CORONAVIRUS DISEASE 2019 (COVID-19) has had catastrophic effects on all aspects of health care, including cancer care. Oncology practices, just like all health care providers, have focused on reorganizing their operations to adjust to the changes driven by the pandemic. Providing a safe and protected environment for both patients and employees during a worldwide pandemic has become the number-1 priority over the past several months. While quality care is still being delivered to patients with cancer during this chaotic time, it is fair to say that continued practice transformation to meet value-based care initiatives has not been top-of-mind. Indeed, COVID-19 has had a dramatic impact on the significant progress being made regarding value-based cancer care, adding uncertainty and postponing the introduction of new reimbursement models.

With no quick fixes on the horizon to prevent or cure COVID-19, the pandemic will linger. Although some bandwidth previously dedicated to advancing value-based care may have been momentarily absorbed by the pandemic, that does not mean value-based care should be forgotten. Providers still must think about value. With the initial emergence of the virus in the rear-view mirror, it is fair to say that continued practice transformation to meet value-based care initiatives has not been top-of-mind. Indeed, COVID-19 has had a dramatic impact on the significant progress being made regarding value-based cancer care, adding uncertainty and postponing the introduction of new reimbursement models.

There are 3 important ways this public health emergency ultimately makes this model and others like it more appealing.

Prospective Management Fees Bring Reliable Payment
Providers in capitated or semi-capitated payment arrangements are paid predetermined amounts to care for a population of patients.

IN THE MONTHS SINCE the Oncology Care First (OCF) Informal Request for Information (RFI) comment period closed in December 2019, America’s health care system has faced a reckoning. A series of alternative payment model (APM) updates made by the Center for Medicare & Medicaid Innovation (CMMI) in the wake of coronavirus disease 2019 (COVID-19) included a yearlong extension to the Oncology Care Model (OCM) and a delayed start of the OCF program. While downside risk exposure in voluntary APMs might give potential participants pause as they recover from the impact of COVID-19, there are 3 important ways this public health emergency ultimately makes this model and others like it more appealing.

IN THE GUIDELINES. Tafasitamab plus lenalidomide is added quickly to the NCCN guidelines following FDA approval in relapsed or refractory diffuse large B-cell lymphoma (DLBCL), meeting the needs of patients who are not eligible for an autologous stem cell transplant.

Understanding the Challenges of Rural Cancer Care
Mary Caffrey

PARIS, TEXAS, WITH A POPULATION of about 25,000, is a long way in both miles and culture from Detroit, Michigan, where Sucharu “Chris” Prakash, MD, completed a fellowship in oncology and hematology. The city near the Red River that forms Texas’ boundary with Oklahoma offered an easier pace of life, friendly people, and a good place to raise a family, so 20 years ago Prakash and his wife made it their destination.

In 2019, Sucharu “Chris” Prakash, MD, and Kelly Preston, center, accepted a donation to the Texas Oncology Foundation for Breast Cancer Awareness Month from employees of Turner Industries, Paris, Texas.
A breakthrough for patients with advanced CSCC

LIBTAYO® is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.¹

For patients with mCSCC or laCSCC receiving 3 mg/kg every 2 weeks in Study 1540:

<table>
<thead>
<tr>
<th>Objective response rate*</th>
<th>31% PR (partial response)</th>
<th>15% CR (complete response*)</th>
</tr>
</thead>
</table>

ORR: 63 out of 137 patients (95% CI, 37%-55%)

79% of responders (50 out of 63 patients) reached a DOR of ≥6 months¹,²
54% of responders (34 out of 63 patients) reached a DOR of ≥12 months¹,²

Median DOR was not reached (range: 1.9–24.2+ months)¹,³

*Median duration of follow-up was 11.1 months for combined CSCC in Study 1540.⁴ See additional study design details below.

Only includes patients with complete healing of prior cutaneous involvement; patients with laCSCC in Study 1540 required biopsy to confirm CR.⁵

In an additional cohort in Study 1540, 56 mCSCC patients received LIBTAYO at a dose of 350 mg intravenously every 3 weeks for up to 54 weeks. With a median duration of follow-up of 8.0 months, the confirmed ORR was 41% (95% CI: 28, 55), and 65% of responders had a DOR ≥6 months.¹

Median DOR was not reached (range: 2.1–11.1+ months)⁶

Plus sign (+) denotes ongoing at last assessment.

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.¹

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1-blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistry, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent), or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-mediated pneumonitis: Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg/day or equivalent. Pneumonitis resolved in 62% of patients. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated colitis: Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 5 (0.4%) and Grade 2 (0.6%). Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 62% who received prednisone ≥40 mg/day or equivalent. Colitis resolved in 80% of patients. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated hepatitis: Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg/day or equivalent. Hepatitis resolved in 64% of patients. Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 2) after corticosteroid taper.

Immune-mediated endocrinopathies: Withhold LIBTAYO if clinically necessary for Grade 2, 3, or 4.

• Adrenal insufficiency: Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%)
• Hypophysitis: Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis
• Hypothyroidism: Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%), no patients discontinued hormone replacement therapy

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
LIBTAYO® (cemiplimab-rwlc) demonstrated meaningful tumor reduction in clinical trial patients1,2

Partial responses
These are examples from the 31% of patients who had a partial response in clinical trials. Individual patient responses may vary.

Important Safety Information (continued)

Warnings and Precautions (continued)

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated endocrinopathies (continued):

• Hyperthyroidism

Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%), or thyrotoxicosis resolved in 38% of patients

• Type 1 diabetes mellitus

Type 1 diabetes mellitus, which can present with diabetes-ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

Immune-mediated nephritis with renal dysfunction:

Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone >40 mg/day or equivalent. Nephritis resolved in all patients. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated dermatologic adverse reactions:

Immune-mediated dermatologic reactions, including erythema multiforme and pemphigus, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%). In addition, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone >40 mg/day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-administration of LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO or were reported with the use of other PD-1–blocking and PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

• Neurological: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, and autoimmune neuropsychiatric disorder.

• Cardiovascular: Myocarditis, pericarditis, and vasculitides.

• Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various Grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

• Gastrointestinal: Pancreatitis, increase in serum amylase and lipase levels, gastritis, and duodenitis

• Musculoskeletal and connective tissue: Myalgia, myositis, and associated sequelae, including renal failure, arthritis, and polyarthalgia rheumatica

• Hematological and immunological: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Emphysema-related toxicity

LIBTAYO can cause fatal hemolysis when administered to a pregnant woman due to an increased risk of immuno-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

Adverse reactions

• Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in ≥2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia.

• LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptica meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, paresthesia, rash maculopapular, pruritis, and confusional state.

• The most common adverse reactions (incidence ≥20%) were fatigue, rash, diarrhea, musculoskeletal pain, and nausea.

Use in specific populations

• Lactation: Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

• Females and males of reproductive potential: Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO.

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

References

To learn more about LIBTAYO, speak with your sales representative or visit LIBUTAYOhcp.com.

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LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE
LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

2 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Severe and Fatal Immune-Mediated Adverse Reactions
LIBTAYO is a monoclonal antibody that belongs to a class of drugs that binds to the programmed death receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response with the potential for breaking of peripheral tolerance and induction of immune-mediated adverse reactions.

Important immune-mediated adverse reactions listed under Warnings and Precautions may not be inclusive of all possible immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ or system. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions.

Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions [See Dosage and Administration (2.2)]. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over one month [See Dosage and Administration (2.2)]. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immun-mediated Pneumonitis
Immun-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), Grade 4 (0.2%) and Grade 2 (1.3%) [See Adverse Reactions (6.1)]. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥ 40 mg per day or equivalent. Pneumonitis resolved in 62% of patients.

Immun-mediated Colitis
Immun-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%) [See Adverse Reactions (6.1)]. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥ 40 mg per day or equivalent. Colitis resolved in 80% of patients.

Immun-mediated Hepatitis
Immun-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%) [See Adverse Reactions (6.1)]. Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥ 40 mg per day or equivalent. Hepatitis resolved in 64% of patients.

Immun-mediated Endocrinopathies
Adrenal Insufficiency
Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%) [See Adverse Reactions (6.1)].

Hypothyroidism
Hypothyroidism, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of one patient with Grade 3 hypothyroidism.

Hypothyroidism
Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%). No patients discontinued hormone replacement therapy.

Hypertension
Hypertension occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%). Type 1 Diabetes Mellitus
Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

Immune-Mediated Nephritis with Renal Dysfunction
Immun-mediated nephritis occurred in 8.6% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%) [See Adverse Reactions (6.1)]. Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥ 40 mg per day or equivalent. Nephritis resolved in all patients.

Immune-Mediated Dermatologic Adverse Reactions
Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%) [See Adverse Reactions (6.1)]. In addition, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 88% who received prednisone ≥ 40 mg per day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO.

6 ADVERSE REACTIONS
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 data described in Warnings and Precautions reflect exposure to LIBTAYO in 534 patients in two open-label, single-agent, multicohort studies (Study 1443 and Study 1540), including 98 patients with mCSCC (nodal or distant), 65 patients with laCSCC, and 371 patients with other advanced solid tumors. LIBTAYO as a single agent in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks (n=27), 3 mg/kg every 2 weeks (n=446), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=6), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=23). Among the 534 patients, 38% were exposed for ≥ 6 months and 16% were exposed for ≥ 12 months.

The data described below reflect exposure to LIBTAYO in 218 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1443 and Study 1540 [See Clinical Studies (14.1)]. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 1 week (n=1), 3 mg/kg every 2 weeks (n=1), 10 mg/kg every 2 weeks (n=156) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% white and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3-4 adverse reactions (≥ 2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia. LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, septic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, tetany, pruritus, rash, maculopapular, pruritus, and conjunctival stasis. Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia.

Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 2 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

Table 1: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1443 and Study 1540

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>LIBTAYO N=219</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue†</td>
<td>34</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus*</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>25</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain†</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management
receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that binds to the programmed death

534 patients who received LIBTAYO [see Adverse Reactions (6.1)] or were reported with the use of other
The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in
Other Immune-Mediated Adverse Reactions

reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions

Immune-Mediated Colitis

patients.

Grade 4 (0.2%), and Grade 3 (1.7%) [see Adverse Reactions (6.1)]. Hepatitis led to permanent discontinuation

Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%),

≥

Immune-Mediated Endocrinopathies

Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), and

Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2

≥

≥

Fatiguea 34 3

Coughf 14 0

Musculoskeletal paine 24 3

Musculoskeletal and Connective Tissue

Nausea 21 0

Diarrhead 25 0.5

Skin and Appendages

Fatiguea 34 3

Coughf 14 0

Musculoskeletal paine 24 3

Musculoskeletal and Connective Tissue

Nausea 21 0

Diarrhead 25 0.5

Table 1: Adverse Reactions in ≥10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540 (continued)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=1219</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10</td>
<td>8.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>8.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

a. Fatigue is a composite term that includes fatigue and anemia
b. Rash is a composite term that includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction
c. Pruritus is a composite term that includes pruritus and pruritus allergic
d. Diarrhea is a composite term that includes diarrhea and colitis
e. Musculoskeletal pain is a composite term that includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain
f. Cough is a composite term that includes cough and upper airway cough syndrome

Table 2: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased INR</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>4</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v. 4.03

* Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

6.2 Immunogenicity

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

Anti-drug antibodies (ADA) were tested in 467 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.1% using an electrochemiluminescent (ECL) bridging immunoassay; 0.2% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1)). There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice.

Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or alter the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO [see Use in Specific Populations (8.1)].

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 219 mCSCC or uCSCC patients who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

REGENERON | SANOFI-GENZYME

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Creativity is just connecting things. — Steve Jobs

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A new study finds that despite advances in early cancer detection, counties with high poverty levels have greater cancer mortality risk. Disparities persist among those with greater exposure to carcinogens, low educational attainment, and lack of access to care.
FROM THE CHAIRMAN

COVID-19 Shows Oncologists Who Embrace Value Fare Better

THIS IS NOT THE ISSUE we thought we would bring you when 2020 began.

When we gave our October issue of Evidence-Based Oncology™ the theme, “Alternative Payment Models,” oncology practices were buzzing about Oncology Care First, the apparent successor to the Oncology Care Model (OCM), as well as the prospect of a Radiation Oncology (RO) Model. Each represented a step toward episode-based or “bundled” payment, with the idea that doctors and practices would move away from the fee-for-service (FFS), or in medical oncology, the buy-and-bill system that had defined their existence.

While there has been broad agreement this needed to happen, the details of getting there can be easier said than done. And, the future of how cancer care would be funded was still very much in doubt when the unthinkable happened:

What if your business model depends on patients walking through the door, and almost no one does?

That is what medical and radiation oncologists faced in March 2020, when the coronavirus disease 2019 (COVID-19) public health emergency hit like a tsunami, dividing time into Before and After. Lessons emerged quickly: practices that could adapt to change would fare better; many adopted telehealth and new safety measures, and entrepreneurs sprang up to help deliver more care at home. Practices that could deliver a more holistic, value-based set of services—including nutrition, chronic disease management, and survivorship care—would fare better than those wedded to old financial models.

CMS responded, but in different ways to different groups of doctors. It extended the OCM, with its FFS framework, for an additional year, thus giving medical oncologists more time to prepare for the OCF—and more time for everyone to learn what they didn’t know about the effects of a pandemic on 2-sided risk. For radiation oncologists, it was a different story (see SP237), and these physicians now have 90 days to prepare for a new payment model that will take effect when the pandemic will be ongoing. The RO Model was finalized over the objections of practitioners, and at press time the American Society for Radiation Oncology, along with the American Medical Association and other groups, was asking CMS to delay the model’s start until January 1, 2022, at the earliest.

Throughout this issue, we bring you all the ways that COVID-19 has affected the progress toward payment reform while demonstrating that it is ultimately needed.

Sincerely,
Mike Hennessy Sr
Chairman and Founder

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THE CENTER FOR BIOSIMILARS

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Too Much, Too Fast: Providers Push Back on CMS’ Final RO Model

MARY CAFFREY

A NEW ALTERNATIVE PAYMENT MODEL (APM) for radiation oncology (RO) has drawn fire from providers, who say a mandatory shift to bundled payments in the middle of a pandemic is unfair. Transitions cost money, and many have none to spare.

CMS Administrator Seema Verma vowed full steam ahead when she finalized the RO Model on September 18, claiming the change that takes effect January 1, 2021, would save $230 million over 5 years and likely mean lower out-of-pocket costs for Medicare beneficiaries.1

"Today, Medicare payment for radiotherapy is based on the number of treatments a patient receives and where they receive it, which can lead to spending more time traveling for treatment with little clinical value," she said in a statement.1

Radiation oncologists have been bracing for a move to a bundled payment model for a while. But they say the timing—in the wake of staffing shortages caused by the coronavirus disease 2019 (COVID-19) pandemic—could not be worse.

The American Society for Radiation Oncology (ASTRO) argues that the planned start date is too aggressive for a model that would be mandatory for 30% of providers, and the group said it would go to Congress to seek relief.2

"The transition to value-based payment will require significant practice changes and investments to comply with the model’s requirements. ASTRO strongly urges CMS to significantly delay the start date rather than foster unnecessary chaos and burden for the practices this model is designed to support," the group said in a statement.2

The American College of Radiology echoed these concerns.3

The RO Model was in the works well before COVID-19, as CMS has been determined to create a payment structure that is site neutral and rewards outcomes, not the number of treatments a patient receives. Historically, payments have been doled out bit by bit, giving providers an incentive to keep treating and billing. CMS argues that evidence shows "for some cancer types and beneficiaries, a shorter course of [radiotherapy] treatment would go to Congress to seek relief."1

"The transition to value-based payment will require significant practice changes and investments to comply with the model’s requirements. ASTRO strongly urges CMS to significantly delay the start date rather than foster unnecessary chaos and burden for the practices this model is designed to support," the group said in a statement.2

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Elements of the RO Model

The RO Model calls for bundled payments over a 90-day episode of care, which would go to radiotherapy providers who treat 1 of 16 cancer types. CMS said it would require participation from physicians in randomly selected geographic areas covering 30% of all current Medicare fee-for-service episodes (the initial proposal was 40%). The model has a 5-year performance period that would run through December 31, 2025.5

According to a CMS fact sheet, the episode payments would be split into 2 components: the professional and technical pieces, which would allow the existing claims systems for the Physicians’ Fee Schedule (PFS) and the Hospital Outpatient Prospective Payment System (OPPS) to be used to pay claims.

A chief mission of the model, according to CMS, is to emphasize “site-neutral payment by establishing a common, adjusted national base-payment amount for the episode, regardless of the setting where it is furnished.”4

Payment will be linked to quality through performance measures, clinical data reporting, and patient experience factors. The model allows providers to meet Advanced APM requirements under the Quality Payment Program. Beneficiaries must be notified their provider is taking part in the RO Model.

Model Pricing and COVID-19

The RO Model calls for participant-specific payments that take into account a mix of national base rates, trend factors, and "adjustments for each participant’s case mix, historical experience, and geographic location." CMS then applies a complex system of discount factors. But CMS will be basing 90% of the payment on a practice’s historical payments from 2016 to 2018, even though an ASTRO released in May found that 85% of members reported a decline in visits due to COVID-19, by an average of one-third.5

"While these volume declines won’t impact the historical experience data, they likely will impact other aspects of the model, most notably the payment adjustment that accounts for case mix, as we expect more patients to present with more complex disease due to delayed screening. These issues will likely confound at least the first year of CMS’ evaluation of the model,” Dave Adler, vice president for Advocacy, ASTRO, told Evidence-Based Oncology” (EBO) in an email. "Skewed results in the first evaluation report would start the program off on the wrong foot and jeopardize the future of the model. This is an important reason to delay the model until after the pandemic.”

EBO asked if the amounts of bundled payments in the early part of the model could be under valued, as most experts predict a wave of patients with advanced cancers will be diagnosed in late 2020 or early 2021 due to missed screenings. Adler said this is possible.

In their statement, ASTRO providers said they remained committed to working toward a value-based payment model, but under the current circumstances they believe a voluntary phase is needed first. “ASTRO has worked with CMS and bipartisan legislators for several years toward a viable payment model for radiation oncology that would support stable and fair payments, drive adherence to..."
nationally recognized clinical guidelines, and improve patient care,” the statement said. “We are hopeful that CMS and Congress are open to reconsidering a start date that would be realistic and not derail this unique opportunity.”

Adler said ASTRO will seek a delay of implementation until July 1, 2021—and potentially later if the pandemic persists—and to reduce the discount factor payment cuts to 3%. This would put the discount factor cuts in line with other models from CMS, he said.

Lower Out-of-Pocket Costs?
CMS’ details suggest that along with bundled payments to providers, the current 20% coinsurance paid by beneficiaries would be configured differently. “Since CMS applies a discount to each component of the bundled payment, the agency expects that beneficiary cost sharing would be, on average, lower relative to what typically would be paid under Medicare’s fee-for-service system,” the fact sheet states.

The model covers 16 diagnoses that account for the vast majority of solid tumor cancers: anal cancer, bladder cancer, bone metastases, brain metastases, breast cancer, cervical cancer, central nervous system tumors, colorectal cancer, head and neck cancer, liver cancer, lung cancer, lymphoma, pancreatic cancer, prostate cancer, upper gastrointestinal cancer, and uterine cancer.

“While these declines won’t impact the historical experience data, they likely will impact other aspects of the model, most notably the payment adjustment that accounts for the case mix, as we expect more patients to present with more complex disease due to delayed screening.”

—Dave Adler, vice president, Advocacy, American Society for Radiation Oncology

References

Join The Center for Biosimilars® network at centerforbiosimilars.com

The Center for Biosimilars® was cited in United States Senate testimony on prices and out-of-pocket costs for rheumatoid arthritis drugs. As a preeminent resource, the Center for Biosimilars® provides relevant information on the current biosimilars landscape and its impact on advanced healthcare management.
BEFORE ANY VACCINE for coronavirus disease 2019 (COVID-19) is approved, millions of people will have contracted this virus. Although some will die, others will survive being infected with the virus, only to face long-term consequences to their health. But a vaccine isn’t the panacea many assume it will be. Even when it becomes available, the virus won’t go away. A percentage of people will still contract the illness, so it is vital that we understand how best to detect, trace, and treat it in varying populations.

Even with all the data gathered during this pandemic, there is still so much that we don’t know about the virus and won’t know for years to come.

In response, the health care industry needs to gather as much data about patients and vaccine recipients as possible to guide treatment decisions, identify risks, and inform standards of care. In the near term, this data will help us better understand the acute impact of the disease and the effectiveness of new vaccines. In the long term, real-world data from COVID-19 patients will show us how the virus impairs the body, what new health risks it creates, and what long-term complications will emerge.

Real-world evidence (RWE) gathered from longitudinal studies of patients with COVID-19 and vaccine recipients will play a crucial role in achieving these goals.

RWE Offers a Treatment Road Map

For a virus that has such a heterogeneous presentation, insights from real-world populations are mission critical; we have to know how and in whom this disease presents, as well as the treatments used to combat the illness in the real world, because there is no “standard” presentation or treatment protocol.

As a result, health care professionals are flying blind, making treatment decisions based on clinical experience, short-term outcomes and anecdotal results from peers facing the same sets of challenges. Among the biggest challenges is the confusing variety in presentation—different symptoms, many presenting like the common cold, as well as different outcomes occurring across the patient set. As of this past summer, there was no clear indication who would have the worst prognosis. Many complications from COVID-19 appear to be long lasting, including effects on lung capacity, myocarditis, chronic fatigue, and vertigo. Because the virus is so new, it is difficult to predict who will contract these long-term, problematic symptoms. It is hard to know how they might be prevented and what other long-term consequences exist that have yet to be identified.

Fortunately, transparency in care is high, and shared knowledge about the virus grows daily. RWE is a critical ingredient here, helping to address this lack of clarity by predicting how the virus is likely to behave in different populations so that clinicians can adapt their treatment plans and minimize risks of serious complications related to the virus.

The value of real-world studies has been increasingly recognized in recent years. Their use has been enabled by rapid access to large, diverse health care data sets and advances in artificial intelligence–based analytics platforms. This combination of data and technology makes it possible to conduct near real-time analyses of health care trends and, for the first time, to create a more robust and accurate understanding of disease and treatments.

Despite the novelty of this virus, real-world data—health information collected in real-world health care settings (ie, not in clinical trials) that can be analyzed to generate RWE—have already been collected from millions of patients across the world from electronic medical records, hospital reports, statewide health care utilization reports, testing centers, insurance claims databases, patients, and other real-world sources. Investigators can rapidly analyze these data sets to answer important questions, such as how and why different populations contract the disease, where and where they seek treatment, what outcomes they experience, and how those outcomes vary based on their access to health care, comorbidities, and other factors.

The health care industry didn’t previously have the ability to gather real-world evidence at the speed and scale needed to address urgent public health crises. But we do now. Advances in analytics, technology, and access to broad and diverse real-world data sets have made it possible to rapidly analyze data as its captured to better understand how these events are unfolding.

These studies are mission critical for building a sufficient profile and understanding of the virus and for tracking long-term symptomology in patients who contract the virus. Such insights will inform immediate treatment decisions and support better decision-making when it comes to population health measures, such as vaccine development.

Once vaccines come to market, studying their impact in real-world populations will be critical to assessing their long-term safety and effectiveness as well as uncovering any adverse events that may be too rare to show up in the clinical trials used for approval.

Real-World Study Models

Researchers have many real-world study models to choose from based on the questions they want to answer and the data they can access.

One of the most applicable designs for COVID-19 research is a natural history of disease study, which follows people who’ve had a disease or who are likely to get it to understand their disease journey, symptomology, treatment paths, and outcomes. These studies use clinically rich data from patient registries, electronic health records, surveys, and other primary and secondary sources to determine how people contract a virus, how it impacts different patient populations, and what treatments deliver the best outcomes.

Enriched real-world studies are another model that will be useful for determining long-term outcomes in people who receive the vaccine or a specific treatment. Enriched studies analyze existing health care data to generate a baseline of knowledge and then collect additional prospective data to fill in gaps while putting minimum participation burden on patients. This allows patients to answer more detailed questions about things like —
Generating RWE to Understand COVID-19

We are already seeing valuable RWE gathered about the virus through the innovative use of real-world studies.

In July 2020, the FDA Oncology Center of Excellence published the results of a real-world study that reviewed more than 212,000 health records of people living with cancer. The analysis found that cancer patients who also had COVID-19 were more likely to experience increased rates of hospitalization and invasive mechanical ventilation and faced a 16-fold increased mortality risk.1

In another example, the Observational Health Data Sciences and Informatics community conducted an 88-hour virtual study-a-thon in March to inform health care decision-making in response to the pandemic.2 The event drew 330 global experts who answered critical questions about the virus, including conducting a global characterization study of COVID-19–positive patients from countries around the world.

These are just 2 examples of how RWE can be generated to understand this disease, inform development of new vaccines and treatments, and provide better care for at-risk patients.

The health care industry didn’t previously have the ability to gather RWE at the speed and scale needed to address urgent public health crises. But we do now. Advances in analytics, technology, and access to broad and diverse real-world data sets have made it possible to rapidly analyze data as it’s captured to better understand how these events are unfolding.

If we work together to capture these insights and share them globally, we will be best positioned to meet the needs of patients and communities around the world.

References
The fact that IMM-101 was already being studied to boost immunity in cancer patients led the “synergy” with Auer, who came up with the idea while trying to find ways to protect her surgical patients. “We asked ourselves, ‘Is this not a product that we really should be testing in the context of COVID-19?’” O’Callaghan said.

**At-Risk Patients Included**

Patients in the treatment arm will receive 3 doses of the drug, on days 0, 14, and 45. Patients in a control arm will be observed.

The real-world population with cancer includes many patients with type 2 diabetes (T2D) or seniors, but it’s not uncommon to see these patients excluded from clinical trials. The nature of COVID-19 demands that the IMM-101 be different.

“In the context of investigating whether we can reduce not only the number of infections, but potentially the severity of COVID-19 infections, including patients with diabetes was appropriate,” O’Callaghan said. “In fact, we are specifically looking to include patients with other risk factors, such as [older age].”

Of critical importance, the study has developed protocols to safely and ethically include nursing home patients, using a pragmatic trial design that incorporates the study into existing chemotherapy administration. Any additional data collection would be done remotely, O’Callaghan said. 

**REFERENCES**


### Case Report: Ibrutinib Might Protect Against Acute Lung Injury in Patients With CLL, COVID-19

**JARED KALTWASSER**

**ONE OF THE MOST DIFFICULT** decisions facing oncologists is whether to suspend immunosuppressive therapy due to the risk of coronavirus disease 2019 (COVID-19) infection. In a new case report in *eJHaem*, investigators outlined what happened when they continued a course of ibrutinib (Imbruvica) in a patient who had chronic lymphocytic leukemia (CLL).

Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor and an interleukin-2 inducible T-cell kinase (ITK) inhibitor. The patient had developed a severe case of COVID-19, but was able to successfully continue taking ibrutinib, and the authors suggest the drug may have helped protect the patient.

The subject, a 77-year-old man, is a patient at the Robert H. Lurie Comprehensive Cancer Center, part of the Northwestern University Feinberg School of Medicine. His CLL, 13q del, was diagnosed in 2005. He was started on ibrutinib at a dosage of 420 mg/day in March 2016. He had been stable for 4 years.

In March 2020, he visited an urgent care clinic, reporting a sore throat, fevers up to 101°Fand a slight dry cough; he had recently been on an over-the-counter cold medication. He returned home, where his wife noticed he looked “very ill.” He was started on a higher dose of 560 mg/day in March 2016 and the inflammatory cytokine response in the lungs. So, they started the patient on a higher dose of 560 mg.

On the 12th day of his admission, the patient was started on a high-flow nasal cannula. Day 14 saw him transferred to the COVID-19 unit on a 2L nasal cannula. However, the next day, the patient had recurrent acute hypoxemic respiratory failure with apparent ventilator-associated pneumonia.

He was extubated after 2 days, weaned off oxygen 3 days later, and eventually discharged to acute rehabilitation 28 days after admission. At that point, his dose was returned to 420 mg. After 2 weeks of rehab, he was sent home.

The authors concluded that it is possible ibrutinib played a protective role against ALI, but they said it’s difficult to know for sure, since he was also on other medications, such as tocilizumab (Actemra).

“Although logically BTK inhibitors should have efficacy in preventing or treating [acute lung injury] in COVID-19, further studies in animal models as well as clinical trials are required to define the optimal role of ibrutinib in patients with life-threatening viral infections.”

—Case report, *eJHaem*

"We elected to continue ibrutinib the same day he was intubated, reasoning that BTK inhibition in myeloid immune cells has been shown to reduce or even reverse influenza-mediated acute lung injury (ALI) and that ITK inhibition in T cells has correlated with reduction in viral replication, and therefore may have an advantage in this setting," wrote corresponding author Leo I. Gordon, MD, and colleagues.

They also noted that ibrutinib has been shown to block Src family kinases, which could reduce viral entry and the inflammatory cytokine response in the lungs. So, they started the patient on a higher dose of 560 mg.

Of critical importance, the study has developed protocols to safely and ethically include nursing home patients, using a pragmatic trial design that incorporates the study into existing chemotherapy administration. Any additional data collection would be done remotely, O’Callaghan said.

**REFERENCES**


FDA Draft Study on Biosimilar Disclosures Draws Fire

TONY HAGEN

The second part of the study will evaluate how disclosing that a drug product is a biosimilar affects HCP and consumer perceptions. Participants will also be asked to respond to various informational statements about biosimilars.

Study participants will also be asked for their reactions to multiple versions of language describing biosimilars and their relative safety and efficacy to reference products.

“This approach allows us to examine the effect of disclosing biosimilar status, examines the additive effect of including 1, 2, or 3 additional basic statements of information about biosimilars, and measures the effect of naming the reference product,” the FDA wrote.

In public comments about the study proposal, the Biosimilars (Forum), representing biosimilars developers, said it was concerned about how language used to describe biosimilars may be “vouched in cautious or negative terms,” which hold the potential to be off-putting to HCPs and consumers. It asked for a stronger emphasis in the study on garnering patient perceptions of biosimilar disclosures. “In the 6 years since the Forum was founded, we have found that while knowledge and perceptions of HCPs have increased…knowledge levels of patients are still low,” the group wrote.

Similarly, the drug company Bayer commented that the language of the study as it would be presented to participants sounded clinical and should be rewritten for consumer participants so that it was “patient friendly.”

The Hematology/Oncology Pharmacy Association asked that the study also evaluate the value of adding information about use of biosimilars for all indicated uses, or extrapolations, of the reference product. “Several studies have indicated that understanding, or lack of understanding of, biosimilars in extrapolated indications impacts a health care professional’s use of a biosimilar,” the group said.

A further critique of the study came from the Pharmaceutical Research and Manufacturers of America, which contended that the study will not provide useful information because such information is already available to the FDA from other sources, that the proposed study as designed is “flawed” because secondary end points are more important to a product’s indicated uses than the study design seems to suggest, and that the study unfairly uses a genuine product, Humira (adalimumab), as a case example while using an anonymous or fictitious biosimilar.

That last point also drew an objection from AbbVie, which owns the Humira brand. The “FDA should refrain from using the name of a reference product currently on the market in the questionnaire and instead use a fictitious name for a reference product, as it does for the biosimilar,” the company said.

Importance of Consumer Perception

The importance of getting label language right for biosimilars is illustrated by the problem with consumers’ understanding of alternative health products, the FDA noted. “Research on consumer attitudes has found some people believe that FDA evaluates certain dietary supplement claims despite the presence and consumer awareness of language required by the Dietary Supplement Health and Education Act, which clearly states that FDA has not evaluated those claims.”

Reference


ACP Calls for Biologics Marketplace Reforms

TONY HAGEN

A DYSFUNCTIONAL REGULATORY and market system is responsible for the high prices of drugs and the slim foothold that biosimilars have achieved so far in the US marketplace, according to a position paper from the American College of Physicians (ACP).

The group describes numerous structural impediments that hinder market entry for lower-cost drugs and allow pharmaceutical companies to leverage larger and larger revenues from their original brand products without a commensurate increase in health care professional value.

ACP suggests multiple policy changes that would make it to the market faster, and ensure a robust and competitive market for generic and biosimilar drugs,” ACP said.
The United States produces 57% more new drugs than the United Kingdom, Japan, Germany, and France combined, but many new drugs are simply repurposed old drugs with new indications, and meanwhile, “there are thousands of rare diseases for which treatments exist for only a tiny fraction,” ACP said.

Many Americans have benefited from the development of “orphan drugs” for niche health conditions (≥200,000 patients), but these are generally very costly, and ACP states that an orphan drug might be only a rare disease indication for a commonly used drug. Because of its orphan status, that same drug would be granted an additional 7 years of product exclusivity, preventing lower-cost competition from exerting downward pressure on pricing.

“This puts a strain on patients and families affected by rare diseases who are often already exposed to high direct and indirect costs of medical care,” ACP noted.

ACP described the American marketplace as “unregulated” when it comes to pricing freedom enjoyed by pharmaceutical producers. “The list prices for the originator rheumatoid arthritis drugs Enbrel (etanercept, Amgen), Humira (adalimumab, AbbVie), and Xeljanz (tofacitinib, Pfizer) have increased by more than 100% since 2014,” the group said.

Biosimilars have been approved for etanercept and adalimumab, but because of patent protections these alternatives will effectively be kept off the market until 2029 and 2023, respectively. “Preventing lower-cost biosimilar or generic drugs from entering the market adds billions of dollars in costs to federal health care programs and affects the affordability and accessibility of drugs for patients who rely on them on a day-to-day basis,” ACP said.

**Patent Protections**

Patent protections for biologics extend to 12 years in the United States, which the group said is excessive. Product exclusivity is often considered essential to reward companies for innovating and to compensate them for the costs of developing a new drug. However, ACP argues that even after loss of exclusivity and biosimilar products entering the marketplace, a pharmaceutical company is able to continue making sizeable profits from a drug.

According to the Pacific Research Institute, the first biosimilar for filgrastim—and, in fact, the first biosimilar in the United States—was launched in 2015, and since that time, filgrastim biosimilars have achieved only a 50.4% share of the marketplace for filgrastim, supporting the ACP’s contention that originator brands can continue making money after their patents have expired.

Manufacturers and industry insiders have contended that the 12-year window for product exclusivity is largely an illusion because many factors may shorten that time, such as a delayed approvals process. Insulin product approvals have recently come under regulation via the Biologics Price Competition and Innovation Act, which affords them biosimilar status if they are not originator drugs. It is hoped that this will lead to greater price competition, and ACP noted that the absence of competition for insulin products has allowed manufacturers to control the marketplace and steadily increase prices.

“The annual cost per patient for treatment of type 1 diabetes doubled between 2012 and 2016, from $2864 to $5705,” the group said.

“Shadow pricing” is a type of marketplace abuse that ACP described as particularly damaging to health care consumers. With shadow pricing, a small number of dominant producers raise their prices almost in tandem. “Between 2009 and 2015, the prices of the insulin products Lantus (Sanofi-Aventis) and Levemir (Novo Nordisk) increased at or around the same time 13 times. Similarly, the prices of Humalog (Eli Lilly and Company) and NovoLog (Novo Nordisk) increased in conjunction 17 times over 10 years,” ACP said.

ACP called for legislative reform to the Orphan Drug Act to change incentives for development of these drugs. It supported reducing data and market exclusivity for biologic drugs from 12 years to 7 years and bringing a halt to “excessive patenting” on brand-name and biologic drugs.

The group also called for elimination of direct-to-consumer (DTC) drug advertisements. “There is a lack of consensus in the economics literature about whether DTC advertising improves market performance or undercuts competition,” ACP said.

**REFERENCE**


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**Being Each Other’s Hero:**

**Facing Metastatic Breast Cancer Together**

**Maggie L. Shaw**

**STRONG. VULNERABLE. OPEN.**

Closed off. Depressed. Angry. Optimistic. Happy. Humorous. Spiritual. Together, these describe just a portion of the emotions patients with metastatic breast cancer (MBC) face when they receive a diagnosis of what is the most advanced stage of the disease.¹

No matter the site, or sites, of metastasis—bones, brain, even liver—cancer that originates in breast tissue before spreading is treated as breast cancer because of where it originated.² At diagnosis, approximately 6% of breast cancers are metastatic.³ Experts predicted that 276,480 women and 2620 men would receive such a diagnosis in 2020.⁴

For men especially, MBC can be difficult to talk about, much less open up about. Men represent only 0.95% of the full number of cases of MBC in women. Kirby Lewis of West Virginia, now a stage II breast cancer survivor, had a mastectomy in 2012—but not before firing his first doctor who told him men don’t get breast cancer. However, in 2016, his cancer recurred, spreading to his spine and both lungs. He had MBC from which his “lungs lit up like Christmas trees,” he said.¹

Lewis has managed to remain optimistic despite his diagnosis, which brought with it 15 weeks of treatment with chemotherapy and various other medications, followed by a switch to a different oral medication and a years-long remission before a small tumor began to grow again. He attributes his attitude to his years of experience as an embalmer for a funeral service. Lewis said he understood that death is a part of life.

“My perspective all along has been that we don’t really get to choose or pick things the way we would like things to be in our life,” he said. “We are dealt this hand and what really matters is how we live it. I’ve tried to be a realist.”

Lewis also credits his faith and his combat experience in the military with helping him realize how precious life is and making it easier for him to cope with his MBC diagnosis.
He is 1 of 9 patients, and the only male, with MBC who serve as the faces of Facing MBC Together from Athenex Oncology, a US-based division of global biopharmaceutical giant Athenex, “to provide accessible information and multiple resources to oncology customers, including health care professionals, patients, and caregivers, who may benefit from Athenex’s broad pipeline of innovative oncology products.”

Both the website and mobile app of Facing MBC Together were built to address the isolation patients with MBC often feel by providing practical and emotional support in the forms of educating patients and the public on:

- What the disease is: it’s stage IV, or advanced breast cancer.4
- What a diagnosis means: the disease may not be curable, but life expectancy is on the rise.7
- Treatment options: surgery, targeted therapies, and radiation, among others, are all available, and there are approximately 300 ongoing clinical trials.8

The overarching message of the campaign is that patients with MBC do not have to face cancer alone. Facing MBC Together fosters this message through digital offerings that include a customizable calendar that supporters can consult to fulfill a loved one's everyday requests such as meal or grocery delivery and a real-time video channel, which enables live one-to-one or group chatting. There is also a health update blog and an encouragement-infused photo and video gallery.5

The campaign began when Tim Cook, senior vice president of Global Oncology Marketing at Athenex Oncology, joined the company 2 years ago.

“My group was tasked with preparing to launch the company’s lead molecule, oral paclitaxel and encequidar, in MBC. We wanted to create a culture looking at the whole person, not as an MBC patient, and to fully understand these people’s treatment needs beyond the disease,” Cook explained in an interview with Evidenced-Based Oncology.5 “To do this, we conducted a lot of primary and secondary research, including partnering with the cancer support community to conduct a new study to better understand what people living with MBC struggle with on a daily basis. The study revealed an overwhelming sense of isolation and loneliness felt after diagnosis.”

At the heart of the campaign's success is that it is fully customizable, he points out, thereby providing “a unique experience for anyone impacted by MBC,” especially patients, which helps to address the often overwhelming isolation and loneliness that follows their diagnosis, connects them with various types of support, and inspires them through the experiences of others.

The campaign is also diverse in that the 9 patients who serve as its faces include individuals from all walks of life and whose MBC diagnosis either followed a history of breast cancer (both early- and late-stage disease) or was de novo disease. The patients were found through the partnerships Athenex formed with several patient advocacy groups, Cook noted.

Alongside Lewis, Stephanie Walker of North Carolina is 1 of those 9 patients, and her MBC was a de novo diagnosis, meaning this was her first encounter with breast cancer and it had already spread.9 “I forgot about it!” she recalled when describing how life got in the way beginning in late 2015 and continuing in the months leading up to her diagnosis. As a result, her yearly mammogram around her December physical didn’t happen until June of the following year. “In July, I get the phone call that I need to come back because they had seen something, and of course I hung up on the lady 2 or 3 times because I thought she had the wrong number. “I was diagnosed stage IV right out of the gate. Asymptomatic, no lumps felt, no dimples, no drainage, no nothing. And it has been a hellacious ride ever since,” she continued, explained that she fired her first oncologist following poor treatment by his staff, when Walker insisted on asking “too many questions.”

However, having been a nurse for 40 years meant she knew many oncologists, and she contacted one, who arranged for her to complete all her tests, even though he was out of the country. It also meant a lot of assumptions based on her medical background and not being assigned a nurse navigator because she herself was a nurse. She is learning to ask for help, which is something she tries not to do and finds hard to do.

“At 61 years old, I’m finally learning to reach out for help,” Walker said.

Reaching out and speaking up to help their fellow patients are why Lewis and Walker gladly became faces of this campaign and why they call each other “my hero.”

In particular, Lewis views himself as an advocate for genetic testing among men for a predisposition to breast cancer, which he defines as “breast cancer” and not “male breast cancer.”10 “You don't have to be concerned just with your daughters, you have to be concerned about your sons as well,” he emphasized. “Genetically speaking, DNA passes obviously from our mother, but it can also pass from our father and from our father’s mother or our mother’s father, and those are points of consideration that need to not be overlooked and frequently are.”

Walker, too, believes in putting it all out there, in letting the care team know what you are going through and filling them in on the undertone of it all, because they already know but are waiting for you to open up. “They weren't blind to the depression or the sadness or the exhaustion or the fatigue,” she said. “They had seen it; they were just waiting for me to voice it. And it’s been wonderful. It truly has been a wonderful being able to have a support system.”

Patients being reticent to ask for help but needing support is why Facing MBC Together exists and why it is even more important now during the coronavirus disease 2019 pandemic, which not only magnifies the loneliness and isolation patients with cancer feel but also poses additional health risks, Cook noted. “In some ways, the pandemic provides anyone with a glimpse into what it’s like to live with a disease like MBC, as many people are required to be isolated from loved ones. But the physical isolation and anxiety caused by the pandemic also poses real health risks to those living with MBC,” he stated. “The development of Facing MBC Together started well before we had any glimpse of our new normal, but we take some comfort in knowing that the campaign can help to address the compounded feelings of isolation for anyone impacted by MBC.”

REFERENCES
When the Topic Is Dying: A Conversation With Kashyap Patel, MD

MARY CAFFREY

Kashyap Patel, MD, CEO of Carolina Blood and Cancer Care, associate editor of Evidence-Based Oncology™, and vice president of the Community Oncology Alliance, discusses his new book, Between Life and Death: From Despair to Hope.

KASHYAP PATEL, MD, had known for years that he would write about dying.

The longtime oncologist, now CEO of Carolina Blood and Cancer Care Associates of Rock Hill, South Carolina, had addressed the topic head on with patients, family members, and caregivers. He took a special course in palliative care at Northwestern University so that he could train others. Patel knew there was a great, unmet need to teach medical students and young physicians how to guide patients through the end-of-life process in a meaningful way.

And yet, despite a decade of movement toward greater quality in cancer care, dying remained a mostly taboo subject.

As Patel describes it, his own brush with mortality—a cardiac event in 2008—convinced him that the time had come to finish a book he had long contemplated. Patel turned to his extensive notes and his diary, and he began compiling the stories that became Between Life and Death: From Despair to Hope (Penguin Random House India). Drawn directly from patient stories—in particular, the tale of a former British pilot named Harry Falls—the book is a roadmap for the journey every human being takes, and how we can all do so with greater purpose, and less fear. (A review appeared in the April issue of Evidence-Based Oncology™). 1

The journey to publication took some unexpected turns. In the winter of 2020, Patel expected his book would reach readers sometime in April. But first the coronavirus disease 2019 (COVID-19) hit China, disrupting the book’s initial printing, and then Patel’s publisher feared the original title would fall flat during a pandemic. After finally arriving on August 1, Between Life and Death has received an enthusiastic reception.

Patel spoke with EBO about a topic he now hopes to make a theme of his coming tenure as president of the Community Oncology Alliance. This interview has been edited and condensed for clarity.

EBO: How and when did you decide, ‘I need to write a book on this subject?’

PATEL: As an oncologist, having lived on 3 continents and having practiced for 3 decades, what I found was that every time I had to break bad news to a patient, we had to shift gears to comfort care. The common questions were, why? How? What will happen to my loved ones? Then, as I started getting involved in the health care policy space, I realized that one of the biggest challenges that we have as oncologists is that our patients are not getting prepared for end-of-life care. After becoming a trainer and conducting retreats for other doctors, I realized that there’s not a single medical school in America that has [a] dedicated course on communications for the end-of-life care.

EBO: Tell us about the patient who appears in the book as Harry Falls.

PATEL: This British pilot who fought in the Second World War. And he said, “Doctor, I’m not afraid of my death, but I want to see how it will happen—I want to be prepared for it, I want to prepare my family.” This patient had terminal lung cancer and said, “I don’t want to take chemotherapy.” From then on, I told him, “Your life expectancy is going to be less than 3 months.” He said, “All I want to know is, what will happen to me? What will happen to my body? How do different faiths deal with death and dying? How will my wife and my children deal with that? Will I have enough time to [bring] closure to everything? Will I be in pain?”

I started narrating stories from a few of my patients, so that I could be mentally ready for the whole process of understanding the transition between this life and wherever we’re heading for after life.

EBO: How are audiences responding to the book?

PATEL: Among all those who’ve read it so far, I’ve received about 15 different written reviews. It’s incredible...They are incredibly moved and touched by it; there are very moving accounts, saying, “I wish I’d read this book before my father passed away. I wish I had this book before my mom was on her death bed.”

“...You have a choice of living life to the fullest no matter what comes. What I don’t control is what way my finitude will reach me....What can I choose is, how do I react to that? What I cannot control is, what comes my way? The only thing that’s certain in my life is that I’m going to leave this world.”

—Kashyap Patel, MD, author, Between Life and Death: From Despair to Hope
EBO: Do the responses vary somewhat—do your physician friends have one type of reaction and patients have a different type of reaction?

PATEL: My physician friends are all excited, because this is something that I think people are hesitant to bring up—but when they see that there’s a way that you can openly communicate about it—dealing with the finitude of life, this conversation could start happening more. A lot of my colleagues are encouraging me to look into even starting a movement. And I’m seriously looking at taking this on….I want to bring open-ness to the conversation; how do we bring this topic up while we talk about extending life as well?

One other person who read it is actually a current patient; he also gave testimony about [the] inter-action with this book. So patients who have active cancer are seeing this book as one of the roadmaps to finding peace in your own life as well.

EBO: It sounds like the book is a good way for physici-ans to start the conversation with patients, to open the door for those who are struggling with beginning a conversation about the end of life.

PATEL: Absolutely. And one of the senior leaders of a large pharma company saw that and said, “We want to have all of our leadership see this, because when we talk about [these] issues across the country, we don’t talk about the poor quality of death.” If you look into the Institute of Medicine, they always say that the quality of death is not the best in the United States (Dying in America, 2015).

If you look into the published studies (in Dying in America), there was a phase 3 randomized study where they looked into the type and place of death of the cancer patients, those patients who died in the hospital, in the ICU [intensive care unit] or active acute care setting—their loved ones had much worse psychiatric issues, because of not being able to put it closer to what [the patients] wanted to do. So there are studies that show that dying in a place where patients would not have desired is fraught with adverse outcomes for the family as well as caregivers….But when you bring up the conver-sation, how do you bring up conversation?

EBO: What do you hope is the chief message that people take away from your book?

PATEL: I want everyone to know that you have a choice of living this life to the fullest no matter what comes. What I don’t control is what way my finitude will reach me—whether I’ll be dying of cancer, heart disease, Alzheimer [disease], or kidney failure. What I can choose is, how do I react to that? What I cannot control is, what comes my way. The only thing that’s certain in my life is that I’m going to leave this world. From the day I am born, I’m counting one less day toward that horizon of finitude, and why can’t I be ready for that instead of worrying about it? If I take the fear of death away, I can enjoy life to the fullest.

REFERENCES

PALLIATIVE CARE

A RECENT REVIEW LOOKED AT palliative care in hepatocellular carcinoma (HCC), a cancer with a poor prognosis, increasing incidence, and one that carries with it a certain amount of stigma.

HCC has been rising and is predicted to keep trending upward, according to a review; it is more deadly than pancreatic, lung, and colorectal cancer. The mortality-to-incidence ratio is 0.89 for HCC versus pancreatic (0.83), lung (0.72), and colorectal (0.27).

In 2018, there were 841,080 incident cases of HCC and 781,631 deaths worldwide. After diagnosis, the 5-year survival is under 20%, ranging from 9% in Asia to 19% in the West.

Early in the disease, HCC is often silent, contributing to its late diagnosis. More than half of patients have incurable disease at the time it is discovered. Furthermore, almost all patients with HCC have underlying liver disease, and up to 90% have cirrhosis.

HCC also expensive—US per-person costs are estimated at $29,000 to $44,000 annually, with the greatest burden happening in the end stages of the disease.

Despite advancements in intermediate and advanced HCC, most treatments remain noncurative. Given these factors, the authors sought to review palliative care’s benefits and use, as well as implementation barriers.

Palliative care is known to improve quality of life, reduce depression, reduce health care costs, and prolong survival, according to other studies that examined cancers other than liver.

In liver cancer, palliative care is underused in this cancer and typically has late referrals. For example, looking at one group of patients with advanced or terminal stage HCC, the authors said only 40% were referred and seen by palliative care.

The main indications for referral were pain (44%), end of life care (37%), nausea (11%), and dyspnea (3%). For inpatients, the median time to death after consulting with palliative care was just 3 days (interquartile range [IQR] 0-28.5); for outpatients, it was 21.5 days (IQR 4-146) for outpatients.

Barriers to accessing palliative care in HCC and accompanying cirrhosis include stigma related to hepatitis and alcohol use, the most common cause of the disease. In addition, as with other cancers, some patients and families may think of palliative care as “giving up.”

The authors also said they were concerned by the findings of a survey of gastroenterologists, where 81% believed the misconception that palliative care starts only when active therapy ends.

Gastroenterologists refer to palliative care less frequently than oncologists, the authors said, although they manage HCC more often. In addition, providers caring for patients with advanced or terminal liver cancer cited a lack of time (91%) as well as a lack of cultural awareness to start the referral (81%).

The authors also said that although the American Society of Clinical Oncology recommends palliative care in all cancers, hepatology societies have yet to adopt the same conclusion.

Future action is needed, the authors said, including education, awareness campaigns, increased funding and improved models of care.

REFERENCE

Uptake of Palliative Care in Liver Cancer Needs Improvement, Report Says

ALLISON INSERRO
FDA Accepts Anti-BCMA Ide-cel for MM for Priority Review

THE FDA HAS GRANTED priority review for the biologics license application (BLA) for idecabtagene vicleucel (ide-cel; bb2121), a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell immunotherapy, Bristol Myers Squibb and bluebird bio said September 22, 2020.

If approved, it would be first CAR T-cell immunotherapy for the treatment of multiple myeloma (MM) in adult patients who have not responded or have relapsed after at least 3 other targeted therapies.

The Prescription Drug User Fee Act (PDUFA) date is March 27, 2021. “Today’s [priority review] milestone recognizes the potential of this first anti-BCMA CAR T-cell therapy to address a critical unmet need of patients with multiple myeloma,” Stanley Frankel, MD, senior vice president of cellular therapy development for Bristol Myers Squibb, said in a statement. “We are pleased by the significant progress that is being made in partnership with patients and the multiple myeloma community to bring ide-cel to adults with relapsed and refractory multiple myeloma who are triple-class exposed and may benefit from an important new therapeutic option.”

These patients have previously received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

Ide-cel functions by recognizing and binding to BCMA on the surface of MM cells. This leads to CAR T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

“Today’s acceptance of the BLA for ide-cel for [priority review] by the FDA marks a key moment in our journey to bring this BCMA-directed CAR T-cell therapy to multiple myeloma patients who are in desperate need of new options,” added Joanne Smith-Farrell, PhD, chief operating officer of oncology for bluebird bio, in the statement. “Based on the body of evidence we have generated in an advanced, heavily pretreated patient population, our confidence in the potential of ide-cel as an important treatment option remains high.”

The application is based on data from the pivotal phase 2 KarMMa study (NCT03361748), which included 140 patients, 128 of whom received ide-cel across target dose levels of 150-450 x 10^6 CAR+ T cells. Eighty-four percent of patients enrolled were refractory to all 3 classes of treatments, and 94% were refractory to anti-CD38 antibodies specifically.

Overall response rate was 73% across all dose levels, including 33% of patients who had a complete response (CR) or stringent CR (sCR); nearly all subgroups had an overall response rate of 50% or greater, including older and high-risk patients.

The median duration of response (DOR) was 10.7 months, with a 19-month median DOR for patients who had a CR or sCR, and median progression-free survival (PFS) was 8.8 months, with a 20.2-month median PFS for patients who had a CR or sCR.

Ide-cel was previously granted breakthrough therapy designation by the FDA, and Priority Medicines designation and validation of its marketing authorization application by the European Medicines Agency. Bristol Myers Squibb plans regulatory submissions for ide-cel in additional markets outside the United States and European Union.

REFERENCES

Novel CAR T-Cell Process Shows Promise in Relapsing/Refractory B-ALL

A NEW TYPE OF chimeric antigen receptor (CAR) T cell may be able to overcome resistance in some patients with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL), study results show.

The findings were published in the Journal of Hematology & Oncology Corresponding author Ying Wang, PhD, of the Chinese Academy of Medical Sciences and Peking Union Medical College, et al, noted that while 70% to 90% of patients with B-ALL who are treated with anti-CD19 CAR T cells achieve complete remission (CR), 40% to 50% of patients who respond to the therapy will relapse within 1 year, and nearly half of those patients will have CD19-positive leukemic cells.

“Recent studies indicate that relapse may be due to mutations in CD19 that destroy the cognate epitope recognized by the anti-CD19 single-chain variable fragment (scFv), such as FMC63 clone, thus rendering the tumor cells invisible to CD19 CAR T cells,” Wang and colleagues noted.

One strategy to get around that problem is to develop CAR T cells with scFvs that can bind to different CD19 epitopes. The team has developed a new type of cell derived from the HI19a clone, dubbing it CNCT19. The hope was that the scFv generated by the HI19a clone would locate different binding epitopes on the CD19 extracellular domain than the ones detected by the FMC63 clone. The results of preclinical model evaluations were positive, prompting Wang and colleagues to conduct the present pilot study to evaluate the safety and efficacy of CNCT19 in both pediatric and adult patients with B-ALL.

They enrolled 20 patients in the study and gave them infusions of CNCT19 cells. Of those, 90% of patients achieved CR or complete remission with incomplete count recovery (CRi) within 28 days. Two relapsed patients saw their extramedullary leukemia disease disappear completely after the infusion.

At a median follow-up of 10.09 months, the median overall survival for the patients was 12.9 months, and the relapse-free survival was 6.93 months.

“Differences with respect to immune profiles associated with a long-term response following CAR T-cell therapy were also addressed,” the authors wrote. “Our results revealed that a relatively low percentage of CD8+ naïve T cells was an independent factor associated with a shorter period of relapse-free survival.”

The authors said their results suggest that CD19 CAR T cells derived from the HI19a clone can promote high antileukemic efficacy and may help curb the poor prognosis faced by patients with R/R B-ALL.

However, Wang and colleagues also sounded a note of caution, pointing out that a high number of their patients, 14 of 20, subsequently underwent hematopoietic stem cell transplantation, which they said may play a significant role in maintaining the long-term response to treatment.

“As such, the duration of the response associated specifically with CNCT19-based T-cell therapy requires further investigation,” they said.

And while their new cells may help counteract the shortcomings of anti-CD19 CAR T cells, the investigators said the new cells do not overcome 1 other problem with CAR T-cell therapy—the high rate of toxicities. In the study, 45% of patients experienced high-grade cytokine release syndrome (CRS), a rate similar to other studies. Severe CRS seemed to correlate with a high tumor burden, so the authors said the results underscore the importance of decreasing tumor burden prior to CAR T-cell infusion.

Still, the authors concluded that their new therapy appears to be highly effective against malignant cells in patients with R/R B-ALL, and they concluded they may have also identified a notable biomarker.

“Our results also suggest the percentage of circulating CD8+ T cells may be developed as a biomarker to predict the long-term prognosis of patients undergoing CAR T-cell therapy,” they said.

REFERENCE
Tafasitamab Plus Lenalidomide Is Added to NCCN Guidelines

THE NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) has added tafasitamab to its clinical practice oncology guidelines for B-cell lymphomas. The addition follows the FDA’s July decision to grant accelerated approval of tafasitamab (Monjuvi) in combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), meeting the needs of patients who are not eligible for an autologous stem cell transplant.

The NCCN classified the treatment under its category 2A designation, which means that there is uniform consensus that the therapy is appropriate, based on lower-level evidence.

Tafasitamab is a humanized Fc-modified cytolytic CD19 monoclonal antibody being studied in several B-cell malignancies. As described in the journal Blood, the treatment uses Xencor’s proprietary XmAb technology, which deploys a different technique to boost affinity for the antigen and make various receptors especially capable of binding to it. In 2018, authors in Annals of Oncology described how this sets off particularly effective processes that target cancer cells and regulate cell death.

Tafasitamab is marketed by MorphoSys and Incyte. “We are very gratified the NCCN acted quickly to include [tafasitamab-cxix] in combination with lenalidomide with a Category 2A designation in its Clinical Practice Guidelines in Oncology as a treatment for patients with relapsed or refractory DLBCL who are not candidates for transplant. This targeted therapeutic option helps address an immediate medical need for patients who previously had limited treatment options,” Malte Peters, chief research and development officer of MorphoSys, said in a statement. “There is no other FDA-approved second-line treatment for these patients with a 2A designation within the NCCN guidelines.”

Among non-Hodgkin lymphomas, DLBCL is the most common subtype, accounting for 22% of cases in the United States and 40% worldwide, with about 18,000 US cases per year. People are at higher risk if they have HIV, an autoimmune disease, or if they have had an organ transplant. More common in older people, DLBCL can be very aggressive. Although well-known treatments have been developed, there are gaps—and one is when DLBCL cannot be kept in remission after chemotherapy but the patient is not eligible for an autologous stem cell transplant. Some of these patients have had chimeric antigen receptor (CAR) T-cell therapy, but this process is costly with significant adverse effects.

REFERENCES

Treatment, Access to Caregivers Among Factors Affecting QOL in MM

A RECENT STUDY HAS PAINTED a portrait of the factors that lead to lower quality of life after a patient has been diagnosed with multiple myeloma (MM).

The research, published in Cancer Medicine, is based on a survey of more than 400 people with MM in China. The authors found that difficulties experienced during the diagnosis and treatment process, psychosocial factors, and the effects of the disease and its treatment all had a significant negative effect on the health-related quality of life (HRQOL) of these patients.

In the study, the authors sent a questionnaire to people with MM in all 27 provinces of China. A total of 430 people responded, and they were an average of 55.7 years old.

The results of the survey showed a number of factors can affect HRQOL. Among them, patients who underwent autologous stem cell transplantation (ASCT) had higher HRQOL than those who did not have the transplant.

However, toxicities were a major concern. A vast majority (91.5%) of patients on maintenance therapy said they intended to stop the treatment, mostly due to adverse events and the high cost of treatment.

“The application of ASCT has significantly improved the prognosis of patients with MM and prolonged the OS of patients,” Li and colleagues wrote. “However, as patient survival is prolonged, patients experience different levels of pain due to treatment-related toxicities.”

HRQOL scores were improved when patients were diagnosed quickly, though the study results showed only 16.7% of patients were diagnosed within 1 month of the onset of symptoms. The reasons for the delayed diagnosis included lack of awareness of the severity of the condition, failure by the hospital to confirm the diagnosis quickly, and inability to pay for care.

Access to a caregiver benefited patients’ HRQOL, but more than one-third (38.4%) did not have a caregiver. More than half of the patients (56.3%) said they had to travel to another city to receive care, another factor that negatively affected their scores on functional and symptom measures, though it did not affect overall HRQOL, the authors said.

Four in 10 patients in the study reported psychosocial challenges, such as anxiety and depression.

“Patients live with the uncertainty of a treatable but incurable cancer; they worry about how their illness will progress and are concerned about death and dying,” the authors said. “Overall, these findings suggest that patients need more psychological support during all phases of treatment.”

Basic demographic factors, such as age and sex, yielded mixed results. In a univariate analysis, both factors appeared to be associated with HRQOL. However, when investigators performed a multiple linear regression analysis, neither factor emerged as an independent predictor of HRQOL.

The authors said these data should provide clinicians with tools to identify patients who are at risk of diminished HRQOL.

“Efforts should be made to identify persons at risk of low HRQOL earlier and improve the overall quality of life of these patients in China,” they concluded.

REFERENCE
25% of Patients With CLL Have Disease Flare When Ibrutinib Therapy Pauses

**EVEN A TEMPORARY HOLD** of ibrutinib therapy can lead to disease flares in patients with chronic lymphocytic leukemia (CLL), according to a new study.

The report, published in *The Oncologist*, suggests that physicians need to be aware of the risk of flares when making decisions about whether to pause the therapy.

Ibrutinib (Imbruvica), the first-in-class Bruton tyrosine kinase inhibitor, has led to a significant shift in the prognosis for patients with relapsed/refractory CLL. Long-term follow-up studies confirm that the drug brings a durable benefit in terms of both progression-free survival (PFS) and overall survival (OS). However, corresponding author Sameer Parikh, MBBS, of the Mayo Clinic and colleagues noted that the benefits come with a caveat.

"Unfortunately, therapy with ibrutinib is associated with various [adverse] effects, including bleeding and hematologic and nonhematologic toxicities, as well as drug-drug interactions, that may necessitate dose modifications or interruption of treatment," they said.

Earlier studies have suggested that discontinuation of ibrutinib leads to a risk of disease flares in patients with Waldenström macroglobulinemia, and the authors said evidence has been reported suggesting the same thing is true in CLL.

In an effort to better understand the risk of disease flare in CLL cases, the authors conducted a study of the Mayo Clinic's electronic records database.

The investigators identified 372 patients who received care for CLL at Mayo's flagship Rochester, Minnesota, clinic between 2012 and 2019 and were prescribed ibrutinib. They found that 143 patients (38%) had had at least 1 temporary interruption in therapy, with a median duration of interruption of 8 days. Overall, the temporary holds ranged from 1 to 59 days, and the number of holds per patient ranged from 1 to 7. The most common reason for medication hold was periprocedural, Parikh and colleagues reported.

Of those who experienced a hold, disease flare was reported in one-fourth of the patients (35 people). Most of those patients (21) experienced mild flares, which were defined as constitutional symptoms only. The remaining 14 patients experienced severe flares, defined as constitutional symptoms along with exam/radiographic findings or laboratory changes. In all cases, the flares resolved once the patient was put back on ibrutinib.

The finding was notable in part because interruptions of ibrutinib are a common strategy to deal with potential adverse effects. While between 15% to 30% of patients on ibrutinib had their doses reduced, estimates of ibrutinib interruptions range from 35% to 65%, depending on the setting.

The finding is notable in part because interruptions of ibrutinib are a common strategy to deal with potential adverse effects. While between 15% to 30% of patients on ibrutinib had their doses reduced, estimates of ibrutinib interruptions range from 35% to 65%, depending on the setting (clinical practice or clinical trial).

Yet, while less common, dose reductions do not seem to lead to disease flares.

"Across varied patient cohorts evaluating dose reductions, consistent findings of no significant differences in PFS or OS have been reported," the investigators wrote.

By contrast, ibrutinib interruptions led to shorter event-free survival (HR 2.3; 95% CI, though they did not appear to affect OS.

Parikh and colleagues said patients with progressive disease at the time of the hold were more likely to experience disease flare during an interruption, as were those with 24 months or more of exposure to ibrutinib.

The investigators concluded that while ibrutinib can have significant adverse effects, physicians need to carefully consider the individual patient's situation when deciding whether to pause therapy with the drug.

"It is critical for practicing hematologists and oncologists to be aware of the potential for this phenomenon during even transitory periods of treatment discontinuity, and further investigation into predictive factors and methods to mitigate risk are needed," they said.

**REFERENCE**


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**More Coffee, Longer Survival? Study Highlights Benefit in Metastatic Colorectal Cancer**

**DRINKING LARGE AMOUNTS** of coffee by patients with advanced or metastatic colorectal cancer (CRC) was linked with both overall survival (OS) and progression-free survival (PFS), according to a study published in *JAMA Oncology*.

The study analyzed 1171 patients. Results showed that those who drank 4 or more cups of coffee a day had the best survival odds as well as slower disease progression.

The research looked at both caffeinated coffee and decaf; when analyzed apart, the association with PFS was stronger with caffeinated coffee, but both types were linked to OS.

Coffee may contribute to anticancer activity through various ways. Several compounds in coffee have antioxidant and anti-inflammatory effects. In addition, insulin resistance is believed to worsen CRC outcomes; coffee can sensitize tissues to the effects of insulin and decrease blood insulin levels.

While other studies have noted links to increased coffee consumption and decreased recurrence and deaths from colon cancer, the association between drinking coffee and survival in patients with advanced or metastatic disease is unknown.

The patients were queried about their diet as an option included in a phase 3 clinical trial comparing the addition of cetuximab and/or bevacizumab with standard chemotherapy. They answered a semiquantitative food frequency questionnaire within the first month of enrollment and from 2005 to early 2018.

Of the 1171 patients, 694 were men (59%) with a median age of 59; 86% of the participants were White. A multivariable model controlled for additional factors known or suspected to affect survival in patients with CRC.

The median follow-up time among living patients was 5.4 years (10th percentile, 1.3 years; interquartile range [IQR] was 3.2 to 6.3 years). A total of 1092 patients (93%) had died or had disease progression.

The results showed that higher levels of coffee drinking, as measured by cups per day, was associated with a decreased risk of cancer progression (HR for 1-cup/d increment, 0.95; 95% CI, 0.91-1.00; *P* = .04 for trend) and death (HR for 1-cup/d increment, 0.93; 95% CI, 0.89-0.98; *P* = .004 for trend).

Compared with those who did not drink coffee, the multivariable analysis showed that drinking at least 4 cups of coffee per day led to a 36% increased chance of improved OS (HR, 0.64; 95% CI, 0.46-0.87) and 22% increased odds of better PFS (HR, 0.78; 95% CI, 0.59-1.05).

At least 2 cups per day of decaffeinated coffee had a positive result as well for both OS (HR, 0.64; 95% CI, 0.43-0.95; *P* = .003 for trend) and PFS (HR, 0.75; 95% CI, 0.52-1.09; *P* = .05 for trend).
Although the authors said it is the first study to find a protective effect of coffee in metastatic CRC, several things about the association remain unknown. For instance, the majority of people who drink coffee during cancer treatment likely drank it before their diagnosis, so a question remains as to whether coffee drinkers tend to develop less aggressive disease, or if coffee exerts an effect on active tumors.

**Reference**

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**Education Level Linked to Outcomes in Patients With MM**

**Study Results of Patients** In China with multiple myeloma (MM) showed those with high education levels had better progression-free survival (PFS) and overall survival (OS) compared with patients with low education levels.

The study underscores the importance of access to care and financial resources in patients diagnosed with the disease. The findings were published in *BMC Cancer*.

A team of investigators, including corresponding author Juan Li, PhD, of the First Affiliated Hospital, Sun Yat-sen University, wanted to gain a better understanding of the role of socioeconomic factors in MM outcomes. They decided to perform a retrospective analysis of 773 patients with MM who visited 9 cancer centers between 2006 and 2019.

The majority of patients in the study (69.2%) had a low level of education, which was defined as secondary education or lower. A high level of education was defined as having a bachelor’s degree or higher. Those with low levels of education also tended to be older, live in rural areas, lack insurance, and have unstable employment, the study’s results showed.

“Additionally, compared [with] patients with high education levels, patients with low education levels had a higher proportion of international staging system (ISS) stage III classification and elevated lactate dehydrogenase (LDH) levels and underwent transplantation less often,” Li and colleagues wrote. Those factors translated into significant differences in outcomes. In patients with high education levels, median PFS was 67.5 months. In those with low education levels, median PFS was 30.6 months. Likewise, median OS in patients with high education was 122.27 months, compared with 58.83 months in patients with low education levels.

The reasons for the apparent link are complicated. The authors noted that the more-educated cohort tended to be younger, and they also tended to be diagnosed closer to the onset of symptoms, compared with the less-educated patients. Thus, the group might have better survival because they may have lower tumor loads. However, the authors said education might also play a role in the treatment decisions made by patients with MM.

“[P]atients with high education levels were more likely to choose effective treatments, such as transplantation, than patients with low education levels, and these patients more often received regular treatment,” the investigators wrote. “Therefore, the above factors may partly explain why education levels affect patient survival.”

Li and colleagues said a patient’s prognosis is based on numerous factors, and thus it cannot be said that education is the only important factor. However, they said the findings of their study could help physicians to better tailor care patterns to patients, particularly if the patient has lower socioeconomic status and/or a low level of education.

**Reference**

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**Counties Experiencing Persistent Poverty Have Higher Cancer Mortality Rates**

**Throughout the United States**, counties experiencing persistent poverty have disproportionately higher rates of cancer mortality, according to a study published in *Cancer Epidemiology, Biomarkers & Prevention*.

In recent decades, advances in early cancer detection tests and treatment have contributed to lower overall mortality and higher survival rates. However, disparities persist across the cancer control continuum among individuals living in poverty. Increased exposure to carcinogens, low educational attainment, and lack of access to care all contribute to the association of individual-level poverty and substantial cancer risk.

“In addition, people living in poverty have high rates of cancers caused by occupational, recreational, or lifestyle exposures (eg, colorectal, laryngeal, liver, and lung) and by human papillomavirus infection (eg, anal, cervical, and oral),” the authors wrote.

Although cancer mortality has been found to be increased in counties with high levels of current poverty, less is known about mortality rates in counties which have experienced persistent poverty, defined as at least 20% of residents in poverty (below the federal poverty level) from 1980, 1990, and 2000. Roughly 10% of all counties in the United States experience persistent poverty, and they are primarily located in the rural South. “Compared with other areas, persistent poverty counties have higher minority populations, more children under the age of 18, less formal education, and greater unemployment,” researchers said.

Investigators analyzed county-level data on cancer mortality from the National Center for Health Statistics collected between 2007 and 2011. Mortality rates were calculated as number of deaths per 100,000 people. For breast and cervical cancers, rates were calculated per 100,000 women; for prostate cancer, rates were calculated per 100,000 men.

Counties were classified as experiencing current poverty based on American Community Survey 5-year estimates. Sample tests and multivariate linear regression were used to assess mortality by persistent poverty and compare rates with counties experiencing current poverty. A total of 395 counties were classified as experiencing persistent poverty, encompassing 20,668,552 residents, while 871 counties were classified as experiencing current poverty between 2007 and 2011.

Analyses revealed:

- Overall cancer mortality was 179.3 (standard error [SE] = 0.55) deaths/100,000 people/year in nonpersistent poverty counties and 201.3 (SE = 1.8) in persistent poverty counties (12.3% higher; P < .0001).
- Cancer mortality was higher in persistent poverty vs nonpersistent poverty counties for overall cancer mortality as well as for several type-specific mortality rates: lung and bronchus, colorectal, stomach, and liver and intrahepatic biliary duct (all P < .05).
- Among counties experiencing current poverty, those also experiencing persistent poverty had elevated mortality rates for all cancer types as well as lung and bronchus, colorectal, breast, stomach, and liver and intrahepatic biliary duct (all P < .05).

In addition to the impacts of limited access to care and social determinants of health, researchers noted that “people living in persistent poverty counties may have higher levels of chronic stress (due to factors such as insecure employment, adverse experiences, social isolation, etc) that could give rise to physiologic aberrations (eg, chronic inflammation) that result in elevated cancer incidence.”

**Reference**
Uncertainty From COVID-19 Delays Progress on the Road to Value-Based Cancer Care

MARCUS NEUBAUER, MD; AND BEN JONES, BS

CONTINUED FROM COVER

COVID-19’s Impact on the Oncology Care Model

COVID-19 has created a significant distraction from normal practice operations. Real transformation to value-based care and performing at a high level in the Oncology Care Mode (OCM) takes time, energy, and dedicated resources, and that focus can be easily blurred when dealing with a pandemic.

The uncertainty that comes along with the pandemic is a huge worry. The OCM is a very detailed, complex model that requires a predictable environment in which practices have control. It is built around the concept of baseline practice patterns and measuring quality and cost metrics over time. However, comparing performance during this crisis against performance in a normal year is problematic. Another major element of the OCM is data collection and reporting. These activities require time and resources, much of which have been diverted to COVID-19 response. Expecting practices to have improved outcomes while spending less in the middle of a pandemic is simply not a realistic goal.

COVID-19 has greatly altered the landscape, making it very difficult—if not impossible—for practices to predict and control what happens to their patients. Cancer providers are well aware of the disruption the pandemic has caused when it comes to delivering care. A recent survey of cancer patients and survivors verifies what was already suspected:

1. 51% of all respondents reported some impact on their care due to the virus.
2. Of those whose care was affected, nearly 1 in 4 reported a delay in care or treatment. The most common delays included:
   • in-person provider appointments (58%);
   • imaging services to see if a cancer had grown or returned (20%); and
   • supportive services, such as physical therapy or mental health care (20%).

Some surgical procedures have been classified as nonessential and, therefore, postponed; this has been especially true of diagnostic procedures. Unfortunately, this can delay the start of treatment, and with some aggressive cancers, a delay of just a few weeks can negatively influence outcomes. This, in turn, can affect performance in the OCM. Some patients are canceling appointments because they are fearful of being exposed to the virus. These patients are not getting the care they need, and many will end up in the emergency department or the hospital. Others may not even be able to get to the hospital when it is necessary, so their condition worsens at home. These situations, which greatly increase the cost of care, have an impact on performance in the OCM.

Adjustments Made to the OCM in Response to COVID-19

The US Oncology Network (The Network) and other stakeholders have been working hard over the past several months to inform the Center for Medicare and Medicaid Innovation (CMMI) about the interruption to patient care that COVID-19 has caused and how it might impact OCM results. There is a strong likelihood that COVID-19 could disadvantage practices beyond their control. Many are operating under the 2-sided risk option and may have to return funds if expenditures are higher than benchmark.

Fortunately, CMMI has been receptive, and it recently announced adjustments to the OCM for performance periods affected by the COVID-19 public health emergency (PHE). The adjustments pertain to financial methodologies, quality reporting, and model timelines. To the credit of CMMI, these relief options add greater flexibility to the program and will be an enormous help to practices that want to remain in the OCM but are concerned about their results due to the pandemic.

On June 3, CMMI announced these changes:

Payment methodology
1. Practices in the OCM can elect to forgo upside and downside risk for performance periods affected by the PHE.
2. OCM practices that remain in 1- or 2-sided risk for the performance periods affected by the PHE will have COVID-19 episodes removed from reconciliation for those performance periods.

Quality reporting
1. Aggregate-level reporting of quality measures and beneficiary-level reporting of clinical and staging data are optional for the affected periods.
2. The requirement for cost and resource utilization reporting and practice transformation plan reporting in July/August 2020 is removed.

Timeline
1. The OCM is extended for 1 year through June 2022, allowing for a delay of the Oncology Care First (OCF) model.

The Network is pleased that CMMI recognized the concerns that were raised, then took action. Although we are several months into the pandemic, the impact on practice performance in the OCM is still unknown. Consequently, the adjustments that provide some flexibility, particularly concerning downside risk, are greatly appreciated.

OCF Details Are Sketchy but Concerning

The launch of the OCF model has been postponed for at least a year due to the pandemic. This is in line with a request made by The Network and a number of other stakeholders. We felt that extending the OCM was important, as practices in The Network were worried about rapidly transitioning into a new model during this chaotic time. Out of anxiety caused by the uncertainty of the pandemic, practices would be reluctant to participate in a new model that might add even more unpredictability. A lack of participation would not be in the best interest of either the practices, who want to lead the way in payment reform, or CMMI, which has a vested interest in ensuring that value-based care models evolve and succeed.

A year from now, if some sort of normalcy has not returned, practices may still have reservations about participating in the OCF. Whether they are willing to take on this new voluntary model will largely depend on what remnants of the pandemic still exist. If the virus is still widespread, practices will likely be hesitant to
take on more risk, particularly if the way they must manage risk is not clearly defined. CMMI may choose to hold off launching the OCF until the PHE is completely over, although its leaders are anxious to shift away from the OCM to a model with an approach that focuses more on bundled payments. If CMMI proceeds while the pandemic is lingering, many aspects of the program will need a second look. Must COVID-19–positive patients be factored into the equation, or not? Obviously, proceeding while the virus is still present would add to the complexity of developing and managing the model. The PHE would drastically change the model CMMI originally envisioned.

Practice-level decisions about whether to participate in the OCF will ultimately depend on what the model looks like. All that is known so far comes from a preliminary 12-page document that is limited on details and difficult to fully and accurately assess. However, from this brief information, practices across The Network have expressed concerns. Consequently, we offer the following suggestions to CMMI on how the model could be improved:

1. Provide greater transparency into the calculation of the OCF baseline, benchmark, and trend factor;
2. Improve transparency of the Monthly Population Payment (MPP) methodology and provide practices with an estimate of the MPP prior to application;
3. Provide more data on a real-time basis to improve both patient care and physician satisfaction with the model;
4. Allow all participating practices to start with 1-sided risk and continue through at least 2 full performance periods before deciding whether to continue as 2-sided;
5. Allow OCF practices that are participating in 2-sided risk the ability to opt out of other CMMI demonstration models if there is a clear conflict in model scope; and
6. Allow another opportunity for stakeholder feedback after more details of the OCF model have been released.

We are hopeful that CMMI will consider our suggestions, as over the past several years, the agency has been very collaborative in dealing with issues surrounding the OCM. On a number of occasions, they have listened to our concerns and made significant adjustments that improved the model. They deserve credit for their willingness to seriously consider our input, and, hopefully, they will take this same approach when building out the OCF. Practices will be more likely to participate if they feel their voices have been heard.

Value-Based Cancer Care in the Time of a Pandemic

While COVID-19 may have interrupted progress on the road to value-based care, practices need to continue delivering high-quality, high-value care through value-based models—even if the pandemic persists. It can be done. Across The Network, OCM practices are circumventing obstacles created by the virus by using personal protective equipment, Plexiglas shields, social distancing, and new policies to protect patients and staff. Furthermore, The Network practices readily employed telehealth to stay connected with patients but to minimize exposure to others in busy clinic settings. This strategy is working, as infusion volume is down less than 5%, and radiation volumes, although decreased, are down less than predicted.

Shying away from value-based care in turbulent times is not the answer, as value-based care is not going away. We know the CMS is strongly committed to transforming the health care landscape away from fee-for-service, and the models we are seeing now are simply stepping stones to the future. The OCF delay is merely a temporary interruption in the path forward.

Looking ahead, the need for value-based care will only become more important and urgent as the government looks for ways to recoup the trillions of dollars spent on the COVID-19 response. Arbitrary cuts can be imposed, but the more thoughtful way is to pursue reimbursement models that incentivize good care but do so in a value-based manner that promotes buy-in from the physician community. Hopefully, common sense will prevail.

The OCM is an example of a successful value-based program in oncology. It attempts to drive genuine transformation in how cancer care is delivered to Medicare beneficiaries by incentivizing practices to provide more comprehensive, cost-effective care. The 15 practices in The Network that are participating in the OCM have greatly enhanced their patient care. For example, OCM patients receive comprehensive care management and treatment plans, assistance from navigators and social workers, advance care planning, survivorship advice, information on estimated total out-of-pocket costs, and enhanced team care.

Across The Network, these reforms and investments have:
1. reduced hospital admissions by 7%;
2. reduced emergency department visits by 4%; and
3. driven a 5% increase in hospice stays longer than 3 days.

A key component of this success is adherence to evidence-based Value Pathways powered by the National Comprehensive Cancer Network, which have been proven to lower the overall cost of care with equal or better outcomes.1 Collectively, The Network practices alone have realized more than $80 million in savings for Medicare through participation in the OCM, while being able to appropriately manage all aspects of care delivery, including drug utilization. Many practices have also shared in the cost savings provided by delivering high-value care, helping them maintain financial stability in the challenging health care landscape.

Commercial Payers Can Help Drive Value-Based Care

As an integral component of the health care system, commercial payers are playing an important role in responding to COVID-19. They must keep up with the evolving needs created by the pandemic. Once the PHE has passed and the dust has settled, we are hopeful they will follow the lead of CMS in driving and participating in value-based cancer care.

In the past, commercial payers have expressed an interest in value-based models, but legacy claims systems designed around fee-for-service make it difficult for commercial payers to implement bundled case rates or episodic payment structures.4 Hopefully, payers and providers can collaborate to build value-based arrangements.4

Generally what works for Medicare can successfully be pursued by commercial payers. This approach would help avoid some of the draconian measures upon which payers often rely to control costs, such as expanded prior authorization, utilization management, restrictive formularies, and fail-first/step-therapy policies. The cost savings they are seeking can be achieved through value-based care, while also providing a more patient-friendly experience that recognizes the critical role physicians play in delivering quality care.

Flexibility and Collaboration Are Critical for Value-Based Care Success

Over the past several years, great progress has been made in transitioning cancer care to value-based models. While COVID-19 has created many challenges, providers are working around the obstacles, getting back into the rhythm of delivering high-quality, value-based care. CMS has set a goal of increasingly tying reimbursement to value, and the pandemic has not diminished the desire to reach this objective. Consequently, we must keep moving forward despite the pandemic, so the significant progress made so far is not lost.

Value-based care works best in a predictable setting where practices have control over outcomes, but unfortunately, COVID-19 has added an enormous layer of uncertainty. Providers are patiently waiting to see what the true impact of the pandemic is, especially concerning patient behavior patterns and other factors that directly impact performance in value-based models. The US Oncology Network encourages CMMI to continue to maintain an open dialogue with providers. Value-based care in today’s ever-changing landscape can only succeed with high levels of adaptability, collaboration, and continuous stakeholder engagement.

REFERENCES
Three Ways COVID-19 Makes the Oncology Care First Model More Attractive

KEELEY MACMILLAN, MSPH

CONTINUED FROM COVER

In these prospective payment arrangements, providers have incentives to deliver the most efficient care possible and benefit from a predictable source of funds amid fluctuation in volume. A long-standing barrier to adoption of these and other value-based payment arrangements has been the sheer convenience of fee-for-service (FFS) reimbursement. However, COVID-19 showed that, in a matter of weeks, complacency in fee-for-volume payment was upended as elective services plummeted. While most providers faced debilitating drops in previously reliable revenue, organizations participating in prospective or global budget types of payment arrangements were better positioned to weather the impact of COVID-19.

The revenue impact of COVID-19 on oncology is less severe than in clinical service areas such as orthopedics and primary care, but oncology is not immune. Data from the COVID and Cancer Research Network (CCRN), published by the Journal of Clinical Cancer Informatics in July, "clearly suggest a significant decrease in all cancer-related patient encounters as a result of the pandemic."3

Calls for legislative reform to drive adoption of alternative payment model (APM) participation have resonated. In late July, the Value in Health Care Act was introduced in the House of Representatives. The bipartisan bill aims to accelerate Medicare’s move to value-based payment and increase participation in APMs through a number of financial and reporting incentives.

In retrospect, the OCF RFI reads as poetical foreshadowing in its description of CMMI’s goal to “eliminate reliance on volume-drive, FFS revenue cycle management” and test whether “predictable revenue streams through an alternative payment mechanism” improve care coordination and management for cancer patients. As conceptualized, the model would pay participants a prospective, monthly payment for an assigned population of patients being treated for cancer. This fixed amount would cover evaluation and management (E/M) services, drug administration services, and other enhanced services such as care management and coordination. Participants also would be eligible for performance-based payments for quality and total cost of care accountability. Amid ongoing challenges to control the pandemic, a more reliable source of revenue may be welcome.

Legislation to Better Support APM Participation

COVID-19 provided real time feedback on the importance of value-based care (VBC) initiatives. Much of the care redesign activity and care management infrastructure that providers put in place for the purposes of being successful in VBC models enhanced providers’ ability to provide ongoing care for patients during the pandemic. While working with hundreds of providers across the country, Archway Health found that VBC participants were more likely to have in place hotlines staffed 24 hours a day, 7 days a week, with registered nurses; remote patient engagement tools; standardized use of a risk assessment tool to identify higher-risk patients; a process to review admit-discharge-transfer feeds from PatientPing or MemberMatch to determine which patients need follow-up; and other population health management strategies.

To inform these activities, VBC participants were more likely to have analyzed data for their patient populations and had a better understanding of the risk profile and prevalence of comorbidities among their patients. CMS recognizes the crucial role VBC has played in meeting patient needs during this pandemic. During a Deep Dive webinar on the “Future of APMs,” hosted in May by America’s Physician Groups (APG), CMMI Director Brad Smith noted, “The public health emergency we’re going through shows the importance of value-based care.” He also emphasized that because of the “type of skills and type of capabilities that organizations have built up as part of being part of value-based [models],” continuing to stay in these programs is “the right thing to do for patients.”

In June, 6 former CMS leaders, including Mark McClellan, MD, PhD; Don Berwick, MD; and Andy Slavitt wrote congressional leadership calling for financial relief to help providers “adapt to the continuing threat of the virus and to rebuild care that keeps the best ideas for improving care in the pandemic.” They also recommended that relief funding be tied to provider efforts to move into value-based payment (VBP) models, and they “expect longer-term savings and better outcomes from greater participation in payment approaches that are better alternatives to FFS.”

Calls for legislative reform to help drive adoption of APM participation have resonated. In late July, the Value in Health Care Act of 2020 (Value Act) was introduced in the House of Representatives. The bipartisan bill aims to accelerate Medicare’s move to VBP and increase participation in APMs through a number of legislative priorities, including extending the 5% bonus for advanced APM participation for an additional 6 years and lowering the Qualifying APM Participant (QP) thresholds for performance year 2021 and onward. Specifically, the Value Act would set the QP payment threshold at 50% in performance year 2021 and limit the increase to no more than 5% each performance period thereafter—a substantial improvement compared with the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) payment threshold of 75% in performance year 2021, and an opportunity for OCF participants to earn additional upside revenue beyond the prospective monthly management payments and performance based payments.

Leveraging Forced Innovation in Care Delivery

Ready or not, COVID-19 forced providers to adopt innovative ways to deliver care more efficiently. A prime example is the rampant adoption of telehealth, which allows cancer patients with compromised immune systems and high risk of infection to safely receive health care services. A McKinsey COVID-19 consumer survey found that telehealth adoption more than quadrupled.

Managed Healthcare
between 2019 and April 2020, growing from 11% to 46% of US consumers using telehealth. During the virtual Community Oncology Association (COA) 2020 Conference in April, a virtual panel of leaders from oncology practices all agreed telehealth was a key pillar of their organization’s strategy to provide safe critical care for their patients under crisis conditions. Sibel Blau, MD, medical director of Northwest Medical Specialties, noted that telemedicine “improves patient care in ways that we couldn’t have imagined.” With implementation accomplished and plans for CMS to permanently expand telehealth for E/M Services, practices can leverage their existing infrastructure for care coordination in OCF.

Other COVID-19 initiated investments made to care redesign, such as home-based chronic care management, remote patient monitoring, partnerships with pharmacies that can deliver medications to patient homes, optimization of a rotating remote workforce, and ways to address lack of transportation for patients, may also generate earnings in OCF. The workforce, and ways to address lack of transportation for patients, may also generate earnings in OCF.

Understanding the Challenges of Rural Cancer Care

Mary Caffrey

Prakash joined the Paris office of Texas Oncology, which serves patients across Texas’ Northeast corner, as well as some from Oklahoma. Now the area medical director, Prakash is passionate about bringing better care to his patients, and he serves on state and national-level committees to address the challenges of rural health care, including the American Society of Clinical Oncology’s Rural Cancer Care Task Force.1

Rural health care delivery faces many challenges—from logistics, to finances, to keeping abreast of the scientific revolution in cancer care. Prakash points out that 60 million people, or about 19% of the US population, live in areas considered rural based on the Census Bureau’s definition, and that’s too many people too ignore.2

From his vantage point, he sees the many disparities among rural patients—the residents are older, with less education and income than their urban counterparts. When cancer occurs, the outcomes are generally worse.3 “They are diagnosed later,” he said. “Access to care is a major issue—that change is regrettable. Worse would be our failure to continue moving in a better direction. In an April Health Affairs article, Mark McClellan, MD, PhD, and coauthors explained, “Continued payment reform progress is in the current interests of public health.”4 If designed well, OCF could be 1 of many worthwhile steps to take in that journey.

References

Rural patients are diagnosed later and less likely to receive stand-alone care, follow-up or supportive services than patients in metropolitan areas. In addition, the ASCO report highlighted the challenge of geography is connecting patients with providers. While the percentage of oncologists in rural counties has expanded somewhat since 2014, data from 2019 show that 12% to 15% of oncologists work in rural settings, and about 20% of rural Americans live more than 60 miles from an oncologist. ``These higher percentages of oncologists practicing in rural areas, however, remain smaller than the share of US population residing there," the report said.\(^3\)

### Rural patients are willing to take part in clinical trials if they are available

They are tough and smart and highly adaptable—they reach down and gather strength. If they trust in God, they trust their physician.\(^2\)

---Suchanu "Chris" Prakash, MD, area medical director, Texas Oncology, Paris, TX

#### Gaps in Coverage and Financial Burdens

A major challenge, for both patients and providers, is insurance coverage and reimbursement. The Affordable Care Act (ACA), passed in 2010, was designed with the idea that Medicaid expansion would reach each household with incomes up to 138% of the poverty level. When the Supreme Court allowed states to decide whether or not to expand Medicaid, only half did in 2014, and 12 still have not as of October 1, 2020—including Texas.\(^4\) In states with Medicaid expansion, safety-net hospitals saw large drops in uncompensated care, but this was not so in non-expansion states.\(^5\) Over the past decade, the closure of rural hospitals has been a story across the United States—and Northeast Texas has been hit especially hard, according to data from the University of North Carolina.\(^6\)

Even when patients have Medicaid, it might not be enough. Depending on where patients live, if reimbursements are too low, not all doctors will accept this form of coverage.\(^7\)

Prakash sees these effects at the individual patient level, as well as the snowball effect that lack of coverage creates across the health system. Many families do not qualify for the tax credit that would allow them to buy coverage on the ACA exchanges, but either they cannot afford coverage, or they do not get it through an employer. "This lack coverage limits access," he said. "They cannot get their form of care."

When these patients are eventually diagnosed with cancer, providers must figure out how to absorb the costs, whether it’s through foundation help or patient assistance programs. Add in pressures from the 340B program and pharmacy benefit managers, and the situation can make it hard to attract the best talent, despite the good quality of life in the area. "The hospital is struggling to recruit, because everyone is aware of the problem," he said.\(^8\)

#### Clinical Trial Participation

Historically, fewer patients from rural areas have taken part in clinical trials because they lived too far from academic centers.\(^9\) Being part of the Texas Oncology/US Oncology network has allowed Prakash to enroll his patients in clinical trials, and he finds them eager to participate. Rural patients, he said, "are tough and smart and highly adaptable—they reach down and gather strength. If they trust in God, they trust their physician," he said.

Willingness on the patients' part is only part of the equation. Trials need enough patients to support a research nurse, for example. Prakash said that ASCO recognizes the inequity that rural patients have experienced, and leaders have worked with rural providers to ease eligibility criteria and protocol design, so that rural patients can participate.

#### Rule Changes at CMS

CMS has experimented with rural health care models, but past efforts were limited to certain states. In August, as part of an effort called "Rethinking Rural Health," the agency updated the Inpatient Prospective Payment System (IPPS) to take effect for fiscal year 2020 (October 1, 2020), which officials said were designed with rural providers in mind.\(^10\) Although not specific to cancer care, the rule changes purport to address financial disadvantages that rural providers experience. And CMS then launched a payment model, called CHART, that addresses a long-standing complaint about the definition of "originating site" in telehealth, which had been a barrier for providers. The IPPS rules changes are designed to:

- address wage index disparities by improving the accuracy of the calculation, and change the way the "rural floor" is calculated;
- increase the wage index for hospitals below the 25th percentile; and
- implement a required increase for hospitals taking part in a quality reporting program.\(^11\)

With CHART, which stands for Community Health Access and Rural Transformation, CMS will provide funding to support new payment models, regulatory flexibility, and technology support to implement value-based capped payment models that will allow an outpatient department or emergency room to be reimbursed as if they were a hospital.\(^12\)

#### Telehealth and Staying Connected

The latest game changer has been the coronavirus disease 2019 (COVID-19). The pandemic has opened the door to telehealth on a scale not seen previously. Not every visit is appropriate for telehealth, as some patients still use a flip phone or want to see their doctor in person. But like many others, Prakash believes there’s no going back, and CMS has proposed making some aspects of the telehealth rule change permanent.\(^13\)

Telehealth is poised to have a "profound impact," beyond patient care and research, he said, because it offers possibilities for provider education and training for rural physicians, to "reduce the isolation, especially for early career oncologists." He sees virtual training as a tool to ensure there is better mentorship and support, and opportunities for young oncologists to more fully participate in major scientific meetings when they simply cannot take time off.

Long term, Prakash sees a need for development of the oncology workforce in rural areas; this will require regulatory relief to improve the clinical trial staff and provide the psychological, nutrition, and support services that patients should expect.

Meeting the needs of patients who often cannot afford their care is not easy, he said. "It is challenging. They need someone who is dedicated." But spending time with each patient, and learning their social and psychological needs has its benefits, too. "You do make a difference in the community. And people appreciate what you do." \(^14\)
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