is affected by drugs, liver disease, etc |
| | | Low MCV may indicate iron deficiency (microcytic) |

TSAT: transferrin saturation.
Treatment of Iron Deficiency Anemia

The short-term goal of treating CRA is correcting the quantitative deficits of Hb and erythrocytes to meet oxygenation requirements of tissues. If successful, meeting these goals may allow for increased QOL through less fatigue and improved cognition and exercise tolerance. Depending on a patient’s prognosis throughout treatment, goals may shift from correction of anemia to maintain overall QOL by preventing worsening anemia and dependence on RBC transfusions. Currently, available treatments focus on increasing RBC production to counterbalance the treatment effects. Fewer than half of patients receive treatment with drugs, potentially sparked by the decline in the use of erythropoiesis-stimulating agents (ESAs) due to growing concerns of safety in patients with cancer. Treatment must be evaluated for each patient based on individual factors including risk versus potential benefit.

Iron Therapy

ORAL VERSUS IV IRON

Iron formulations available to patients with cancer include both oral and parenteral forms (low-molecular-weight [LMW] iron dextran, ferric gluconate, iron sucrose, ferumoxytrol, ferric carboxymaltose, and ferric derisomaltose). In terms of oral formulations, bivalent (ferrous) forms of iron have better bioavailability than trivalent (ferric) forms. Although both oral and IV formulations of iron replacement therapy can be considered in patients with cancer, there has been insufficient evidence that oral iron is effective. Oral iron also has a higher risk for reaction. The short-term goal of treating CRA is correcting iron deficiency and anemia. Patients with cancer who have functional iron deficiency anemia (TSAT <20% and serum ferritin >100 ng/dL) may qualify for monotherapy IV iron therapy. ESMO guidelines also state that IV iron treatment should be limited to patients with cancer who are on active chemotherapy treatment. Despite these guideline recommendations favoring IV iron supplementation, due to insurance mandates, oral iron is often a first choice for iron supplementation in patients with cancer with iron deficiency, except in patients with profound absolute iron deficiency anemia. Patients with cancer who receive oral iron may be exposed to needless AEs and loss of time due to ineffective treatment and will often need to be transitioned to IV iron supplementation. Due to chronic inflammation and hepcidin release resulting in poor absorption in patients with cancer, oral supplementation with iron should be considered inappropriate as it is less effective.

GUIDELINE RECOMMENDATIONS

National Comprehensive Cancer Network (NCCN) guidelines recommend IV iron supplementation be used in most clinical circumstances over oral iron. IV iron can overcome the abrasive inflammatory blockade of iron common in patients with cancer and is the preferred treatment of choice for CRA. IV iron supplementation should also be recommended and considered in patients who do not respond to or cannot tolerate oral iron supplementation. NCCN guidelines state that IV iron has superior efficacy and should be considered for supplementation, especially when used in combination with ESAs.

According to recent updates to the European Society for Medical Oncology (ESMO) guidelines published in 2018, IV iron is recommended for patients receiving ongoing chemotherapy who present with anemia (Hb ≤11 g/dL or Hb decrease ≥2 g/dL from baseline level ≤12 g/dL) and absolute iron deficiency is present (serum ferritin <100 ng/dL).

Patients with cancer who have functional iron deficiency anemia (TSAT <20% and serum ferritin >100 ng/dL) may qualify for monotherapy IV iron therapy. ESMO guidelines also state that IV iron treatment should be limited to patients with cancer who are on active chemotherapy treatment.

Iron formulations available to patients with cancer include both oral and parenteral forms (low-molecular-weight [LMW] iron dextran, ferric gluconate, iron sucrose, ferumoxytrol, ferric carboxymaltose, and ferric derisomaltose). In terms of oral formulations, bivalent (ferrous) forms of iron have better bioavailability than trivalent (ferric) forms. Although both oral and IV formulations of iron replacement therapy can be considered in patients with cancer, there has been insufficient evidence that oral iron is effective. Oral iron also has a higher risk for reaction. The short-term goal of treating CRA is correcting iron deficiency and anemia. Patients with cancer who have functional iron deficiency anemia (TSAT <20% and serum ferritin >100 ng/dL) may qualify for monotherapy IV iron therapy. ESMO guidelines also state that IV iron treatment should be limited to patients with cancer who are on active chemotherapy treatment. Despite these guideline recommendations favoring IV iron supplementation, due to insurance mandates, oral iron is often a first choice for iron supplementation in patients with cancer with iron deficiency, except in patients with profound absolute iron deficiency anemia. Patients with cancer who receive oral iron may be exposed to needless AEs and loss of time due to ineffective treatment and will often need to be transitioned to IV iron supplementation. Due to chronic inflammation and hepcidin release resulting in poor absorption in patients with cancer, oral supplementation with iron should be considered inappropriate as it is less effective.

IV IRON PRODUCTS

Table 2 describes IV iron products, including dosing and clinical pearls, used for CRA. As far as tolerability with IV iron products, patients may experience nausea, vomiting and/or diarrhea, hypotension, pain, hypertension, dyspea, pruritus, headache, and dizziness. High-molecular-weight iron dextran had much higher rates of serious AEs, including allergic/anaphylactoid reactions, hypertension, cardiac arrest, and death, but is no longer used routinely in clinical practice.

A recent meta-analysis evaluated the safety and risk of hypersensitivity reactions in more than 5000 patients, comparing iron dextran-containing products (LMW iron dextran, ferumoxytrol, and ferric derisomaltose) versus non-iron dextran products (ferric carboxymaltose and iron sucrose). The meta-analysis results revealed no meaningful clinical differences in risk of reactions, hypersensitivity or anaphylactic, among the various iron products. Another meta-analysis published in 2015 showed that anaphylactic type reactions with IV iron products are extremely rare (<0.1%), but the estimated cumulative risk when receiving a total iron dose of 1000 mg administered within a 12-week period is highest with LMW iron dextran (82 per 100,000 patients) and is the lowest for iron sucrose (21 per 100,000 patients).

Iron dextran (Infed). LMW iron dextran was first approved for treatment of iron deficiency anemia in the United States in 1992. Due to potential severe reactions even with the test dose, it is recommended to administer premedications 30 minutes before the LMW iron dextran test dose. The use of antihistamines, such as diphenhydramine, as premedication with IV iron is also controversial due to risk of exacerbation or ability of diphenhydramine to mimic signs and symptoms of hypersensitivity reaction. Because of this, antihistamines are not recommended for premedications with IV iron products and instead corticosteroids should be used.

Ferric gluconate (Ferrlecit). Ferric gluconate was first approved by the FDA in 1999 as a follow-up to LMW iron dextran for adult patients with iron deficiency anemia and in pediatric patients aged 6 years or older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy. Ferric gluconate does not require premedications, unless desired by prescribing physician based on risk for reaction. It is important to note that ferric gluconate contains benzyl alcohol (9 mg/mL) as an inactive ingredient and therefore should not be used in neonates.

Iron sucrose (Venofer). Iron sucrose was first approved in 2000 by the FDA for treatment of iron deficiency anemia in patients with chronic kidney disease (CKD). Along with all other IV iron products, iron sucrose is used off-label to treat iron deficiency anemia in patients with cancer. There are some data with iron sucrose in patients with cancer.

TABLE 2. IV Iron Products

<table>
<thead>
<tr>
<th>Elemental iron</th>
<th>Test dose required</th>
<th>BBW*</th>
<th>Dose</th>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>LWM iron dextran – 1992</td>
<td>50 mg/mL</td>
<td>Yes</td>
<td>Yes</td>
<td>• 100 mg x 10 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• TDIL x1000 mg over 1-6 hours</td>
</tr>
<tr>
<td>Ferric gluconate – 1999</td>
<td>12.5 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 125 mg IV weekly x 8 doses</td>
</tr>
<tr>
<td>Iron sucrose – 2000</td>
<td>20 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 200 mg IV x 5 doses over 15 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 300 mg IV over 90 min</td>
</tr>
<tr>
<td>Ferumoxytrol – 2009</td>
<td>30 mg/mL</td>
<td>Yes</td>
<td></td>
<td>• 510 mg IV over 15 min x 2 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 1020 mg IV over 30 min x 1</td>
</tr>
<tr>
<td>Ferric carboxymaltose – 2013</td>
<td>50 mg/mL</td>
<td>No</td>
<td>No</td>
<td>For patients ≤50 kg:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 750 mg IV over 15 min x 2 doses</td>
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<td></td>
<td>• 1000 mg IV over 15 min x 1</td>
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<td></td>
<td>For patients &gt;50 kg:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 15 mg/kg x 2 doses</td>
</tr>
<tr>
<td>Ferric derisomaltose – 2020</td>
<td>100 mg/mL</td>
<td>No</td>
<td>No</td>
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</tr>
</tbody>
</table>
patients with CRA. The analysis showed that IV iron is likely a safe and effective option for patients with CRA.

Administration of ferumoxytol may also transiently affect the diagnostic ability of magnetic resonance imaging (MRI) scans. If MRI scans are necessary in patients receiving ferumoxytol, the MRI should be conducted before initiating ferumoxytol, as alteration of MRI studies may persist for up to 3 months following the last dose of ferumoxytol. The most common AEs of ferumoxytol are abdominal pain, diarrhea, and nausea.

Ferric carboxymaltose (Injectafer). Ferric carboxymaltose (FCM), first approved in 2013, is an IV iron formulation used to treat iron deficiency anemia in multiple clinical settings including pregnancy-related anemia and patients with anemia and chronic renal failure. FCM can restore up to 1500 mg of iron over at least 20 minutes. A recent study aimed to investigate the effects of FCM without ESAs in CIA. This study stratified 84 patients based on their risk for reaction. The most common AEs of ferric carboxymaltose are headache, or trouble walking.

Ferric derisomaltose (Monoferric). Ferric derisomaltose was compared with FCM and it was determined that ferric derisomaltose demonstrated a significantly higher percentage of patients in the FCM group maintained Hb within 0.5 g/dL of baseline (50.8%) compared with the placebo group (35.3%; treatment difference: 15.6% [95% CI, 8.0% to 23.1%]; P = .01). The FCM/placebo odds ratio was 0.51 (95% CI, 0.30-0.87; P = .01). Additionally, increases from baseline in Hb were observed as early as 7 days in patients receiving FCM therapy, while patients on placebo remained almost unchanged for the first 6 weeks. No significant safety concerns were noted with no significant differences in AEs between groups. Hypophosphatemia occurred in 16% of FCM patients and 3% in placebo patients but was transient and asymptomatic. This study adds support for the use of IV iron therapy in the form of FCM monotherapy for patients receiving myelosuppressive chemotherapy to maintain Hb levels who may be unsuitable candidates for ESAs and/or blood transfusions. FCM does not require premedications, unless desired by prescribing physician based on patient risk for reaction.

Patients receiving FCM should be closely monitored for hypophosphatemia. There are increases in AEs and safety issues related to ESA therapy. Patients receiving ESA therapy have a higher rate of thromboembolic events for CRA. Higher baseline Hb has been associated with increased occurrences of thromboembolism in some trials. Additional AEs of ESAs include hypertension, thrombocytopenia, hemorrhage, and seizures. The FDA published a warning statement in 2007 limiting the use of ESA only for the indication of CIA and discouraging use once antineoplastic therapy is completed, and while the Risk Evaluation and Mitigation Strategy (REMS) program was discontinued in 2017, the warnings surrounding ESAs in patients with cancer still exist. Additionally, there is evidence that ESAs may improve QOL, fatigue, and other specific anemia symptoms such as dizziness, chest discomfort, headache, or trouble walking. Crawford et al found that the highest improvement in QOL was found if Hb values were 11 to 12 g/dL.

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improvements in QOL. Both risk (shorter survival, no effect on time to hematopoietic response nor hematopoietic response, fewer RBC transfusions, and potentially fatal allergic reactions, transmissions during the procedure). One study demonstrated that patients who reach a certain Hb value with blood transfusions have survival rates similar to those who reached that Hb value spontaneously.

RBC Transfusions
RBC transfusions are highly successful in raising Hb levels and oxygen transport capacity of blood. This makes transfusions a fast and effective therapeutic option to optimize care. Figure 2 summarizes benefits versus risks or limitations of the various treatment options for CRA.

Managed Care Considerations
Cancer affects approximately 8.4 million Americans, and accounts for 10% of total healthcare costs. The true economic burden of CRA has been minimally explored. One study aimed to assess the impact of early anemia within 6 months of cancer diagnosis on utilization and expenditures in patients with cancer also receiving chemotherapy treatment. Data used in the study were pulled from the MarketScan database consisting of approximately 3 million covered employees and their dependents, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continues, and Medicare-eligible retirees. Outpatient prescription data were linked to patient identifiers with inpatient and outpatient files. Expenditures for all service types included total gross payment to a provider for a specific service before application of deductibles, co-pays, and coordination of benefits, but after applying pricing guidelines such as discounts. The study included 2760 patients with a diagnosis of cancer during January to June 1999 who also had a 3-month “clean” period free of cancer diagnosis, referred to as the “pre-period.” Patients were followed for 6 months after the cancer diagnosis called the “study period.”

A total of 731 patients (26%) had anemia in the 3 months before or 6 months after the initial cancer diagnosis. The rates for inpatient, outpatient, and outpatient prescription drug utilization were significantly higher for the anemia group than the non-anemia group. Patients with anemia had twice as many hospital admissions and emergency department visits and one-third more outpatient service-days and prescription drug claims than patients without (all P<.0001). Mean length of stay was 10.9 days for patients with anemia versus 6.4 days.

FIGURE 2. Benefit-risk Profiles for Anemia/Iron Deficiency Treatment in Patients With Cancer

Risks:
• Increases risk of thrombosis
• Increases mortality in patients not receiving cancer treatment
• Insufficient efficacy (50% of patients)
• Decreases effect over time

Benefits:
• Effective in correcting iron deficiency
• Reduces RBC transfusions
• Increases response to ESAs

Risks:
• Increases risk of thrombosis, transfusion reactions, transmission of bloodborne pathogens, infections due to immunosuppression
• Potential reduced survival in select cancer types treated by surgery

CRA: cancer-related anemia; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; IV, intravenous; RBC, red blood cell.

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Economic Burden
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for patients without anemia ($P<0.001). Expenditures were significantly higher for patients with anemia. Mean 6-month unadjusted total expenditures were $562,496 for patients with anemia versus $36,871 for patients without anemia ($P<0.001). Although patients with anemia represented 26% of the study population, they accounted for 46% of total hospitalization expenditures and 38% of expenditures across the full study population. EPO treatment accounted for 2% of total expenditures for patients with anemia. The largest driver of differences between groups were inpatient services. Mean inpatient costs for patients with anemia were more than twice that of patients without anemia at $30,639 and $13,152, respectively. This study demonstrates the significant cost burden that patients with cancer and anemia bring to the healthcare system and the need for focus on treatment that is effective.

### Challenges With Managing CRA

Managing patients with CRA can be challenging from clinical, operational, and economical perspectives. A patient experiencing CRA may not be able to receive their scheduled chemotherapy treatment, which may have negative consequence on infusion room and infusion pharmacy operations and may potentially necessitate the consumption of additional laboratory, pharmacy, or blood bank resources. Other consequences could include wasted chemotherapy doses and/or the admission of patients with severe anemia to the inpatient service. A primary challenge for hospital management is balancing wide-range objectives in an ever-changing environment of best practices. Due to the serious safety concerns with ESAs, including an increased risk for thromboembolic events and worsening survival in patients with cancer, their use has been declining in oncology since the late 1990s and early 2000s.

Patients are also undergoing transfusions at an increased rate, which is expensive and resource-intensive for healthcare facilities as blood product supplies continue to be constrained. In an oncology setting, efficient use of blood products poses unique clinical effectiveness, patient safety, operations, and financial challenges. Blood product management practices must be optimized to ensure clinically effective and safe use of blood products. As mentioned previously, transfusions are also not without risks, such as allergic and febrile reactions, which are rarely life threatening, contamination of platelets, acute transfusion-related injury to the lungs, and errors related to incorrect matching or infusion to the incorrect patient. Transfusions additionally are a more complex process as they require an informed consent process with the patient, outlining the spectrum of potential risks associated with receiving the transfusion.

Blood products are also costly, at a mean price of $213.94 (2006 dollars) for one unit of leukocyte-reduced RBCs. The cost of ESA therapy can have an estimated 6-month cost of $10,000. Based on average wholesale price (AWP) data for IV iron products, a treatment course of FCM would be approximately $3000, ferumoxytol about $2800, ferric gluconate about $610, iron sucrose about $440, iron dextran about $380, ferric carboxymaltose about $3050 (LexiComp AWP pricing listed for course of treatment of 1000 mg). Price differences are regional, with hospitals in the northwest paying significantly more than the nation mean, and hospitals in the southwest and central regions paying significantly less. Note that patients with CRA may require utilization of multiple treatment options including ESA therapy and IV iron therapy. Patient assistance programs exist for both IV iron products and ESAs that can be used to help patients with out-of-pocket expenses as well as programs to help address reimbursement and payer issues for health systems.

Although some clinicians are emphasizing the use of supplemental iron use in the management of patients with both cancer and anemia, these unified approaches to guide the use of supplemental iron products have not been universally accepted by the oncology community. Use of supplemental iron is likely not optimized in patients with cancer. This may be a result of a lower comfort level of physicians and understanding how to use these agents, especially parenteral agents, and how they can play a key role in the management of this patient population compared with either use of ESAs or blood transfusions. Additionally, policies addressing the use of supplemental iron may not be as frequently encountered as policies addressing ESA or transfusion use. An anemia management strategy must consider the severity of anemia and the potential for AEs.

### Role of the Pharmacist

A crucial role of the pharmacist in managing anemia in patients with cancer is therapy management, including appropriate product selection and monitoring for efficacy and safety. With multiple IV iron products available, it can be challenging to determine the most appropriate option for patients and for organizations to make formulary selections. IV iron products are equally effective in treating iron deficiency and all currently available IV iron formulations have a similar iron core but vary in terms of physicochemical and pharmacokinetic properties.

Factors that should be taken into consideration for product selection include:

- Infusion time
- Length of course and number of doses
- Premedication/test-dose requirement
- Risk of AEs such as hypersensitivity reaction or allergic reaction (anaphylaxis)
- Cost of product/contracts and formulary preferences

A study was conducted to determine the appropriateness of ESA use following initiation of a pharmacist-managed clinic at a Veterans Affairs medical center. Physicians referred all patients beginning or currently receiving ESA therapy to a clinic for pharmacist management. Pharmacists initiated therapy for patients with a TSAT<20% and serum ferritin concentrations<100 ng/mL, which signified low iron stores. Results showed Hb levels improved significantly after 1 month, and cost savings were substantial. Six months after the clinic protocol was established, ESA therapy for 27 of 29 patients followed drug use evaluation criteria. This study suggests pharmacist management of patients receiving ESA therapy, including adjunctive IV iron therapy, is effective for improving Hb levels and compliance with ESA criteria for safe use, in addition to providing cost savings.

Collaborative practice agreements between pharmacists and physicians could have a profound effect on the safe and appropriate use of ESAs as well as optimizing reimbursement. Multiple issues arise when managing anemia, specifically in the oncology population, including clinical, operational, and economic considerations. These complexities signify the need for strong multidisciplinary pharmacist involvement in patient care to ensure optimal outcomes and patient satisfaction. A survey of patients with cancer demonstrated a strong interest in regular visits with pharmacists for therapy management and counseling and strong patient willingness to pay for pharmacist services. These data can be extrapolated and applied to patients across the health system and show the need for specialty (hematology/oncology), ambulatory care, hospital, and practice management pharmacists collaborating for patient management and transitions of care.

An internal audit exploring the cost-effectiveness of ESA therapy and patient outcomes found that physicians were not appropriately monitoring the use of ESAs. The drug use evaluation involved a retrospective chart review of 520 patients treated with epoetin alfa or darbepoetin alfa over 12 weeks and found that iron stores were not assessed in approximately 70% of the patients. At week 4, a recommended ESA dosage increase was prescribed for only 6% (2/32) patients for whom therapy was indicated, and at week 12, 58% (30/52) were continued on subtherapeutic dosing (Hb increase <1 g/dL). This study led to the standardized approach of managing hematology/oncology patients receiving ESA therapy by improving the monitoring of iron status and ESA therapy. An anemia clinic was created to manage ESA, iron, and B vitamin therapy for patients with CIA. Implementation of a pharmacist-managed anemia clinic has the potential to decrease physician workload, allowing physicians more time for direct patient-care activities.

Having a dedicated clinical pharmacist to monitor patients ensures timely and appropriate documentation of pharmacist-provided services that allow physicians to remain well informed of patient progress. In addition, a pharmacist-managed anemia clinic has the potential to increase reimbursement rates by providing all necessary information to medical codes. Pharmacist management would ensure adherence to national guidelines and reduce the risk of subtherapeutic doses of ESAs. Pharmacists provide clinical expertise and reduce burden on providers through assessment of laboratory monitoring, risk factor identification, and patient monitoring. Pharmacists are also strategically positioned to offer preventive modification counseling to patients, assess available treatment options, make recommendations, and counsel patients to help improve adherence and decrease adverse drug events.
Conclusions
In conclusion, anemia in patients with cancer is a complex condition affecting a majority of patients. It has substantial negative impacts on prognosis of patients, including decreased survival and poorer QOL, compared with patients without anemia. In patients with cancer, those with anemia also have shown to incur greater healthcare expenditures compared with patients without anemia, such as inpatient services, emergency department visits, outpatient services, and outpatient prescription drugs. Guidelines are not conclusive in recommending treatment strategies, but review the advantages and disadvantages of ESAs, IV iron therapies, and RBC transfusions. In patients with cancer and anemia, IV iron therapies are likely more effective than oral iron replacement options, which can potentially result in reduced healthcare costs due to more effective treatment and reduced inpatient stays. The development of pharmacist-led programs and managed care initiatives are needed to improve patient care and healthcare efficiencies.

REFERENCES
4. Lyman GH, Berndt ER, Kallich JD, et al. The economic burden of anemia and reduced inpatient stays. The development of pharmacist-led programs and managed care initiatives are needed to improve patient care and healthcare efficiencies.
INSTRUCTIONS FOR RECEIVING CONTINUING PHARMACY EDUCATION (CPE) CREDIT

TESTING INFORMATION: This lesson is free online; request your CE credit at www.PharmacyTimes.org/anemia-onc

TESTING DIRECTIONS
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To request your CE credit, scan the code or visit: www.PharmacyTimes.org/anemia-onc
1. Which statement is true regarding the impact of anemia in patients with cancer?
   A. Iron deficiency was highest in patients with lung cancer.
   B. Anemia is a predictor of overall poor prognosis and may negatively impact survival.
   C. Symptoms of anemia include pain, nausea, and dyspnea.
   D. Increased hemoglobin (Hb) levels help resolve anemia symptoms, but do not improve quality of life.

2. According to a MEDLINE data review by Caro and colleagues, which of the below cancer types has the highest increase in relative risk of death in patients with anemia compared with those without anemia?
   A. Head and neck cancer
   B. Lung cancer
   C. Pancreatic cancer
   D. Breast cancer

3. Which of the following is a contributing factor to the development of iron deficiency anemia in patients with cancer?
   A. Increased erythropoietin release
   B. Increased folic acid dietary intake
   C. Inflammation and cytokine release
   D. Reduced hepcidin production by the liver

4. A 68-year-old man with stage IV non–small cell lung cancer receiving chemotherapy is here today for follow-up and labs as the patient has been feeling more fatigued the past several weeks. The following labs are reported in clinic today related to complete blood count and iron panel:
   - Hb: 10.1 g/dL; hematocrit: 31.3%
   - Iron: 40 mcg/dL
   - TIBC: 270 mcg/dL
   - TSAT: 15%; serum ferritin: 23 ng/mL
   Based on the lab values for this patient, how would you classify his anemia?
   A. Absolute iron deficiency anemia
   B. Functional iron deficiency anemia
   C. No iron deficiency present; patient has chemotherapy-related anemia
   D. Moderate iron deficiency anemia

5. A 43-year-old woman with stage III pancreatic cancer is here today for her next cycle of chemotherapy. Iron deficiency anemia is noted on the patient’s labs in clinic today and the provider would like to initiate ferumoxytol. What important clinical pearl related to ferumoxytol is important to consider before initiating?
   A. Ferumoxytol is given as small doses over 3 to 5 treatments and must be given at least 72 hours apart between doses.
   B. Premedication with acetaminophen and diphenhydramine are recommended with ferumoxytol.
   C. Ferumoxytol can alter magnetic resonance imaging studies for up to 3 months following the last ferumoxytol dose.
   D. Electrolyte abnormalities are common with ferumoxytol and should be monitored closely during and after treatment.

6. What effects can patients with both cancer and anemia have on healthcare expenditures?
   A. Patients with anemia may have longer hospital stays, increasing the number of inpatient services compared with patients without anemia.
   B. Patients with anemia often have shorter recovery times than patients without anemia and thus have lower healthcare expenditure.
   C. Patients with anemia have lower outpatient prescription drug costs compared with patients without anemia.
   D. Patients with anemia have not been shown to have increased healthcare costs.

7. Why is intravenous (IV) iron therapy for appropriate oncology patients not currently being optimized?
   A. Parenteral iron therapy is considered high risk compared with erythropoietin-stimulating agents or red blood cell transfusions.
   B. Therapies have not been proven as effective at correcting anemia.
   C. Guidelines recommend usage of oral iron therapy.
   D. There is low comfort level of physicians and understanding how to use these agents.

8. Which monitoring parameter is important to evaluate and follow during treatment of iron deficiency anemia in patients with cancer who are receiving ferric carboxymaltose?
   A. Renal function
   B. Phosphorous levels
   C. Hepatic function
   D. Calcium levels

9. A 72-year-old woman with stage 2 triple-negative breast cancer is initiated on chemotherapy for curative intent with dose-dense AC (doxorubicin plus cyclophosphamide) for 4 cycles followed by paclitaxel weekly for 12 cycles. After 2 cycles of AC therapy, the labs are as follows:
   • Hb 9.2 g/dL; Hct: 27%; platelets: 350,000/µL
   • MCV: 72 fL
   • TSAT: 10%; serum ferritin 15 ng/mL
   Based on her baseline anemia and iron stores present on labs today, which of the following is the best option for this patient for treatment?
   A. Oral ferrous fumarate 325 mg by mouth twice daily
   B. Darbepoetin alfa 300 µg subcutaneously once every 3 weeks
   C. Withhold chemotherapy based on patient’s labs today
   D. Ferric derisomaltose 1000 mg IV x 1 dose

10. Based on the recent IRON-CLAD study, which IV iron product has prospective randomized clinical data as monotherapy in patients with chemotherapy-induced anemia?
    A. Ferumoxytol
    B. Ferric derisomaltose
    C. Ferric carboxymaltose
    D. Ferric gluconate
Value-Based Care Will “Continue to Evolve” Even if OCM Expires

MARY CAFFREY

CONTINUED FROM COVER

Lessons From the OCM

Some larger practices have pushed back against reports saying the OCM was not a success—they say once practices learned to use the model correctly, they achieved savings for Medicare over predicted benchmarks. More importantly, the quality of patient care improved. To start the discussion, Wilfong asked how practices could retain the successes of the OCM and especially how commercial payers have responded to the movement toward value-based care, because they will be carrying the movement forward.

Staggs ran through the numbers for The US Oncology Network: the OCM has brought $240 million in savings for Medicare and going into 2020 the network had seen a 24% decrease in emergency department (ED) visits, a 37% decrease in hospitalizations, and an 11% increase in use of hospice care for more than 3 days. Just as important, he said, “We’ve established key things [such as] patient navigation, team-based care, better conversations around shared decision-making, and better access to enhanced services.” The OCM, he said, has created “a good foundation” for commercial plans to build value-based models in oncology, and for regulators to pursue the next wave of reform in Medicare.

Henschel said the OCM caused commercial payers to give more attention to managing the total cost of care, adding that 2 things stand out. “No. 1, we can drive the delivery of high-value care by aligning payer and provider incentives that ensure the right care is delivered at the right time and the right place of service,” she said. “And No. 2, the OCM highlights the different levers...such as care coordination or inpatient or ED reduction strategies and therapeutic interchanges that can reduce the cost of care by engaging with providers and aligning the different incentives.”

Wilfong agreed that creating payer and provider alignment to improve care—and cut costs—was essential. But increasingly, drugs form a large part of oncology care costs. Wilfong asked Jones to comment on how the OCM encouraged the use of biosimilars to drive down total care costs.

Providers, Jones said, often have limited control over drug costs; a novel therapy that is the best treatment available may not have a competitor. But when a biosimilar is available for a commonly used treatment, providers can help patients achieve savings—and Jones said policymakers are looking for incentives to encourage their use. “Patient care obviously comes first, but costs are in everyone’s minds,” he said. Among the federal agencies such as CMS, the US Department of Health & Human Services, or the Center for Medicare and Medicaid Innovation, “You can already see a lot of interest in the use of biosimilars—and a lot of hope for those patients in your clinic, so that you could get them in and take care of them.”

Practices had to ensure staffing was available to help patients after hours, to provide access to records, and to inform individuals about more cost-effective therapies that might mean lower out-of-pocket costs. Wilfong asked Staggs what would happen if MEOS payments ended. He noted that patients—and even some in the healthcare system—may not realize that navigation and nutrition services are not reimbursed.

“That’s something that’s not just a concern of mine, but also the concern of our practices,” Staggs said. With the monthly payments as a foundation, practices invested in “patient-facing” resources such as navigation, nutrition, and social work—and they have seen the value. Having these additional staff available also allowed practices to make better use of nurses while capturing all the data needed to evaluate patients’ experience.

Staggs said practices are finding that “their patients have been making the best use of all these resources over the past 5 years. So, really, we’re trying to figure out a good bridge for them to maintain those resources and make them sustainable.”

Commercial Payers and Employers

How has the OCM changed the way other payers and employers approach value-based oncology care? Henschel said many payers have tried to adapt versions of the OCM to their infrastructure, but none are identical to the original. And “none or very few of them have any type of downside risk component for providers,” she said.

Value-based payment design is intensive, and the work involved has caused some to abandon the task. The lack of alignment across payers is tough for practices, and as a result the Community Oncology Alliance and the American Society of Clinical Oncology have worked to develop the Oncology Medical Home model, which would create standardization and “minimize the resource burden” for payers, Henschel said. Bundled payments and oncology case rates are becoming more common, she said, with some of this being handled by third-party administration.

What are the challenges for practices? Staggs concurred with Henschel’s comments about alignment, adding, “It’s really about stickiness,” meaning practices need to have a model they can count on using for several years instead of frequently changing course. Government models tend to last 5 years, whereas commercial models change more frequently, he said.

Wilfong said these burdens can distract from the goal of value-based care. “You can’t spend all of your administrative time focused solely on reporting requirements for various programs, because that takes away from your ability to take care of patients, which is our point,” he said. Sticking with a model long enough for it to work matters because it can take time to see the benefits. This was the case with the OCM. Early on, many practices struggled, but then there were 6 performance periods of sustained improvement. “And if we’d stopped too early, we wouldn’t have gotten there.”

The most important thing providers need from commercial payers, Jones said, is the “freedom to innovate.” The rise of vertical integration of payers and pharmacy benefit managers (PBMs), “particularly in the payer space where they’re bundling that,” he said. “And the (OCM) changed all that. All of a sudden, the incentives were there for you to make sure that you had access for those patients in your clinic, so that you could get them in and take care of them.”

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In the meantime, many of our practices have gone on to develop their own types of value-based agreements and incentive programs with the commercial payers in their region. So even those practices that are waiting for what’s coming next in CMS are going forward and continuing to enhance their care coordination programs; they are making other investments in care coordination so that they can be successful as this journey from fee-for-service to value-based reimbursement continues.

EBO: How does the Decision Path make treatment evaluations easier for providers?

VALLEY: The Decision Path tool is very unique. It’s certainly not the first clinical decision support tool in oncology; there are several of these tools out there. Many tools, though, have a hindrance in terms of adoption or utility in that they require the provider to go into a separate program to navigate and select the treatment regimens. And providers are really, really keen on doing things within their current workflow whenever possible.

So one of the key aspects of Decision Path is that it is integrated into the clinical workflow. The second aspect, where we really focused heavily in our initial...
product launch, is the ability to pull financial information on the cost of the treatment regimens into that decision support tool. So Decision Path is unique in that it is right within the clinical workflow and it does both of those things: decision support in the workflow and including financial information.

**EBO:** Does the tool specifically focus on drugs under the medical benefit or can this work in the pharmacy benefit setting as well?

**VALLEY:** Yes, it includes both, actually. Our financial tools within Cardinal Health Specialty have always been rather unique in that as we approached the market, we were very focused on having a more holistic view of treatment costs. That includes both infused, reimbursable drugs for the medical benefit as well as the pharmacy benefit. And so we follow the same methodology with Decision Path. You're able to see costs of oral and injectable or infusible drugs.

**EBO:** Does the tool identify treatment options based on payer formulary lists or does the tool prioritize the least expensive alternative, such as a biosimilar, regardless of formulary placement?

**VALLEY:** We also are able to show the ability or the impact of swapping out biosimilars. That's a very key component and something that is still of avid interest. Although our recent work here at Cardinal Health and looking at biosimilar adoption is showing that in oncology, it's just not new territory anymore to be thinking about that in terms of the biosimilar. It's probably getting a little more complex because we have the luxury now with some [reference products] with multiple biosimilars. That's where we think that the value will be as competition in that market and prices, cost, and patient support services are evolving to help providers get a little bit of a better handle on that in an easier, more efficient way.

**EBO:** Which financial aspects does the technology prioritize the most: the expense to the patients, the expense to the payers, or the expense to the practice?

**VALLEY:** It prioritizes the total cost. Then, as a corollary to that, it would be the patient's out-of-pocket that would be estimated. Our patient out-of-pocket estimates, I'd say, at launch, are a little bit more global and there we'll be able to be more specific as we continue to develop the product. For example, we're already making this tool very smart in that if a payer has a certain preferred pathway regimen, we're able to surface that to the provider easily so they don't have to say, "Oh, well, what payer does Mrs Jones have?" We'll service that up to them based on the information that Decision Path is obtaining from the practice management system and the patient demographic information. So we're able to prioritize that by payer as well.

**EBO:** How does the technology take into account rebates and reimbursements on drugs when helping providers make treatment-based decisions?

**VALLEY:** We're able to pull that information into the net cost of drug therapies. And so that really gets more at the providers' level costing more so than the patient's level costing for some of those areas. But we've always had the ability in all of our tool sets for providers and administrative and business personnel within the practice to understand net cost of drugs with and without GPO [group purchasing organization] rebates factored in, and that'll continue to be an element in all of our financial tools. Within Decision Path, since we're mostly focused on total cost of therapy and patient out-of-pocket costs, those GPO rebates and discounts aren't as much of a factor.

**EBO:** How would this tool take into account interchangeable products? Would biosimilars with interchangeable designations get a higher priority over others?

**VALLEY:** We haven't really thought through that piece of it yet. I think, at this point, with interchangeability being at its current state, we don't have as much of a need to have that automated within the tool at this point. But again, with our strength in biosimilars, it's certainly something that our VP [vice president] of biosimilars is supporting our team regularly to think through the when and how of how we'll be able to service those insights.

**EBO:** How can technology be updated to include new therapies and indications as they're approved? Will the updates have to be entered manually or will there be regular system-wide updates?

**VALLEY:** There will be regular system-wide updates. That's our current practice today. We don't really wait always for the new regimens to be entered into the system until NCCN [National Comprehensive Cancer Network] has had time to update. Although I think they're getting faster and faster at their updates. But sometimes a new therapy is approved and we want to be able to have that in there right away. And so we do have sort of a supplement, if you will, until things are reflected in the NCCN guidelines. But that's something we do on a regular basis and those will be automatically updated within the system.

**EBO:** Does the tool also take into account any drugs that are often used off label?

**VALLEY:** It does in the same manner that NCCN would think of those. There are many drugs throughout the NCCN guidelines that aren't necessarily officially indicated from an FDA labeling standpoint but have compendial listings and, of course, with NCCN being a compendial listing. So I think the definition for that has already been developed in our regular business and so we would continue to follow those.

**EBO:** Do you have any concluding thoughts?

**VALLEY:** I think it’s very interesting as we have been developing Decision Path, talking with providers, and looking at some of the wonderful work that’s been done by the National Cancer Institute and by other groups that have really done a lot to define what financial toxicity is. So we have a really good definition of the problem, but we don’t have a lot of solutions that help us navigate the issues. And it’s just such a big issue in oncology.

So I think what we’re excited about is being able to provide a solution. One of the things we commented on publicly recently was recent data showing that over 70% of oncologists and providers view it as part of their responsibility to have these economic discussions in the treatment planning process, but fewer than 25% of them do that. And the reason is that they don’t have tools like this to put the information at their fingertips for them to consider as they’re doing treatment plans to support their conversations with patients. So we’re really excited about the potential to have a really usable, practical tool in the hands of providers and start moving to having solutions to make a difference in how we navigate financial toxicity in cancer care.
WE ASPIRE TO CURE CANCER.

At Takeda Oncology, we aspire to cure cancer, with inspiration from patients and innovation from everywhere.
Crowdfunding for Cancer: What Financial Toxicity Among Young Adults Says About the US Health Care System

SKYLAR JEREMIAS

CONTINUED FROM COVER

In 2019, a survey from NORC at the University of Chicago found that 1 in 5 Americans reported that they or a household member had contributed to a crowdfunding campaign set up to fund someone's medical bills or treatment. Additionally, approximately 8 million Americans started a campaign for themselves or a household member, and about 12 million Americans started a campaign for someone else during the same year.

Adults in their 20s and 30s diagnosed with cancer can have a staggering financial burden, largely resulting from the high costs of medical treatments and the financial vulnerability that many people in this age range experience.

One study published in the Journal of Cancer Survivorship that investigated the experience of medical crowdfunding among young adults aged between 21 and 39 years found that despite how immensely helpful donations to campaigns were, medical crowdfunding also brought a lot of shame, stigma, and stress.

The study was the first to examine how crowdfunding impacted young adult survivors of cancer.

The study was conducted by researchers from The Samfund, a nonprofit organization dedicated to providing support to patients recovering from cancer treatments, and its goal was to survey patients about their opinions on their medical crowdfunding experiences. (In 2019, The Samfund merged with Expect Miracles Foundation.) The participants had a mean (SD) age of 27.65 (6.55) years and 84.8% were women. A majority were White, lived in suburban areas, had a bachelor's degree or higher at the time of their diagnosis, and had their campaigns started by a friend or family member.

“It’s a great thing that people can contribute, and that hopefully they find the help they need, but in what universe should that to have even happen in the first place?” said Samantha Watson, a study co-author, manager of stewardship at Expect Miracles Foundation and founder of The Samfund, in an interview with Evidence-Based Oncology (EBO).

Why Young Adults Gravitate to Crowdfunding

The high costs related to health care, insurance, treatments, and hospital care are worrisome for Americans regardless of age, especially regarding oncology. After cancer, patients may require regular screenings and subsequent treatments after overcoming their initial battle. But what makes beating cancer as a young adult extra-challenging, and why are so many young adult patients with cancer turning to crowdfunding?

“Navigating cancer as a young adult, is most likely [their] first major interaction with the health care system. So, young adults in their 20s are the age group least likely to have health insurance, and they have low financial health literacy, which is not a fault of their own,” said Lauren Ghazal, PhD, FNP-BC, a postdoctoral research fellow at the University of Michigan School of Nursing and study co-author, in a separate interview with EBO.

Additionally, young adults—who may still be attending school or are new to the workforce—have likely not had sufficient time to establish themselves in their careers. Young adults are more likely to face greater job insecurity, work lower-wage jobs, and have higher education-related expenses (ie, student loans).

The average amount of student loan debt for a bachelor's degree holder has more than tripled since the 1990s, from $10,000 to more than $37,000, and more than 43 million Americans currently have student debt, according to the Education Data Initiative.

Watson encapsulated the financial concerns of young adults with cancer: “It’s medical costs on top of everyday living expenses, on top of insurance concerns, on top of just everything all at once—at a time when you [often] don’t have enough money to pay for all of your bills anyway,” she said. “When you take into account someone’s life stage more so than specific age, someone in their early to mid-20s who is just starting out, if all of a sudden everything working against them, it becomes that much harder to catch up financially.”

Ghazal and Watson both have an in-depth perspective and special expertise on this topic: They are cancer survivors as well as researchers. Ghazal, who was diagnosed when she had recently begun her PhD studies, found the experience to be an eye-opener about how the US health care system functioned—and how lucky she was to have the support and background to help navigate it.

“When you take into account someone’s life stage more so than specific age, someone in their early to mid-20s who is just starting out, if all of a sudden everything is working against them, it becomes that much harder to catch up financially.”

—Samantha Watson, manager of stewardship, Expect Miracles Foundation; founder of The Samfund

Both Watson and Ghazal “recognized our privilege and our literacy in this, and [yet] it was still so overwhelming. What did it mean for others who didn’t have the background and clinical education, who didn’t have parental support, who didn’t have a community that could financially support them when they needed it?” said Ghazal.

For some young people with cancer, crowdfunding can feel like their only option.

The Pros and Cons of Crowdfunding

Crowdfunding can be considered a “life saver,” as one participant described it. Others added that crowdfunding was a stress reliever, a way to cover immediate expenses, and a tool that allowed them to focus on their health rather than bills. In addition, crowdfunding provided a convenient method of collecting donations, “Any funds that are raised or donated, also can be used to help someone pay their rent or pay for the gym membership that is critical to their healing but financially out of reach. There are a lot of things that people need money for during and after cancer treatment that they just can’t afford to pay on their own,” explained Watson.

Some study participants noted that crowdfunding may be helpful only for those who have established networks with or proximity to wealthy people. The ability to meet donation goals...
was found to be easier for those who had a larger following on social media or belonged to several communities, lived in wealthier areas, were from a higher socioeconomic background, and were White. Also, patients who have or are pursuing higher education may have an easier time networking with higher-income earners.

On the other hand, participants who had friends or family who didn’t have much disposable income reported struggling to meet donation goals.

Ghazal mentioned the concept of “crowdfunding campaign fatigue,” meaning that social media users may have seen so many crowdfunding campaigns that the ones for medical reasons may get lost in the shuffle. During the COVID-19 pandemic, especially, an abundance of crowdfunding campaigns arose for those who needed extra funds for food and shelter after losing their job or being hospitalized.

“If you’re scrolling Facebook, for example, and you see 20 people crowdfunding for something, they all get lost. I think that dilutes some of the importance of each one, because there are just so many people crowdfunding for something,” said Watson.

Most (52.2%) of the participants in the study did not meet their fundraising goal and the majority of those who did took 6 months to achieve their goal. Many of the participants saw donations dwindle after the first few months; one reported that a friend advised them to stop asking for donations after their treatment cycles were completed.

Additionally, crowdfunding websites carry privacy concerns. Patients with cancer who seek to start a campaign are forced to disclose a lot of personal medical information to a large amount of people, to convince them that their cause is worth donating to. Understandably, this can be stressful for patients. Patients may not have the time or emotional bandwidth between treatments to write up their story, or they may feel uncomfortable with the idea of marketing their illness or exposing vulnerable information about their medical conditions on the internet.

Many study participants “acknowledged fears related to publicly sharing personal health information, which has been found in other studies and labeled either as a privacy paradox or publicity tension,” described Ghazal. “[Questions] like ‘What would the campaigns do with this information?’ came up pretty often, as did, ‘How much information was just enough to share? How much information did I have to share to show that I’m in need?’”

Additionally, donations to crowdfunding websites are not tax-deductible, Watson mentioned, which can limit the number of people who have the means to donate to a person’s medical campaign. Some participants also expressed frustration that crowdfunding websites take a portion of the donations, a fact many donors may not realize prior to giving.

“I think [the fees] make sense to a certain extent, because with the volume of transactions that a site like GoFundMe is processing, there’s a cost to that donation process,” said Watson. “I think most people still don’t realize that. And so, transparency is key,” said Watson.

Several participants reported that they wouldn’t have been able to afford treatment and other necessities without medical crowdfunding. Crowdfunding was also reported as an easy way to allow loved ones to help, even if they don’t live nearby.

“The best thing that crowdfunding provides is the opportunity to do something. When you see someone you care about going through something very challenging, everybody’s first question is, ‘What can I do to help?’ And usually there’s nothing. But [crowdfunding] gives people a very easy, very tangible way to do something to help that person,” Watson continued.

However, other participants reported that feeling the need to ask family and friends for money made them feel “shameful,” “uneasy,” or “humiliated.”

“Looking at the financial toxicity faced by cancer patients has increased dramatically over the years....The partnership with Annexus Health will help overcome these financial barriers and reduce these burdens.”

—Todd Schonherz, CEO, American Oncology Network

According to an Annexus Health news release, the partnership will allow the Adparo team of “experienced financial counselors, who leverage the Annexus Health workflow platform, AssistPoint,” to help AONs practices obtain financial assistance for patients receiving cancer care by streamlining the application process.

“The financial toxicity faced by cancer patients has dramatically increased over the years,” said AONs CEO, Todd Schonherz, in the release. “At AON, we’re committed to minimizing the financial impact of cancer on families. This partnership with Annexus Health will help overcome these financial barriers and reduce these burdens.”

AON Partners With Annexus Health to Help Patients Gain Financial Assistance

AJMC Staff

AMERICAN ONCOLOGY NETWORK (AON) has formed a partnership with Annexus Health, which will allow oncology practices in the network to access the Adparo technology solution to help patients in the financial assistance process.

“The financial toxicity faced by cancer patients has increased dramatically over the years....The partnership with Annexus Health will help overcome these financial barriers and reduce these burdens.”

—Todd Schonherz, CEO, American Oncology Network

Health will help to overcome these financial barriers and reduce these burdens.”

As the cost of new cancer therapies has climbed, more and more patients need financial assistance or free drug programs to receive the best possible care. When executed well, patient assistance can make a tremendous difference. But the process for qualifying for these programs can be arduous, and many small practices cannot afford to pay staff members to focus solely on patient applications.

In their statement, Annexus Health officials said that the Adparo service will allow proactive contact with each patient to evaluate financial need, followed by eligibility verification and a search into what benefits might apply. If patients are eligible for programs, these can be managed through the AssistPoint platform.

“Annexus Health is in hyper-growth mode, and we’re excited to partner with AON for an incredible expansion of efforts to generically disrupt how the patient access journey is managed,” said Joe Baffone, Annexus Health co-founder and CEO.

Founded in 2018, AON is an alliance of 107 physicians and 85 physician assistants in practices across 16 US states. It allows practices to achieve economies of scale while pursuing value-based reimbursement models, and it creates protocols for practice management and administrative procedures.

REFERENCE

The US Health Care System and What Needs Fixing

A big takeaway from Ghazal and Watson’s study was that crowdfunding consistently questioned why they had to pursue crowdfunding as a possible solution to their cancer-related financial struggles.

“We live in a country where the costs of care falls on the shoulders of friends and family donating $5 and $10 at a time. It blows my mind that that’s where we’re at….our system needs a total overhaul,” proclaimed Watson.

In 2020, $208 billion was spent on cancer care in the United States, a number that is expected to increase to $246 billion by 2023, according to an analysis published in Trends in Cancer. Furthermore, up to 48% of patients with cancer reported financial toxicity, and up to 73% face subjective financial toxicity, including worries about paying bills and other costs of living.¹

Over the past decade, researchers have focused on financial toxicity, a term coined by Syed Younus Zafar, MD, and Amy Abernathy, MD, in 2013. The concept describes how financial distress can contribute to worse clinical outcomes and reduced quality of life in patients with cancer.²

Zafar and Abernathy referenced study results indicating that 19% of the patients surveyed believed that cost of their treatments caused their families a large amount of distress, 11% took treatment costs into consideration when deciding on whether to receive a therapy, and 9% decided not to receive a therapy because of the cost. All these patients had health insurance, dipped into their savings, and worked longer hours to be able to afford therapy.

Since the rise in awareness of financial toxicity, other researchers have explored its effects on the health of patients with cancer, including a landmark study that found an association with increased mortality.³ A patient-focused page published by the National Cancer Institute warns of the risks of depression and stress that can be associated with a filing for bankruptcy.⁴

Getting coverage for cancer therapies, especially newer ones, can be difficult to obtain for patients, as health systems may choose not to cover emerging therapies that have not yet been proven to provide significant value to patients and that exceed a certain monetary threshold.

From a business standpoint, pharmaceutical companies often offer rebates that can make expensive medications more affordable for health systems. However, because insurance plans are responsible for setting patient co-pays and co-insurance percentages, which are based on drug list prices without accounting for potential rebates, patients do not benefit from rebate programs and are subject to higher out-of-pocket costs.

Watson expressed worries about patients skipping or rationing medications as a means of avoiding high co-pays and neglecting follow-up care out of fear that they can’t afford it. “What does crowdfunding say about us? That’s exactly where we landed, but it doesn’t say anything good, in my opinion,” she said.

Results from the aforementioned NORC survey found that 60% of respondents said the government should bear “a great deal” or “a lot” of responsibility for providing help when medical care is unaffordable.

“It is clear that Americans want government and providers to work together to provide charity or assistance when needed,” said Susan Cahn, DrPH, MHS, MA, senior research scientist at NORC, regarding the survey. “Fewer Americans think that family, friends, or even strangers should shoulder the costs of care that patients and their families cannot afford.”

Watson, Ghazal, and authors of the Trends in Cancer analysis propose several solutions to address financial need for adults with cancer:

- Allowing the federal government to negotiate with companies to set drug prices
- Instituting a beneficiary out-of-pocket cap under Medicare Part D
- Allowing low-income Medicare enrollees who do not qualify for Medicaid to have their drug coverage improved
- Implementing pharmaceutical-led patient assistant programs with a straightforward and simplified application process
- Improving access to at-home health care services to avoid costs related to hospitalization and emergency department visits
- Implementing routine screening for financial toxicity in patients
- Providing financial counseling to physicians to help them approach sensitive topics with patients
- Providing financial navigation programs for patients in need of help with bill management

In their study on crowdfunding, the investigators cited earlier work that established a call for ethics-focused social science research into medical crowdfunding that put the issue into a larger perspective.

“When medical crowdfunding is described as a solution to the problem of inadequate access to medical care through these websites and the feel-good stories they encourage in the media, they help to divert attention from the much harder but necessary work of reforming health systems to ensure efficient and equitable access to medical care.”⁵

Ghazal emphasized the importance of having social and medical safety nets in place to allow young adult survivors of cancer to enjoy their lives after they beat cancer.

“They have felt that they’re a group that’s left behind, and that’s in between the pediatric and adult worlds,” Ghazal said. “We must ensure that we keep young adult cancer survivors on their treatment regimens in their homes, ensure they have the food that they need, and also have funds to be young adults—that is to socialize, be with their peers, and participate in the economy.”

References

8. Cadogan T. GoFundMe CEO: Hello Congress, Americans need help and we can’t do your job for you.” written by Tim Cadogan, the CEO of GoFundMe. Cadogan commented that despite the growing number of GoFundMe campaigns that were started to help people who were negatively affected by the COVID-19 pandemic, the website was never intended to be a replacement for a federal pandemic aid package.
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