SPECIAL ISSUE: **OBESITY AND CANCER**

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ALSO IN THIS ISSUE

SHIFT TO YOUNGER PATIENTS. Two review articles published in the past year, including one in *JAMA Network Open*, have highlighted how cancers related to obesity are increasingly appearing in younger patients. The shift has implications for payers, SP312.

LACK OF DIVERSITY LIMITS TRIALS. A study in *JAMA Oncology* finds that African American and Hispanic patients are underrepresented in clinical trials, which limits the ability to develop personalized approaches for patients, SP314.

VOLUNTARY FIRST. The American Society of Radiation Oncologists responds to CMS' proposed Radiation Oncology Model, which the group says would unduly punish practices that are already efficient. A board member calls for a voluntary-first approach and other changes to the proposal, SP317.

ENGAGE, ENABLE, EMPOWER. The most recent session of the Institute for Value-Based Medicine in Philadelphia challenged cancer care leaders to give health systems the tools to measure how well quality care is being delivered, and then charge physicians with improving care based on how well they fare against benchmarks, SP322.

PATIENT-REPORTED OUTCOMES (PROS). A session at the National Comprehensive Cancer Network's fall policy conference in Washington, DC, looked at the importance of PROs and the challenge of comparing them across different groups of cancer patients, SP319.

OVERVIEW

Obesity and Cancer Risk: A Public Health Crisis

Alexander J. Alvarnas; and Joseph C. Alvarnas, MD

OBESITY IS BECOMING AN increasingly common health condition in the United States and other Western nations. This condition is defined as an individual having a body mass index (BMI) of 30 kg/m^2 or greater.[1] Although some data suggest that other measures of obesity, such as percentage of body fat or fat mass index, might be better predictors of obesity-related complications such as metabolic syndrome, BMI is still the most commonly used metric to estimate individual obesity.[2] A BMI greater than 40 kg/m^2 indicates extreme obesity.[3]

The United States has the highest obesity rates in the world.[4] According to a *JAMA* paper published in 2016 based on data from 26,468 participants from 2 previous National Health and Nutritional Examiner Survey (NHANES) trials, the crude rate of obesity for data year 2013 was 35.2% for men and 40.5% for women. The overall age-adjusted obesity rate was 37.7%. The prevalence of class 3 obesity (BMI ≥40 kg/m^2) was 5.5% for men and 9.9% for women.[5] When comparing obesity rates in 2015 with those of the 1980s, one study found that average body weight had increased by 10%.[6] By comparison, in 1990, the US obesity rate of obesity was just 15%.

CONTINUED ON SP332 »

ADVOCACY PERSPECTIVE

NASH and Liver Cancer: The New Cancer Headline

Donna Cryer, JD

DESPITE MUCH PROGRESS in the war on cancer, the continued rise of obesity in the United States remains a significant contributing factor to cancer incidence and death.[1] The term *obesogenic cancers*, which refers to cancers driven by our fat-promoting environment, nutritional policies, and lifestyle, is still relatively unfamiliar outside the medical literature. However, this issue needs to be at the top of the agenda for public health, policy, and payer professionals.

Obesogenic cancers include esophageal, colon, breast, and liver cancer. The most common primary liver cancer, hepatocellular carcinoma (HCC), driven by fatty liver disease, is among the most prevalent and deadly of obesogenic cancers.[2] In 2014, overweight- and obesity-associated cancers accounted for 40% of cancer diagnoses in the United States, totaling about 630,000 diagnoses.[3] Rising rates of overweight and obesity parallel increased obesogenic cancer rates, which increased 7% between 2005 and 2014.[3] With nonobesogenic cancer rates declining over the same period, it is evident that there is cause for concern.[3]

CONTINUED ON SP334 »

PATT

INTERVIEW

How Obesity Affects Cancer Treatment—and How to Talk With Patients About Prevention

An Interview With Debra Patt, MD, MPH, MBA, by Jaime Rosenberg

AS OBESITY RATES HAVE CLIMBED in the United States over the past 2 decades, so has the incidence of cancers related to obesity.[1,2] Debra Patt, MD, MPH, MBA, an oncologist who specializes in breast cancer and who serves as executive vice president at Texas Oncology, sees this phenomenon among her patients in the Austin, Texas, area. Patt spoke with *Evidence-Based Oncology*™ (*EBO*) about the effect that obesity has on cancer rates and how it can reduce the effectiveness of some therapies, as well as the need for clinicians to encourage patients to eat healthy food and exercise to both improve outcomes and prevent recurrence.

Patt, a member of the editorial board of *EBO*, is a national leader in healthcare policy and clinical informatics who has testified before Congress about the importance of protecting access to care for Medicare beneficiaries.[3] She is the editor-in-chief of the *Journal of Clinical Oncology—Clinical Cancer Informatics*.

CONTINUED ON SP336 »

AJMC® Managed Markets Network®
ACCC Association of Community Cancer Centers
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IMBRUVICA® (ibrutinib): #1 PRESCRIBED THERAPY IN FRONTLINE* AND PREVIOUSLY TREATED CLL[1†]

*Based on market share data from IMS from November 2016 to February 2019.
†Based on market share data from IMS from May 2014 to February 2019.

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Major hemorrhage (≥Grade 3, serious, or central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA® in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. In IMBRUVICA® clinical trials, 3.1% of patients taking IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA®

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janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

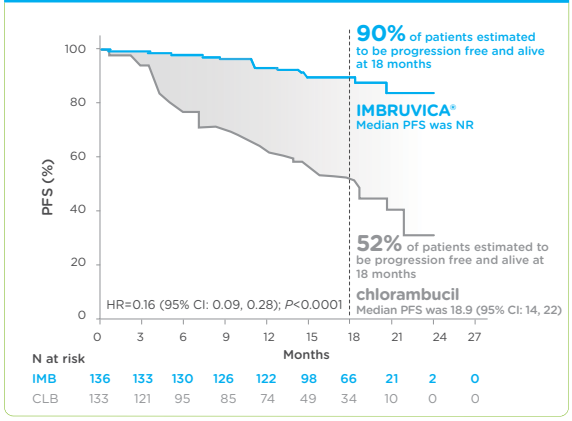
RESONATE™-2 PRIMARY ENDPOINT: PFS WITH IMBRUVICA® VS CHLORAMBUCIL[3]

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269).[2,3] Patients with 17p deletion were excluded.[3]

OVERALL FOLLOW-UP OF 55 MONTHS

Primary analysis: Superior PFS by IRC assessment with IMBRUVICA® with a median follow-up of 18 months[2,3]

84% statistically significant reduction in risk of progression or death[2,3]



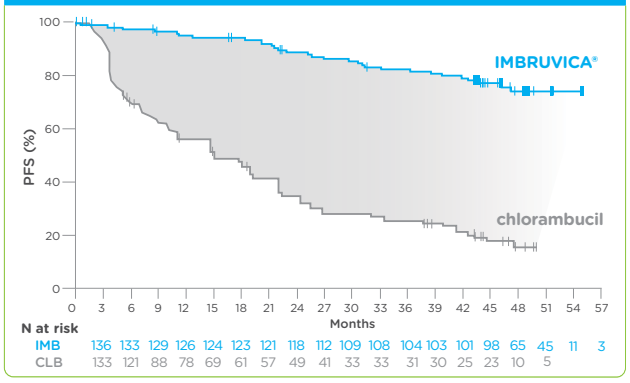
Secondary endpoint: OS with IMBRUVICA® vs chlorambucil[2,3]

Based on a median follow-up of 28 months, IMBRUVICA® resulted in a 56% statistically significant reduction in the risk of death vs chlorambucil (HR=0.44 [95% CI: 0.21, 0.92])[1]

- The estimated survival rate at 24 months was 95% with IMBRUVICA® (95% CI: 89, 97) vs 84% with chlorambucil (95% CI: 77, 90)
- 41% of chlorambucil-treated patients crossed over to IMBRUVICA® upon disease progression

Long-term follow-up: Investigator-assessed median PFS was not reached with IMBRUVICA® with an overall follow-up of 55 months[1,2]

Investigator-assessed long-term follow-up of risk of disease progression or death[1]



Complete long-term follow-up results are not included in the Prescribing Information for IMBRUVICA®. The timing for long-term follow-up was not prespecified and the analysis was descriptive in nature.

Median PFS was not reached with IMBRUVICA® with an overall follow-up of 55 months[1,2]:

- Median time on study was 48.1 months (0.1 - 55.2 months)
- 74% of patients estimated to be progression free and alive at 4 years in the IMBRUVICA® arm (95% CI: 65, 81)
- 16% of patients estimated to be progression free and alive at 4 years in the chlorambucil arm (95% CI: 9, 24)

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain‡ (36%)
- Cough (22%)
- Rash‡ (21%)
- Bruising‡ (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection‡ (15%)

‡Includes multiple ADR terms.

in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, diarrhea (41%), anemia (38%)*, neutropenia (35%)*, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)*, thrombocytopenia (16%), and pneumonia (14%).

Approximately 7% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included pneumonia (1.1%), hemorrhage (1%), atrial fibrillation (0.9%), rash (0.7%), diarrhea (0.6%), neutropenia (0.5%), sepsis (0.4%), thrombocytopenia (0.4%), interstitial lung disease (0.3%), and bruising (0.2%). Nine percent of patients had a dose reduction due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Modify IMBRUVICA® dose as described in USPI sections 2.4 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

CI=confidence interval, CLB=chlorambucil, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, IMB=IMBRUVICA®, NR=not reached, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC. 2019. **3.** Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients exposed to IMBRUVICA in 27 clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 39% of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. In IMBRUVICA clinical trials, 3.1% of patients taking IMBRUVICA without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA in clinical trials *[see Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. Advise women to avoid becoming pregnant while taking IMBRUVICA and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Cardiac Arrhythmias *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and four randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS, and iLLUMINATE) in patients with CLL/SLL (n=1,506 total and n=781 patients exposed to IMBRUVICA). Patients with creatinine clearance (CrCl) ≤ 30 mL/min, AST or ALT ≥ 2.5 x ULN (upper limit of normal), or total bilirubin ≥ 1.5x ULN (unless of non-hepatic origin) were excluded from these trials. Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 386 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 267 randomized patients with treatment naïve-CLL or SLL who were 65 years or older and received single agent IMBRUVICA or chlorambucil, HELIOS included 574 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab, and iLLUMINATE included 228 randomized patients with treatment naïve CLL who were 65 years or older or with coexisting medical conditions and received IMBRUVICA in combination with obinutuzumab or chlorambucil in combination with obinutuzumab.

The most commonly occurring adverse reactions in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, rash, musculoskeletal pain, bruising, nausea, fatigue, pyrexia, hemorrhage, and cough.

Four to 10 percent of patients with CLL/SLL receiving IMBRUVICA discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia. Adverse reactions leading to dose reduction occurred in approximately 7% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 1 and 2.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies	10	2†
Vascular disorders	Hypertension	16	8

†One patient death due to histiocytic sarcoma.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.
Treatment-emergent Grade 4 thrombocytopenia (8%) and neutropenia (12%) occurred in patients.

RESONATE: Adverse reactions and laboratory abnormalities described below in Tables 3 and 4 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 3: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	2†
Infections and infestations				
Upper respiratory tract infection	16	1	11	2†
Pneumonia*	15	12†	13	10†
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0

Table 3: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given adverse reaction (ADR) term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 8% in the ofatumumab arm) occurred in patients.

RESONATE-2: Adverse reactions described below in Table 5 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE-2

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular disorders				
Hypertension*	14	4	1	0
Nervous system disorders				
Headache	12	1	10	2

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

HELIOS: Adverse reactions described below in Table 6 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

IMBRUVICA® (ibrutinib)

Table 6: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	56†
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular disorders				
Hemorrhage*	19	2†	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

iLLUMINATE: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA + obinutuzumab with a median duration of 29.3 months and exposure to chlorambucil + obinutuzumab with a median of 5.1 months in iLLUMINATE in patients with previously untreated CLL/SLL.

Table 7: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE

Body System Adverse Reaction§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Blood and lymphatic system disorders				
Neutropenia*	48	39	64	48
Thrombocytopenia*	36	19	28	11
Anemia	17	4	25	8
Skin and subcutaneous tissue disorders				
Rash*	36	3	11	0
Bruising*	32	3	3	0
Gastrointestinal Disorders				
Diarrhea	34	3	10	0
Constipation	16	0	12	1
Nausea	12	0	30	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain*	33	1	23	3
Arthralgia	22	1	10	0
Muscle spasms	13	0	6	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	27	1	12	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	25	2	58	8
Vascular disorders				
Hemorrhage*	25	1	9	0
Hypertension*	17	4	4	3
Infections and Infestations				
Pneumonia*	16	9	9	4†
Upper Respiratory Tract Infection	14	1	6	0
Skin infection*	13	1	3	0
Urinary tract infection	12	3	7	1
Nasopharyngitis	12	0	3	0
Conjunctivitis	11	0	2	0
Metabolism and Nutrition Disorders				
Hyperuricemia	13	1	0	0

Table 7: Adverse Reactions Reported in at Least 10% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in iLLUMINATE (continued)

Body System Adverse Reaction§	IMBRUVICA + Obinutuzumab (N=113)		Chlorambucil + Obinutuzumab (N=115)	
	All Grades (%)	Grade 3 or Higher (%)	All Grades (%)	Grade 3 or Higher (%)
Cardiac Disorders				
Atrial Fibrillation	12	5	0	0
General Disorders and Administration Site Conditions				
Pyrexia	19	2	26	1
Fatigue	18	0	17	2
Peripheral edema	12	0	7	0
Psychiatric disorders				
Insomnia	12	0	4	0

§ The data are not an adequate basis for comparison of ADR rates between treatment arms.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
† Includes one event with a fatal outcome.

Additional Important Adverse Reactions: *Cardiac Arrhythmias:* In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.5% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 9% versus 1.4% and for Grade 3 or greater was 4.1% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), diarrhea of any grade occurred at a rate of 39% of patients treated with IMBRUVICA compared to 18% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range, 0 to 708) versus 46 days (range, 0 to 492) for any grade diarrhea and 117 days (range, 3 to 414) versus 194 days (range, 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 85% versus 89% had complete resolution, and 15% versus 11% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 7 days (range, 1 to 655) versus 4 days (range, 1 to 367) for any grade diarrhea and 7 days (range, 1 to 78) versus 19 days (range, 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance: In randomized controlled trials (n=1605; median treatment duration of 14.8 months for 805 patients treated with IMBRUVICA and 5.6 months for 800 patients in the control arm), blurred vision and decreased visual acuity of any grade occurred in 11% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (6% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 91 days (range, 0 to 617) versus 100 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 60% versus 71% had complete resolution and 40% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 37 days (range, 1 to 457) versus 26 days (range, 1 to 721) in IMBRUVICA-treated subjects compared to the control arm, respectively.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome *[see Warnings & Precautions]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis, panniculitis
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Data)*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

IMBRUVICA® (ibrutinib)

Data: Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 20 times the exposure in patients with CLL/SLL administered the dose of 420 mg daily. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.8 times the exposure (AUC) in patients with CLL/SLL administered the dose of 420 mg daily.

Lactation: *Risk Summary:* There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for IMBRUVICA and any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: *Pregnancy Testing:* Conduct pregnancy testing in females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception: Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

PATIENT COUNSELING INFORMATION

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

- *Hemorrhage:* Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions]*.
- *Infections:* Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions]*.
- *Cardiac Arrhythmias:* Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions]*.
- *Hypertension:* Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions]*.
- *Second primary malignancies:* Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions]*.
- *Tumor lysis syndrome:* Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions]*.
- *Embryo-fetal toxicity:* Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA *[see Warnings and Precautions]*.
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information]*.
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose *[see Dosage and Administration (2.6) in Full Prescribing Information]*.
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions]*. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION .
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions]*.
- Advise patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration *[see Adverse Reactions]*.

Active ingredient made in China.

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PRC-05666

FROM THE EDITOR-IN-CHIEF

Reality Isn't That Simple

Reality seems so simple. We just open our eyes and there it is.
But that doesn't mean it is simple.

Penn and Teller


ALVARNAS

OVER THE PAST DECADE, we have developed an extraordinary pipeline for innovative anticancer therapeutics. This period of unprecedented innovation in oncology has been profoundly edifying for patients and cancer physicians who have watched the seemingly unchanging poor prognosis for several cancer types improve dramatically based upon the rapid identification of targets and the emergence of lifesaving therapeutics. The greatest optimist would not have predicted this pace of change 2 decades ago. Yet, in the midst of this progress, we have missed a golden opportunity: The best anticancer treatments are those we *never* have to administer.

After a deep dive to understand the link between obesity and cancer risk for this issue, only in retrospect did I realize the full depth of my ignorance. Obesity is a significant, growing, and avertable cause of cancer for a large number of patients. The scope of the problem is daunting, and the human toll of the current obesity epidemic is extraordinary. Since 1990, US obesity rates have risen from 15% to approximately 37%. Sadly, the United States has the dubious distinction of having the highest obesity rates in the world. Whereas the role of obesity in increasing the risk of hypertension, diabetes, dyslipidemia, cardiovascular disease, stroke, and musculoskeletal disorders is well recognized, there is far less awareness about the impact of obesity upon cancer risk.

Obesity is on the verge of becoming the most common preventable cause of cancer in the United States. Data from large-scale population studies demonstrate a greater cancer risk due to obesity for more than 20 cancer types, and additional data demonstrate inferior cancer care outcomes for patients considered obese. Beyond the immense human toll, the societal costs of the obesity epidemic are extraordinary, with one estimate of obesity-related excess healthcare expenditures totaling more than $200 billion annually.

The majority of my professional career has been spent delivering anticancer treatments; I am a blood and marrow transplant physician. Either by training, avocation, or plain inclination, I have devoted far less of my professional energy to the equally important work of cancer prevention. Unlike our anticancer armamentarium that can be unleashed quickly, discretely, effectively, and stereotypically based upon clinical evidence and standardized treatment approaches, undoing the obesity epidemic represents a much more complex set of tasks that requires both a wholesale change in human behavior and a deep societal commitment to bring about fundamental cultural change. Sometimes the public discourse around this issue simplifies the level of commitment required, and not in a positive way. There are no quick fixes to the epidemic of obesity. In examining root causes of childhood obesity, the challenges of getting this right are as much cultural as clinical. Addressing key contributing factors, such as childhood screen time, consumption of fast food, lack of physical exercise, and environmental hazards is not a set of activities that fit well within our current encounter-based reimbursement system.

The simple truth is that that there is nothing simple about cancer prevention. To do this well involves a wholesale commitment to things that are a challenge to our healthcare system under the best of circumstances: communicating with patients in a way that moves them deeply enough to change their behavior, reinforcing that message even when it seems that initial efforts are not working, engaging the community around the patient to support healthier behaviors, and making an impact upon the popular culture to support the message.

Yet, this can be accomplished. We are now in the midst of a time in which cancer-prevention endeavors are showing striking signs of success. Smoking cessation efforts are finally translating into decreases in cancer incidence rates. The methodical nature of this success and the multidecade incremental investments of time, energy, resources, and effective public policy required to get to this moment are monumental. (The first report to the US Surgeon General appeared in January 1964, and it took over 5 decades to get it right). Here at *Evidence-Based Oncology*™, we are committed to fostering conversations that hope to change systems. We are the leaders, physicians, and healthcare professionals who can lead the charge, no matter how daunting. Let us begin.◆

Joseph Alvarnas, MD
EDITOR-IN-CHIEF

EDITORIAL MISSION

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

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SPECIAL ISSUE / OBESITY AND CANCER
OCTOBER 2019
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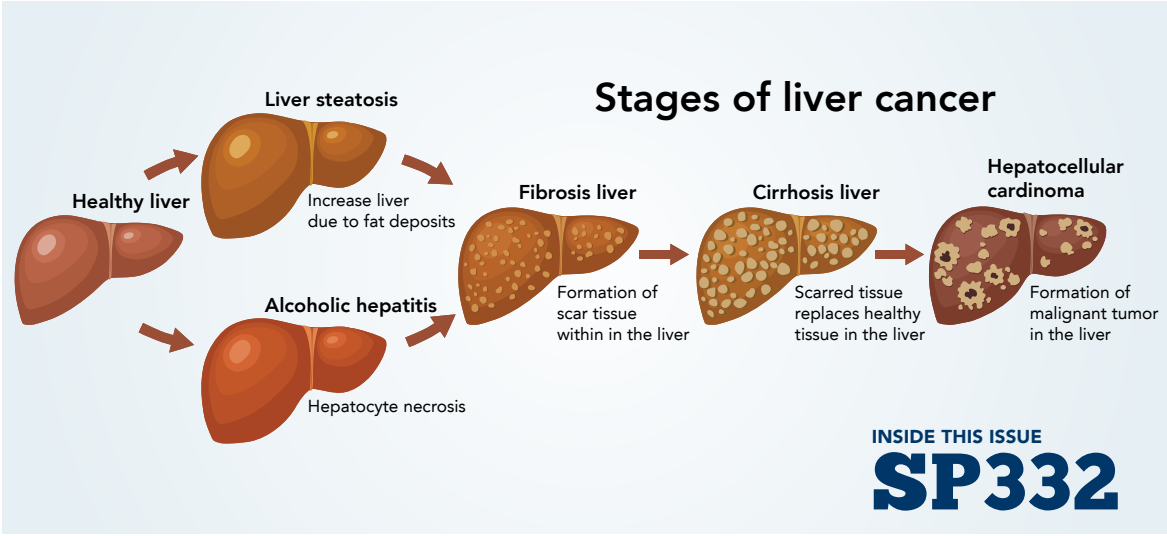

The illustration above outlines the stages that occur from alcoholic hepatitis to liver cancer, one of the obesity-related cancers that is on the rise in the United States, even as overall cancer survival improves.

FEATURES

INSIDE THE ISSUE

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Obesity and Cancer: Fat Is Not Idle

FIVE YEARS AGO, it might not have seemed obvious to present an issue of *Evidence-Based Oncology*™ (*EBO*) on obesity and cancer—and certainly not to readers involved in managed care. Today, coverage of the topic is essential. In 2019 we have seen 2 important review articles in *Lancet Public Health*[1] and *JAMA Network Open*[2] that report alarming trends: Although cancer survivorship rates are improving, more cancer incidence is now tied to obesity, and more of these obesity-related cancers are being diagnosed in younger patients. As Alexander Alvarnas and *EBO* Editor-in-Chief Joseph A. Alvarnas, MD, report in our cover article, obesity-related malignancies are on track to replace smoking-related malignancies as the leading preventable cause of cancer.

How does this occur? The authors detail the accumulating science on the role of inflammation, which is responsible for diabetes, rheumatoid arthritis, and so many other diseases. With obesity, the presence of excess adipose tissue creates the inflammatory state that sets in motion the conditions for the development of tumors. In other words, fat is not idle; there is much happening, and it's not healthy. In an interview, *EBO* editorial board member Debra Patt, MD, MPH, MBA, of Texas Oncology, discusses how excess fat can diminish the effectiveness of aromatase inhibitors for certain patients with breast cancer and increase the likelihood of cancer recurrence.

These trends have implications for the healthcare system and managed care, starting with Medicare. As the authors noted in the *JAMA Network Open* study, if more patients in their 40s and 50s are given diagnoses of obesity-related cancers, more cancer survivors will enter Medicare, with greater need for monitoring and therapy and an increasing possibility of relapse. Thus, managed care has a keen interest in turning the tide. Solutions like bariatric surgery can prevent cancer in patients who are severely obese, and some state Medicaid programs are paying for surgery in light of this evidence.[3] For others, even modest weight loss makes a difference, in both preventing initial cancers and avoiding secondary cancers. As Patt notes, this means physicians must talk to patients about weight loss, although she is candid that collaborating with patients on lifestyle choices is not easy. It all starts with value-based payment models: Physicians must have incentives to address obesity and lack of exercise if we are to reverse these alarming trends. ◆

Sincerely,

Mike Hennessy, Sr
Chairman and CEO

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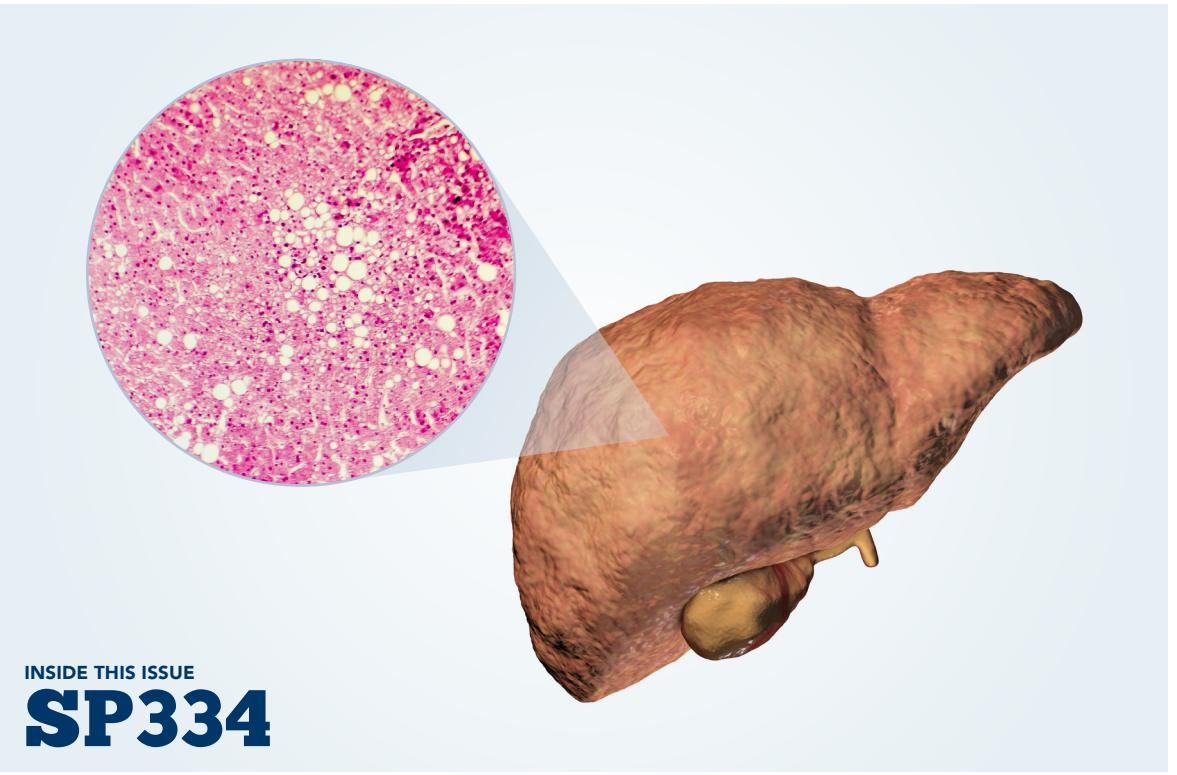

INSIDE THIS ISSUE

SP334

This photo inset shows large vacuoles of triglyceride fat accumulated inside liver cells, which can occur in alcohol over use and lead to liver steatosis. Fatty liver disease is a cause of liver cancer, one of the obesity-related cancers that is on the rise.

EFFECTIVE **OCTOBER 1, 2019**, THE FOLLOWING PERMANENT J-CODE CAN BE USED FOR BILLING AND OTHER ADMINISTRATIVE PURPOSES:

LIBTAYO®
(cemiplimab-rwlc)
Injection 350 mg

J9119, INJECTION, cemiplimab-rwlc, 1 mg

How supplied[1]

LIBTAYO is supplied in a carton containing 1 single-dose vial of 350 mg/7 mL (50 mg/mL).

Recommended dosage[1]

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. Please see brief summary of prescribing information on the following pages for additional dosing and administration information.

Strength[1]
350 mg/7 mL (50 mg/mL)
NDC[1]
61755-008-01

The Centers for Medicare & Medicaid Services assigned a 1 mg billing unit for LIBTAYO (1 mg of LIBTAYO = 1 unit). Coding requirements may vary by payer; please verify coding requirements before submitting claims.

Indication

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

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. 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 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. 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 3 (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 60% 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 0.9% 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 1) after corticosteroid taper.

(Continued)

Please see additional Important Safety Information and accompanying Brief Summary of Prescribing Information on the following pages.

Important Safety Information

Warnings and Precautions (continued)

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
- **Hyperthyroidism:** Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%); hyperthyroidism resolved in 38% of patients
- **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: 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 pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%). In addition, SJS and 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-initiation of LIBTAYO. 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.

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 neuropathy
- **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 to include increases in serum amylase and lipase levels, gastritis, and duodenitis
- **Musculoskeletal and connective tissue:** Myositis, rhabdomyolysis, and associated sequelae, including renal failure, arthritis, and polymyalgia 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.

Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-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 28% of patients. Serious adverse reactions that occurred in ≥2% of patients were cellulitis, sepsis, pneumonia, pneumonitis, and urinary tract infection. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection, and fatigue
- LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness
- The most common adverse reactions (incidence ≥20%) were fatigue, rash, and diarrhea

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 accompanying Brief Summary of Prescribing Information on the following pages.

Reference: LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PD-1=programmed death receptor-1; NDC=National Drug Code.

REGENERON | SANOFI GENZYME

LIBTAYO®
(cemiplimab-rwlc)
Injection 350 mg

LIBTAYO® (cemiplimab-rwlc) Injection 350 mg

LIBTAYO® (cemiplimab-rwlc) injections, 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 (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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.

2.2 Dosage Modifications for Adverse Reactions

Withhold or discontinue LIBTAYO to manage adverse reactions as described in Table 1. No dose reduction of LIBTAYO is recommended.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	LIBTAYO Dosage Modifications
Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis	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.	Withhold†
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, or 4	Withhold if clinically necessary
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold†
	Grade 4	Permanently discontinue
Recurrent or persistent immune mediated adverse reactions	• Recurrent Grade 3 or 4 • Grade 2 or 3 persistent for 12 weeks or longer after last LIBTAYO dose • Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last LIBTAYO dose	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

*Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

2.3 Preparation and Administration

- Visually inspect for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of translucent to white particles.

Preparation

- Do not shake.
- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused medicinal product or waste material.

Storage and Infusion Solution

- Store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion.
- Allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

Administration

- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

4 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 system or tissue. 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.

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.

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%) *[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.

Immune-Mediated Colitis

Immune-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.

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%) *[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.

Immune-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)]*.

Hypophysitis

Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of one 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.

Hyperthyroidism

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

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

Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%) *[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, SJS and 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 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.

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 *[see Adverse Reactions (6.1)]* or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Neurological: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Cardiovascular: Myocarditis, pericarditis, 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 to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

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

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO *[see Adverse Reactions (6.1)]*. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction *[see Dosage and Administration (2.2)]*.

5.3 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. 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. 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 *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*

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-arm, multicohort studies (Study 1423 and Study 1540), including 98 patients with metastatic (nodal or distant) CSCC, 65 patients with locally advanced CSCC, and 371 patients with other advanced solid tumors. LIBTAYO as a single agent or 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 163 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=139) or 350 mg every 3 weeks (n=23) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 20 weeks (3 days to 1.4 years).

The safety population characteristics were: median age of 71 years (38 to 96 years), 85% male, 96% white, and ECOG performance score (PS) of 0 (44%) or 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash and diarrhea. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection and fatigue. LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness. Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in at least 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection.

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

Table 2: Adverse Reactions in ≥10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	LIBTAYO N=163	
	All Grades %	Grade 3-4 %
Skin and Subcutaneous Tissue		
Rash*	25	1.2
Pruritus†	15	0
Gastrointestinal		
Diarrhea‡	22	0.6
Nausea	19	0
Constipation	12	0.6
General and Administration Site		
Fatigue§	29	2
Musculoskeletal and Connective Tissue		
Musculoskeletal pain#	17	3
Metabolism and Nutrition		
Decreased appetite	10	0

*Rash is a composite term that includes rash maculopapular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction.
†Pruritus is a composite term that includes pruritus and pruritus allergic.
‡Diarrhea is a composite term that inlcudes diarrhea and colitis.
§Fatigue is a composite term that includes fatigue and asthenia.
#Musculoskeletal pain is a composite term that includes: musculoskeletal pain, back pain, myalgia, neck pain, pain in extremity.

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

Laboratory Abnormality	Grade 3-4 (%)†
Chemistry	
Increased aspartate aminotransferase	3
Increased INR	2
Hypoalbuminemia	1
Hematology	
Lymphopenia	7
Anemia	2
Electrolytes	
Hypophosphatemia	4
Hyponatremia	3
Hypercalcemia	1

†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 398 of 534 patients who received LIBTAYO and the incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.3% using an electrochemiluminescent (ECL) bridging immunoassay; 0.3% 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. 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 altering 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 163 patients with metastatic and locally advanced CSCC who received LIBTAYO in clinical studies, 72% were 65 years or older and 37% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Advise patients that LIBTAYO can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that LIBTAYO can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of LIBTAYO *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking LIBTAYO and for at least 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

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LIBTAYO® (cemiplimab-rwlc) Injection 350 mg

More Data Reveal Shift to Obesity-Related Cancers in Younger Patients

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AN ANALYSIS OF US CANCER DATA published in *JAMA Network Open* shows that cancers related to obesity are on the rise in younger adults, and the investigators said the impact on Medicare and Medicaid in the coming decades will be severe unless screening programs can better pinpoint who is likely to develop the disease.

Siran Koroukian, PhD; Weichuan Dong, MA; and Nathan A. Berger, MD, examined records from more than 2.6 million obesity-related cancer cases and more than 3.4 million non–obesity-related cases in the Surveillance, Epidemiology, and End Results Program database from 2000 to 2016, looking not only at the age distribution but also at how obesity-related and non–obesity-related cancers were distributed by race and gender during that period.[1]

Although results of other recent studies have noted the rise in the rate of obesity-related cancers among younger adults, this is the first study to also find a concurrent decrease in the rate of new cancer cases among patients 65 years and older. "It is possible that changes in cancer surveillance over time have improved early cancer detection," the investigators wrote.

In other words, the good news is that the screening protocols in Medicare are working. The bad news is that a different, more personalized screening approach is needed for younger adults, especially those aged 50 to 64 years. In this group, the rate of obesity-related cancers in particular is rising.

> **"The shift of the cancer burden to younger age groups has important public health, research, and policy implications."**
>
> —*JAMA Network Open*

This latest study adds to concerns that the US obesity epidemic is thwarting gains in preventing and curing cancer. Overall, cancer survival rates have improved over the past quarter century, aided by declining smoking rates.[2] In 2017, the CDC published data showing that 40% of all cancer diagnoses were of 13 types of cancer associated with obesity: adenocarcinoma of the esophagus; cancers of the gastric cardia, colon and rectum, liver, gallbladder, pancreas, breast (in postmenopausal women), ovaries, uterus, kidney, and thyroid; meningioma; and multiple myeloma.[3]

The *JAMA Network Open* study was the second this year to report a trend of obesity-related cancers among young patients. A February study in the *Lancet Public Health* by the American Cancer Society and the National Cancer Institute found that cancer incidence rose for 6 of 12 obesity-related cancers between 1995 and 2014 in adults aged 25 to 49 years, with steeper increases in younger generations.[4]

For the *JAMA Network Open* study, investigators defined obesity-related cancers as those of the colon and rectum, female breast, uterus, gallbladder and other biliary systems, esophagus, stomach, liver, pancreas, ovary, kidney and renal pelvis, and thyroid, as well as myeloma.[1]

The investigators noted the following findings:

- Of the obesity-related cancers in the study, 70.3% were among women, a result of the inclusion of breast, uterine, and ovarian cases.
- The study broke out incidence rates by age, gender, and race. In most cases, although the overall number of obesity-related cases among those 65 years and older rose because of the aging population, the incidence rate decreased. Among all race/gender groups in the population 65 years and older, obesity-related cancers decreased; other cancers increased or declined at lower rates.
- For the group aged 50 to 64 years, a statistically significant increase across the study period was observed in both obesity-related and non–obesity-related cancers; this was seen across all race/gender groups. The increases were larger in obesity-related cancers than in other cancers.
- Among those aged 20 to 49 years, the overall risk of cancer fell over the time, but all race/gender groups, with the exception of Hispanic men, saw a higher risk of obesity-related cancers than other cancers.

What types of cancer are on the rise? Although the data showed a variation by age, race, and gender, liver and thyroid cancers rose sharply among many groups. Liver cancer is one of the fastest-rising cancer diagnoses in the United States, according to CDC.[3]

"The shift of the cancer burden to younger age groups has important public health, research, and policy implications," the investigators wrote. When cancer is diagnosed in younger adults, the disease may already be more advanced and more aggressive.

Also, the authors noted that if more young adults develop obesity-related cancers in their 40s and 50s, more cancer survivors will join the ranks of Medicare, having endured the physical, financial, and emotional hardships of living with the disease. Because of the expense of current therapies and the cost-sharing designs of some health plans, many may also qualify for Medicaid.

"Together, these findings suggest an increasing cancer burden on Medicare and Medicaid programs in the future," the investigators wrote.

Reducing obesity may be the best solution, but short of that, the investigators recommended improving screening programs to catch cancer earlier or prevent it among younger adults. "The findings have important public health implications and suggest that interventions to reduce obesity and to implement individualized screening programs are needed," the authors concluded. ◆

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Research Reveals a Lack of Racial Diversity in Clinical Trials for Cancer Drugs

Matthew Gavidia

RAGHAV

Kanwal Raghav, MBBS, MD, is an assistant professor, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center

CLINICAL TRIALS FOR CANCER drugs lack racial and ethnic diversity in their populations, according to findings published in August in *JAMA Oncology*.[1]

Researchers from the University of British Columbia (UBC), The University of Texas MD Anderson Cancer Center, the Fred Hutchinson Cancer Center, and Baylor University sought to evaluate the frequency of race reporting and representation in 230 trials supporting FDA oncology drug approvals from July 2008 to June 2018. The study authors analyzed 112,293 participants from the 4 major racial and ethnic groups in the United States: white, black, Asian, and Hispanic. Taking into account that some trials reported on more than 1 group, these are the results:

- 144 (62.6%) trials reported on the white population
- 110 (47.8%) trials reported on the Asian population
- 88 (38.2%) trials reported on the black population
- 23 (10%) trials reported on the Hispanic population

Among the 230 trials, 145 (63%) reported on at least 1 group, 18 (7.8%) reported on the 4 major groups, and 58 (25.2%) reported on racial and ethnic subgroups. The differentiation of race reporting in trials between July 2008 and June 2013 versus July 2013 and June 2018 changed nominally (45 trials [56.6%] vs 100 trials [67.1%]; odds ratio [OR], 1.63; 95% CI, 0.93-2.87; $P = .09$), as did race subgroup analysis (13 trials [16.1%] vs 45 trials [30.2%]; OR, 2.26; 95% CI, 1.16-4.67; $P = .03$).

The data also revealed a stark contrast in representation for the black and Hispanic populations, at 3.1% and 6.1%, respectively. Black and Hispanic participants also were underrepresented in trials in regard to rates of cancer incidence, at 22% and 44% of their expected rate of cancer; by contrast, whites were enrolled at 98% and Asians at 438% of their expected rate of cancer incidence. The lack of representation by black and Hispanic enrollees was further exemplified by the minimal change in proportion from each race enrolled between July 2008 and June 2013 versus July 2013 and June 2018 (blacks, 3.6% vs 2.9%; Hispanics, 5.3% vs 6.7%).

A lack of diversity in cancer studies was previously documented. Scientists from Johns Hopkins' Bloomberg School of Public Health wrote in 2018 how fewer than 5% of breast cancer studies were stratified by race and socioeconomic factors.[2] These researchers emphasized the need to prioritize social factors like race to understand correlating vulnerability and mortality rates with specific ethnicities.

For many years, assessment devices like the Breast Cancer Risk Assessment Tool were only validated for white women, which significantly underestimated the risk of breast cancer in black women, who have higher rates of breast cancer at younger ages.[2] By utilizing data from a primarily white study group, scientists ignore the impact of cancer drug efficacy on the other 3 major race groups, which may prove detrimental to survival rates.

Lead study author Jonathan Loree, MD, assistant professor in the Department of Medicine, Division of Medical Oncology at UBC,[1] provided an instance in which a medication used to treat lung cancer showed mediocre trial results in the general population but exhibited incredible responses among nonsmoking young women in a study in Asia due to a genetic mutation common in this population.[3] Asked in an interview how physicians reacted to his findings, Loree expressed his own astonishment.

"I think physicians were aware that disparities might exist based on prior work; however, the magnitude of disparity noted in our study is something that is quite surprising," he said.

Delving into the distinctions found in each race can unveil personalized approaches to treating patients based on social factors, but the disparity in race enrollment inhibits this interpretation. Senior investigator in the study Kanwal Raghav, MBBS, MD, assistant professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer, provided additional insight on how to combat these disparities.

"A potential step in this direction would be if the regulatory agencies request post approval studies fueled with real-world data to help generate evidence and fill the disparity gaps for otherwise underrepresented subgroups in initial studies," Raghav said in an email.

Raghav's idea for real-world data involvement is an approach the FDA called for in a framework released in December 2018.[4] Back in 2016, Congress passed the 21st Century Cures Act, which directed the FDA to develop processes for using real-world evidence (RWE) in the course of drug regulation.[5] The FDA joined COTA Healthcare in a 2-year research and collaboration agreement to reform treatment through RWE and electronic health records (EHRs). Starting with breast cancer, the FDA and the healthcare data and analytics company created a study protocol to guide approaches to handling treatment within subpopulations.[6]

COTA is a technology company founded by oncologists and data scientists on the idea that harnessing the vast amounts of information from disorganized EHRs will enable data interpretation so that doctors can relate these findings toward current patients with cancer. In the August issue of *Evidence-Based Oncology*™, COTA Chief Medical Officer Andrew Norden, MD, MPH, MBA, highlighted the steps being taken within the FDA's partnership to work in populations that are often excluded from clinical trials.[7]

The use of EHRs and RWE to combat racial disparity in clinical trials is providing innovative steps to include underrepresented races, like black and Hispanic patients, in their data. Through the ongoing effort by the FDA and COTA to correct race representation, doctors can understand what cancer treatments are best for their patients.

"Real-world evidence is one of many tools that we can use to help address variation in subpopulations and to learn more about how to best utilize cancer treatments to improve outcomes in patients," said Loree. ◆

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FROM OUR CONTRIBUTOR

Who's Next in Line for New Payment Models? Everybody!

Rhonda Henschel, MBA

HENSCHEL

Rhonda Henschel, MBA, is director of commercial value-based care programs for The US Oncology Network.

HHS AND CMS RECENTLY unveiled the CMS Primary Cares Initiative, a group of voluntary payment models that CMS officials hope will move primary care farther down the road to value-based care. Recognizing that primary care resources are stretched, CMS hopes the initiative will improve access, quality of care, and outcomes for Medicare patients by encouraging primary care physicians (PCPs) to play a more prominent role in caring for patients with complex conditions.

Although the Primary Cares Initiative focuses on PCPs, it has implications for all providers, particularly specialists. Simply put, the initiative is just one more indication that CMS is moving forward on its promise to transition healthcare to value-based care, and it is just a matter of time before CMS sets its sights on specialty-focused Advanced Alternative Payment Models (APMs).

The majority of today's healthcare delivery systems are designed to be reactive and address problems once they exist. The new models reward providers for delivering proactive care and keeping patients healthy, helping to prevent chronic conditions and identifying conditions that require specialty care earlier. Theoretically, fewer and less costly resources should be required to manage conditions, and better patient outcomes should be achieved. For example, in oncology, fewer patients may receive diagnoses of cancer or patients may be referred to an oncologist earlier, resulting in cost savings and better outcomes.

Oncology has already seen the emergence of a CMS-driven APM, the Oncology Care Model (OCM), a 5-year pilot program designed to reduce the cost of care while improving quality, care coordination, and patient outcomes. The OCM will most likely lead to a more sophisticated APM when the pilot ends in June 2021.[1]

CMS-Led Programs Have Similarities

Many of the new CMS programs have numerous common elements and goals. The PCP programs, the OCM, and the newly proposed Radiation Oncology APM all focus on reducing Medicare expenditures while ensuring quality care.[2] All models also include a patient experience component, keeping patients at the forefront.

Like the OCM, several PCP models support transformation activities with payments to redesign care management services. Practice transformation is critical for success in any of these models. Practices will likely have difficulty achieving program goals or earning incentives using current workflows and care delivery models. Models also include performance-based incentive payments for reducing use and improving quality and patient experience.

Participants in the OCM now face the decision on whether to engage in 2-sided risk, whereas participants in the PCP and Radiation Oncology models are required to assume financial risk at initiation of the program. In the radiation model, providers receive a bundled payment for most radiation services furnished during a 90-day care episode. The program includes a 3% withhold for quality and patient satisfaction measures, which must be met to earn back this amount. As a result, if practices do not perform, they receive less reimbursement than they would under fee-for-service, whereas the PCP models include varying levels of risk by offering options with reduced fee-for-service payments, flat primary care visit fees, and partially or fully capitated population-based payments.

In all programs, CMS is rewarding practices that assume financial risk by lessening administrative requirements associated with traditional fee-for-service models and upside-only agreements. We have yet to see what decreasing administrative burden means in practice. Moving forward, CMS will likely incorporate strategies into new models that provide greater predictability of healthcare expenditures and require providers to assume financial risk. As CMS collects more clinical and claims data through these early programs, it will be able to establish bundled care rates per condition, requiring specialty providers to diligently manage patients and coordinate care.

New Models Influence the Commercial Sector

Each time CMS creates an APM, it stirs activity among commercial payers who usually align their reimbursement guidelines closely with CMS policies. Commercial payers tend to focus on a subgroup of program requirements they believe drive high-value care and are realistic for them to monitor and report. Most likely, they will continue to mirror CMS programs.

CMS is rewarding practice that assume financial risk by lessening administrative requirements associated with traditional fee-for-service models and upside-only agreements. Moving forward, CMS will likely incorporate strategies into new models that provide greater predictability of healthcare expenditures and require providers to assume financial risk.

Success Depends on Continual Improvement

Specialty providers are already participating in the Merit-based Incentive Payment System, and many oncologists are taking part in the OCM. Although these providers have a good start on value-based care, they must continue to improve performance, especially as programs become more challenging and begin to incorporate cost components or 2-sided risk. To help ensure ongoing success with value-based models, providers should focus on several key areas:

Holistic transformation. Regardless of which program providers participate in, there must be a constant and progressive focus on holistic transformation. Many practices have targeted the low-hanging fruit during these initial years. Soon they will be required to tackle more services along the continuum of care. One example is greater and more consistent integration of enhanced services (in oncology, this equates to palliative care, advance care planning, social work, and nutrition therapy). Providers will need to build mechanisms, such as care paths or remote patient-reported outcomes tools, to identify unmet needs and connect patients with appropriate services at the right time and place. This personalized approach helps prevent adverse

FROM OUR CONTRIBUTOR

effects, complications, and avoidable emergency department visits and hospitalizations—all leading to better outcomes, lower healthcare expenditures, and improved patient experience.

Total cost of care. Clinical decision support tools can help guide providers in developing evidence-based treatment plans, addressing uncontrolled symptoms, and ordering appropriate diagnostic studies. Clinicians will need to identify high-quality providers for referral who offer affordable care. Diligence in this area will help practices manage the total cost of care. For instance, a computed tomography scan is typically more expensive in a hospital setting versus an outpatient imaging center due to hospital fee schedules and additional facility fees.

Accountability and training. Some critical components of value-based care require long and potentially difficult patient conversations. Staff and providers need to be equipped to introduce and explore challenging topics with patients. Expectations also should be established, with care team members held accountable for addressing components of care in a timely manner. Enhanced services tend to have inconsistent integration into care plans because it takes time to introduce and educate patients on the value of these additional visits. Cancer patients, for instance, are often overwhelmed by the number of medical appointments and are not always willing to schedule these visits. Unfortunately, this can lead to complications, poor quality of life, and subpar care. As an example, patients who are enrolled in hospice for less than 3 days are more likely to die in a hospital or intensive care unit, based on data from the OCM. Building advance care planning into the continuum of care can smooth the transition into hospice and provide a better end-of-life experience for patients and loved ones.

The Bottom Line: Value-Based Care Is Here to Stay

Providers who are in denial about the value-based care evolution should take note of the new primary care Advanced APMs. They are continued evidence of CMS' commitment to transform the delivery of healthcare. Three of the models involve capitated rates, likely indicating that PCPs can expect this as the standard reimbursement structure in the future. Providers who hold back from engaging in value-based care should carefully consider the long-term implications of not being an early adopter. There will be a time when learning periods no longer exist and providers will have no choice but to assume full financial risk. Those who hesitate to embrace value-based care will find themselves in a state of rapid transformation, competing with others who already have significant experience and practice. ◆

AUTHOR INFORMATION

Rhonda Henschel, MBA, is the director of commercial value-based care programs for The US Oncology Network. She has 15 years of oncology experience, including value-based care delivery, novel managed care contracts, quality program development, and clinic operations. Henschel has led design efforts and implemented new programs to support delivery of survivorship, palliative care, advance care planning, and oncology medical home certification.

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COMMENTARY

ASTRO Calls for Voluntary Start, Scaling Back Excessive Cuts in CMS' Proposed Radiation Oncology Model

Paul Harari, MD, FASTRO

IN JULY 2019, CMS proposed the Radiation Oncology (RO) Model,[1] an important step forward in allowing the nation's 4500 radiation oncologists to join in the transition to value-based healthcare, as envisioned by the 2015 Medicare Access and CHIP Reauthorization Act (MACRA).[2]

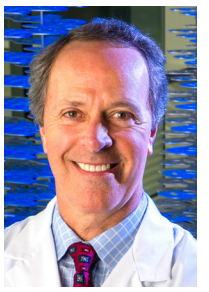
The American Society for Radiation Oncology (ASTRO)—the leading medical society for members of the RO care team—submitted comments to CMS in September 2019 to express its appreciation with the agency's decision to move forward with an alternative payment model (APM) for the specialty.[3] However, ASTRO leaders have shared multiple concerns about the proposal, such as the model's mandatory nature and its excessive payment cuts to practices. Below is a review the strengths and shortcomings of the proposed RO Model, as well as suggested policy solutions to ensure the model can achieve its intended goals of improving patient outcomes while generating savings for Medicare.

Compared with the current fee-for-service structure that incentivizes volume over value in Medicare reimbursement, an APM for RO could realign incentives to encourage the use of guideline-concordant and efficient patient care. A successful RO Model also could create stable and predictable payment rates that avoid jeopardizing patient access to life-saving treatments, and support medical innovation while reducing administrative burden.

Our organization appreciates that CMS recognizes the effort that radiation oncologists have put into the development of an APM for their specialty, as evidenced by the fact that several elements of the proposed CMS RO Model align with the Radiation Oncology Alternative Payment Model concept paper that ASTRO submitted to CMS in April 2017.[4] The positive aspects of the CMS model include the prospective payment; the episode trigger mechanism, timeline and clean period; establishment of distinct professional component and technical component payments; the inclusion of all modalities of treatment; and key quality measure elements.

We are concerned, however, that the proposed CMS RO Model falls short of meeting 3 key goals that ASTRO identified in comments submitted to CMS[3] as necessary for successful, longstanding payment reform. From our perspective, an APM for RO should:

- Reward radiation oncologists for participation and performance in quality initiatives that improve the value of healthcare for patients;
- Ensure fair, predictable payment for the radiation oncologist in both hospital and freestanding cancer clinics to protect patients' access to care in all settings; and
- Incentivize the appropriate use of cancer treatments that result in the highest quality of care and the best patient outcomes.[3] »



HARARI

Paul Harari, MD, FASTRO, is professor and chairman, Department of Human Oncology, University of Wisconsin School of Medicine and Public Health.

An ASTRO analysis estimates that the RO Model would cut payments to participants by approximately $320 million during the 5-year period—an excessive amount that would undermine this unique opportunity.[3] Cuts of this magnitude could strain RO practices that have little choice but to take part in the model, which could put access to safe and effective radiation treatments at risk. For the RO Model to be successful, ASTRO recommends specific, significant changes that will incentivize the use of high-quality, efficient radiation therapy treatments that drive value-based reform and generate savings for Medicare. A summary of the key issues and recommended ASTRO policy solutions to address them follow:

The American Society of Radiation Oncology believes that the Radiation Oncology (RO) Model, with significant modifications, could represent a meaningful and viable first step toward enabling the field of RO to participate in the evolving world of healthcare payment reform.

- **MANDATORY PARTICIPATION** that extends to 40% of RO episodes is excessive for an untested model.

  ASTRO recommends that CMS should begin with voluntary participation before moving to a mandatory model, while allowing opt-outs for low-volume practices and hardship exceptions.
- **NATIONAL CASE RATES.** Calculations for the national case rates contain flaws that would result in significant and unfair payment penalties. ASTRO leaders are concerned that the methodology fails to appropriately account for a range of complex clinical scenarios and average treatment costs for many clinics.

  ASTRO recommends that CMS include some costs from the Medicare Physician Fee Schedule, properly attribute palliative care cases, and ensure adequate payments for patients receiving standard-of-care multimodality treatments, such as combination therapy for gynecological cancer.
- **DISCOUNT FACTOR AND EFFICIENCY ADJUSTMENT.** Proposed adjustments could result in significant funding cuts to all participants and unfairly harm practices that are already efficient.

  ASTRO recommends that CMS adjust the efficiency factor to avoid penalizing efficient practices and scale back the discount factors, which put patient access at risk by causing significant financial issues for such a capital expenditure–intensive specialty.
- **APM INCENTIVE PAYMENT.** CMS' selective waiver of the 5% APM incentive payment on freestanding center technical payments does not align with either the spirit or the letter of MACRA, which calls for giving providers incentives to take on risk by participating in APMs.

  ASTRO recommends removing this waiver.
- **INNOVATION.** Advances in RO have increased cure rates and reduced adverse effects from treatment. Yet, the RO Model does not adequately account for future innovation in the delivery of RO. Practices should be able to continue to invest in technology and other changes that provide clinical benefit for patients.

  ASTRO recommends that CMS pay for new technology at fee-for-service rates and adopt a rate review mechanism for new service lines and upgrades.
- **BURDEN.** The proposed RO Model would heap additional administrative tasks and costly requirements on already burdened RO practices that are required to participate in the model.

  ASTRO recommends that CMS delay many of these requirements and rely instead on recommendations from the RO community to ensure that only information that is most meaningful and least burdensome is collected.

ASTRO believes the RO Model, with significant modifications, could represent a meaningful and viable first step toward enabling the field of RO to participate in the evolving world of healthcare payment reform, as initiated by MACRA. The proposed model has serious flaws, but none of these issues are insurmountable. Radiation oncologists are committed to working with CMS to modify the model in such a way that it meets the stated goals. ◆

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This commentary is adapted from comments submitted by ASTRO to CMS on September 16, 2019.

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Lessons From the Field: How Practices Are Succeeding Under OCM

Jaime Rosenberg

THREE YEARS INTO CMS' Oncology Care Model (OCM), with feedback from 4 performance periods, practices participating in the value-based model continue to strive for successful practice transformation that drives appropriate utilization and contains costs while keeping patients and oncologists at the forefront.

However, as drug costs take up an ever-growing share of the total cost of care, practices find themselves in control of a smaller portion of costs, according to speakers from an academic medical center and a community-based practice who took part in the National Comprehensive Cancer Network (NCCN) Policy Summit held September 12 in Washington, DC.

In the last decade, there has been a more than 5-fold increase in incremental anticancer drug costs: Average annual costs rose from $30,000 in 2006 to $161,000 in 2015. There has not been a corresponding increase in practice efficacy, according to scores from both the American Society of Clinical Oncology and the European Society for Medical Oncology,[1] explained Kerin Adelson, MD, associate professor, chief quality officer, and deputy chief medical officer for Smilow Cancer Hospital at Yale New Haven/Yale Cancer Center.

Despite the challenge, approximately one-third of practices have been able to lower their total costs and achieve savings under the OCM.[2] Adelson and Diana Verrilli, MS, senior vice president of strategy and practice solutions at McKesson Specialty Health, which is part of The US Oncology Network, shared their experiences with the model and what they've learned since they entered.

Addressing What You Can

Comparing costs of care from 2012 through 2015, before the OCM was implemented, with performance periods 1 through 3, the overall cost of care increased from $28,000 to more than $32,000 for Smilow Cancer Hospital; however, this was less than what CMS expected, so the network was able to achieve savings. To date, it has received over $6 million in performance-based payments.

Looking within the total cost of care, spending significantly increased for drugs, which accounted for 53% of costs between 2012 and 2015 and jumped to 60% in performance period 3. However, by focusing on the remaining 40% of other healthcare costs, Smilow Cancer Hospital was able to exert tighter control. The hospital did this by honing in on utilization patterns, specifically in the emergency department, with inpatient care, and in postacute care. Through a new revenue stream under the OCM, Smilow Cancer Hospital implemented infrastructure focused on those areas by building a care management program, increasing access to palliative care, and opening an urgent care center.

The US Oncology Network has also seen success with the model. With 15 practices participating in the OCM, 14 fell below the benchmark during performance period 4; only 5 practices received performance-based payments. Together, the practices achieved $36 million in Medicare savings, totaling $89 million in savings over a 2-year period, explained Verrilli.

Although most of the network's efforts focused on reducing utilization, practices were able to target certain areas where they noticed large variation in utilization, including supportive care drugs. Looking at pegfilgrastim, for example, the group implemented appropriate use policies, which yielded positive results and brought the practices closer in line to, even below, other OCM practices' utilization rates.

Changing and Standardizing the Way Doctors Practice

"Never underestimate how long it takes to change physician behavior and maintain that level of change," said Verrilli.

It's one thing to build supports around oncologists; it's much harder to change the way doctors practice, added Adelson. "There's a black box around what goes on between a doctor and a patient in an exam room," she said.

Smilow Cancer Hospital tried to uncover how its doctors were practicing things like goals-of-care discussions, which drive earlier use of hospice; communication skills; and patterns of practice.

The most important piece to driving new behaviors, and reinforcing good ones, is through data, said Adelson. Working with Flatiron, Smilow Cancer Hospital implemented an end-of-life dashboard that every 4 months sends doctors data that reflect their care practices for their patients who died.

Within the data is what percentage of those patients got cytotoxic chemotherapy, oral therapy, and immunotherapy. The doctors are also able to see their cost measures, including where they landed compared with other doctors, as a whole, by cancer type, and by drug use.

"We can then get a conversation going about which drugs to use, and when, in order to drive more appropriate behavior," said Adelson, who emphasized the importance of drilling down to the patient level and providing doctors with individual anecdotes.

Verrilli echoed Adelson, saying, "Starting the OCM has led to a significant paradigm shift in how care is provided." She explained that her group also emphasized sharing data with its doctors each quarter and giving them goals of where utilization rates should be.

Behavior change also came from embracing clinical pathways at the point of care through a partnership with NCCN. For example, several oncologists in the network rarely see patients with pancreatic cancer, she said. By using value pathways implemented through the partnership, when an oncologist sees one of these patients, they're equipped with the tools needed to treat them.

Recognizing the Challenges and Pain Points

Despite its success, the OCM does present challenges for the 2 networks. In addition to the high cost of drugs, the networks also face these challenges:

- Rolling out practice transformation
- Identifying and enrolling patients, especially those on oral drugs
- Entering all facts for quality measures into the electronic medical record
- Ensuring clear definitions for new roles, such as patient navigators ◆

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Defining, Standardizing, and Acting on Patient-Reported Outcomes in Cancer Care

Jaime Rosenberg

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Ronald S. Waters, MD, MBA, MHA, MS, The University of Texas MD Anderson Cancer Center.

DURING A PANEL DISCUSSION on defining, standardizing, and reporting quality in cancer care during a National Comprehensive Cancer Network Policy Summit, held September 12, 2019, in Washington, DC, it became clear that stakeholders of all backgrounds have set a focus on a single type of metric in particular: patient-reported outcomes (PROs).

However, although all stakeholders can agree that capturing and acting on these measures is important, bringing the concept to life has proved much more difficult. Lawrence N. Shulman, MD, FACP, FASCO, deputy director for clinical services, Abramson Cancer Center at the University of Pennsylvania, called it a "huge deficiency" in the healthcare system.

Although there are universal measures of patient-reported outcomes that apply to all patients, such as being able to work if they choose, there are more specialized measures that vary based on the disease type, the stage of cancer, and what matters to different demographics of patients.

"I spend a lot of time looking at the National Cancer Database, and I have a huge amount of survival data—our ultimate outcome data—but currently, none of that is linked to PROs," Shulman said. "We know that patient got treatment A or that patient got treatment B and they lived each 12 months; we don't know anything about the quality of their life during that period of time."

"As a nation, we need to get there," he said, warning that it will take a fair amount of work. According to Shulman, the change is more heavily concentrated on the process side of things rather than the cost.

"I think the cost is acceptable, but clinics are all working 110%, and it's just one more thing to do," he explained, but added that it can be done.

The Penn Medicine oncology team now measures PROs at every visit for patients with cancer, with a capture rate of more than 90%. The feedback gets inputted into the electronic health record in a structured format for providers to see at the time of the patient visit and to compare the measures with the treatment and outcomes of those patients.

The team is now starting to differentiate the questionnaires that patients answer, which means customized reports for different disease types, where the patients are within the care continuum, and so on.

In the long run, Shulman hopes to see this be replicated across the country and for practices to be able to link PROs with a large data set like the National Cancer Database or Medicare Surveillance, Epidemiology, and End Results database.

Bryan Loy, MD, MBA, corporate medical director of Humana's Oncology, Laboratory, and Personalized Medicine Strategies Group, agreed that the country is still in the early days of incorporating PROs into actionable information. Currently, Humana collects information on the patient experience through clinical programs or through complaints relating to member experience. However, he noted, the insurer is still on the front end of this.

Representing CMS, Reena Duseja, MD, MS, who serves as the chief medical officer of Quality Measurement and Value-based Incentives Group, reflected on the agency's "Meaningful Measures" framework that it launched 2 years ago to make sense of the measures used in federal programs.

"As we were developing this program, one of the areas that we recognize and that we have gaps in, is PROs, and since then, there's been more emphasis in the agency on collecting outcome measures," said Duseja. She explained that, looking at the proposed measures on the consideration list for the agency's programs, there has been a bigger presence of outcomes measures. Of these measures, a subset are PROs.

Duseja also highlighted an important challenge that makes it difficult to transform the healthcare system into one that fully incorporates and acts on PROs: the need for standardization.

Ronald S. Walters, MD, MBA, MHA, MS, Department of Breast Medical Oncology, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center, agreed, noting that PROs are collected from nearly every patient participating in a study and are beginning to be collected on patients in the clinic; however, it is not done in an organized fashion.

Walters elaborated more on the issue, explaining that although there are universal measures that apply to all patients, such as being able to work if they choose and their overall quality of life, there are also more specialized ones that vary based on the disease type, the stage of cancer, and what matters to different demographics of patients. These latter measures, he explained, are the more controversial ones.

"We keep trying to come up with the nirvana list of things that apply to everyone, and that just doesn't apply to everyone," he explained.

Instead, he said, there should be a program where there is a mix of measures that include both universal measures and more specialized measures and in which providers can mix and match.

Duseja agreed, emphasizing that there needs to be flexibility and choice to allow providers to choose the measures that matter to them and their patients. Nevertheless, there still is a need for standardization for there to be comparison across providers, and there is still the question of how to collect these PROs in a way that addresses this challenge, she said. ◆

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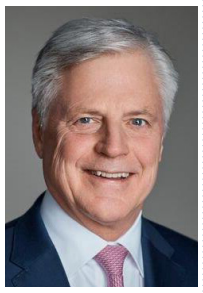
Facilitating the Qualitative Improvement of Oncology Through Value-Based Care

Matthew Gavidia

SHULMAN

Lawrence N. Shulman, MD, FACP, FASCO, deputy director, clinical services, Abramson Cancer Center, University of Pennsylvania.



SNYDER

Richard Snyder, MD, executive vice president, Facilitated Health Networks; chief medical officer, Independence Blue Cross.

BEKELMAN

Justin E. Bekelman, MD, director, Penn Center for Cancer Care Innovation, Abramson Cancer Center.

AS HE STARTED THE MEETING alongside cancer care leaders from the Philadelphia, Pennsylvania, area, moderator Lawrence N. Shulman, MD, FACP, FASCO, deputy director for clinical services at the Abramson Cancer Center of the University of Pennsylvania, highlighted the central quandary of the US healthcare system:

"In cancer, our outcomes in this country are not as good as they are in other places," he said, opening the September 19, 2019, of the Institute of Value-Based Medicine®, an initiative of *The American Journal of Managed Care*®. "In spite of the fact that we're spending huge amounts of money, somehow our patients aren't doing quite as well, and I think that is a very disturbing finding."

Getting better outcomes—without more spending—will mean doing things differently. To further discuss this, Shulman turned to Richard Snyder, MD, executive vice president of Facilitated Health Networks and chief medical officer of Independence Blue Cross; and Justin E. Bekelman, MD, director of the Penn Center for Cancer Care Innovation at the Abramson Cancer Center.

Payer Perspectives on Advancing Value-Based Care Agreements

Focusing on the high healthcare prices in Philadelphia and other regional metropolitan areas, Snyder discussed the impact these costs have in keeping and attracting business. "For many P&Ls [Profit and Loss statements], the second line item behind labor is healthcare cost," said Snyder. Currently, US healthcare spending per capita accounts for approximately 18% of the nation's gross domestic product, which Snyder says is dangerously close to 20%, and a line the country cannot cross.[1]

For employers, the transition from fully insured to self-funded healthcare is an issue that arises as companies grow. Snyder stressed that when healthcare claims cause reinsurance costs to become more than a business can bear, funding for healthcare becomes derailed. When patients experience cost shifting and a lack of cost transparency, it can cause them to delay treatments and preventive care, even though this can lead to increased treatment costs in the future. The rise in co-pays and member out-of-pocket costs occurs with high-deductible plans. For many patients, Snyder said, high out-of-pocket costs and a lack of healthcare knowledge contribute to healthcare-related bankruptcy.

To address the public's limited understanding of how the healthcare system works, quality information is vital to allow for more informed decisions to be made. Snyder emphasized the need to publish more information about the quality of care, although this process has been met with lawsuits from medical centers claiming defamation. "How many people ask their physician: How many cases do you treat and what are your outcomes? Patients are scared to do that; they're fearful it will insult the physician, even when it is their life," said Snyder.

Nevertheless, inviting patients to discuss treatment options for their conditions and providing them with ample information to make good decisions is a process that is expanding. In Pennsylvania, some hospitals are designated as Blue Distinction Centers, meaning they are recognized for their expertise in delivering specialty care.[2] Snyder says that these newer models can assist in ameliorating costly treatments by prioritizing the concept of value-based contracting. How patients experience care is a variable Snyder said is growing in importance. Heightened accountability toward physicians and medical centers is being achieved through tools such as the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) patient satisfaction survey.[3]

In lowering costs and improving care, Snyder described the concept of "Engage, Enable, and Empower," which are steps that can be used to shift the focus toward patients:

- **ENGAGE** focuses on the value-based contract and the total value of care, promoting the responsibility of the health system to work with physicians for at least 1 year to take better care of insured patients. These contracts promote value-based care through tools like HCAHPS, and quality targets that would promote a 50:50 share for surpassing them and a 50:50 loss when missed.
- **ENABLE** represents the process of gathering information and exchanging data for analytical processing. The expanded data exchange would include variables such as electronic health record extracts, claims, lab results, and Admit-Discharge-Transfer messages in their databases, while additionally including opportunity analyses for analytics-based monitoring and reporting.
- **EMPOWER** uses the obtained information to increase opportunities for the use of innovative services (eg, telehealth to manage postacute care and home care) in order to increase care delivery options for patients. Snyder describes this as the most powerful step.

"This concept of doing everything the way we've always done and getting a different outcome just doesn't work, we've got to change the way we think, we've got to break the old mold and build anew if we ever hope to get out of the mess that we've found ourselves in this country," said Snyder.

Advancing Cancer Care Innovation Through Value-Based Care

As he opened his section of discussion, Bekelman emphasized that, regardless of the discernible innovations in cancer care, it continues to be suboptimal. "I would argue that we are at a turning point in cancer care today. We've made major strides improving survival, quality of life, but cancer care remains a multispecialty, multisetting, fragmented specialty with huge administrative complexity," he said. In the United States, Bekelman continued, suboptimal care is attributed to one-third of the $3 trillion spent on healthcare every year.

Providing an example of one patient who had an unsatisfactory experience, Bekelman described a myriad of contributing factors that led to this level of suboptimal care. As the patient was diagnosed with prostate cancer, he had to undergo more than 8 weeks of both chemotherapy and hormone therapy at the facility and, given the demands of his occupation as a truck driver, he had to limit his routes to those close to home.

Given that the local care provider for the patient was separate from the healthcare system in which Bekelman worked, it impaired the coordination of the patient's care. Several urgent care visits, and a nearby emergency department (ED) visit, were attributed to complications from the hormone therapy, which interfered with the patient's glucose and affected his diabetes.

The stress placed on the patient and his family was "totally avoidable," said Bekelman.

Improvement through heightened glucose management during hormone therapy, and evidence that now points to 5.5 weeks of treatment as equal in effectiveness to 8.5 weeks, proved to be invaluable for Bekelman. "This gentleman's experience was formative for me. As we confront this turning point in cancer care today, we need to challenge where we are," said Bekelman.

To confront suboptimal care, Bekelman suggested that the goal should be to aim for multispecialty cancer care that is accountable for the total cost. Bekelman provided 5 elements of risk sharing, bundled care, or effective capitation for cancer care to achieve this goal: (1) Providers need to work as a team; (2) Providers should be responsible for all care and total costs; (3) Providers should tie payment to quality and outcomes; (4) Adjust payment for risk; and (5) Price in lean healthcare in an appropriate margin for providers.

"Working as a team triggers a reorientation of how we work together," said Bekelman. By collaborating as a team, as opposed to separate departments, Bekelman stresses that consistent expectations will be set for each specialized care physician. Furthermore, the incorporation of allied health professionals, nurses, and nonlicensed coordinators will heighten efficiency in the pursuit of value-based targets.

Once team-based care is in place, Bekelman highlights the need to partner with generalists to ensure that comprehensive care does not get overlooked. "If we think back to this gentleman with diabetes, in the world of silo care, he falls through the cracks. In the world of multispecialty accountable care for cancer—the ideal world—he's taken care of," said Bekelman. By essentially becoming the general contractor for patients with cancer, Bekelman says it allows providers to manage total costs. This process of risk sharing will achieve a sought-after care model for payers and patients, noted Bekelman.

Tying payments to quality and outcomes is an issue that Bekelman describes as both a challenge and an opportunity. Starting off with a limited set of measurements and expanding them was recommended in the discussion, with patient experience serving as the primary factor. Press Ganey, a healthcare performance analytics provider, was highlighted for increased use as this rating system would motivate physicians to improve care through details provided by patients.

Adjusting for risk is an additional challenge. Although most oncologists may be put off by bundled payments due to variations in the health of their assigned patients, Bekelman suggests incorporating this practice onto patients with diseases who do not need much risk adjustment, such as those with early-stage breast cancer. Bekelman concedes that this cannot be done instantly, even if he desired to, but in utilizing a staged approach, adjusting for risk will grow in healthcare.

For the last element, pricing in lean healthcare in appropriate margins can be achieved through increased provider knowledge of costs, indicates Bekelman. "We have to understand [costs] to understand: how does the ask from the payer side comport with how we make margin?" By understanding the costs at main hospitals and community-based practices, providers can assist in steering patients to cost-effective treatments.

Once these costs are known, it delineates value of care through pricing in the appropriate margin. "Those providers that get ahead of this and provide a true value equation to insurers or employers, those are the ones who end up being the market leader," said Bekelman. ◆

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Implementing Practice Transformation, Integrating Primary Care to Raise the Quality of Cancer Care

Jaime Rosenberg

AS PRACTICES STRIVE TO offer patients the best care while also containing costs, it has become clear that following the old methods won't cut it. As a result, practice transformation has become a norm for many practices looking to succeed under value-based care models, such as the Oncology Care Model (OCM).[1]

For Jefferson Health, headquartered in Philadelphia, Pennsylvania, the process began a decade ago, when the health system decided to develop a multidisciplinary geriatric oncology evaluation center, Andrew E. Chapman, DO, FACP, chief of cancer services at Sidney Kimmel Cancer Center at Jefferson, said during the second half of *The American Journal of Managed Care*®'s Institute for Value-Based Medicine® (IVBM) session held September 19, 2019, in Philadelphia.

The cancer center implemented a team-based model, bringing together social work, pharmacy, nutrition, and medical oncology. What leaders learned, Chapman explained, was that the group of patients accounting for the majority of cancer diagnoses, deaths, and survivors—those 65 years and older—are a significantly vulnerable population due to confounding factors, such as comorbidities and polypharmacy.

Faced with these facts plus a fragmented healthcare system, Jefferson Health officials stepped back to ask, "How can we think about how to address these cracks and think about this patient population in this fragmented system, and can we do something better?"

From there, the health system started down the path of practice transformation. The pace accelerated as the National Committee for Quality Assurance introduced its Patient-Centered Medical Home Model[2] and picked up even more with CMS' introduction of the OCM.

As health system leaders considered what needed to be addressed during this process, Jefferson Health identified multiple aspects of care to be implemented, including team-based care, patient care management, and care coordination.

From there, Jefferson Health worked on building a system infrastructure that could withstand the changes needed, one that could facilitate engagement with providers by creating a culture in which they understood how interrelated they are to the healthcare delivery system. Leaders also offered assessments to providers by providing data and feedback.

"The Oncology Care Model for us has been this test tube for us to try to test really different opportunities in terms of building this infrastructure, sharing these data analytics, and trying to really evolve as a practice," Chapman said.

Making Progress With Providers

Fast-forward to 2019 and Jefferson Health has laid out a series of goals:

- Develop and execute a strategy for addressing care needs across the continuum of care through navigation and supportive medicine.
- Execute a strategy to reduce cost and care variation. »

- Demonstrate improvement in guiding patients to the appropriate site of care and creating meaningful care goals.
- Disseminate this data through a community strategy so that providers understand what is being measured and why each measure is important.
- Share this information with providers.

Throughout the year, Jefferson Health has worked toward several goals. The health system has addressed unnecessary care variation by creating a data operationalization strategy to identify the factors that drive clinical and cost outliers in practice. An oncology navigation team will focus on care coordination and outcomes and outreach, as well as implement a pathway system.

Jefferson Health has also worked on guiding patients to the appropriate site of care by looking at how to reduce avoidable emergency department (ED) use. Baseline data on patients visiting the ED who did not got admitted showed that just shy of 50% of those patients go the ED while the clinic is open.

"We saw this as a huge opportunity to say, 'How can we leverage the triage algorithms that we built for all the different symptoms, and how can we leverage our same-day clinic where patients can be immediately plugged into when they call the practice?'" Chapman said.

The health system, in response, started a campaign to educate both providers and patients about the importance of calling a practice beforehand to ensure direction to the appropriate site of care.

Taking on a third goal, the health system opened up the Neu Center for Supportive Medicine & Cancer Survivorship, which this year has screened nearly 900 patients for distress and facilitated advanced care planning discussions early on between providers and their patients.

Looking ahead, Chapman outlined several challenges for the coming year, including scaling capabilities, implementing programs to manage high-risk or targeted populations, and engaging primary care and specialty practices.

A Focus on Primary Care

Integrating and engaging primary care in cancer care and survivorship has been of keen interest to other health systems, too. During IVBM, Kelly Filchner, MSN, director of Fox Chase Cancer Center Partners, traced the cancer center's steps to integrate primary care into oncology patient management.

"Primary care physicians believe they are an integral part of cancer care, but they need the tools to be part of that team," she explained. For Fox Chase Cancer Center, this plays an especially important role in survivorship.

Realizing that many patients transitioning out of oncology care did not have a primary care provider (PCP), the cancer center created Fox Chase Cancer Center Care Connect. The team started by identifying and building relationships with PCPs in the area.

Fox Chase also set clear goals regarding the value it intended to get out of the program. For providers, the cancer center wanted to ensure effective access and communication, improve physician metrics, and enhance shared collaboration and support of a growing survivorship population. For the cancer center itself, goals included improving the transition of patient to survivor; providing an opportunity for screening, risk, and diagnostic services; and dispelling the notion that Fox Chase is limited to cancer treatment.

"You can't just create a program and then let it be on its own. You have to constantly be doing something; you have to constantly be monitoring," Filchner said.

Currently, the program comprises 33 PCP practices representing 50 family medicine or internal medicine physicians and 22 midlevel practitioners; it also includes 3 obstetricians and gynecologists, Filchner noted. To date, the program has referred 300 patients who did not have a PCP. ◆

CHAPMAN

Andrew Chapman, DO, FACP, chief of cancer services, Sidney Kimmel Cancer Center, Jefferson Health

FILCHNER

Kelly Filchner, MSN, director, Fox Chase Cancer Center Partners

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Reporting by Matthew Gavidia, Laura Joszt, and Alison Rodriguez

New Liquid Biopsy Test Identifies Patients Who May Respond to Immune Checkpoint Blockade

A LIQUID BIOPSY TEST, developed by Personal Genome Diagnostics, was shown to possibly detect microsatellite instability (MSI) and tumor mutational burden (TMB), which may help determine which patients are likely to respond to immune checkpoint inhibitors, according to a September study published in the journal *Clinical Cancer Research*.[1]

In May 2017, the FDA approved the immune checkpoint inhibitor pembrolizumab, sold as Keytruda, for patients with unresectable or metastatic tumors that tested high for MSI (MSI-H) or mismatch repair deficiency (dMMR).[2] Although this approval addressed the treatment of MSI-H or dMMR in these patients, detecting these conditions can be difficult.

Current MSI detection processes include tissue biopsies and technologies such as polymerase chain reaction–based amplification or next-generation sequencing. These approaches have been found to be complicated and contain sensitivity limitations, which can exclude patients whose tumor samples lack enough tissue for accurate testing.

"A liquid biopsy test assessing [microsatellite instability] could reach a larger subset of patients, such as those where tissue is limited or where there are safety concerns around additional surgical intervention."

—Andrew Georgiadis, MS,
Personal Genome Diagnostics

Study coauthors Andrew Georgiadis, MS, a scientist at Personal Genome Diagnostics, and Dung Le, MD, associate professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, sought to evaluate the sensitivity and specificity of a liquid biopsy test that would help create an alternative for MSI detection and cater to patients affected by these complications. "A liquid biopsy test assessing MSI could reach a larger subset of patients, such as those where tissue is limited or where there are safety concerns around additional surgical intervention," Georgiadis said.

The study included 61 patients with metastatic cancer and 163 plasma samples from healthy subjects. Investigators developed a 98 kb pan-cancer 58-gene panel, then employed a multifactorial error-correction method and a novel peak-finding algorithm to identify MSI frameshift alleles in the study group's cell-free DNA. As the authors explained, MSI can be detected by measuring the length of altered microsatellite sequences in tumor DNA compared with normal DNA:

- Investigators flagged certain sequence data for error correction, then subjected data to the peak-finding algorithm that identified instability in the loci.
- If 20% or more of loci contained MSI, samples were classified as MSI-H.

The liquid biopsy test produced a specificity of greater than 99% and a sensitivity of 78%, which speaks to its prowess for identifying MSI levels in patients.

Investigators then tested for TMB, in which next-generation sequencing data were processed, and variants were identified using VariantDx software. The threshold for identifying a high TMB in the analyzed tumors was set at 5 mutations in the targeted plasma panel. The liquid biopsy test produced similar results toward TMB to that of MSI as a specificity of greater than 99% was achieved, although the liquid biopsy's sensitivity was lower, at 67%. The VariantDx test identified MSI-H in 18 of the 23 MSI-H patients (78.3%) and correctly detected the 6 microsatellite stable cases.

For patients treated with programmed cell death protein-1 blockade, a type of immune checkpoint blockade, MSI and high TMB levels in pretreatment plasma predicted progression-free survival (hazard ratios, 0.21 and 0.23; $P = .001$ and .003), the investigators found.

Le emphasized the potential of the liquid biopsy test to enhance MSI-H detection in more at-risk patients who can benefit from the immune checkpoint blockade. "If tests become more accessible, less expensive, and require fewer resources such as tissue acquisition and pathology resources, more patients could be tested," Le said.

Study limitations included the small population of cancer patients analyzed. The authors noted that further research on a broader range of tumor types is warranted to confirm their results. ◆

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Study Explores Brentuximab Vedotin Efficacy in Patients Expressing High CD30 Levels

BRENTUXIMAB VEDOTIN (BV) performed acceptably in patients with high-CD30–expressing non-Hodgkin lymphoma (NHL), according to recent study results. Investigators sought to find out which patients will most likely benefit from using the agent.

The phase 2 trial enrolled relapsed or refractory high-CD30–expressing NHL, with BV administered intravenously at 1.8 mg/kg every 3 weeks. The primary end point was a disease control rate of more than 40%, consisting of complete response (CR), partial response (PR), or stable disease.

BV, sold as Adcetris, has several FDA approvals, including for use in combination with chemotherapy for adults with certain types of peripheral T-cell lymphoma (PTCL) and for the treatment of adults with previously untreated stage III or IV classical Hodgkin lymphoma (HL), systemic anaplastic large cell lymphoma (ALCL) after failure of at least 1 prior multiagent chemotherapy regimen, and primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides (MF).

The efficacy of BV was previously evaluated in various subtypes of NHL, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, PTCL, MF, and various cutaneous T-cell lymphomas. These studies enrolled patients with a wide range of CD30 expression levels, and their response rates were unrelated to the CD30 expression level of tumor cells.

High CD30 expression was defined as 30% or greater tumor cells positive for CD30 by immunohistochemistry. CD30 is uniformly expressed in HL and ALCL.

The purpose of the study was to determine the overall disease control rate from BV administration among heavily pretreated relapsed or refractory patients with various subtypes of NHL, other than ALCL and HL. Because the study sample was based on CD30-positive tumor cells being equal to or greater than 30%, regardless of histologic subtype, patients with various subtypes of NHL, from DLBCL to MF, could enroll. High-CD30–expressing NHL patients (n = 33) were enrolled, except for those with ALCL. »

The disease control rate was 48.5% (16 of 33), including 6 CRs and 6 PRs; 6 patients (4 CRs, 2 PRs) maintained their response over 16 completed cycles. Response to BV and survival were not associated with CD30 expression levels.

Over a median of 29.2 months of follow-up, the median progression-free and overall survival rates were 1.9 months and 6.1 months, respectively. The most common adverse events were fever (39%), neutropenia (30%), fatigue (24%), and peripheral sensory neuropathy (27%).

In a *post hoc* analysis for the association of multiple myeloma oncogene 1 (MUM1) on treatment outcome, MUM1-negative patients showed a higher response (55.6%; 5 of 9) than MUM1-positive patients (13.3%; 2 of 15).

BV performance as a single agent was acceptable in terms of disease control rates and toxicity profiles, the researchers said, especially in MUM1-negative patients. ◆

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New Treatment Can Benefit Patients With MM Refractory to Multiple Other Therapies

PATIENTS WITH MULTIPLE MYELOMA (MM) whose disease is refractory to available treatments may have better a better response if they are treated with selinexor plus dexamethasone, according to a study published in the *New England Journal of Medicine*.[1]

Investigators from Mount Sinai found that patients taking the oral combination therapy saw a response within 2 months. Selinexor causes cancer cells to die by blocking the export of the cells' protein and messenger RNA to the cytoplasm.

"This study is meaningful for patients with multiple myeloma who haven't had success on multiple other therapies," the study's first author Ajai Chari, MD, director of clinical research in the multiple myeloma program at the Tisch Cancer Institute at Mount Sinai, said in a statement. "An increasing number of patients have resistance to the standard drugs used in the treatment of multiple myeloma, and the overall survival in these patients is short, sometimes less than 3 months."

Patients in the STORM Part 2 study had MM and had been treated previously with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids, and an alkylating agent. The patients had disease progression during treatment or within 60 days after completing treatment or had less than a 25% response to therapy.

A total of 122 patients were included, with a median age of 65.2 years and a median disease duration of 6.6 years. The vast majority of patients (118; 97%) discontinued the treatment, with the most common reasons being disease progression and adverse events (AEs). However, 5 patients (4%) continued to receive treatment at the last date of follow-up, and another 34 (28%) discontinued treatment and remained in follow-up for long-term survival.

Approximately one-fourth (26%) of patients had a partial response (PR) or better. Of those, 2 patients had stringent complete responses, 6 had very good PRs, and 24 had PRs. However, 48 patients (39%) had stable disease and 26 (21%) had progressive disease or disease that could be not evaluated.

The researchers found that the median progression-free survival was 3.7 months and the median overall survival (OS) was 8.6 months. Patients with a minimal response or better had a median OS of 15.6 months.

Thrombocytopenia was the most common AE, occurring in 73% of the patients, followed by nausea in 72% and anemia in 67%. Thrombocytopenia was also the most common grade 3 or 4 AE (59%). AEs considered to be related to selinexor or dexamethasone led to 18% of patients discontinuing treatment.

The authors reported that 16 patients died during the study from disease progression and another 12 from an AE, including 2 cases that were considered to be related to treatment.

"This study proved that a novel, first-in-class drug with a new mechanism of action can kill a patient's cancer cells," said the study's senior author, Sundar Jagannath, MBBS, director of the multiple myeloma program and a professor of medicine (hematology and medical oncology) at the Tisch Cancer Institute. "This proved that the drug worked in patients who had exhausted every other treatment and who would have been placed on hospice care otherwise." ◆

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Phase 1 Pancreatic Cancer Trial Points to Effective Combination Treatment

WITH 5-YEAR SURVIVAL RATES below 35%, pancreatic cancer is among the deadliest cancers. However, a phase 1 clinical trial testing a new drug—an inhibitor designed to block an enzyme called Wee1—has shown promising results for this disease, suggesting a need for additional investigation.

The trial results, published in the *Journal of Clinical Oncology*,[1] included 34 patients with locally advanced pancreatic cancer who received four 21-day cycles of gemcitabine with the inhibitor AZD1775, or adavosertib. The second and third cycles were administered with radiation; cycles 5 to 8 were optional.

"AZD1775 was dose-escalated using a time-to-event continual reassessment method on the basis of the rate of dose-limiting toxicities within the first 15 weeks of therapy. The primary objective was to determine the maximum tolerated dose of AZD1775 given in conjunction with gemcitabine and radiation," the authors noted. "Secondary objectives were to estimate overall and progression-free survival and determine pharmacodynamic activity of AZD1775 in surrogate tissues."

The results revealed that 24% of patients experienced a dose-limiting toxicity, such as anorexia, nausea, or fatigue. Additionally, the investigators found that the median overall survival for all patients was 21.7 months, and the median progression-free survival was 9.4 months. Analysis of samples from hair follicles demonstrated that Wee1 inhibition had decreased phosphorylation of cyclin-dependent kinase 1 staining by immunohistochemistry after AZD1775 administration at the recommended phase 2 dose.

Gemcitabine has been a therapy for pancreatic cancer for more than a decade, and these results show that the agent will be effective when combined with radiation. The researchers recommend a phase 2 dose of 150 mg daily for AZD1775.

"If we can disable the DNA damage response in pancreatic cancer cells, it might eliminate treatment resistance and sensitize the cancer to the effects of both radiation and chemotherapy," lead study author Kyle Cuneo, MD, associate professor of radiation oncology at Michigan Medicine, said in a statement.[2]

Despite the efficacy of the treatment in the trial, the authors emphasized the need to further investigate the treatment combination. "If we're ever going to cure pancreatic cancer, we're going to need effective systemic treatment as well as local therapy. Our data suggests that AZD1775 can do both," concluded senior study author Ted Lawrence, MD, PhD, Isadore Lampe Professor of Radiation Oncology and chair of radiation oncology at Michigan Medicine. ◆

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Produced by Jaime Rosenberg

NOTE: this section has been edited for clarity

Richard Snyder, MD, Executive Vice President, Facilitated Health Networks; Chief Medical Officer, Independence Blue Cross

With more novel, costly therapies being approved and patients being responsible for more costs, how do you think this will impact the prevalence and popularity of value-based agreements?

I think it will absolutely increase the speed to value-based care and also the kinds of arrangements that we will see going forward. There are quite a few creative ideas emerging. Amongst them, the Blue Cross Blue Shield Association has a number of direct contracting models to eliminate the need for a provider to invest in the cost of a medication, [which will] thereby gain perhaps somewhat of a discount and facilitate the patient care delivery without incurring as much out-of-pocket costs for the patient.

How do value-based agreements benefit all stakeholders, including providers, patients, and payers?

If they're done correctly, a value-based contract should benefit all 3. So, I'll give you a few examples. First of all, from a patient perspective, we can define the benefits to reward patients with lower out-of-pocket costs if they go to a Blue Distinction Center or a center of excellence to get their care, and by steering them to such a location, they're virtually guaranteed to have better clinical outcomes at a lower cost. That is the basis for the Blue Distinction Centers program that the Blue Cross Blue Shield Association has been promulgating in and around things like [chimeric antigen receptor] CAR T-cell therapy and Luxterna and other expensive drugs.

Typically, they reward the payer with lower total cost of care, and oftentimes a warranty in the event the medication does not effectively control the diagnosis. Obviously, that is a good thing since a large proportion of the care today is being paid for by employer groups through self-funded arrangements, and these very, very costly drugs that are emerging from the pipeline put a significant stress on their [profit and loss statements], so from a payer perspective and ultimately our customers, the employer group, it helps to control costs and ensure quality outcomes and reward us with a warranty in the event the outcome is not optimal.

In the case of the provider, a lot of these arrangements do not require the provider to pay out the cost of stocking or storing these medications until a patient is waiting for them. With some of these programs, precertification barriers or limits can be reduced, since they're very unusual circumstances—rare diseases where the medication otherwise wouldn't be used. So, I think there are plenty of reasons why the member—the patient, the payer—the ultimate customer the employer group or the government, and ultimately the provider delivering the service can benefit from value-based contracts.

How important are population health management and coordination of care in value-based contracting?

They're actually integral to value-based contracting. When we do episode of care payments, we are paying for a period of time and everything that happens in that period of time, so it's critically important that the right patients are chosen for that episode, that there's extremely good coordination to prevent leakage out of the system of care to other systems, and ultimately that patients adhere to any medication regimens that they're prescribed and that post-acute care when the patient goes home for a period of time, that's included in the episode, is well managed so they don't bounce back to an emergency room or a hospital or end up having a complication that could have been otherwise avoided if we had been monitoring them more closely.

In today's world, we have technology, whether it's video capabilities or Bluetooth-enabled monitoring devices to determine whether patients are adhering to their treatment plans and whether they're having any early signs of a complication that could result in a readmission to the hospital or emergency room or avoidable testing and treatment. ◆

Stephen Schleicher, MD, MBA, Medical Oncologist, Tennessee Oncology

What are your thoughts on the proposed Radiation Oncology Model and the fact that CMS wants it to be mandatory?

The big hype right now is this proposed radiation oncology bundled payment. This would be the first true bundled payment to come in oncology. The [Oncology Care Model] OCM is an episode-based payment, but it is not a bundle, and then the other experiments like Medicare's [Bundled Payments for Care Improvement], the comprehensive joint replacement model—both had nothing to do with oncology. So far in oncology, outside of [Merit-based Incentive Payment System], the OCM was voluntary, so this is a big change in oncology to have a mandatory payment model, and as we've seen in OCM, there are unpredictable consequences of the methodology, such as the novel therapy drugs coming out after the baseline.

So, in my opinion, I'd prefer a voluntary model where groups that are excited about being on the cutting edge can be a part of that and help us learn where the challenges are in bringing a bundle to radiation oncology and then perhaps make it mandatory in the future, based off the initial feedback.

How does the implementation of high-cost, novel drugs into clinical practice after the baseline period cost calculations further add to the challenge of lowering costs under OCM?

This remains a challenge since the baseline period was up until 2015 and we had this, really, immunotherapy boom happen after that. So, it is a challenge and Medicare does a great job trying to predict what costs should be based off these new novel therapies, but we have some data that was presented at [the 2019 American Society of Clinical Oncology annual meeting] ASCO and is going to be published shortly showing that this is still not a perfect methodology to account for these, so I think understanding those challenges and trying to understand the risk that those challenges have on us going forward is important.

I will say performance period 4, which included the first half of 2018, was when immunotherapy came to the front line of non-small cell lung cancer, so it was kind of a test case for the model, and I think I was pleasantly surprised that the prediction had been better than expected when we got our performance period 4 results. ◆

Nina Chavez, MBA, FACMPE, Chief Operating Officer, New Mexico Oncology Hematology Consultants, Ltd

Now that we are a few years into the OCM and other value-based models, have community oncologists become better at practicing the business of oncology?

It's a difficult question in the sense that community oncology [aren't] businessmen. Doctors don't go to medical school to get a business degree, and, unfortunately, in our healthcare environment, if you're going to be an independent practice, you have to understand the business of medicine that you're in. I think that the OCM over the past couple of years has helped us look at things that we didn't really think of from an oncology perspective.

You're always looking at the patient first, you're always looking at that patient outcome, but now we have to look at the total cost of care, we have to look at that patient engagement piece—not just saying that we did it but also documenting it and having those documented interactions, which is something more for the payers than, really, the patient.

So, I do think that oncologists have become better businesspeople.…They've had to in order to survive in this environment and be able to take care of their patients in a better way.

With therapies like CAR T-cell therapy entering the market, will reimbursement present significant challenges to providers?

CAR T…I was talking to my doctor about this because I'm not clinical, and I want to make sure I got her opinion, and she said that with CAR T, the insurers are not paying for it right now; we don't know what's going to happen. It really should be happening in a hospital, but if you're not partnering with your hospital and you're trying to do it in an independent practice, it's not going to be easy.

I think from a cost perspective, we don't know what the market's going to do; we don't know what the payers are going to do. We do know that we can't get that medication—we can't get CAR T therapies very easily in community oncology. We can't even get it from the [group purchasing organization] we currently have. You have to go through a certain specialty, and it is very costly, so I think that remains to be seen. It's something that we'll have to kind of see how it goes. ◆

Lee Schwartzberg, MD, FACP, Executive Director, West Cancer Center; Chief Medical Officer, OneOncology

The US Preventive Services Task Force (USPSTF) recently updated its recommendations for *BRCA1/2* screening and testing and included women with a history of several cancers and women with ancestry associated with the mutations. What are your thoughts on this?

Who should be screened for genetic testing for cancers is an ever-evolving issue, and we recently saw the USPSTF come out with a new recommendation. To me, this was very interesting, because they tend to be a very conservative group, and they actually got ahead of some of the other guideline committees by mentioning that all women who have a personal history of breast, ovarian, or other cancers should be tested. So, we're starting to see this movement toward universal testing. We're not quite there yet, but this is a broadening of who should be tested.

Testing for germline mutations for hereditary cancers is getting cheaper all the time. It's getting easier to talk about, although we still need our genetic counselors, and we need a workflow that works with this because genetic testing doesn't just affect our patient, it affects the whole family. So, it's a little different concept from the way we take care of patients. I think there's more and more comfort with disseminating this information, so I strongly endorse that recommendation. Not every payer has agreed to that yet, but it's definitely moving in that direction.

The reason this is important is that up to 5% to 10% of women who have cancer, one of the female cancers, will have a mutation, and that's a pretty substantial number when you're dealing with a quarter of a million breast cancer diagnoses per year. So, this old sort of arbitrary "do triple-negative breast cancer if they're under 60"—there's a lot of arbitrariness in who we're defining should be tested. The broader we make it, the better it is.

"I believe that all men who have breast cancer, for example, should be tested. About 10% of them will have a hereditary risk factor, usually a *BRCA1* or *BRCA2* gene. The number of genes that contribute to hereditary breast or ovarian cancer is broadening, so we're learning more over time. …"

—Lee Schwartzberg, MD, FACP

What are your thoughts on USPSTF leaving men out of its updated recommendation for *BRCA1/2* screening and testing?

Well, I believe that all men who have breast cancer, for example, should be tested. About 10% of them will have a hereditary risk factor, usually a *BRCA1* or *BRCA2* gene. The number of genes that contribute to hereditary breast or ovarian cancer is broadening, so we're learning more over time as we move from the very high penetrant cancer syndromes to somewhat less, but we're learning a lot, so I think men will be included in the near future. ◆

Jeff Patton, CEO, Tennessee Oncology; President of Physician Services, OneOncology

What are your thoughts on the Community Oncology Alliance's (COA's) proposed OCM 2.0? Does it address concerns that providers have with the current model?

COA has had a lot of input and a lot of help from Tuple Health and Kavita Patel [Brookings Institution] to help address the flaws in the current model, but also it includes some things that should probably have been in the initial model. Again, [I have] a lot of confidence with what's coming out of COA. I just hope we can get them to implement it.

Is there concern or anticipation among providers about what might come after OCM ends?

I think [there is] less concern about what might come after OCM. It's clear that we're going in that direction with value, and so we have confidence that OCM will be iterated and 2.0 will be better than 1.0 was. We have a fair amount of influence on that. I'm on the COA board, so I have a lot of input into the COA feedback. We also use Tuple Health as our consultants; they have the ears of CMS. I actually know personally the soon-to-be-named director of the Center for Medicare and Medicaid Innovation, who is really smart and will give us a lot of confidence in building on the successes, and I think OCM has been a success. There are some flaws, like in any initial system, but we have confidence that 2.0 will be better than 1.0. ◆

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OVERVIEW

Obesity and Cancer Risk: A Public Health Crisis

Alexander J. Alvarnas and Joseph C. Alvarnas, MD

A. ALVARNAS

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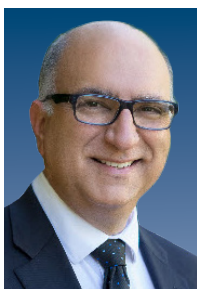

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CONTINUED FROM COVER

Risk factors for obesity vary by age. For children younger than 11 years, screen time/hours per day of media exposure is a statistically significant risk factor. For individuals 12 years and older, risk factors include consumption of fast-food meals, lack of physical exercise, spending more than 8 hours daily engaged in sedentary activity, and female gender.[4] Race, income level, education levels, and geographic location within the United States are all associated with obesity risk. The large states of the South and Midwest have the highest levels of adult obesity, with rates of 32.4% and 32.3%, respectively, whereas states located in the West and Northeast have the lowest obesity rates, 26.1% and 27.7%, respectively.[7] Children living with a parent without a high school degree had an obesity rate 3 times higher than those living with parents who had obtained a higher degree of education. As noted above, disparities continue along racial lines, as well, with Asian Americans adults having the lowest rate of obesity (12.7%), followed by non-Hispanic white adults (37.9%), African American adults (46.8%), and Hispanic adults (47%).[8]

The mechanisms through which obesity leads to an increased risk of cancer are multiple and complex. They reflect the sometimes synergistic impact of altered hormone and cytokine secretion, changes to the tumor microenvironment, and intracellular alterations to regulatory proteins.

Obesity is associated with a number of adverse health-related complications and carries an elevated individual all-cause mortality risk.[9,10] It would be hard to overstate the increased adverse health outcomes for obese individuals. In one study, the risk of type 2 diabetes (T2D) for individuals with a BMI >30 kg/m^2 was 28 times higher than it was for individuals of normal weight; for those with a BMI >35 kg/m^2, the risk rose to 98 times higher.[11] The authors of the study noted, "The national prevalence rates of diabetes have increased in parallel with the rates of obesity."[10]

Obesity also carries a markedly elevated risk of other chronic health conditions, including hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, and stroke.[9] Beyond the direct health implications of the obesity epidemic, the worldwide economic burden related to obesity is estimated to be nearly $2 trillion.[9] The authors of a 2009 *Health Affairs* paper on the escalating economic impact of obesity in the United States said, "Our overall estimates show that the annual medical burden of obesity has risen to almost 10% of all medical spending and could amount to $147 billion per year in 2008."[12] Current estimates of our current national health care costs related to obesity are as high as $210 billion.[8]

What is far less well recognized by the general public is the significant link between obesity and increased cancer risk. Data from the United Kingdom indicate that, in the next 15 years, obesity may overtake smoking as a leading cause of preventable cases of cancer.[13] Population-based data from 10,038,812 patients enrolled in the UK Clinical Practice Research Datalink were analyzed for a statistical evaluation of the relationship between 24 cancer types and an overweight or obese level BMI.[14] This study demonstrated a statistically significant association between obesity and 13 cancer types, including cancers of the breast, ovary, uterus, cervical, ovary, renal, gallbladder, liver, colon, and thyroid and acute leukemias. The relationship between BMI and several cancer types was linear.[14] In an accompanying editorial, the authors noted:

> Each 5 kg/m^2 increase in BMI was associated with higher risks of cancers of the uterus (hazard ratio [HR] 1·62, 99% CI 1·56–1·69), gallbladder (1·31, 1·12–1·52), kidney (1·25, 1·17–1·33), liver (1·19, 1·12–1·27), colon (1·10, 1·07–1·13), cervix (1·10, 1·03–1·17), thyroid (1·09, 1·00–1·19), ovary (1·09, 1·04–1·14), postmenopausal breast (1·05, 1·03–1·07), pancreas (1·05, 1·00–1·10), and rectum (1·04, 1·00–1·08), and of leukemia (1·09, 1·05–1·13).[15]

In addition, there are data demonstrating a less pronounced but statistically significantly increased risk of multiple myeloma, meningioma, esophageal, and pancreatic cancers.[16-19]

Numerous studies from the United States also demonstrate that obesity has become a leading preventable cause of cancer. Data from the American Cancer Society demonstrate that obesity is responsible for about 8% of all cancers in the United States and about 7% of all cancer deaths.[20]

The mechanisms through which obesity leads to an increased risk of cancer are multiple and highly complex. They reflect the sometimes synergistic impact of altered hormone and cytokine secretion, changes to the tumor microenvironment, and intracellular alterations to regulatory proteins. The biological activity of adipose tissue is enormously complex. Authors of one study note that, "In obese patients, excessive accumulation of adipose tissue leads to elevated levels of circulating free fatty acids and increased expression of serum adipokines, such as leptin, visfatin, and cytokines…"[21] As such, obesity creates a pro-inflammatory state. The obesity associated pro-inflammatory state results in the elevation elaboration of cytokines, such interleuken-6 (IL-6) and tumor necrosis factor α (TNFα), which are elaborated at higher levels than in individuals who are not obese. This chronic inflammatory state results in changes to both the cellular microenvironment and to numerous intracellular molecular pathways.[21-23]

While the precise cellular and molecular biological changes underlying obesity-related cancer may vary considerably between patients, recent research highlights some of the key mechanisms through which obesity may promote tumorigenesis. For men with high fat diets and prostate cancer, murine models demonstrate that a high fat diet alters phosphorylation of the signal transducer and activator of transcription-3 (STAT3) regulatory protein and palmitic acid levels in tumor cells.[22] For women with endometrial cancer, the presence of obesity and metabolic syndrome likely increase cancer risk through a variety of mechanisms. Increased estrogen levels produced by the effects of both hyperinsulinemia and an increase in adipocyte-derived estrogen likely play a role. In addition, increased activity of rapamycin (mTOR)/vascular endothelial growth factor (VEGF) and changes to the tumor microenvironment mediated by cancer-related fibroblasts also play a role. In addition, adipose tissue-related proinflammatory cytokines such as IL-6 and TNFα likely play a role in tumorigenesis.[21]

OVERVIEW

Given the concerning increase in the prevalence of obesity and the frightening growth rate of obesity-related cancers, solutions have thus far proven elusive. Just as obesity-related cancer risk is projected to overtake smoking-related cancer risk as the leading preventable set of cancers, the success of the nation's long-term smoking cessation efforts provide an evidence-based perspective on a potential path forward toward mitigating the risk of obesity-related cancer.[24] Indeed, just as data demonstrate that smoking cessation reduces cancer risk, there is also an evolving body of data that demonstrate that reducing individual obesity may produce a commensurate fall in cancer risk rates. In one trial, investigators found that, "a history of bariatric surgery and maintained normal weight after surgery is associated with a 71% and 81% reduced risk for uterine malignant tumors."[25]

The increased prevalence of obesity reflects the impact of both individual behavior and the massive societal changes of the past 5 decades that have contributed to this phenomenon. This includes the proliferation of calorie-rich inexpensive fast foods, a shift toward increasingly sedentary forms of work and recreation, and the presence of "food deserts" in many communities from the lower end of the socioeconomic spectrum.[26] Efforts to reduce obesity rates are further hampered by an alarming lack of public awareness of the hazards of obesity. Data from the American Institute for Cancer Research demonstrate that only 50% of Americans are aware for the link between obesity and increased cancer risk.[27] A study from the United Kingdom found that 75% of adults were not aware of the obesity-cancer link.[13] Improving public awareness is a first and essential step toward ensuring more effective cancer prevention efforts.

Beyond concerted efforts to cultivate a greater level of awareness regarding the hazards of obesity, there are both individually-targeted and broader social strategies for reducing obesity rates. Primary care physicians can and should play a central role in patient education and focusing upon risk reduction. This includes integration of obesity screening and discussions related to obesity risk reduction and management as part of routine clinic visits, beginning in childhood.[28] Authors of a recent commentary in *Family Medicine* noted that, "A study in the United States suggested family physicians regularly failed to acknowledge weight problems in over half of consultations with adult patients who had a weight-related comorbid condition, yet when they did counsel them, patients were much more motivated to change health behaviors and have a greater awareness of health risks."[28,29] By focusing upon this issue when patients are young, physicians are more likely to foster better food and activity choices by their patients.

There also opportunities for broader society efforts at fostering better dietary and activity choices. These include both coercive measures, such as the adoption of sugary beverage taxes as a means of creating financial incentives for avoidance of high calorie/low nutritional value foods and beverages.[30] Although there are some early data that suggest that these coercive methods may be having an impact, efforts such of these have been controversial and met with a great deal of skepticism as well as concern that they may inadvertently prove to be disproportionately punitive to low-income families.[31,32] Other efforts have been fraught with less controversy. In some communities, concerted efforts to create healthier food options within urban food deserts demonstrate early signs of success.[33]

Rising obesity rates have emerged as a key public health threat. Both obesity-related cancers and the numerous adverse chronic health conditions that are related to obesity take an enormous human toll and consume more than $200 billion annually in avertable healthcare costs. The link between obesity and numerous cancer types is well-established. Research into the underlying biology has identified numerous obesity-related inflammatory, cellular, and extracellular mechanism behind this phenomenon. Through more personalized care focusing upon obesity risk reduction, more effective patient and family education, and a concerted series of efforts that parallel those that have proven effective at reducing tobacco, we may be able to reduce the immense human suffering and extraordinary economic costs of this epidemic. ◆

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ADVOCACY PERSPECTIVE

NASH and Liver Cancer: The New Cancer Headline

Donna Cryer, JD

CRYER

Donna Cryer, JD, is president and chief executive officer of the Global Liver Institute.

CONTINUED FROM COVER

Fatty Liver Disease: The Link Between Obesity and Liver Cancer

The obesity epidemic in the United States has been highlighted over the past few decades, with obesity rates consistently increasing. In 2011-2014, more than 70% of adults were classified as overweight or obese, compared with 56% in 1988-1994.[2]

A strong relationship between fatty liver disease and obesity has been discovered. Investigators found that between 30% and 90% of obese patients had nonalcoholic fatty liver disease (NAFLD).[4] In severely obese patients having bariatric surgery, more than 90% had NAFLD.[4,5] For NAFLD to be diagnosed, there must be imaging or histology evidence of hepatic steatosis (HS) and the lack of a secondary cause of hepatic fat accumulation.[5] The more advanced form of fatty liver disease, nonalcoholic steatohepatitis (NASH), is marked by the presence of ≥5% HS and inflammation with injury to liver cells.[5]

Compared with individuals who have a normal body mass index (BMI), overweight patients have a greater than 20% increased risk of developing liver cancer. Likewise, obese patients have an 87% increased risk of developing the disease compared with those of normal BMI.

NAFLD and NASH are widely considered the hepatic manifestations of metabolic syndrome, alongside diabetes and high cholesterol. NAFLD affects up to 30% to 40% of adults in the United States, and NASH affects 3% to 12%.[3] Although these numbers are high, just a small percentage of NASH cases are diagnosed, with even fewer confirmed by biopsy.[5] More concerning: The number of patients presenting with 2 or more risk factors for NAFLD or NASH, including obesity, type 2 diabetes, high cholesterol, and high triglycerides, is steadily increasing.[4,5]

NAFLD and NASH are not the only liver diseases marked by alarming trends. Liver cancer has the fastest-rising incidence in men and women of any cancer type in the United States.[6] This year, more than 42,000 people in the United States will receive a diagnosis of liver cancer,[6] and nearly 32,000 people will die from the disease.[5] Additionally, at 18%, the 5-year survival rate for liver cancer is among the lowest of any cancer type in the United States.[6] When liver cancer is diagnosed at later stages with distant metastasis, the 5-year survival rate drops to just 2%.[6]

Historically, the majority of HCC cases have been viral hepatitis related. As the number, effectiveness, and accessibility of hepatitis C virus (HCV) curative treatments rises, the number of cases of HCV-related cirrhosis and HCC falls. With HCV-related HCC decreasing in incidence and prevalence, experts have been examining the roles that obesity, metabolic syndrome, and NAFLD/NASH play in the development of HCC.[7]

Although the exact mechanisms associating NALFD and NASH and the development of liver cancer need further investigation, research has consistently shown a relationship between the diseases. NAFLD has been recognized as a trigger for liver cancer, with related risk factors for both diseases including elevated body mass index (BMI), abdominal obesity, insulin resistance, and other metabolic factors.[7,8] In fact, compared with individuals who have a normal BMI, overweight patients have a greater than 20% increased risk of developing liver cancer.[8] Likewise, obese patients have an 87% increased risk of developing the disease compared with those of normal BMI.[8]

Current Challenges

The liver cancer world has been marked by challenges, including but not limited to cost burden, fragmentation in healthcare and health policy, and issues associated with liver cancer risk factors, especially related to obesity, NAFLD, and NASH.

The direct and indirect costs of managing liver cancer, especially obesity-related liver cancer, are significant. In 2014, direct and indirect obesity healthcare costs in the United States reached $1.42 trillion, with an estimated $63 million in liver cancer costs attributable to obesity.[9] Of those costs, $35 million reflect direct liver cancer medical treatment cost and $28 million represent indirect costs, including the combination of absenteeism, or lost workdays, and productivity loss or underperformance at work due to the disease.[9] Costs associated with NAFLD and NASH are also marked with high, and are increasing. Current estimates state that in the United States, annual direct costs associated with NAFLD have reached $103 billion.[10]

The worlds of healthcare and health policy have been divided over liver issues in the past. This is especially evident in screening policies and programs for patients at risk of developing HCC. Although some experts recommend screening for at-risk patients every 6 months, using ultrasounds with or without serum α-fetoprotein, these recommendations do not hold consistent across liver and oncologic specialties.[11,12]

Liver diseases have been marked by clinical and research difficulties, and NAFLD and NASH present a new set of challenges. Although it is estimated that one-third of adults in the United States have NAFLD, very few people know what the disease is or that they may be at risk. NAFLD and NASH are largely asymptomatic diseases that go undiagnosed. Because of the lack of both public education and awareness and troubling symptoms, patients are progressing to later-stage disease before intervention occurs.

Another challenge we face is the lack of simple, noninvasive, cost-effective diagnostics in NAFLD and NASH, leading to late diagnosis and patient burden. The gold standard diagnostic test is a liver biopsy, a procedure that is invasive and burdensome and carries risk, including death. Noninvasive technologies for diagnosis do exist, but their adoption is likely years away due to regulatory pressure, clinical inertia, and health system procurement processes.

Meeting the Challenges

The Global Liver Institute, other advocacy groups (cancer, liver disease, and obesity), patients, and clinical experts are collaborating to meet these challenges and change the trajectory of

obesogenic liver cancer. Massive strides have been made in the past few decades in the fights against cancer and obesity. Public awareness and education organizations and campaigns, increased funding for research and innovation, and policy changes are leading to progress in cancer and obesity.

To tackle obesity-driven liver cancer, we must address the link between NAFLD and NASH; then we may see an increase in disease management and treatment and a decrease in patients developing NAFLD- and NASH-associated liver cancer. The first step in this process is public awareness and education, a need that has been met by advocacy organizations across the globe. With campaigns, educational materials, events, and now an international awareness day, held on June 12, the public is gaining more and more access to information.

Another pillar in the fight against NAFLD and NASH involves overcoming barriers to diagnosis. This is addressed in Beyond the Biopsy, an awareness-raising campaign with the goals of speeding the acceptance and adoption of noninvasive technologies as an alternative to liver biopsy.[13] As NAFLD and NASH become more prevalent, it is imperative that patients have access not only to accurate diagnoses but also to diagnoses that do not require the invasiveness, burden, and risk associated with liver biopsy.

Other stakeholders involved in noninvasive technologies include the Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE)[14] and Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS)[15], operating in the United States and the European Union, respectively. The NIMBLE project aims to standardize and validate a set of noninvasive biomarkers to the diagnosis and staging of NASH and identify patients at risk of disease progression to cirrhosis and in need of intervention. The LITMUS project's goal is to develop, validate, and advance toward regulatory qualification biomarkers that diagnose, risk stratify, and monitor NAFLD and NASH progression and fibrosis stage.

Targeting the disease states that lead to liver cancer offers hope that the number of obesity-driven liver cancer diagnoses will begin to drop, but liver cancer must be a target, as well. Cancer screening saves lives, and when HCC is diagnosed at an early stage, there is the greatest hope for curative treatment.[11,12]

October is Liver Cancer Awareness Month, celebrated with #OctoberIs4Livers, a monthlong awareness campaign that addresses topics in the liver cancer continuum. The campaign delves into liver cancer basics, diagnostics, treatment options, research, and support. This year, #OctoberIs4Livers revolves around a common goal of doubling the 5-year survival rate for liver cancer to 36%. The current 18% rate means that this year, more than 30,000 people will die of the disease.[6] Recent trends in liver cancer drug approvals and research are promising, but more effective therapies and screening protocols are needed to ensure that all liver cancer patients have access to these lifesaving resources.[11,12]

Continuing to grow the nation's investment in liver cancer research will be pivotal in reaching our goals and improving health outcomes in this population. In 2019, the first liver cancer Specialized Program of Research Excellence (SPORE) was established at Mayo Clinic in Rochester, Minnesota.[16] We look forward to additional liver cancer SPORE programs gaining approval and coming online quickly to continue the movement of basic science findings into the clinical setting.

The Liver Illness Visibility, Education, and Research (LIVER) Act of 2019 (HR 3016), introduced in May, is crucial to progressing liver cancer research.[17] The LIVER Act will authorize funds for liver cancer and hepatitis B research at the National Institutes of Health and elevate the Liver Diseases Branch of the National Institute of Diabetes and Digestive and Kidney Diseases to a division. The act would also direct the National Cancer Institute to establish an interinstitute working group and create programs to coordinate research agendas focused on finding better outcomes and cures for liver cancer and other liver diseases. In addition, the act authorizes funds for prevention and awareness grants at the CDC, including grants for screening, vaccination, and treatment for liver cancer, NAFLD, and cirrhosis of the liver.

Another step forward in health policy comes from Hawaii, where Hawaii House Bill 654 was signed into law.[18] It appropriates funds to the University of Hawaii Cancer Center in Honolulu to determine the etiologies of the high incidence of liver and bile duct cancer in the state and establishes reporting requirements. The bill also highlights NASH as a cause of liver cancer.

More research is needed to understand the relationship between the NAFLD and NASH epidemic and liver cancer incidence and mortality trends so that more can be done to elevate and, ideally, solve these related health problems. Peter Campbell, PhD, strategic director of gastrointestinal tract cancer research at the American Cancer Society states, "Along with reducing known risks—excess alcohol consumption and hepatitis infection—maintaining a healthy body weight, eating healthy, and staying physically active to reduce the risk of diabetes may be important preventive strategies to reduce the risk of liver cancer."[8]

If policy and research trends continue in the right direction, we expect to see liver cancer diagnoses and deaths steadily decrease. But this won't come without widespread public awareness and education on liver cancer, NAFLD, and NASH. Looking forward, policy makers, thought leaders, research experts, clinicians, and patients must come together to change the narrative of liver cancer and alter the trajectory of this disease while saving lives. ◆

AUTHOR INFORMATION

Donna R. Cryer, JD, has channeled her personal experience as an irritable bowel disease and liver transplant patient into professional advocacy as founder of CryerHealth, LLC consulting firm on patient–industry partnerships; the Global Liver Institute (GLI), the only patient-driven liver health non-profit operating in the United States and Europe; and now as interim executive director of the People-Centered Research Foundation, the central office for PCORnet. In addition to leading the GLI Liver Cancer Council, Cryer's oncology experience includes serving as a managing director for the Association of Community Cancer Centers, building a multicultural clinical trial recruitment function for a public relations agency, and assessing patient advocacy and public affairs capabilities and opportunities for top pharmaceutical clients in the oncology space. She is a frequent speaker on patient centricity in research and healthcare delivery at meetings of major pharmaceutical, biotechnology, and oncology research and industry organizations.

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INTERVIEW

How Obesity Affects Cancer Treatment—and How to Talk With Patients About Prevention

An Interview With Debra Patt, MD, MPH, MBA, by Jaime Rosenberg

PATT

Debra Patt, MD, MPH, MBA, is executive vice president, Texas Oncology

CONTINUED FROM COVER

The interview is edited slightly for clarity.

EVIDENCE-BASED ONCOLOGY™ (EBO): The United States has made gains in cancer survivorship and preventing cancers related to smoking, but cancers related to obesity have climbed over the past 10 to 15 years. Do you think there is enough awareness of this challenge among primary care physicians, payers, and oncologists?

PATT: It's a great point. We are seeing several trends. The first trend is that we are better at treating and preventing smoking-related malignancies, but the second is that obesity-related malignancies are growing as the epidemic of obesity is continuing to increase and also that obesity-related cancers are happening earlier and earlier in people's lives, as obesity is happening earlier and happening in more of the country.

To your question, there is awareness of the obesity epidemic; what is harder is effective action. There are so many components in the [patient's] lifestyle in which patients must engage in their health and wellness to have a lean body mass—things like exercise, diet, nutrition, healthy behaviors—that it becomes hard [for the clinician] to partner with patients effectively.

"In postmenopausal women, obese patients have an increased risk of recurrence of breast cancer and uterine cancer. That's a different risk than for premenopausal patients. It may be multifactorial. There may be some inherent risk, and then some of our mechanisms of cancer treatment may be less effective in obese patients."

—Debra Patt, MD, MPH, MBA,
Executive Vice President, Texas Oncology

EBO: Is the health system addressing the issue of disparities in obesity-related cancers? Are some parts of the country doing a better job than others?

PATT: Yes, the health system is addressing the issue of disparities and obesity-related cancers. Interestingly, some early research suggests that sometimes obesity can act differently, contributing to risk among different ethnic groups.[4,5] So, there is research in that area, and I think that is really important. And yes, there are parts of the country that are doing a better job than others. I'm sure you've seen things that are simple, like wellness scores in communities.[6] To what degree are individuals that live in [given] communities walking, exercising; is health and wellness part of their regular routine? Are some communities more obese than others? There certainly are places that tend to be more fit than others. A lot of those are manifestations of policies and interventions to have a healthier population.

EBO: It can be difficult for a provider to address obesity with patients. Can you walk us through how you handle these conversations? We have heard from providers who worry about offending patients but also want to give them the facts.

PATT: It can be tricky talking to patients about a very sensitive subject like obesity. I tend to think of myself as a clinician as someone who provides facts and helps patients have a good outcome. In doing that, I try to be as fact based as possible, because I think people fear judgment about obesity or their body habitus in general. So, if you can be a fact-based partner on a collaborative strategy, that's in the best interest of patients, and frequently [this] will diminish their likelihood of being offended.

I may say something like, "I notice that your weight has increased on our scale, and your body mass index [BMI] is 31, which plots out as obese, and we know that is a risk for you as a breast cancer survivor. I want you to be happy and healthy. How do you think we can partner to reduce your risk?"

EBO: There's so much work being done with genetic testing and biomarkers in cancer. Is any work being done in biomarkers for obesity and how it can increase existing cancer risk?

PATT: There is a lot of thought around end points of obesity being inflammation, and there are a lot of markers of inflammation like IL-6, among others, that are surrogate end points for biomarkers of obesity. How that influences cancer risk is being evaluated. We are trying to understand it better because it is complex; there are so many factors that play in. It's not only what you eat by caloric content or the composition of what you eat or how frequently you eat but also how much energy you are expending. What does your exercise platform look like? It's important to use biomarkers to try to contribute to the understanding, as we want to know how the various features of things that contribute to obesity can influence cancer risk.

EBO: In looking at different groups of women, can you discuss how obesity affects cancer risk in postmenopausal women?

PATT: In postmenopausal women, obese patients have an increased risk of recurrence of breast cancer and uterine cancer. That's a different risk than for premenopausal patients. It may be multifactorial. There may be some inherent risk, and then some of our mechanisms of cancer treatment may be less effective in obese patients. So, for example, we know postmenopausal breast cancer patients who are obese have a higher risk of recurrence; it may be because when you make natural estrogen in a postmenopausal women, you're converting androstenedione and testosterone to estrogens. And that reaction is catalyzed by an enzyme called aromatase, which we block with drugs called aromatase inhibitors to treat breast cancer. If you have more fat because you're obese, we know that the same dose of aromatase inhibitors may not effectively block the enzymatic conversion to estrogen; those patients may not have their estrogen successfully blocked as well as a normal-weight patient.

INTERVIEW

EBO: What supports should payers be offering women in menopause to help them address weight changes?

PATT: I think it's complex. I know many payers have tried to have healthy living campaigns in many different ways—encouraging diet, encouraging weight loss among obese patients, and trying to facilitate exercise. I wish I knew what the right answer was. The truth is, I think it's all very important.

Here's what we know: Eating lean is important. I try to give people generic guidance. I will credit Michael Pollan for the guidance: Eat food like nonprocessed, real food, mostly green, and not too much.[7] That's a reasonable way to approach nutrition. I think in this society, we eat a lot of primary carbohydrates and breads that contribute to weight gain, and so I think following the Michael Pollan mantra is a really reasonable way to approach healthy eating.

But it's not just about eating—it's also about exercise, so I think trying to facilitate ways that patients will exercise 3 to 5 hours per week is important. Having some balance of cardiovascular training and strength training is important.[8] I try to explore with patients what they're interested in, because the truth is, any strategy that they're not interested in—that they're bored with, that they find too difficult—they're just not going to do. I counsel people [to try] anything—[maybe] walking the mall, if window shopping seems exciting to them, or swimming. I live in Texas, where it's frequently hot outside, so swimming seems attractive. But I try to discern from them what they think is appealing. Those are important features of fitness that influence health outcomes, but also exercise contributes, because for many patients who undergo surgery for the treatment of cancer, recovery is much faster if they had been exercising and their cardiovascular health is improved.

What we see here is that diet, exercise, and physical fitness can influence cancer outcomes in many ways.

EBO: What do we know about the importance of weight loss once a patient survives cancer treatment? How do you address this with the breast cancer patients you see in clinical practice?

PATT: We know that postmenopausal patients who have survived breast cancer have a lower risk of recurrence if they are not obese, so I tend to give nutritional guidance and guidance around exercise. Again, I try to explore with them what will work, because I find any strategy that they are not interested in is going to be challenging, and any strategy that's too difficult they might deem a failure and then not do anything. So, I try to see what they're predisposed to do.

Again, I tend to give the guidance of: Eat food, mostly green, not too much, and try to exercise 3 to 5 hours per week. I try to find out what they're doing and push them to do a little bit more. With every patient I see in clinic, we have some discussion about their wellness and what they are doing to make sure they get adequate sleep, are exercising, and are making good nutritional choices.

EBO: Is there evidence that obesity limits the effectiveness of cancer therapies? If so, why does this occur?

PATT: There is evidence that obesity limits the effectiveness of some cancer therapies. A great example is that in postmenopausal women with breast cancer, we frequently treat estrogen-positive cancers with aromatase inhibitors—drugs like letrozole, or Femara; anastrozole, or Arimidex; exemestane, or Aromasin—those drugs act by preventing the peripheral conversion of testosterone or androstenedione into estrogens. It's the same dose for every patient. If you have a 150-kg patient [330 lb] or a 60-kg patient [132 lb], you're giving them the same dose of drug. What we've learned is that the obese patient is at higher risk of recurrence, and it appears to be directly related to this. If you have more fat, you can have more aromatization of testosterone products without being blocked appropriately.

EBO: Does obesity's effect on a person's mental health also affect their cancer risk or survival if they receive a diagnosis?

PATT: It becomes very complex; we don't understand as well today which part of obesity influences the outcome. Is it diet or is predominantly exercise? Is it predominantly percentage of fat? Is it BMI? I think we don't know the answers to those questions yet, and I think that more research is very important in that area. At the end of the day, what we bring to practice as clinicians is an obligation to talk to our patients about nutrition, wellness, and exercise, to try to get them on the right path to having a good outcome. ◆

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