PAYMENT MODELS

Kavita Patel: Drug Pricing, Care Access Priorities in Federal Health Care Policy
Rose McNulty

AS A NEW ADMINISTRATION FINDS its footing, cancer care stakeholders are raising questions about the fate of many federal policies that will make an impact on health care as well as on oncologists, payers, and patients. Kavita Patel, MD, MS, FACP, a non-resident fellow at the Brookings Institution Center for Health Policy, addressed several of those policies to kick off the Association of Community Cancer Centers (ACCC) 47th Annual Meeting and Cancer Center Business Summit.

Patel, who served as a director of policy for the White House under President Barack Obama, gave a reminder that a decade later and during a global pandemic, the root issues in health care remain the same.

“All in all, no matter what, you can safely say that 10 years after the passage of the Affordable Care Act (ACA), we’re still faced squarely with the issues of cost, as well as quality, that we tried to address in 2010,” Patel said. She noted that with a US Supreme Court decision on the ACA’s validity expected in spring or summer 2021 following oral arguments in November 2020,1 her presentation was based on the assumption that the ACA will still stand.

Noting that both the House of Representatives and the Senate have very slim Democratic majorities, Patel pointed out that although executive orders have become common for presidents to enact change, some of the biggest health care policy reform changes will require legislative action.

TARGETED THERAPIES

Identifying Small Cell Lung Cancer Subtypes and Potential Therapeutic Targets
Rose McNulty

NEW RESEARCH FROM the University of Texas MD Anderson Cancer Center has identified 4 distinct subtypes of small cell lung cancer (SCLC) based on gene expression, providing possible targets for treatment in a notoriously aggressive cancer type with a limited therapy armamentarium.2

Lung cancer is the second most common type of cancer in the United States, and SCLC makes up about 13% of lung cancer cases.3 Compared with the more common non–small cell lung cancer (NSCLC), which has seen new, more effective therapy options and improved patient outcomes, SCLC has lacked therapeutic advances.

FOR EMPLOYERS

The Impact of Reinsurance of Gene Therapies on Employer Financial Risk
Marc Hixson, MBA; Neil Minkoff, MD; Kim Gwiazdzinski, MBA, RPh; and Jim Clement, MHA

THE EXPLOSION OF INNOVATION in health care comes with a price tag. While the cost of an individual product or service may be small in the scheme of national health expenditures, a single event can be financially devastating to a self-insured plan sponsor. This is especially true for the growing proportion of smaller employers that assume the financial risk for providing health care benefits to their employees.

CONTINUED ON SP110 »

CONTINUED ON SP112 »

CONTINUED ON SP107 »
INDICATION

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS.

Billing Unit Conversion

<table>
<thead>
<tr>
<th>HCPSC J9037 (Injection, belantamab mafodotin-bmif, 0.5mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5mg</td>
</tr>
<tr>
<td>100-mg vial</td>
</tr>
</tbody>
</table>

*Please check with individual payers and carriers for specific documentation and guidance when billing for a new drug.

HCPCS=Healthcare Common Procedure Coding System


The decision by a payer to pay for a specific product is based on many factors. It is always the prescriber’s responsibility to determine the appropriate treatment and submit appropriate codes, charges, and modifiers for treatments provided.
IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS

Ocular Toxicity: Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 24% had both ocular symptoms and visual acuity changes.

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

BLENREP REMS: BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity. Notable requirements of the BLENREP REMS include the following:
• Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
• Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
• Patients must be enrolled in the BLENREP REMS and comply with monitoring.
• Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
• Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available at www.BLENREPREMS.com and 1-855-209-9188.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose.

ADVERSE REACTIONS

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

The safety of BLENREP as a single agent was evaluated in DREAMM-2. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcaemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 ≤5% laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

USE IN SPECIFIC POPULATIONS

Lactation: There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

Females and Males of Reproductive Potential: BLENREP can cause fetal harm when administered to pregnant women. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP.

Pregnancy Testing: Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Infertility: Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats but were reversible in female rats.

Geriatric Use: Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

Renal Impairment: No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation). The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis.

Hepatic Impairment: No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin super limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST). The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Please see Brief Summary of Full Prescribing Information, including BOXED WARNING, on the following pages.
BRIEF SUMMARY

BLENREP
(belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate [see Clinical Studies (14) of full Prescribing Information] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

Perform an ophthalmic exam prior to initiation of BLENREP and during treatment [see Warnings and Precautions (5.1)].

Advise patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist [see Warnings and Precautions (5.1)].

2.2 Recommended Dosage

The recommended dosage of BLENREP is 2.5 mg/kg of actual body weight given as an intravenous infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.

2.3 Dosage Modifications for Adverse Reactions

The recommended dose reduction for adverse reactions is:
• BLENREP 1.9 mg/kg intravenously once every 3 weeks.

Discontinue BLENREP in patients who are unable to tolerate a dose of 1.9 mg/kg (see Tables 1 and 2).

Corneal Adverse Reactions

The recommended dosage modifications for corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA), are provided in Table 1 (see Warnings and Precautions (5.1)). Determine the recommended dosage modification of BLENREP based on the worst finding in the worst affected eye. Worst finding should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity (KVA) scale.

Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale (continued)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Corneal examination finding(s):</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Severe superficial keratopathy* Change in BCVA: Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200</td>
<td>Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.</td>
</tr>
<tr>
<td>4</td>
<td>Corneal epithelial defect* Change in BCVA: Snellen Visual Acuity worse than 20/200</td>
<td>Consider permanent discontinuation of BLENREP. If continuing treatment, withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.</td>
</tr>
</tbody>
</table>

* Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

Moderate superficial keratopathy with or without patchy microcryst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

Corneal epithelial defect such as cornea l ulcers.

Other Adverse Reactions

The recommended dosage modifications for other adverse reactions are provided in Table 2.

Table 2. Dosage Modifications for Other Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia [see Warnings and Precautions (5.3)]</td>
<td>Platelet count 25,000 to less than 50,000/mL</td>
<td>Consider withholding BLENREP and/or reducing the dose of BLENREP.</td>
</tr>
<tr>
<td></td>
<td>Platelet count less than 25,000/mL</td>
<td>Withhold BLENREP until platelet count improves to Grade 3 or better. Consider resuming at a reduced dose.</td>
</tr>
<tr>
<td>Infusion-related reactions [see Warnings and Precautions (5.4)]</td>
<td>Grade 2 (moderate) or Grade 3 (severe)</td>
<td>Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%.</td>
</tr>
<tr>
<td>Grade 4 (life-threatening)</td>
<td>Permanently discontinue BLENREP and provide emergency care.</td>
<td></td>
</tr>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 3</td>
<td>Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Consider permanent discontinuation of BLENREP if continuing treatment, withhold BLENREP until improvement to Grade 1 or better and resume at reduced dose.</td>
<td></td>
</tr>
</tbody>
</table>

2.4 Preparation and Administration

BLENREP is a hazardous drug. Follow applicable special handling and disposal procedures.

Calculate the dose (mg), total volume (mL) of solution required, and the number of vials of BLENREP needed based on the patient’s actual body weight. More than 1 vial may be needed for a full dose. Do not round down for partial vials.

Reconstitution
• Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).
• Reconstitute each 100-mg vial of BLENREP with 2 mL of Sterile Water for Injection, USP, to obtain a final concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. Do not shake.
• If the reconstituted solution is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) or at room temperature (68°F to 77°F [20°C to 25°C]) for up to 4 hours in the original container. Discard if not diluted within 4 hours. Do not freeze.

(continued on next page)
• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to opalescent, colorless to yellow to brown liquid. Discard if extraneous particulate matter is observed.

Dilution

• Withdraw the calculated volume of BLENREP from the appropriate number of vials and dilute in a 250-mL infusion bag of 0.9% Sodium Chloride Injection, USP, to a final concentration of 0.2 mg/mL to 2 mg/mL. The infusion bags must be made of polyvinylchloride (PVC) or polyolefin (PO).

• Mix the diluted solution by gentle inversion. Do not shake.

• Discard any unused reconstituted solution of BLENREP left in the vial(s).

• If the diluted infusion solution is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours. Do not freeze. Once removed from refrigeration, administer the diluted infusion solution of BLENREP within 6 hours (including infusion time).

• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted infusion solution should be clear and colorless. Discard if particulate matter is observed.

Administration

• If refrigerated, allow the diluted infusion solution to equilibrate to room temperature (68°F to 77°F [20°C to 25°C]) prior to administration. Diluted infusion solution may be kept at room temperature for no more than 6 hours (including infusion time).

• Administer by intravenous infusion over approximately 30 minutes using an infusion set made of polyvinyl chloride (PVC) or polyolefin (PO).

• Filtration of the diluted solution is not required; however, if the diluted solution is filtered, use a polyethersulfone (PES)-based filter (0.2 micron).

Do not mix or administer BLENREP as an infusion with other products. The product does not contain a preservative.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 or 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instructions

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3)].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1)].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

5.2 BLENREP REMS

BLENREP is only available through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)].

Notable requirements of the BLENREP REMS include the following:

• Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.

• Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.

• Patients must be enrolled in the BLENREP REMS and comply with monitoring.

• Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.

• Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENREPREMS.com and 1-855-209-9188.

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3)].

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3)]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

• Ocular toxicity [see Warnings and Precautions (5.1)].

• Thromboembolic [see Warnings and Precautions (5.3)].

• Infusion-related reactions [see Warnings and Precautions (5.4)].

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

(continued on next page)
Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 weeks or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP, keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytopenia decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyltransferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

Table 3. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Keratopathy</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>53</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>22</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>14</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong>&lt;br&gt;Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong>&lt;br&gt;Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
</tr>
<tr>
<td><strong>Procedural complications</strong>&lt;br&gt;Infusion-related reactions</td>
<td>21</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong>&lt;br&gt;Athalgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong>&lt;br&gt;Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
</tr>
</tbody>
</table>

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.
* Visual acuity changes were determined upon eye examination.
* Blurred vision included diplopia, visual blurring, visual acuity reduced, and visual impairment.
* Dry eyes included dry eye, ocular discomfort, and eye pruritus.
* Fatigue included fatigue and asthenia.
* Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.
* Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

**Eye Disorders:** Photophobia, eye irritation, infective keratitis, ulcerative keratitis.

**Gastrointestinal Disorders:** Vomiting.

**Infections:** Pneumonia.

**Investigations:** Albinurnuria.

Table 4 summarizes the laboratory abnormalities in DREAMM-2.

Table 4. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blimf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blimf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. 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 reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blimf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

(continued on next page)
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception

Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility

Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats [see Nonclinical Toxicology (13.1) of full Prescribing Information].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years or older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 or older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <upper limit of normal [ULN] and aspartate aminotransferase (AST) >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].

• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Path to Better Payment System to Be Clear Over Time

ON MY DESKS AT HOME and at work, I keep copies of a 2012 internal medicine text written by several esteemed professors from my medical school. It is not there to remind me what they got right, but rather, to remind me how, in retrospect, so much of what we took as indisputable knowledge is now plainly wrong. As Joshua Y. Yang, MD, notes, few of his fellow medical students appreciated the prescience of their professor’s first-year prediction that, “Ninety percent of what we will learn over the next 4 years will be wrong in a couple of decades from now.”

This misalignment is especially true in the domain of cancer care. From the perspective of someone practicing oncology in the late 1990s, there was no way to accurately predict how radically oncology and hematology would be transformed in the subsequent 2 decades by advances in genomics diagnostics/risk stratification, targeted therapeutics, immuno-oncologic drugs, and gene-modified therapeutics. My 2012 textbook serves as a reminder to remain humble and embrace a broader perspective when making sweeping pronouncements about the future of cancer care.

Instead, we must embrace this hyperdynamic period of innovation with the perspective that the best way to create a system path that ensures these discoveries are delivered sustainably, equitably, and effectively may only become clear in time through the persistence of those who are passionately engaged in bringing care to patients and families. There are more than 8000 new medications in development; up to 75% may represent new therapeutic classes. The failure to embrace this dizzying pace of change will exacerbate care disparities, produce more misaligned payment systems, and erect more barriers to life-saving, life-transforming care.

In 1984, CMS created the Prospective Payment System. Inasmuch as this represented an advance from prior payment systems, it now seems antiquated in light of the dramatic advances in cancer care. In 1984, 5-year relative cancer survival rates were only 52.74%. Since then, cancer survival rates have risen by the greatest increments ever, fueled in light of the dramatic advances in cancer care. In 1984, 5-year relative cancer survival rates

“This doesn’t mean that the perfect model of care payment should paralyze the pace of progress, nor should it result in patients and families encountering additional barriers to life-saving access in their respective cancer journeys. In this issue of Evidence-Based Oncology®, we look forward, humbly, toward how our systems may more effectively evolve to become more patient centered, more effective, more innovative, and more sustainable.

As we move forward through this unprecedented period in cancer care innovations, the quest for grand strategies and elegant systems should not be our principal goals. The growing disparities in care access coupled with a growing portfolio of therapeutics require that we act now to ensure that patients, oncologist, and health systems can move with unlettered speed in bringing hope to those whose lives have been affected by a cancer diagnosis.

As long as we keep this as our truth north and continue to push past the systemic imperfections and incorrect assumptions that stand in our way, the connected dots of a robust care delivery system will become increasingly clear in time. The first step is to humbly embrace this level of uncertainty—and to then move with speed.”

Joseph Alvarnas, MD
Editor-in-Chief

“Evidence-Based Oncology®: You can’t connect the dots looking forward; you can only connect them looking backward. So you have to trust that the dots will somehow connect in your future.”

Steve Jobs

Joseph Alvarnas, MD
The failure to include members of minority groups in clinical trials means the promise of precision medicine is falling short, according to panelists taking part in the first discussion of the Oncology Value Coalition.
Sp89
Policy
Disparities in Cancer Care: Has Precision Medicine Widened the Gap?
Mary Caffrey

SP91-SP92
Conference Coverage
Geisinger’s “Soft Demo” Proves Key for a Successful Clinical Pathways Rollout
Integrating Remote Symptom Management With ePROs in Cancer Care
Better Phone Call Triage Leads to Faster Decision-Making

SP94-SP97
Clinical Updates
Sustained MRD Negativity Is Predictive of Long-term Outcomes in RRM
Cosela Is Approved for Protection Against Myelosuppression From SCLC Treatment
Combination Treatment Maintains Quality of Life in Relapsed/Refractory MM

SP105-SP106
AJMC TV
Dr Apar Kishor Ganti Explains Why Lurbinectedin Is Important for Patients With SCLC
Dr Ashley Ross on Genomic Testing Post Prostatectomy
Dr Sibel Blau Discusses the Impact of Delayed Cancer Diagnoses on Community Cancer Practices
Dr Whitney Goldsberry on the Future of PARP Inhibitors in Ovarian Cancer

FROM THE CHAIRMAN

Paying for Cancer Care in the Age of Innovation

As Evidence-Based Oncology™ went to press, the FDA approved the first chimeric antigen receptor (CAR) T-cell therapy for patients with multiple myeloma, idecabtagene vicleucel (ide-cel), to be sold as Abecma. It’s a breakthrough, no question. But the cost of each treatment will make some shudder: $419,500. This news comes after Bristol Myers Squibb, which is developing ide-cel with bluebird bio, announced that its other new CAR T-cell therapy, lisocabtagene maraleucel (liso-cel, Breyanzi), will sell for $410,300.

Life-saving gene and cell therapies with six-figure price tags are no longer rare. The therapies are great news for patients, but the wonders of science bring new challenges to self-funded employer health plans. Increasingly, employers and business groups are learning how to balance the need for the workforce to have access to innovation with the need to manage the risk of catastrophic claims.

In this issue, our friend Neil Minkoff, MD, and his coauthors Marc Hixson, MBA; Kim Gwiazdzinski, MBA, RPh; and Jim Clement, MHA; discuss approaches that self-funded plans can take, and why pharmaceutical manufacturers should take a role in these discussions. They explain how the traditional role of stop-loss carriers is shifting, noting that the rise of these high-cost therapies can no longer be considered “random.” Thus, employers and other payers risk losing what has been an essential element in managing health care delivery and their own bottom line.

The authors explain how the rise of high-cost therapies will force everyone to rethink the role of reinsurancen. And, the future may force smaller players or call on small employers to give employees a voucher to shop for coverage instead of managing it in-house.

Is this a bad sign? Not necessarily. Competition can bring creativity, and the most enterprising thinkers will come up with new ways to deliver services and manage risk. The idea of paying over time for a curative therapy has been discussed for some time (and in these pages), so those entities that can master the active therapy has been discussed for some time (and manage risk. The idea of paying over time for a curative therapy has been discussed for some time (and

Finding a financing model that rewards innovation will come up with new ways to deliver services and manage risk. The idea of paying over time for a curative therapy has been discussed for some time (and in these pages), so those entities that can master the financing and risk management aspects of cancer care are destined for success.

What is needed is the recognition that cancer care is a highly individualized and fast-moving process, one for which backward-looking modeling is often, to be blunt, backward. Yes, I’m talking about the Oncology Care Model which was extended last year due to coronavirus disease 2019. This was necessary, but now the model will have its day of reckoning. As the Brookings Institution’s Kavita Patel, MD, said recently at the Association of Community Cancer Centers, it has been “a debacle.”

Finding a financing model that rewards innovation and gives patients access without burdening doctors will be no small task, but it’s a necessary one.

Sincerely,
Mike Hennessy Sr
Chairman and Founder
First-line maintenance treatment of urothelial carcinoma

BAVENCIO® (avelumab) is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

Based on overall survival (OS) data

The FIRST and ONLY immunotherapy approved in the first-line maintenance setting

National Comprehensive Cancer Network® (NCCN®) Recommendation

Avelumab maintenance therapy (category 2A) is recommended as part of a preferred regimen as an option for first-line systemic therapy in patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy.¹

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

LEARN MORE at BAVENCIO.com

IMPORTANT SAFETY INFORMATION (continues on following pages)

BAVENCIO can cause severe and fatal immune-mediated adverse reactions in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

BAVENCIO can cause immune-mediated pneumonitis. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 12% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause immune-mediated colitis. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
BAVENCIO® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone

**Study design:** The JAVELIN Bladder 100 Trial was a Phase 3, randomized, open-label, multicenter study of BAVENCIO as a first-line maintenance treatment in 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=700).²

**BAVENCIO® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone**

**Most common adverse reactions in the JAVELIN Bladder 100 Trial**

The most common adverse reactions (≥20%) in patients receiving BAVENCIO + BSC vs BSC alone were:

- Fatigue (35% vs 13%)
- Urinary tract infection (20% vs 11%)
- Musculoskeletal pain (24% vs 15%)
- Rash (20% vs 2.3%)

For information on warnings and precautions, see Important Safety Information starting on the previous page.

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² PD-L1 expression was assessed in tumor samples using the VENTANA PD-L1 (SP263) assay.³

³ Using the VENTANA PD-L1 (SP263) assay, PD-L1-positive tumors were defined as PD-L1 expression in ≥25% of tumor cells in ≥25% of tumor-associated immune cells if the percentage of immune cells was ≤1% or ≤1%, respectively. If none of these criteria were met, PD-L1 status was considered negative.⁴

⁴ BSC was administered as deemed appropriate by the treating physician, and could include treatment with antibiotics, nutritional support, and other patient management approaches with palliative intent (excludes systemic antitumor therapy).⁵

⁵ For patients with autoimmune diseases or medical conditions requiring systemic immunosuppression were excluded. Patients were randomized to BAVENCIO 10 mg/kg intravenous infusion every 2 weeks + best supportive care (BSC) (n=350) or BSC alone (n=350) until disease progression or unacceptable toxicity. Treatment was initiated within 4 to 10 weeks after chemotherapy. OS was the major efficacy outcome measure in all randomized patients with PD-L1-positive tumors.⁶

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LEARN MORE at BAVENCIO.com
**IMPORTANT SAFETY INFORMATION (continued)**

**BAVENCIO** can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

**BAVENCIO** can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

**BAVENCIO** can cause **immune-mediated hyphophysitis**. Hyphophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hyphophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

**BAVENCIO** can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hypothyroidism or institute medical management of hypothyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

**BAVENCIO** can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

**BAVENCIO** can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

**BAVENCIO** can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rush with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids were used to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

**BAVENCIO** can result in other **immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For myocarditis, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For neurological toxicities, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

**BAVENCIO** can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade 3 reactions were treated with intravenous corticosteroids.

Fatal and other serious complications of allogeneic hematopoietic stem cell transplantation (HSCT) can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

**BAVENCIO** can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman not to breastfeed during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

A **fetal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving BAVENCIO + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonitis, respiratory failure, sepsis, urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

The **most common adverse reactions** (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 16%), musculoskeletal pain (24% vs 15%), and dyspnea (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving BAVENCIO, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

**Selected laboratory abnormalities** (all grades, ≥20%) in patients with **locally advanced or metastatic UC** receiving BAVENCIO + BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

Please see Brief Summary of Prescribing Information on following pages.

Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or pituitary disorders occurred in 0.1% (1/1738) of patients receiving BAVENCIO which was a Grade 2 reaction. Adrenal insufficiency did not resolve in any patient (0/8). Of the 2 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 3 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of dermatologic adverse reactions.

Other Immune-Mediated Adverse Reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received BAVENCIO 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. Cardiovascular: Myocarditis, pericarditis, vasculitis. Gastrointestinal: Pancreatitis to include acute pancreatitis, pancreatitis associated with severe or persistent hypertriglyceridemia, immune-mediated colitis. Hematologic: Lymphadenopathy (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immunoblastic lymphoma, necrotizing lymphadenitis (Kikuchi lymphadenitis), sar
Adverse reactions resulting in permanent discontinuation of BAVENCIO in >1% of patients were myalgia/myofascial pain (including acute myopericardial and thoracic pain), cough, diarrhea (including severe), rash (including eczema, dermatitis, rash maculo-papular, papulovesicular, eczematous), and infusion-related reaction (including urticaria). The incidence of grade 3/4 adverse reactions was highest for infusion-related reactions (18%). Other grade 3/4 adverse reactions included dermatologic adverse reactions (15.5%), fatigue (15.5%), and respiratory, thoracic and mediastinal disorders (12.3%).

Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO, including fatal cases (0.1%). Adverse reactions resulting in death occurred in 0.5% of patients (9/1738) receiving BAVENCIO and included respiratory, thoracic and mediastinal disorders (0.3%), cardiovascular disorders (0.1%), infections and infestations (0.1%), and gastrointestinal disorders (0.1%).

Table 5: Adverse Reactions (≥10%) of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BAVENCIO plus BSC (N=334)</th>
<th>BSC (N=345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
<td>All Grades %</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Rash*</td>
<td>20</td>
<td>1.2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>20</td>
<td>6</td>
</tr>
</tbody>
</table>

* Fatigue is a composite term that includes fatigue, asthenia, and malaise. 
* Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain. 
* Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis, urticaria, eczema, erythema multiforme, rash, erythematosus, rash macular, rash papular, pruritc, drug eruption and lichen planus. 
* Urticarial tract infection is a composite term that includes urticarial tract infection, uruosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection, bacterial, and Escherichia coli urinary tract infection. 
* Cough is a composite term that includes cough and productive cough.

Table 6: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BAVENCIO plus BSC*</th>
<th>BSC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade %</td>
<td>Grade 3-4 %</td>
<td>Any Grade %</td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>34</td>
<td>2.1</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>30</td>
<td>2.9</td>
</tr>
<tr>
<td>Blood sodium decreased</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>11</td>
<td>1.7</td>
</tr>
<tr>
<td>Blood potassium increased</td>
<td>24</td>
<td>3.8</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>24</td>
<td>2.6</td>
</tr>
<tr>
<td>Blood cholesterol increased</td>
<td>22</td>
<td>1.2</td>
</tr>
<tr>
<td>Serum aspartate increased</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>CPK increased</td>
<td>19</td>
<td>2.4</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>19</td>
<td>3.2</td>
</tr>
</tbody>
</table>

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO plus BSC group (range: 339 to 344 patients) and BSC group (range: 329 to 341 patients).

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on its mechanism of action, BAVENCIO 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. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. In the U.S. general population, the estimated background risk for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Other adverse reactions: Pregnancy: Pregnancy, data animal: Animal reproduction studies have not been conducted with BAVENCIO 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 BAVENCIO 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 BAVENCIO may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Lactation: Risk Summary: There is no information regarding the presence of avulamab in human milk. The effects on the breastfed infant, in addition to the effects on the mother, are unknown. The decision to breastfeed should be based on the importance of the drug to the mother versus the potential risk to the breastfed infant. Based on the mechanisms of action, BAVENCIO may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Geriatric Use: Locally Advanced or Metastatic Urothelial Carcinoma: Of the 344 patients randomized to BAVENCIO 10 mg/kg plus BSC in the JAVELIN Bladder 100 trial, 63% were >65 years or older and 24% were >75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. The antigenicity of BAVENCIO is unknown.

Table 7: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

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<tbody>
<tr>
<td>Any Grade %</td>
<td>Grade 3-4 %</td>
<td>Any Grade %</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>28</td>
<td>4.4</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>20</td>
<td>0.6</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>18</td>
<td>0.6</td>
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Adverse effects were generally mild to moderate in severity. The most commonly reported adverse effects included infusion-related reactions, rash, and pyrexia.

Data, Animal Data: Animal reproduction studies have not been conducted with BAVENCIO 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 BAVENCIO 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 BAVENCIO may increase the risk of developing immune-mediated disorders or altering the normal immune response.

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Genomic Cancer Profiling: Setting a New Standard in Lung Cancer Treatment

MARTIN DIETRICH, MD, PHD

GENOMIC PROFILING HAS REVOLUTIONIZED the way cancer care is being approached. Following the completion of the Human Genome Project in 2003, which provided the DNA reference blueprint, many actionable genomic alterations have been identified.

Non-small cell lung cancer (NSCLC) is a genetically diverse disease, with at least 9 genetic alterations that are clinically accessible for targeted therapy. Some of these are virtually exclusive to NSCLC, such as EGFR mutations. Others span a broad spectrum of cancer types, like BRAF and NTRK alterations.1

Additional biomarkers, including PD-L1, mismatch repair deficiency or microsatellite instability, and tumor mutational burden are FDA-approved markers of immunotherapy, a third therapeutic pillar of NSCLC beyond targeted therapy and conventional chemotherapy.2

With the breadth of targetable mutations, next-generation sequencing provides a highly sensitive, parallel approach to identifying the complete set of relevant biomarkers to guide therapy, allowing clinicians to match biology with the appropriate therapy and refining the one-size-fits-all approaches previously applied in NSCLC.3

Results of genomic testing are a critical component of the diagnosis, complementing previous histology-based assessments, according to key national cancer treatment guidelines, including those published by the American Society of Clinical Oncology and National Comprehensive Cancer Network.4 These complete results guide critical therapy decisions and, ideally, they are available prior to initiation of any systemic therapy.

The number of actionable mutations in NSCLC is ever-expanding, and approvals to target alterations in KRAS, HER2/neu and NRG1/HER3 are expected in the near future.5,6 Most nonsquamous NSCLC diagnoses will be characterized by the presence of a driver mutation. Therefore, the yield and effect of genomic testing will continue to grow and improve outcomes in NSCLC.

The nature of genomic alterations is complex and diverse. It can include simple alterations, such as point mutations in EGFR or NTRK, or higher genomic rearrangements, like splicing variants in the MET gene or fusion products of 2 seemingly unrelated genes.

Gene fusion is the joining of 2 genes, and when the binding partner upstream of the actual gene is responsible for activation of a typically dormant gene it results in malignant transformation.

One of these genomic alterations is the NTRK gene fusion product. Fusion of 1 of the NTRK genes to an activating promoter gene can activate NTRK-related signaling in NSCLC.7,8 As with other oncogenes, no clinical or histological characteristic hints at the presence of an NTRK fusion, and agnostic testing of all patients with NSCLC is critical to identify the mutation.

Several challenges have made stringent genomic testing for all patients with NSCLC difficult, including lack of sufficient biopsy specimen, viability of biopsy specimen, tissue utilization during histological work up, insurance coverage, and delays in turnaround time for laboratory results when there is a clinical urgency to initiate systemic therapy.9,10 Although the challenges are clearly affecting real-world care delivery for lung cancer, the following case is a good example of why it is worthwhile, even in later lines of therapy.

A 41-year-old female patient received a diagnosis of adenocarcinoma of the lung after presenting with shortness of breath. Her biopsy revealed a PD-L1 level of 80% and no actionable mutation was seen on liquid biopsy. No additional tissue was available for genomic testing. The patient was initiated on single-agent immunotherapy and showed disease progression on the first follow-up scans. Chemotherapy was then added to immunotherapy, stabilizing her disease for 3 months prior to clinical progression. A repeat tissue biopsy was obtained and retested on an RNA-based tissue platform. An NTRK3 fusion was identified, and the patient was started on targeted therapy with near complete response on the first follow-up scan (Figure).

While liquid biopsy is a convenient and ubiquitously available testing modality for the detection of point mutations and small deletions, fusions and other more complex genomic alterations are more sensitively detected on tissue-based assays. A negative evaluation by liquid biopsy should be followed by a tissue-based assay, and a negative tissue-based evaluation on a DNA platform should be complemented by an RNA-based tissue analysis. This effort of comprehensive tissue testing maximizes the probability of oncogene detection, facilitates the selection of appropriate therapies, and helps avoid ineffective therapies and their associated medical and financial toxicities.

Improved outcomes following genomically guided therapy have been extensively demonstrated, and a reduction in adverse effects has demonstrated superior quality of life and significant cost savings for patient care delivery.11-13 From a patient perspective, it is an improvement in quality and quantity of life, with
synchronous reduction in cost of care delivery. Or as one oncologist put it, genomic testing assures “the right therapy for the right patient at the right time.”

AUTHOR INFORMATION
Martin F. Dietrich, MD, PhD, is a medical oncologist at Florida Cancer Specialists & Research Institute and an assistant professor of internal medicine at the University of Central Florida in Orlando. He is a board-certified internist and medical oncologist. He has a special research interest in lung and breast cancer treatment, as well as genomic evaluation and counseling of somatic and hereditary syndromes.

REFERENCES

Looking at Long-term Results, New Opportunities With CAR T-Cell Therapies

MARY CAFFREY

MORE THAN 3 YEARS have passed since FDA approved the first chimeric antigen receptor (CAR) T-cell therapy to treat patients whose B-cell lymphoma had not responded to other treatments. Since 2017, researchers have learned more about controlling side effects and which patients make good candidates for therapy; but one question remains: why does this process work for some patients but not others?

“Is there a question we struggle with,” said Stephen J. Schuster, MD, who on March 19, 2021, offered an overview of developments in CAR T-cell therapy during the National Comprehensive Cancer Network’s (NCCN) 2021 Virtual Annual Meeting.

Schuster, director of the Lymphoma Program at the Abramson Cancer Center, University of Pennsylvania, was the principal investigator for the trial that led to the approval of isatuximab-od钁, or tisa-cel (Kyrumia). He has also led trials involving bispecific antibodies, and said he’s given them to patients when CAR T-cell therapy failed.

Since July 2020, 2 more CAR T-cell treatments have been approved: they are brexepacabtagene autoleucel (Tecartus), a new treatment for mantle cell lymphoma, and lisocabtagene maraleucel, or liso-cel (Breyanzi), which is also approved for refractory B-cell lymphoma but uses a manufacturing process that promises less toxicity that previously approved CAR T-cell therapies.

Schuster discussed differences among the 3 approved anti-CD19 therapies, tisa-cel, liso-cel, and axicabtagene ciloleucel, or axi-cel (Yescarra), and also discussed the path ahead, which will involve deciding which patients will benefit from CAR T-cell therapy, how early to give it, and how to combine it with other drugs for the best result. “We’re going to be combining CAR T cells with other therapies, and moving it up earlier in therapy for patients,” Schuster said. “I think it’s going to change the landscape.”

Added choices and recent advances reflected in the March 2021 update of the NCCN guidelines for lymphoma include:

• In follicular lymphoma, there are now distinctions between second-line and subsequent treatments and third-line and subsequent treatments for the elderly or infirm.
• Liso-cel was added in 5 different places as a category 2A recommendation: in follicular lymphoma, marginal zone lymphoma, DLBCL, and for forms of high-grade B-cell lymphoma.

Schuster highlighted the approval in mantle cell lymphoma, saying in this condition, “recurrence was the norm.” Schuster cited 2020 data published by Michael Wang, MD, of The University of Texas MD Anderson Cancer Center, showing the 61% complete response rate at 12 months when a BRAF inhibitor is used a bridge therapy, which Schuster said was “clearly better than any of the other agents approved for relapsed/refractory mantle cell lymphoma.”

CAR T-cell therapy has saved the lives of patients who had been extremely ill, but it still fails in about two-thirds of patients who receive it, for reasons that are not fully understood. This is of great concern to payers, given the initial prices of $373,000 to $475,000.

Schuster co-authored research in the New England Journal of Medicine that progression-free survival at 5 years was 31% in patients with diffuse large B-cell lymphoma (DLBCL) and 43% in patients with follicular lymphoma; 60% of patients were in remission at 5 years. They wrote, “Of the patients who had a relapse, only one had no expression of the CD19 target antigen.”

The customized approach of CAR T-cell therapy—in which a patient’s T cells are harvested and engineered to attack cancer before being reinfused into the body—brings with it pluses and minuses; a key downside is the time it takes to manufacture individual treatments for each patient. But a big plus is that CAR T-cell therapy now has more than 5 years of long-term data behind it, Schuster said. Despite the cost, Schuster said payers have largely come on board with the early CAR T-cell therapies, at least at academic medical centers where the reimbursement process has been fine-tuned.

Success in CAR T-cell therapy will come from gaining more understanding of key steps in the treatment process: patient selection, apheresis and cell manufacturing, selection of bridge therapy, and management of toxicities.

There’s room for advancement in the role of bridging therapy, which Schuster called “the art of oncology,” with the arrival of new third-line agents and advances in other drug classes used as bridge therapy. Deciding the order of when to use immune checkpoint inhibitors, bispecific antibodies—whether it’s before, during, or after CAR T-cell administration—will open new possibilities.

“We’re talking about the two-thirds of patients that aren’t responding to the CAR Ts, and maybe getting a third of them to respond to a bispecific [antibody] so I’m optimistic that bispecifics are going to have a role here,” he said. “We’re looking at that in a more systematic fashion.”

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SP85
Delays With Payers Mean Some Patients Miss Window for CAR T-Cell Therapy, Findings Show

MARY CAFFREY

When a physician makes the call that chimeric antigen receptor (CAR) T-cell therapy offers the best chance for survival in patients with relapsed large B-cell lymphoma (LBCL), there isn’t time to spare. But data gathered over the past 2 years by a team from Cardinal Health Specialty Solutions revealed that community oncology practices can encounter roadblocks when trying to navigate payer approvals for CAR T-cell therapy. These barriers can lead to time running out before patients can receive the therapy—and the situation isn’t improving, even though the first CAR T-cell treatments were approved more than 3 years ago.¹,²

With a new, less toxic CAR T-cell therapy now approved³ and more in the pipeline—including treatments for multiple myeloma—the findings raise concerns that disconnects among payers, providers, and patients are stalling, and could continue to stall, timely implementation of this lifesaving treatment.

Data from hematologists/oncologists were gathered a year apart, first in February 2019 and then between November 2019 and February 2020. The initial survey covered 59 physicians, who were all in some type of community practice; the second included 168. Each time, almost one-third of patients who were referred for CAR T-cell therapy ultimately were unable to receive it. “High cost and toxicity continue to be potential deterrents to CAR-T consideration and appear to be increasing in significance,” the authors concluded.

For insights, Evidence-Based Oncology™ (EBO) spoke with lead author Ajeet Gajra, MD, MBBS, FACP, vice president at Cardinal Health, about identifying and removing the barriers for offering CAR T-cell therapy at the community practice level. The interview is edited for clarity.

EBO: It’s normal to have challenges with payers when a new therapy is approved. However, your findings show that the percentages of patients who were unable to receive CAR T-cell therapy after referral were about the same nearly a year apart, with the second survey coming more than 2 years after approval. What accounts for this?

GAJRA: These are complex therapies—they are essentially living cells derived from a particular individual, then engineered to be used as therapy for that individual. Obviously, the therapies are challenging in terms of logistics, and there’s also the cost factor. The issues are twofold. The first rests with the providers: They need to be very clear in terms of who they’re referring for CAR T therapy. The labels are very explicit: [the patient needs to have had] 2 prior therapies and progression, and [must meet requirements] also in terms of medical comorbidities. This is not just something that you can try [on a whim], because CAR T therapy needs planning and it requires following each step of a detailed process.

The second issue, as we all know, is the complex prior authorization process with payers. For some of these patients, it can be daunting for the managing team to collect all the information needed in a timely fashion to satisfy a payer’s requirements. [To start] the payer needs the records of the diagnostic biopsy; the history of therapies and regimens received thus far, [whether] they’ve had bone marrow transplant.

If care has been fragmented—especially if the patient was treated at another facility or, say, a tertiary center where they went for care or a transplant—all that information has to be populated. That is a potential barrier, which leads to delays. Diffuse LBCL is not a disease that you can temporize with simple measures. If it’s recurring a third time, these patients tend to be quite ill. A delay of a week or two sometimes can force the hand of the provider to take an alternative route, because they feel, “My patient is deteriorating, I still don’t have the authorization, so what am I to do?” And they have to craft an alternative plan. So, we may be capturing some of those issues when it comes to the patient, provider, and payer factors leading to delays.

EBO: As you noted, the payer delays can lead to the to the patient not receiving the therapy at all. Do providers need more support to navigate the process, whether from a professional organization or from the manufacturers themselves?

GAJRA: Absolutely. I feel strongly that additional support would be valuable. We found that most providers thought that they were quite well versed with the science behind CAR T. Many of them, though, may not actually be aware of the [full] complexity of the process involved in getting a patient on to CAR T and then managing them afterward. I feel it still starts with education—you don’t want to refer the wrong patients, because ultimately, they’re going to go through the rigmarole and not end up getting the treatment. That’s another piece we captured, where patients were being referred to CAR T centers, but ultimately not getting the treatment.

Second is support, support, support. We [generated] these results [at a time when] only 2 CAR T products [were available]. We now have 3 CAR T-cell products approved, with 1 for mantle cell lymphoma. CAR T therapies [must] be administered at designated CAR T centers, but about 1 in 6 providers didn’t have a CAR T center in their geographic vicinity, which is a barrier. Also, there’s a question of whether there can be reciprocity. Must each center be approved for every therapy that they’re going to administer? Manufacturers can help with that piece. Patient support and access services sponsored by pharma companies can help with streamlining the prior authorization process, to expedite how quickly patients can check all the boxes—get all the I’s dotted and the T’s crossed so that they can at least be evaluated sooner. Hopefully, patients can be approved by the payer sooner, when appropriate, to move to the next step.

EBO: We talked about toxicity as being among the big challenges with CAR T-cell therapy; that’s been the case from the time it was approved. Is this a bigger challenge at the community level, in terms of the patient in this setting being more concerned about the looming threat of [cytokine release syndrome] CRS? Is it more the provider who has the concern? Or is it a combination?

GAJRA: It’s a great question. I certainly agree that the specter of toxicity is still [quite] strong, and that community practices have a lower threshold or a greater concern for toxicity than the academic centers. This has come out loud and clear at [live meetings] when we engage with providers. [The audiences] often include a mix—largely community oncologists, but with some academic representatives as well.

Patients are concerned, but for the most part, with appropriate counseling, they’re willing to receive therapy because they realize...
they are running out of options. I would also highlight that as the field evolves, remarkable improvements have been made in the management of toxicity, so a lot of it can be mitigated and managed early. The thresholds have improved in terms of identifying CRS as well as neurotoxicity; [the latter] can be quite scary and devastating.

The scientific literature shows that management of toxicity has definitely improved, especially now with real-world use of CAR T being reported. Patients, for the most part, are quite eager to receive what many of them probably perceive as lifesaving and/or significantly life-prolonging therapy. But [it's a different challenge] for community physicians, especially those who aren't attached to a large tertiary care hospital. They don't have immediate access to critical care—[to an intensive care unit (ICU)]—and if your patient's health is declining [due to CAR T toxicity], they are going to [need to] land in the ICU. A lot of work [has been done] on the disparities in rural settings and smaller communities, and I think there's definitely more apprehension.

GAGIRA: We learned from our initial work that cost was a major concern in the minds of the treating oncologists. Thus, we decided to reassess as a follow-up: We had a larger sample size than in [the first survey], and it was more than 2 years since the approval of the initial therapies. However, [our results] showed that in addition to intake and toxicity concerns, cost remained a major barrier, or major concern, in the minds of the providers [due to gaps between the treatment list price and reimbursement rates, especially from Medicare]. That gap has perhaps never been completely bridged. [As far as] we know, the [list price] is about $373,000 for treatment. Certainly, attempts have been made with NTAP, the New Technology Add-on Payment [in Medicare], to reduce that burden; [the goal is to not rely on the hospitals] where the majority of CAR-T is being administered just to supplant the funding for the facilities. [Still,] it cannot be denied that it is still a very high-cost therapy.

Some of this cost sensitivity may arise from the fact that providers are looking at longer-term outcomes. If providers are [committing] to a complex process and an expensive therapy, then do the outcomes bear that out? Especially if there are a lot of early failures of therapy, then perhaps this is a barrier. I don't have evidence for this, but it has been brought up by providers as a possible barrier during discussions at live meetings on the subject.

In my mind, if a greater confidence [develops] in being able to safely administer these therapies in the clinic vs in the hospital, there will be greater interest in these therapies. Otherwise, it's really the hospital that's bearing the cost. If you do it as an outpatient infusion, though, then it becomes a proposition for the practice, given that it's a very expensive infusion. …The community practice planning on outpatient administration has to assess the risk of the patient getting sick and getting admitted for toxicity. As we learn more, though, community oncologists will become more confident about preventing toxicity and ensuring that they can safely administer these treatments on an outpatient basis. That's where the future is, and I think that will really help CAR T-cell therapies take off.

EBO: You mentioned the gap in Medicare funding. How does this compare with reimbursement for patients with commercial coverage?

GAGIRA: We don't have an answer for this question yet. We haven't teased that out. That's just the honest truth—it wasn't part of what we've surveyed thus far. This question will be more suited for CAR T centers performing the actual infusions.

EBO: Fair enough. I'd like to ask about coronavirus disease (COVID-19). It would seem that during the pandemic, there would be an interest in not keeping patients in the hospital any longer than necessary. COVID-19 emerged since you gathered your information, but I'm wondering what it's been like since then—has the pandemic made it more favorable to administer CAR T-cell therapy in the community setting?

GAGIRA: Absolutely. We're actually redoing the survey as we speak. We hope to get a decent sample size of current practices; we wanted to redo it in the context of having 3 products now approved. And, hopefully, we'll see more CAR T therapies coming down the pipe in 2021; some data looked really good coming out of ASH 2020. There seems to be anecdotally a lot of interest, especially among larger practices that are geographically close to a hospital setting, in taking on outpatient infusion of CAR T-cell therapies. We certainly got that [impression] during our discussion the last time, [last spring, so we're trying to see if that change has actually transpired. [COVID-19 is a driver for outpatient care and for almost everything else], including CAR T. [Please note] that the label of one of the initial 2 products indicated that it should be given in the hospital, while that was not the case for the other product. The labeling, or the implications of the label, also impacts practice. As we see new products emerge, if there's no direction that they should be given in a hospital, I think that will encourage the use of these therapies in the outpatient setting. But the COVID-19 pandemic, as we all know, has been a driver to push care away from the hospital and into the clinic.

EBO: We've covered a lot of ground. Would you like to add anything that we didn't cover?

GAGIRA: First of all, even though now it's been 3-plus years since the original approval, there is still room for educating and keeping the community provider especially engaged. It's not every day or every other day that a community provider will have the opportunity and will have the appropriate patient for a CAR T-cell therapy. It's not like, say, hormone-positive breast cancer, which they [commonly] see. So, I think, as more and more indications become amenable to CAR-T therapy, that ongoing engagement with be essential, [whether it stems] from the manufacturers, from organizations, or from [health care media]—whatever avenue there is.

Second is the prior authorization process. Streamlining that process for the appropriate patient is so critical, and anything that can be done to simplify and facilitate that, both from the payer perspective and the manufacturer side, would really help drive this therapy further.

Third, perhaps manufacturers can help identifying the pain points at the CAR T centers. These are typically large academic or tertiary-care cancer centers. We've encountered concerns from community oncologists, including that the patient was referred for CAR T, but was ultimately treated with a transplant; that a finite percentage of patients never ended up getting CAR T at the CAR T center; and that communication wasn't adequate in terms of what the community provider should do when the patient returns after CAR T-cell therapy.

[In short,] we've heard that the intake of the CAR T was so slow. Here, you have a patient for whom you've moved heaven and earth for prior approval authorization, and you referred them, but then they couldn't get in or it took too long. So, I think that's another area where we can share some time off in terms of getting the patient in line for CAR T.

Another potential barrier to CD-19–directed CAR T therapies in LBCI is the recent approval of tafasitamab (Monjuvi), a CD-19–directed monoclonal antibody, which is easy to give in the office and technically targets the same antigen. What is not known clearly is whether prior exposure to tafasitamab leads to impaired response with CAR T-cell therapy and vice versa.

One other thing that we learned—and I think the community physicians are learning this as well—is that patients are likely to need bridging therapy while they are awaiting CAR T-cell therapy. In the early days, they were sort of taken aback: “Oh, what am I supposed to do now? You're not going to have your product for another 6 to 8 weeks?” But now they're learning that yes, something else is needed to hold the disease—ie, bridging therapy—while awaiting the CAR T product, so it's really a multi-pronged approach. And I feel the manufacturer, CAR T center, provider, and the patient, then the payer, are in it together, and little tweaks can streamline the process [to work] somewhat better than it does now. 

REFERENCES
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Disparities in Cancer Care: Has Precision Medicine Widened the Gap?

MARY CAFFREY

TO START A DISCUSSION ON DISPARITIES in cancer care, oncologist Kashyap Patel, MD, opened with a troubling review of recent history: In 2015, when President Barack Obama unveiled the country’s Precision Medicine Initiative in a State of the Union address, some $200 million was directed through the National Institutes of Health (NIH) to facilitate data-sharing and bring together experts in oncology care for online discussions in topics of interest to payers and policy makers. Our first discussion, “Disparities in Cancer Care: Sources and Solutions,” took place March 22, 2021, with moderator Kashyap Patel, MD, chief executive officer of Carolina Blood and Cancer Care Associates, based in Rock Hill, South Carolina. Patel is the current president of the Community Oncology Alliance (COA) and associate editor of Evidence-Based Oncology™. Joining the discussion were Debra Patt, MD, PhD, MBA, an Austin-based breast cancer specialist with Texas Oncology who is secretary of COA; and Karen Winkfield, MD, PhD, a radiation oncologist who last year became executive director of the Meharry-Vanderbilt Alliance in Nashville, Tennessee.

A NEW INITIATIVE of The American Journal of Managed Care®, the Oncology Value Coalition, brings together experts in oncology care for online discussions in topics of interest to payers and policy makers. To address disparities in outcomes in topics of interest to payers and policy makers. To address disparities in outcomes in topics of interest to payers and policy makers.

Many Factors Involved, Including Medicaid

Debra Patt, MD, PhD, MBA, joined the discussion, adding that the issue of disparities in cancer is “multifactorial,” as it can cover not only race, ethnic, and cultural issues, but also gender identification. “Some issues are cultural and some are about trust. Some issues are socioeconomic and some are our exclusion criteria,” Patt said. As for challenges with accessing clinical trials, Patt recommended an approach similar to the one taken for getting past language barriers. “We need to figure out what’s right for the patient,” even if that means presenting the options using a doctor or nurse from the same background.

Winkfield said communication is key—everything from body language to the physician’s approach. She has a colleague in an oncology practice where the majority of the patients are Black, and 50% of her colleague’s patients are on a clinical trial. A clinical trial should be treated like other items of consent, she said. If it’s recommended an approach similar to the one taken for getting past language barriers. “We need to figure out what’s right for the patient,” even if that means presenting the options using a doctor or nurse from the same background.

Patt brought up a topic familiar to the whole panel: Medicaid access, or lack of it. Patel and Patt are based in states that have not expanded Medicaid, and Winkfield recently relocated from Wake Forest University in North Carolina, which is among them. Patt agreed that multiple factors, including biologic ones, contribute to disparities in health and cancer outcomes. Black patients are more likely to have aggressive breast and prostate cancer and multiple myeloma, while Hispanic populations are likely to have higher rates of cervical and hepatobiliary cancers. But as a physician in 1 of 12 the states that have not expanded Medicaid, she knows geography plays a role, too.

“We have a large portion of adult Texans who don’t have access to health care, period. And so, between ages 19 to 65, that’s about 25% of adults in Texas who don’t have access to insurance. We know in that patient population, that they’re 6 times more likely to present with advanced cancer, and they die more rapidly of their disease because they present with advanced cancer,” Patt said. “I think the access issue is a real hurdle that has to be overcome. We have to talk about it transparently, because it factors into this.”

“Those are certainly biologic reasons, and socioeconomic ones and cultural ones, and they are complicated,” she said. •
“But if you can’t pay for a mammogram, if you can’t pay for colon cancer screening, you know, the buck stops there.”

Later in the discussion, the panelists said missed screenings and deferred care due to COVID-19 will likely make disparities in cancer worse, both because of the need for social distancing and the loss of coverage.

Implications of Undersampling Minority Patients
Patel moved the conversation to an area that he has raised in recent commentary: If patients in minority groups have less access to care and are underrepresented in trials, then they are also underrepresented in genome-wide association studies that are used in drug development. According to a recent study, the degree to which they are underrepresented is astonishing: By 2017, of 35 million samples, 80% were of Northern European ancestry, even though this population is less than 10% of the population worldwide.5,6

“The there are great examples of community oncologists who are doing the good work of bringing clinical trials into people’s backyard to make it better for them...to make it more accessible....It’s been a long time coming.”

—Karen Winkfield, MD, PhD, executive director, Meharry-Vanderbilt Alliance

The implications for patients and for payers are significant. “What shocks me is that when you look into the personalized medicine, just biologically. I’m different than you, you’re different than Karen—we all are different biologically. So the starting point of the designer drug development process does not have information on who we are.” Patel said, further emphasizing the points Patt made on the differences in disease predisposition among patients. How can pharmacogenomic analysis be accurate with this kind of inequity?

“Precision medicine has widened the gap to the point that patients of minority [groups] may live [shorter lives] compared to those who are represented in the drug development process,” Patel said. “How do we address that?”

As a breast cancer specialist, Patt sees how this happens up close: If the payer doesn’t cover the test, the test doesn’t happen. In metastatic breast cancer, that’s a lot of missed opportunity. Communicating the need for a test can be more challenging if there are economic and cultural barriers. “Is policy actually a coverage determination policy?” she asked. “I think if we could change those things that it would help.”

Patel cited a recent court ruling in Hawaii against Bristol Myers Squibb and Sanofi, which were ordered to pay the state $834 million for failing to disclose for a decade that the drug Plavix was not effective in reducing the risk of heart attacks, strokes, and blood clots in patients of Asian and Pacific Islander descent.7

“This is a first—a milestone in what’s going to come for the industry if they do not wake up now,” he said.

Bringing Clinical Trials to People
Patel spoke of the need to bring clinical trials to underserved areas and involve community oncologists, the “boots on the ground,” not only to reduce travel times for rural patients, but also to reduce the level of intimidation some may feel in dealing with an academic center. Winkfield, who earlier in her career was a clinical fellow at Harvard, said there are equally impressive examples of trials close to patients who live far from academic centers.

“There are great examples of community oncologists who are doing the good work of bringing clinical trials right into people’s backyard to make it better for them...to make it more accessible,” Winkfield said. Institutions and national organizations should look for ways to support this work, and she agreed with Patt that “it’s been a long time coming.”

Patt, who manages breast cancer trials for Texas Oncology, said there’s considerable administrative work to bring them to the community level, but it’s worth it. “We have 70 to 80 clinical trials at any given time, and it’s a lot of sweat equity,” she said. “It’s IVs every week and a lot of administrative time and support. But I think it’s really meaningful that community oncologists need to have this as a priority.”

The doctors agreed that more digitization of the administrative work would ease that burden and make trials more cost-effective. Winkfield noted that a “silver lining” of coronavirus disease 2019 is that oncology practices have learned they can do some administrative steps remotely, such as consents.

Change in Washington
Is there opportunity for the Biden administration to expand Medicaid access to more patients, or can more be done to help oncology practices reduce disparities? The most obvious recent step is the new round of incentives in the American Rescue Plan of 2021 for the 12 states that have not expanded Medicaid. The panel discussed “carrots” and “sticks” that can be used in the drug approval process if manufacturers are not doing enough to enroll minority patients, and Winkfield noted the recent spate of withdrawn indications in lung and bladder cancer as a sign that FDA is enforcing requirements.8,9

Reducing disparities in cancer care has been a major agenda item for every major cancer group in the past year. Patel noted that the second part of the 21st Century Cures Act features an inclusivity mandate—meaning that drugs cannot be approved until they treat diverse populations. It will be up to the research community to help hold the pharmaceutical industry’s feet to the fire, Patel said.

He repeated the well-known quote from President Ronald Reagan, “When you can’t make them see the light, make them feel the heat.”

REFERENCES
**Geisinger’s “Soft Demo” Proves Key for a Successful Clinical Pathways Rollout**

**CLINICAL PATHWAYS IN CANCER CARE** are beyond the “new” phase, but oncology practices and health systems are still learning all the ways they can bring greater standardization to care, eliminate unnecessary care, improve data collection, and drive value.

That’s what Mark Wojtowicz, MS, MBA, the administrative director for Oncology Research and Innovation at Geisinger Cancer Institute, Danville, Pennsylvania, shared during a session of the 47th Annual Meeting & Cancer Center Business Summit Association of Community Cancer Centers (ACCC), held March 1 to 5, 2021.

Geisinger implemented Elsevier’s ClinicalPath in medical and radiation oncology in April 2019, starting with a “soft demo” and a weeklong training process. The pathways product was rolled out at all sites a month later. The health system decided to integrate ClinicalPath into its Epic electronic health record (EHR) management system, because incorporation into the workflow was seen as critical to getting physicians to adopt pathways.

Pharmacists oversaw a process in which the pathway regimen library was “harmonized” with Epic, to systematically update new workflows in hematology and oncology. This was a key process, because Geisinger actively takes part in clinical trials.

“**We know that clinical pathways will oftentimes not cover every single scenario that’s out there, or every decision that an oncologist needs to make. So, you have to be able to map that out.**”

—Mark Wojtowicz, MS, MBA, administrative director, Oncology Research and Innovation, Geisinger Cancer Institute

"Accruing to clinical trials is an important part of what we do, and we know that it means a great deal that our clinicians have clinical trial information at that decision-making point," Wojtowicz said. To have all options available when clinicians were talking to patients, "we wanted to implement across all these specialties, and we wanted to do it as rapidly as possible."

"A lot of the credit goes to the team that really made that happen," he said. The soft demo was key, Wojtowicz said. "Everybody was at the starting line, the tool was actually launched; it just wasn't promoted to the broad practice in the right fashion, and merging it back with some of our clinical data to make the data, to add clicks to their day, Wojtowicz said. Adoption rates have been good, and the process continues to improve.

During this period, the physician champions worked with the pathways to achieve buy-in among the others—and allow time for adjustments and integrating with other workflows. A month later the new program was ready to go live. Over a week, the pathways team met with clinicians and let them try the pathways system to give them opportunities for training and practice.

Wojtowicz shared a decision-tree slide that showed each step, starting with whether a diagnosis was or was not on a pathway. The mapping system was critical, he said.

“We know that clinical pathways oftentimes will not cover every single scenario that’s out there, or every decision that an oncologist needs to make. So, you have to be able to map that out—what’s that pathway look like? Or, what do those workflows look like when it’s a nonpathway related decision versus pathway related.”

This “visualization” process allowed the team, and by extension, physicians, the chance to think through what the workflow would look like and helped with implementation.

Integrating workflows in medical oncology with the EHR definitely presented some challenges, but physicians were determined to have one way to interact with the system. In the beginning, extra information had to be tailored and removed. “And that did require that [for] some regimens they had to be different, and we had to build new ones. But I think that was a worthwhile exercise, because everyone required consensus, discussion, and agreement around that direction.”

The final step was to ensure that the pathways were multidisciplinary—that physicians could work with a system that would allow transparency between medical and radiation oncology so that treatment options could be presented together to patients. "What worked for us was that the system allowed for this transfer of data," so if a decision was made in medical oncology, it was shared with radiation oncology.

“That was a huge thing as far as workflow goes, because we really had to be prepared to have not only the individual clinician be able to handle the workflow, but then you kind of get to that next level where its, “How about the multidisciplinary workflow?” he said. “You’ve got to make it simpler for, for those things to happen.”

The next step is to make use of new data on the pathway system that allows artificial intelligence to use predictive analytics to inform decision makers in the practice.

“It doesn’t really stop there,” he said. More value will come from investments health systems are making in predictive analytics. "We started bringing our clinical pathways decision data to the discrete elements that come out of that decision, we started bringing that into data tables, and linking it back with our clinical information to gain better insights about when decisions were made, and what’s happening after that.” This allows clinicians to decide what care plans should look like and how much monitoring should occur.

Geisinger also opted to include prognostic questions. Tough as it is, physicians are asked if they would be surprised if the patient were to die in the next year. The answer helps drive more palliative care referrals.

The health system is cognizant that it is asking doctors to take time to gather data, to add clicks to their day, Wojtowicz said. Adoption rates have been good, and the process continues to improve.

From the health system’s perspective, “they’re extracting data in discrete fashion, and merging it back with some of our clinical data to make the most out of it.”

**Integrating Remote Symptom Management With ePROs in Cancer Care**

**BOTH CANCER AND ITS TREATMENTS** are highly symptomatic, making it difficult at times for clinicians to closely monitor every symptom a patient experiences outside of the office walls. But advances in technology are making it easier to use patient-reported outcomes (PROs) as a tool for remote symptom management (RSM). A presentation at the ACCC 47th Annual Meeting & Cancer Center Business Summit titled “The Role of Remote Cancer Symptom Management in an Evolving Reimbursement Landscape” gave virtual attendees an overview of the latest research on PROs and how RSM can be incorporated into an oncology practice.

The discussion began with a presentation from Ethan Basch, MD, MSc, director of the Cancer Outcomes Research Program at University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, chief of the Division of Oncology and physician-in-chief at N.C. Cancer Hospital, and professor of health policy and management at the UNC Gillings School of Global Public Health. The panel also included Nadia Sill, DNP, RN, senior director of client services at Carevive Systems, Inc; Madelyn Trupkin Herzfeld, co-founder and vice chair of Carevive; and Bruno Lempnerres, chief executive officer of Carevive.
“A mainstay of quality cancer care is symptom management. It’s core to what we do because cancer is so symptomatic, and our treatments are highly symptomatic, as well,” said Basch. “And early in my career, I began to observe that, unfortunately, we often miss symptoms that patients may be experiencing that emerge later on. We realized that really, they were presenting themselves much earlier—but they evaded our notice.”

This realization led him and his research group to conduct early studies on whether utilizing PROs and clinician reporting simultaneously would reveal gaps in reported symptoms. They found that there were significant differences between the incidence of symptoms reported by patients vs clinicians, with symptoms underreported by clinicians compared with PROs. “This is a missed opportunity to catch symptoms early to intervene and to improve the patient experience and potentially to avoid downstream complications,” Basch said.

Basch highlighted electronic patient-reported outcome (ePRO) systems as one way to implement patient reporting and symptom management. Patients self-report symptoms with the system, whether through a web interface, smartphone, or an automated telephone questionnaire. He noted that a traditional telephone system is most accessible to patients, especially in community practices and rural areas. The system can automatically reply with information on how to self-manage the symptoms while conveying the information to providers and electronic health records.

Providing multiple interface options for patients and preset reminders for them to input their surveys are 2 key best practices that can help ensure adherence on the patients’ end, Basch said.

One randomized controlled trial from Basch’s research group found that compared to standard care, patients utilizing ePRO were 7% less likely to visit the emergency department. Median survival was also 5.2 months longer among patients in the self-reporting arm of the study.

“In this study and in other studies, patients have been able to stay on chemotherapy longer when using this kind of ePRO intervention,” Basch added. Better quality of life and functionality was also seen in those patients.

Basch noted that patients have generally reported satisfaction with ePRO systems, and so have nurses. He cautioned that it does increase upfront work for nurses but will save work down the line if fewer patients have hospital visits thanks to the systems. Therefore, workflow accommodation should be planned, and clinics must be prepared ahead of beginning to utilize ePROs.

Introducing patients to ePRO systems can be quick, Still explained during her presentation. In the case of Caregiver PROOnpt, for example, a physician could introduce the concept to patients before a nonclinical role such as a patient navigator explains the system to the patient in more depth. By the next week, patients should be comfortable completing weekly surveys from home. Based on their survey responses, the system responds with a self-management plan that includes evidence-based methods to manage their symptoms. Where provider notifications are concerned, practitioners can set the threshold to avoid being bogged down with alerts.

Herzfeld discussed reimbursement, highlighting reimbursement codes that were created specifically to address the boom in telehealth over the pandemic. Some examples she provided were codes for e-visits, which are set up by providers to address situations where a clinic visit is not necessary; codes for virtual check-ins initiated by the patient; the Principal Care Management code, which is for comprehensive care management for a single, high-risk disease lasting more than 3 months; and reimbursement for remote monitoring with an FDA-approved device such as a fitness tracker.

RSM is something that may be included as a required enhanced patient service in the upcoming Oncology Care First model, which is expected to begin in June 2022. Herzfeld pointed out. For physicians who plan on participating, it would be a good idea to become accustomed to utilizing ePROs beforehand, she said.

Finally, Lemplennes touched on the importance of patient experience data (PED), which include disease symptoms, the impact on quality of life, experience with treatments, input on the outcomes most important to them, and the relative importance of any given issue to each patient. Use of ePROs provides a full picture of the patient experience, he said.

“So if we look at the implications for the future of cancer care with these data, what do we see? Well, today there’s already several applications and benefits to using this kind of data in cancer care,” Lemplennes said. “These data empower patients as an active stakeholder, with more engagement in their treatment and disease. From the clinician standpoint, the use of data and patient-reported outcomes improves patient-provider communication, informs treatment and symptom pathways, increases vigilance and real-time actions with alerts, and finally, supports personalized care.”

REFERENCE

Better Phone Call Triage Leads to Faster Decision-Making

TEXAS ONCOLOGY’S QUEST TO reduce hospitalizations and emergency department (ED) visits through value-based care started with a single question: can we do a better job with patient phone calls?

Lalan Wilfong, MD, executive vice president of Value-Based Care and Quality Programs, described Texas Oncology’s challenge during the 47th Annual Meeting & Cancer Center Business Summit Association of Community Cancer Centers. Five years ago, when the 200-site community oncology network decided to take part in CMS’ Oncology Care Model, it had to step back and look at areas where patient experience fell short.

A top complaint: when patients called during business hours, it took too long for someone to get back to them. Patients would leave voicemails, and there was no system to track who picked up the voicemail or when.

“We didn’t have any insight at all about that,” Wilfong said. “What are nurses doing during the day? How are we holding them accountable for callback times?”

Studies were also showing the benefits of electronic patient reported outcomes, or ePROs. Texas Oncology physicians asked they could incorporate these new findings into patient care. “How can we understand patients who are calling in with symptoms, and how do we make sure we’re responding appropriately?” Wilfong asked.

The idea was to create operational efficiency to improve triage, better manage patient symptoms, and reduce ED visits and hospitalizations. In July 2019, Texas Oncology selected the Navigating Cancer management solution system to help the network cut down the time it takes to resolve patient phone calls while also collecting feedback.

Launching the system required Texas Oncology physicians to study how patient calling patterns, whether they spoke with a nurse, and what kind of training that person had received. Doctors examined call volume levels at different sites across the network. The result, Wilfong said, is a new system with the following steps:

- Patients report symptoms to a centralized system operator
- The operator manually adds the patient’s report to the triage workboard
- A triage nurse provides symptom management and resolves remotely, with instructions sent directly to the patient.

Wilfong said the new system has cut down incident resolution time by 33%. The Navigating Cancer pathways are a key step in the process, he said. The operator who takes patient calls uses them to log information into the dashboard, and, ultimately, to send care instructions home to the patient.

The improved resolution time has happened despite a 25% uptick in call volume in the second half of 2020, most of which is due to COVID-19. “Our nurses are becoming faster at taking care of patients,” he said. “What’s really impressive is that 60% of these incidents are resolved in less than an hour, which is fantastic. We’re having better, more proactive, timely symptom management with this process.”

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Sustained MRD Negativity Is Predictive of Long-term Outcomes in RRMM

SUSTAINED MINIMAL RESIDUAL DISEASE (MRD) negativity may predict long-term outcomes in relapsed/refractory multiple myeloma (RRMM), according to a recent analysis of the POLLUX and CASTOR studies. In addition, daratumumab-based combinations led to higher rates of sustained MRD negativity compared with the standard of care.

Although patients with MM have had improved response rates due to combination therapies in recent years, the majority relapse and must undergo further therapy. The authors of the new study, published in the *Journal of Clinical Oncology*, assessed sustained MRD negativity and patient outcomes based on data from POLLUX and CASTOR, which represent the largest set of MRD data collected from RRMM patients.

The phase 3 POLLUX study compared daratumumab, lenalidomide, and dexamethasone (D-Rd) with lenalidomide and dexamethasone (Rd) in RRMM. CASTOR, also a phase 3 study, compared daratumumab, bortezomib, and dexamethasone (D-Vd) with bortezomib and dexamethasone (Vd) in RRMM. Overall, 569 patients in POLLUX and 498 in CASTOR were included in the new analysis.

Both studies assessed MRD, a known sensitive measure of disease control, with next-generation sequencing based on the International Myeloma Working Group guidelines, which recommend a sensitivity threshold of $10^{-5}$ (1 tumor cell in 100,000). Patients were assessed at numerous time points: at suspected complete response (CR); at 3 and 6 months after confirmed CR in the POLLUX study; at 6 and 12 months after the first dose in the CASTOR study; and every 12 months following CR in both studies.

The combined analysis included 537 patients on daratumumab-containing regimens and 530 patients given the standard of care (Rd or Vd). Researchers assessed MRD in both the intention-to-treat (ITT) population and in patients who achieved CR or better. Sustained MRD negativity of at least at least 6 months in the ITT population and at least 12 months in the CR population. Median follow-up was 54.8 months in POLLUX and 50.2 months in CASTOR.

For POLLUX, MRD negativity rates in the ITT population were 32.5% in the D-Rd group and 6.7% in the Rd cohort. Patients who achieved CR or better had higher MRD rates, with 57.4% of those patients on the D-Rd regimen and 29.2% on the Rd regimen showing MRD negativity ($P = .0001$). In the CASTOR study, MRD negativity rates in the ITT population were 15.1% in the D-Vd group vs 1.6% in the Vd group. In the CR-or-better population, 52.8% of patients on the D-Vd regimen and 17.4% on the Vd regimen achieved MRD negativity ($P = .0035$).

In both studies, the daratumumab combination treatment saw higher percentages of patients in the ITT and CR-or-better cohorts achieve sustained MRD negativity compared with those receiving the standard of care. In the D-Rd group in POLLUX, 20.3% of patients achieved sustained MRD negativity of at least 6 months vs 2.1% in the Rd cohort ($P < .0001$). At 12 or more months, combination-group patients still had higher rates of sustained negativity (16.1% vs 1.4%; $P < .0001$).

In CASTOR, the D-Vd and Vd groups achieved 6 months or longer sustained MRD negativity at rates of 18.4% and 1.2%, respectively ($P < .0001$). More D-Vd patients also achieved sustained MRD negativity for 12 or more months (6.8%) compared with Vd patients (0%).

MRD negativity was also associated with longer progression-free survival (PFS). In patients who achieved sustained MRD negativity for 6 or more months, PFS was prolonged in both studies, regardless of treatment arm. Patients who achieved sustained MRD negativity for 12 or more months on a daratumumab combination regimen also had longer PFS compared with those who were MRD positive. Overall survival data will be assessed at the end of both studies.

"Achieving durable MRD negativity may predict long-term outcomes, as durable MRD negativity improves PFS and increases the time between treatment relapses for RRMM," the authors wrote. "This supports the concept that sustained MRD negativity may serve as a surrogate end point for PFS in ongoing and future clinical trials."

The authors point out that although findings suggest that MRD monitoring may be predictive of long-term outcomes in RRMM, there is no consensus on how or when to use it. "Prospectively gathered clinical data will be useful in developing future paradigms for MRD analysis as a clinical practice decision tool," they wrote. ●

**REFERENCE**

Cosela Is Approved for Protection Against Myelosuppression From SCLC Treatment

THE FDA APPROVED TRILACICLIB (Cosela; G1 Therapeutics) to be used as a protective agent against bone marrow loss among adults before chemotherapy regimens that contain a platinum agent/etoposide or topotecan for extensive-stage small cell lung cancer (SCLC). This is the first and only such approval for a cyclin-dependent kinase 4/6 inhibitor.

"Bone marrow loss and myelosuppression are well-documented adverse effects (AEs) of chemotherapy, which leave the immune system without some of its most potent fighters: red blood cells, which contain hemoglobin; white blood cells, which help to fight infection; and platelets, which assist in clotting. These losses, in turn, can cause fatigue and increase risk of infection, bleeding, anemia, and thrombocytopenia.

Previous treatments that address bone marrow injury have only attempted to remedy it after the fact. "To date, approaches have included the use of growth factor agents to accelerate blood cell recovery after the bone marrow injury has occurred, along with antibiotics and transfusions as needed," stated Jeffrey Crawford, MD, George Barth Geller Distinguished Professor for Research in Cancer in the Department of Medicine, Duke University School of Medicine, and a member of the Duke Cancer Institute, in G1 Therapeutics’ news release. "By contrast, trilaciclib provides the first proactive approach to myelosuppression through a unique mechanism of action that helps protect the bone marrow from damage by chemotherapy."

G1 Therapeutics’ application was backed by data from 3 double-blind, placebo-controlled studies of 245 patients randomized to intravenous (IV) trilaciclib or placebo, with dual primary outcomes of severe neutropenia and its length during the first chemotherapy cycle. The effectiveness of trilaciclib plus carboplatin/etoposide (with or without atezolizumab) or topotecan was evaluated in these trials. Severe neutropenia was a less likely outcome, and lasted for a shorter time among those for whom it did occur, following treatment with trilaciclib. These findings were deemed clinically meaningful and statistically significant.

Most common AEs (≥10%) of the treatment are fatigue, headache, high asparagine transferase levels, pneumonia, and low calcium, potassium, and phosphate levels. Injection-site reactions, acute drug hypersensitivity, intestinal lung disease/pneumonitis, and embryo-fetal toxicity are also possible.

Serious AEs that occurred (≥3%) were respiratory failure, hemorrhage, and thrombosis; fatal AEs were seen in 5% (pneumonia; 2% respiratory failure; 2% acute respiratory failure; <1% hemoptysis; <1% cerebrovascular accident, <1%); and 9% permanently discontinued the preventive measure for reasons that included anemia, ischemic stroke, and myositis.

"For patients with extensive-stage SCLC, protecting bone marrow function may help make their chemotherapy safer and allow them to complete their course of treatment on time and according to plan," said Albert Deisseroth, MD, PhD, supervisory medical officer in the Division of Non-Malignant Hematology in the FDA’s Center for Drug Evaluation and Research, in a statement from
the FDA. “Cosela will give patients a treatment option that can reduce the occurrence of a common, harmful [adverse] effect of chemotherapy.”

Cosela received a Breakthrough Therapy designation in 2019 and a Priority Review in 2020; a postapproval clinical trial is currently scheduled for 2022. The treatment is administered as a 30-minute IV infusion within 4 hours of the start of chemotherapy.

REFERENCE

Combination Treatment Maintains Quality of Life in Relapsed/Refractory MM

RESULTS FROM PATIENT REPORTS indicate that health-related quality of life (HRQOL) was maintained when treating relapsed/refractory multiple myeloma (RRMM) with daratumumab (Darzalex) in combination with bortezomib (Velcade) and dexamethasone, according to a new study.

Previously reported results from the phase 3 CASTOR trial had demonstrated that adding daratumumab to the combination of bortezomib and dexamethasone extended progression-free survival when compared with the use of the chemotherapy and steroid alone. The additional data on patient-reported outcomes (PROs) from the CASTOR trial, published this month in the British Journal of Haematology, amplify the clinical findings on the benefits of the 3-drug combination.

Daratumumab is an anti-CD38 monoclonal antibody with a direct on-tumor and immunomodulatory mechanism of action. Patients in the group taking daratumumab, bortezomib, and dexamethasone (D-Vd group) reported similar HRQOL changes from baseline in comparison with those taking only bortezomib and dexamethasone (Vd group). Patients received 8 cycles of treatment for the comparative study.

Patients in both groups indicated they experienced long-term improvements in quality of health and pain levels. A total of 498 patients with RRMM participated. The researchers explained that they conducted the study because, first, treatment of MM is recommended for an undetermined amount of time (until the disease progresses), and second, the introduction of novel agents has extended progression-free survival. The study was also intended to provide clinicians with further insight into treating older patients who may have comorbidities such as diabetes or cardiovascular disease.

Study results showed no clinically meaningful changes from baseline in PROs through the 8 cycles. Some patients in the Vd group saw clinically significant improvements in fatigue, pain, or sleep disturbance, but the mean changes for each group were not clinically meaningful.

The authors suggested that the lack of significant differences between the 2 groups may have been due to the benefit of bortezomib treatment, leaving little room for improvement from the daratumumab.

Reports continued to be collected from the D-Vd group for a maximum of 49 weeks. Improvement in QOL and pain continued past the eighth cycle. The authors speculated that those findings may have been due to a change in patients’ expectations after prolonged experience with RRMM. Less frequent visits to the clinic might have improved mood as well. Other possible reasons for the improvement included organ and skeletal recovery, which can lag behind other clinical responses; reduced toxicity from halting dexamethasone; and the fact that adverse effects from daratumumab, unlike those of bortezomib, aren’t cumulative and stay steady over time.

PROs were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) and the EuroQol 5-dimensional descriptive system questionnaire (EQ-5D-5L). The EORTC QLQ-C30 is a cancer-specific questionnaire with 30 items on 5 functional scales (physical, role, emotional, cognitive, and social). The EQ-5D-5L is a generic measure of health status assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. An additional scale rated “health today.”

REFERENCE

Study Explores Costs Linked With Adverse Events in Mantle Cell Lymphoma

A STUDY EXAMINING THE ECONOMIC burden of mantle cell lymphoma (MCL) treatment found that hypertension, anemia, and infection were the most common adverse events (AEs), while the costliest AEs were hepatotoxicity, stroke, and renal failure.

The retrospective study, using data from the Optum Research Database and the Social Security Administration, examined the financial implications of the rare form of non-Hodgkin lymphoma, also found that the most common therapy by far for MCL was the combination of the chemotherapy drug bendamustine and the biologic rituximab (Rituxan).

The authors said the study was undertaken in part because the real-world data available on MCL have been limited, with the number of novel agents arriving on the scene affecting researchers’ ability to keep up with developments. In one other recent study, the data were slightly older; in another, the patients included did not represent an older cohort.

“This study shows that AEs are common during treatment, and [they are] expensive,” the authors wrote in the February issue of Anticancer Research. “Therefore, as new treatments and combinations are being developed and recommended, there must also be focus on management of AEs to achieve the best outcomes for patients.”

AEs and health care costs were significant overall, varying by treatment regimen. Anemia was the only AE that appeared on lists of most frequent AEs and costliest ones: It was the second-most frequent AE, and the fifth costliest, according to the study.

Hypertension (40.5%) was the most commonly developed AE in treatment of MCL, followed by anemia (37.7%), infection (36.1%), neutropenia (36.1%), and thrombocytopenia (13.4%).

Due largely to inpatient care, hepatotoxicity ($19,645) had the highest cost per patient per month (PPPM), followed by stroke ($18,893), renal failure ($9037), atrial fibrillation ($5751), and anemia ($5597), according to the study results. Inpatient costs for nonhematologic AEs were higher than previous studies had indicated.

The study used data from 395 patients (69% male) with a median age of 72 years; 69% were enrolled in Medicare Advantage plans. The data were for patients with multiple claims for MCL whose initial claim was submitted between July 2012 and May 2017.

Chemoimmunotherapy remained the most common treatment regimen throughout the study period. Ibrutinib (Imbruvica) was the most common treatment for patients in their second or third line of therapy.

Patients started therapy a mean of 72 days after diagnosis. Nearly all (95%) underwent systemic therapy within the first year.

The most common regimens administered at initiation of the patient follow-up period (at least 1 month after the initial claim) were bendamustine HCl/rituximab (52%); cyclophosphamide, doxorubicin, vincristine, and rituximab with or without prednisone (R-CHOP; 13%); and ibrutinib (3%).

The majority received rituximab (92%) during the study period either alone or in combination with other drugs. The next most common agents, used in
either alone or in combination, were bendamustine (62%), cyclophosphamide (26%), vincristine (26%), doxorubicin (22%), ifosfamide (17%), and bortezomib (Velcade; 11%).

The study was funded by AstraZeneca and written in cooperation with Optum.

**REFERENCE**

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**Assessing Health Care Policy Reform at the Federal and State Levels**

**IN ADDITION TO CORONAVIRUS DISEASE 2019 (COVID-19), several other factors will play a major role in health care policy reform for federal and state-level health officials this year, including the transition to value-based care and containment of high health care costs.**

Bill Kramer, executive director for health policy at the Pacific Business Group on Health (PBGH), provides his insight into federal and state-level health care reform.

**EVIDENCE-BASED ONCOLOGY (EBO):** Can you tell us about yourself and your work?

**KRAMER:** I’m the executive director for health policy at PBGH, which is a consortium of large employers, a not-for-profit organization that’s committed to improving quality, cost, and equity for health care across the United States.

“There are significant opportunities to work with a Biden-Harris administration on health care policy. The number-1 priority, of course, will be to deal with the COVID-19 pandemic. That’s essential for the health of our country and for our economy, but beyond that, there are a number of opportunities.”

—Bill Kramer, executive director for health policy at the Pacific Business Group on Health

**EBO:** As 2020 saw a rise in virtual care and telehealth services amid the pandemic, as well as a greater focus on mental health and social determinants of health, what goals or objectives will have notable influence on employer action in 2021? Will it be more of the same?

**KRAMER:** COVID-19 has had a tremendous impact, of course, on our entire health care system. One of those [impacts] has been the acceleration of some long-overdue changes in health care. A perfect example of this is the rapid transition to telehealth and other kinds of virtual care.

That’s been long overdue: The technology has been available, and now it’s being put into place to the benefit of patients and physicians and hospitals. But other issues need to be addressed going forward, in addition to, of course, dealing with the COVID-19 pandemic.

Costs continue to be a serious problem for employers and, of course, for their employees and their families who receive benefits through their employers. Costs are through the roof—they continue to be an enormous burden, not only on businesses, but on employees because they also crowd out [increases in] wages. High health care costs have led to a flattening of wage growth over the past 20 years. We need to find ways to contain the cost of health care across the United States in order to strengthen wage and business growth.

Something else we need to do going forward is to strengthen primary care. Primary care has been hit really hard during the COVID-19 crisis, particularly independent primary care practices that were perhaps financially vulnerable, particularly those independent practices that relied a lot on fee-for-service (FFS) revenue.

Now, some steps have been taken to shore up [those practices], but that’s still a very fragile part of our health care delivery system. You need to find ways to preserve primary care, but more importantly, to strengthen it, make it more resilient. It is the foundation of a high-quality, affordable, accountable health care system.

**EBO:** What significance will the transition to the Biden administration have for employers in 2021? And what will be the impact of the shift to a Democratic majority in the Senate?

**KRAMER:** There are significant opportunities to work with a Biden-Harris administration on health care policy. The number-1 priority, of course, will be to deal with the COVID-19 pandemic. That’s essential for the health of our country and for our economy, but beyond that, there are a number of opportunities.

One is payment reform. Again, this is one of these long-overdue reforms that’s been needed for a long time. [Reform should] move us away from FFS payment, and toward more value-based payment where physicians, hospitals, and other clinicians are paid for the quality of care that they provide for improving the health of their patients.

We believe we can work with the new administration to not only develop these kinds of payment reforms, but also implement them more widely. Along with that, there needs to be an emphasis on accountability. Accountability comes through ensuring that patients are getting the care they need and are getting the necessary health outcomes. To do that, we need to have good transparency and good performance measurement. Again, employers are looking forward to working with the Biden administration on stronger performance measures and on accountability tied to payment reforms.

Last, but not least, there needs to be a way to contain health care costs more broadly—not just in Medicare, but throughout the health care system. A main reason for high health care costs has been high prices, not just high utilization, and in many markets, these high prices are driven by dominant health care systems. We need to find a way to either restore competition through stronger antitrust enforcement or by prohibition on anticompetitive practices; also, where necessary, we [should] limit the prices that can be charged by these dominant health care providers.

**EBO:** Beyond the federal level, should employers be monitoring any state-level changes to health care policy?

**KRAMER:** Yes, many opportunities exist at the state level. Again, the states will also need to make COVID-19 their first priority, but beyond that, there are many promising initiatives.

Many states have launched or are considering health care cost containment commissions. Massachusetts was one of the first, California also has a proposal,1,2 Oregon has been developing one—many states have been doing this. Many of them have actually set targets and are monitoring health care costs, looking at the underlying reasons that have been driving up prices, and setting targets to ensure that costs don’t exceed a certain limit.

In addition, to strengthen markets, some states, like California, have taken steps to strengthen antitrust enforcement. A really good example of this is what was done to deal with the problem of Sutter Health Care System in northern California.3 As you probably know, an antitrust suit was launched; it was originally a class action suit led by a labor trust fund and then it was joined by the California attorney general. That suit will be settled and formalized shortly, and it points not only to a problem, but to a solution. If we can strengthen antitrust enforcement and make markets work better, we can bring these costs under control.

Finally, other things that states can be doing—and many are already doing—include development of all-payer claims databases, so we have a clearer picture...
of what costs are being charged, and [creating] initiatives to shore up and strengthen primary care infrastructure. •

REFERENCES


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### Athenex Receives CRL on Oral Paclitaxel Plus Encequidar for Treatment of Metastatic Breast Cancer

**FDA HAS SENT ATHENEKX, INC,** a complete response letter (CRL) regarding the company’s new drug application (NDA) for oral paclitaxel plus encequidar for the treatment of metastatic breast cancer. The company announced the CRL in early March and issued a statement along with other developments as part of its financial update for 2020.1

Regulators called for a new “adequate and well-conducted clinical trial,” marking an about-face from the course Athenex seemed to be on when the company’s NDA was accepted for priority review in September 2020. The targeted action date was February 28, 2021.

FDA cited concerns about the risk to patients of increased neutropenia-related adverse events in the oral paclitaxel arm compared with the intravenous (IV) paclitaxel arm. Regulators also said they were concerned about the uncertainty over results of the primary end point of the objective response rate (ORR) at week 19 conducted by a blinded independent central review (BICR).2

In its statement, Athenex said, “The agency stated that the BICR reconciliation and re-read process may have introduced unmeasured bias and influence on the BICR.”

Athenex officials expressed their surprise at the turn of events and said they would request a meeting with FDA to discuss the response and a plan to move forward.

“Our clinical and regulatory teams are disappointed by the complete response letter,” Rudolf Kwan, MD, chief medical officer of Athenex, said in the statement. “We plan to work with the agency to resolve the issues raised in the CRL and to obtain approval for oral paclitaxel plus encequidar in metastatic breast cancer.”

The application was supported by data from a phase 3 trial that showed oral paclitaxel plus encequidar improved ORR compared with IV paclitaxel in patients with metastatic breast cancer; the ORR for the study drug was 36% compared with 24% for the control arm.3 Duration of response among those who responded to treatment was long as well, at 150 days or 2.5 times longer in those given oral paclitaxel with encequidar compared with IV paclitaxel.

Rates of neutropenia were comparable between the 2 arms, but more patients who took the study drug had grade 4 neutropenia and were more likely to have gastrointestinal adverse effects.

During the conference call, Athenex officials said the issue was whether the study population was representative of a US population also came up during the review process. The study arm of patients taking the combination drug was 90% Hispanic, 1% Black, and 7% White. According to the US Census Bureau, the nation’s population is 18.5% Hispanic, 13.4% Black, and 60% White.

Johnson Lau, MBBS, MD, FRCPath, CEO of Athenex, said, “We remain committed to the breast cancer community and will explore the best path forward to obtain regulatory approval. In the interim, we will identify and undertake the appropriate internal organizational adjustments accordingly.”•

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### REFERENCES


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 at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1 blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to ensure safe use of PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Visit LIBTAYOhcp.com for more information.
Important Safety Information (cont’d)

Warnings and Precautions¹ (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

No dose reduction for LIBTAYO is recommended. In general, withhold LIBTAYO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated adverse reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Immune-mediated pneumonitis: LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.7% (22/591) of patients receiving LIBTAYO, including fatal (0.3%), Grade 4 (0.3%), Grade 3 (1.0%), and Grade 2 (1.9%). Pneumonitis led to permanent discontinuation in 1.9% of patients and withholding of LIBTAYO in 1.9% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 59% of the 22 patients. Of the 11 patients in whom LIBTAYO was withheld, 7 reinitiated after symptom improvement; of these 1/7 (14%) had recurrence of pneumonitis. 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. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.2% (7/591) of patients receiving LIBTAYO, including Grade 3 (0.3%) and Grade 2 (0.7%). Colitis led to permanent discontinuation in 0.2% of patients and withholding of LIBTAYO in 0.7% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 71% of the 7 patients. Of the 4 patients in whom LIBTAYO was withheld, none reinitiated LIBTAYO. 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. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 1.9% (11/591) of patients receiving LIBTAYO, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (1.5%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.8% of patients and withholding of LIBTAYO in 0.8% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 9% (1/11) of these patients. Hepatitis resolved in 64% of the 11 patients. Of the 5 patients in whom LIBTAYO was withheld, none reinitiated LIBTAYO.

For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases in patients with tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated endocrinopathies: For Grade 3 or 4 endocrinopathies, withhold until clinically stable or permanently discontinue depending on severity.

• Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.5% (3/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.3%). No patient discontinued or withheld LIBTAYO due to adrenal insufficiency.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.
Important Safety Information (cont’d)

Warnings and Precautions1 (cont’d)

Severe and Fatal Immune-Mediated Adverse Reactions (cont’d)

Immune-mediated endocrinopathies: (cont’d)

- **Hypophysitis**: LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.2% (1/591) of patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis

- **Thyroid disorders**: LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hypothyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity

- **Thyroiditis**: A single case of Grade 1 thyroiditis was observed in 591 patients receiving LIBTAYO in clinical trials.

- **Hyperthyroidism**: Hyperthyroidism occurred in 1.9% (11/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.5%). No patient discontinued treatment and LIBTAYO was withheld in 0.3% of patients due to hyperthyroidism. Systemic corticosteroids were required in 9% (1/11) of patients. Hyperthyroidism resolved in 46% of 11 patients

- **Hypothyroidism**: Hypothyroidism occurred in 7% (42/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (6%). No patient discontinued treatment and LIBTAYO was withheld in 0.3% of patients due to hypothyroidism. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 7% of the 42 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 2 patients in whom LIBTAYO was withheld for hypothyroidism, both reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy; the other did not experience recurrence of hypothyroidism

- **Type 1 diabetes mellitus, which can present with diabetic ketoacidosis**: Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.7% (4/591) of patients, including Grade 4 (0.5%) and Grade 3 (0.2%). Type 1 diabetes mellitus led to permanent discontinuation in 0.2% of patients and withholding of LIBTAYO in 0.3% of patients. Of the 2 patients in whom LIBTAYO was withheld, both reinitiated LIBTAYO and required insulin treatment

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.5% (3/591) of patients receiving LIBTAYO, including Grade 3 (0.3%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation in 0.2% of patients and withholding of LIBTAYO in 0.3% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in all 3 patients. Of the 2 patients in whom LIBTAYO was withheld, none reinitiated LIBTAYO. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 2.0% (12/591) of patients receiving LIBTAYO, including Grade 3 (1.0%) and Grade 2 (0.8%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.3% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 42% of the 12 patients. Of the 8 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 5 reinitiated LIBTAYO after symptom improvement; of these 60% (3/5) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 591 patients who received LIBTAYO 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.

- **Cardiac/Vascular**: Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis

- **Nervous System**: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids

- **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 steroids to reduce the risk of permanent vision loss.

- **Gastrointestinal**: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- **Musculoskeletal and connective tissue**: Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **Endocrine**: Hypoparathyroidism
- **Other (Hematologic/Immune)**: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, 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.

### Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

### 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

- **In Study 1423 and Study 1540**: Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in ≥2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia. LIBTAYO was permanently discontinued due to adverse reactions in 8% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, proctitis, and confusional state. The most common adverse reactions (incidence ≥20%) were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia. The most common (≥4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyponatremia, and hypophosphatemia

- **In Study 1620**: Serious adverse events occurred in 32% of patients. Serious adverse reactions that occurred in >1.5% (at least 2 patients) were urinary tract infection, colitis, acute kidney injury, adrenal insufficiency, anemia, infected neoplasm, and somnolence. Fatal adverse reactions occurred in 1.5% of patients who received LIBTAYO, including acute kidney injury and cachexia. Permanent discontinuation of LIBTAYO due to an adverse reaction occurred in 13% of patients. Adverse reactions resulting in permanent discontinuation of LIBTAYO in >1.5% (at least 2 patients) were colitis and general physical health deterioration. Dosage delays of LIBTAYO due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage delay in >2% of patients (at least 3 patients) included blood creatinine increased, diarrhea, colitis, fatigue, headache, pneumonitis, and urinary tract infection. The most common adverse reactions reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection. The most common Grade 3 or 4 adverse reactions (>2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hypokalemia and visual impairment. The most common (>3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia

### Use in specific populations

- **Lactation**: Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential**: Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

Please see Brief Summary of Prescribing Information on the following pages.
Immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

### Immune-Mediated Endocrinopathies

Other immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

#### Immune-Mediated Polynuropathies

LIBTAYO can cause immune-mediated polyneuropathy. The definition of immune-mediated polyneuropathy includes the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of polyneuropathy is higher if patients who have received prior thoracic radiation.

Immune-mediated polyneuropathies occurred in 3.7% (22/591) of patients receiving LIBTAYO, including fatal (0.3%), Grade 3 (0.5%) and Grade 2 (1.9%) adverse reactions. Two patients required permanent discontinuation of LIBTAYO in 1.9% of patients and withholding of LIBTAYO in 0.3% of the patients.

#### Immune-Mediated Collitis

LIBTAYO can cause immune-mediated colitis. The definition of immune-mediated colitis includes the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

The primary component of the immune-mediated colitis was diarrhea. Cyclosporine (CVS) infection/mycosis fungoides has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infection workup to exclude other alternative etiologies, including infection. Instruct medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.2) in the full prescribing information).

#### Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immune-mediated hepatitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated hepatitis occurred in 1.9% (11/591) of patients receiving LIBTAYO, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (1.5%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 0.8% of patients and withholding of LIBTAYO in 0.8% of patients.

Systemic corticosteroids were required in all patients with hepatitis. Nine percent (9%) of these patients (1/11) required additional immunosuppression with mycophenolate. Hepatitis resolved in 64% of the 11 patients. Of the 11 patients in whom LIBTAYO was withdrawn for hepatitis, 7 were reinitiated LIBTAYO.

#### Immune-Mediated Endocrinopathies

Adrenal insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity (see Dosage and Administration (2.2) in the full prescribing information).

Adrenal insufficiency occurred in 0.5% (3/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. No patient discontinued LIBTAYO due to adrenal insufficiency. LIBTAYO was not withdrawn in any patient due to adrenal insufficiency.

Hypophysitis

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypothalamic dysfunction. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.2) in the full prescribing information).

Hypophysitis occurred in 0.2% (1/591) of patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis.

#### Thyroid Disorders

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hypothyroidism. Initiate hormone replacement or medical management of hypothyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.2) in the full prescribing information).

Hypothyroidism: Hypothyroidism occurred in 1.9% (11/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.8%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.3% of patients.

Systemic corticosteroids were required in 9% (51/11) of patients. Hyperthyroidism resolved in 46% of the 11 patients.

Hyperthyroidism: Hypothyroidism occurred in 7% (42/591) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (6%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.3% of patients.

Other Immune-Mediated Adverse Reactions

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

- Cardiac/Vascular: Myocarditis, pericarditis, vasculitis
- Dermatologic: Dermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)
- Gastrointestinal: Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)
- Metabolic: Diabetes, metabolic acidosis
- Nervous system disorders: Seizures
- Respiratory, thoracic and mediastinal disorders: Interstitial pneumonitis
- Skin and Subcutaneous Tissue: Toxic epidermal necrolysis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)
- Vascular disorders

### 5. WARNINGS AND PRECAUTIONS

#### 5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monochlonal antibody that belongs to a class of drugs that bind to either the programmed death receptor (PD-1/PD-L1) or its Ligand (PD-L1). This results in modulation of the immune system. Immunemediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibodies. With immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor closely for symptoms and signs that may be classic manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.2) in the full prescribing information).

#### 5.2 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 or permanently discontinue LIBTAYO based on severity of reaction (see Dosage and Administration (2.2) in the full prescribing information).

#### 5.3 Complications of Allogeneic HSCT

Fetal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications may include hematocrit graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome.
Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogenic HSCT.

5.4 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 modulation 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)]
• Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of 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 581 patients in two open-label, single-arm, multicohort studies (Study 1423 and Study 1540), including 131 patients with mCSCC (nodal or distant), 88 patients with locally advanced CSCC, and 372 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=470), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=4), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=56). Among the 591 patients, 47% were exposed for ≥6 months and 27% were exposed for ≥12 months.

Cutaneous Squamous Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 [see Clinical Trials (7.1) for full prescribing information]. Of these 219 patients, 135 had (or distant) and 88 had loco-regional. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=182) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% white, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (36%).

Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, nephritis, sepsis, and pyelonephritis. Permanent discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, exacerbation, aspergillus meningitis, hepatitis, arthropathy, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoasitis, rash mucocutaneous, prophylaxis, and confusional state.

The most common (≥25%) adverse reactions were fatigue, rash, diarrhea, mucositis, pain, and nausea. The most common Grade 3 or 4 adverse reactions (≥2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, anorexia, pyrexia, skin infection, and hypercholesterolemia. The most common (≥4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyponatremia, and hyperphosphatemia.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients and Table 3 summarizes Grade 3 or 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO N=219</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and Administration Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>1</td>
<td></td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Hematologic</td>
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</tr>
<tr>
<td>Anemia</td>
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</tr>
<tr>
<td>Endocrine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Table 4: Adverse Reactions in ≥10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1629

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO N = 132</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>30</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
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<td>0</td>
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<tr>
<td>Infections and infestations</td>
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<td>Upper respiratory tract infection</td>
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<td>Urinary tract infection</td>
<td>12</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1.5</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
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<tr>
<td>Anemia</td>
<td>13</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 5: All Grades and Grades 3-4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients receiving LIBTAYO

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
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<tr>
<td>Increased ALT</td>
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<td>Hematology</td>
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<td>4</td>
<td></td>
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<tr>
<td>Hyperkalemia</td>
<td>2</td>
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</tbody>
</table>

Table 6: All Grades and Grades 3-4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients receiving LIBTAYO

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
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<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
<td></td>
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<tr>
<td>Increased ALT</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
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</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
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 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. 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 219 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.
Dr Apar Kishor Ganti Explains Why Lurbinectedin Is Important for Patients With SCLC

Lurbinectedin is a selective oncogenic transcription inhibitor that is being studied in 9 different tumor types. Can you discuss its mechanism of action? Why does it offer promise for certain patients with small cell lung cancer (SCLC) when a first-line therapy fails?

Lurbinectedin inhibits oncogenic transcription. Basically, it prevents the binding of transcription factors to their sequences. Therefore, it prevents transcription, and transcription is what's responsible for cell division. Preventing transcription eventually leads to cell death or apoptosis. In addition to lurbinectedin blocking transcription in tumor cells, it also inhibits transcription in the tumor-associated macrophages; therefore, it can affect the tumor microenvironment as well.

“[Lurbinectedin] has been studied in other tumor types as well, but this was a report specifically in small-cell lung cancer, and in this group of patients, who had previously received at least 1 line of chemotherapy, about 35% of the entire population responded.”

—Apar Kishor Ganti MD, professor of Internal Medicine, Division of Oncology & Hematology, University of Nebraska Medical Center

It is important, or particularly exciting, because a new trial was published recently in The Lancet in which they looked at lurbinectedin in SCLC. It has been studied in other tumor types as well, but this was a report specifically in SCLC, and in this group of patients, who had previously received at least 1 line of chemotherapy, about 35% of the entire population responded. Historically, in that cohort of patients, response rates range between 15% and 20%. So, when this study reported a 35% response rate, that automatically became pretty big news.

What is the recommendation for lurbinectedin in the National Comprehensive Cancer Network (NCCN) guidelines?

NCCN guidelines recommend lurbinectedin in the relapse setting, meaning in patients who have failed at least 1 previous line of chemotherapy. It’s the second drug that has been FDA approved in this setting, after topotecan. The NCCN guidelines recommend that as the preferred option in patients who have failed SCLC therapy and for whom more than 3 months have passed since their previous treatment. [In other words, they’ve had a chemotherapy-free interval of 90 days; for patients with a chemotherapy-free interval of less than 90 days, it is an option.]

Dr Ashley Ross on Genomic Testing Post Prostatectomy

Can you discuss the current treatment landscape for postprostatectomy patients? What are the benefits of utilizing genomic testing to plan the right approach?

Previously, trials have focused on adjuvant radiation treatment vs just waiting. [Some] trials showed oncologic benefit for giving adjuvant treatment over doing nothing, but the number of men who needed to be treated with therapy was fairly high. More importantly, a lot of those trials looked at adjuvant treatment vs what often was a delayed salvage approach, in which the patients’ prostate-specific antigen (PSA) measurements were actually fairly high. Over the last year or so, clinical trials have been published looking at adjuvant therapy vs early salvage therapy.

What those trials showed is that if you have disease that is Gleason grade group 2 or 3, and particularly if you have seminal vesicle involvement and no lymph node involvement, then an early salvage approach might be favored vs an adjuvant radiation approach. But how about men who don’t [have] those characteristics and who were underrepresented in those trials? Men with Gleason 8 to 10 disease, meaning Gleason grade group 4 or 5, and men with T3b disease, meaning they have disease in the seminal vesicles, were unrepresented in the RADICALS and RAVES trials. And those men still have treatment decisions about whether they should jump on their cancers early or not.

What genomic classifiers do, or genomic information does—particularly the Decipher score—is provide independent prognostic information beyond your clinical pathologic characteristics. Previous retrospective studies have shown that you might be better suited for adjuvant therapy, as opposed to a salvage approach, and potentially even an early salvage approach, if you have a constellation of higher-risk features, at least 2 of the following: Gleason 8 to 10; T3b disease; or a high genomic classifier score, meaning a Decipher score higher than 0.60. That’s going to be fleshed out in prospective clinical trials.

But right now, that’s a sweet spot for genomics. You can help decide: Are you going to use this therapy or not? Let’s pretend that you waited until your [patient’s] PSA started to rise—and particularly now with ultrasensitive PSA checks, a lot of us are doing that, waiting until the PSA gets to some low level—but let’s pretend that it’s even 0.10. And now you’re deciding, based on the clinical trials have been published, that you do want to give a salvage therapeutic approach. The questions that appear now are: Should that salvage therapy be alone, or should it be [in conjunction] with hormonal therapy? A previous...
trial, RTOG 9601, showed that in the salvage radiation setting, adding 2 years of hormonal therapy—in that trial, they used bicalutamide for 2 years—would improve oncologic outcomes. However, that trial included many men with higher PSA levels, and a subset analysis of men with lower PSAs showed that adding on the bicalutamide might be an overall detriment to survival if you're radiating people at low PSAs. So here's another place where the molecular testing really can shine and help you with your clinical decision-making.

A paper in press looks at RTOG 9601 and a subset of the men who had testing with the genomic classifier. It showed that adding hormonal therapy would actually cause an overall survival detriment for men at low genomic risk and who had low PSA. [This] tells us to avoid hormonal therapy if you're going to do salvage radiation in those men, particularly early salvage radiation. On the flip side, you may want to intensify with hormonal therapy, if they have a high genomic risk and you're doing even early salvage radiation. So, [genomic testing] is giving you important prognostic information in addition to your clinical information about whether or not you should do salvage radiation therapy, and [if so], how intense you should make that.

**REFERENCES**


Kavita Patel: Drug Pricing, Care Access Priorities in Federal Health Care Policy

ROSE MCNULTY

CONTINUED FROM COVER

External factors, particularly the coronavirus disease 2019 (COVID-19) pandemic, have been and will continue to shape the Biden administration's health care priorities. In the short-term, increased awareness of inequity throughout the health care system is a pandemic-related priority that has translated to cancer care, another environment with long-documented disparities that have become the focus of recent initiatives. Patel highlighted priorities in health care reform—in particular drug pricing; Medicare and Medicaid coverage and out-of-pocket care costs; and health disparities—that inevitably affect cancer care. Specifically, she noted the Trump administration's blueprint to lower drug and out-of-pocket costs in America, which included provisions such as permitting potential drug importation, allowing for Medicare to negotiate drug prices, and creating an international pricing index.2

“It’s hard enough for physicians to grasp everything in terms of genetic testing implications for treatment; and treatments, which are dose based and have various step-off points depending on adverse effects, etc. How you put that into a value-based model that CMS can administer is nothing short of a debacle.” —Kavita Patel, MD, MS, non-resident fellow at the Brookings Institution

“It’ll be interesting to see what the Biden administration wants to do in terms of most-favored nation [status] and some of the policies and rules that they put either on pause or asked the agencies to kind of rescind—but there will be action on drug prices. There's no doubt in my mind,” Patel said. The most-favored nation rule, which the Trump administration issued 60 days before Biden took office, faced overwhelming blowback from community oncology advocates throughout the country, who raised concerns about its potential effects on community-based practices.3

Some of the major issues in access to care as the Biden administration tackles Trump administration changes include strengthening and expanding the ACA; strengthening Medicaid coverage, which saw new parameters such as work requirement waivers; and improving racial and gender health disparities, according to Patel. She also hopes to see a rejuvenation of the debate surrounding the Medicare 340B Drug Pricing Program, which has faced bipartisan criticism and accusations of some facilities taking advantage of the program meant to provide drugs at a reduced cost in low-income communities.

“We saw some actions in the Trump administration that continued to...chip away at that disparity that people felt was there—that those who the program was intended for did not match who actually got it. I think that trend will continue, but it’s going to have a lot more to do with whether, once we're past COVID-19, the White House puts attention to it or whether it comes from a very kind of aggressive administrator in the form of a [Health Resources and Services Administration] administrator.”

Price transparency, which the Trump administration pushed for, is something that the Biden administration has not indicated whether it will support or reject, according to Patel. Price transparency as it has begun to be implemented in some hospitals, where patients can see prices online ahead of scheduling services, is not working as intended, she added.

“It never really works out that way. It's hard, and we found from a decade-plus of literature that consumers don’t really shop outside of a couple of elective procedures—colonoscopies, knee replacements, radiology, imaging, etc—but it can be hard,” she said. “So, it’ll be interesting to see how Biden takes what I think are clear signs to providers, primarily hospitals, and payers, to make ‘cost transparent.’ But in my opinion, what we see today is not going to make a meaningful change unless there's something built on top of it.”

Once issues of cost and care access are addressed, Patel said, then comes an ever-present topic in discussions of cancer care: payment reform.

Value-based payment models are another trend in cancer care that Patel does not see slowing down. But she did not mince words in declaring the Oncology Care Model—the Center for Medicare & Medicaid Innovation’s (CMMI) episode-based, oncology-focused alternative payment model (APM) that began in 2014 and was extended through 2021 in light of the COVID-19 pandemic—a “debacle.”

“The data and the evaluations to date have been pretty disappointing and showing that despite helping with care coordination efforts, there was really no effect on cost. And I think it has a lot more to do with the flawed mechanism or the design of these models, to be perfectly blunt,” Patel said. “It’s hard enough for physicians to grasp everything in terms of genetic testing implications for treatment; and treatments, which are dose based and have various step-off points depending on adverse effects, etc. How you put that into a value-based model that CMS can administer is nothing short of a debacle.” Despite its shortcomings, though, Patel added that she hopes it will not affect the ability to advance other value-based payment models.

Another APM facing criticism and delays due to the pandemic is the Radiation Oncology (RO) Model, which the American Society for Radiation Oncology (ASTRO) took aim at in a recent announcement of its support for President Biden’s CMS administrator nominee, Chiquita Brooks-LaSure, and his selection of Liz Fowler to direct CMMI.4

“We look forward to working with Ms Brooks-LaSure, Ms Fowler and the Biden administration on a variety of issues, including ways to fix the flawed RO Model and protect access to high quality radiation oncology care for people with cancer,” the organization said in the release. “President Biden is a recognized leader on ways to advance cancer care, and we hope to collaborate with his team to enhance quality and reduce costs for patients.”

Patel concluded her discussion by looking ahead at topics not necessarily addressed in the federal policies, highlighting the importance of awareness surrounding the immeasurable toll the pandemic has taken on oncology providers and patients alike.

“I do think advocacy around the toll it’s taking on providers as a very, very broad term—physicians, advanced practitioners, lay caregivers—has to be prioritized,” she said. “It’s] not necessarily...
something that I’ve seen in some of these federal policies, but I think it has to be included; and advocacy for the kinds of programs for our patient community that has also been just as devastated.”  

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1. Keith K. Supreme Court arguments: even if mandate falls, rest of Affordable Care Act looks likely to be upheld. Health Affairs Blog

FDA Approves Cemiplimab for First-Line Advanced NSCLC With PD-L1 Expression

ROSE MCNULTY

REGENERON PHARMACEUTICALS, INC, and Sanofi announced that the PD-1 inhibitor cemiplimab-rwlc (Libtayo) was FDA approved as a monotherapy for patients with first-line advanced non–small cell lung cancer (NSCLC) with PD-L1 expression of at least 50% as determined by an FDA-approved test. Patient eligibility criteria also include having either metastatic or locally advanced NSCLC that cannot be resected or treated with definitive chemoradiation, and tumors cannot have EGFR, ALK, or ROS1 aberrations.

The approval is based on an analysis of 710 participants in the phase 3, open-label EMPower-Lung 1 trial, which randomized patients 1:1 to receive either cemiplimab or chemotherapy. Patients were intended to have high PD-L1 expression, and the cemiplimab cohort had a 32% lower risk of death than the chemotherapy group in the overall population.

A prespecified analysis was performed on a cohort of 563 patients with confirmed PD-L1–high tumors proven by the PD-L1 immunohistochemistry 22C3 pharmDx kit, and those patients showed a 43% lower risk of death compared with those treated with chemotherapy. The results were published recently in The Lancet.

“Libtayo has demonstrated an impressive level of efficacy in advanced NSCLC with at least 50% PD-L1 expression in its pivotal trial,” study investigator Ahmet Sezer, MD, professor in the Department of Medical Oncology at Başkent University in Adana, Turkey, said in a statement. “As published in The Lancet, in a prespecified analysis in the subset of patients proven to have PD-L1 expression of at least 50%, Libtayo reduced the risk of death by 43% compared with chemotherapy. This was achieved with a greater than 70% crossover rate to Libtayo following disease progression on chemotherapy, as well as the largest population of patients with pretreated and clinically stable brain metastases among advanced NSCLC pivotal trials to date. The approval of cemiplimab for this indication comes after a priority review by the FDA, which is granted when a drug may significantly improve patient outcomes in serious diseases. It is the third cemiplimab approval in the United States and the second in February 2021 alone.

Earlier in the month, the drug was approved for the treatment of advanced basal cell carcinoma (BCC) previously treated with a hedgehog pathway inhibitor (HHI) or in cases when an HHI is not appropriate. It was granted full approval for locally advanced BCC and accelerated approval for patients with metastatic BCC. In 2018, cemiplimab was approved for the treatment of locally advanced or metastatic cutaneous squamous cell carcinoma when curative surgery or radiation is not an option.

“With this third approval for Libtayo, we are proud to deliver on our ambition to bring our PD-1 inhibitor to patients in need with difficult-to-treat cancers, such as advanced NSCLC,” Peter C. Adamson, MD, global development head of oncology and pediatric innovation at Sanofi, said. “As the leading cause of cancer deaths globally, the need for additional therapeutic options in advanced NSCLC is clear. Libtayo allows physicians to further optimize treatment of these patients whose tumors have high expression of PD-L1. We thank all of the trial investigators, patients and their caregivers who helped make this milestone possible.”

In the trial, 355 patients in the cemiplimab cohort and 342 in the chemotherapy group were included. Overall population.

common serious adverse reactions were pneumonia (15% vs 6% and 11% vs 8%, respectively). The most common serious adverse reactions were pneumonia, and neutropenia, which occurred in 5% and 2%, respectively, of cemiplimab patients, and in 6% and 0% of chemotherapy patients. Overall, no new safety signals were found in the cemiplimab cohort. “Libtayo has already changed the treatment paradigm for certain patients with advanced cutaneous squamous cell carcinoma and is poised to do the same for advanced basal cell carcinoma,” said Israel Lowy, MD, PhD, senior vice president of clinical sciences, head of translational science, and head of oncology at Regeneron. “Now, Libtayo has the opportunity to make a meaningful difference for the many US patients battling advanced NSCLC. Libtayo is being investigated in a variety of settings, and we hope to share updates later this year on our pivotal trials in cervical cancer and in combination with chemotherapy in advanced NSCLC.”

REFERENCES
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Identifying Small Cell Lung Cancer Subtypes and Potential Therapeutic Targets

ROSE McNULTY

In SCLC, rapid growth and resistance to treatment contribute to an estimated 5-year survival rate of 27% for patients with limited-stage disease and just 3% for patients with advanced SCLC at diagnosis. The new research, published in Cancer Cell, identifies possible treatment vulnerabilities that will hopefully prove useful in future clinical trials and in planning treatment for SCLC patients and other cancers. Three of the identified subtypes aligned with outcomes of previous research, but a novel fourth type showed an inflammation gene signature with high expression of multiple immune genes.

Recently, Evidence-Based Oncology™ (EBO) spoke with the study’s senior author, Lauren A. Byers, MD, associate professor of thoracic/and head and neck medical oncology at The University of Texas MD Anderson Cancer Center, to discuss the findings and the treatment landscape of SCLC. The interview is edited lightly for clarity.

EBO: Your recently published research in Cancer Cell identified 4 types of SCLC. Can you discuss the importance of stratifying those disease subtypes?

BYERS: As somebody who treats patients with lung cancer, it’s been amazing to see how much progress we’ve had in treating advanced NSCLCs. And the game-changer for those cancers was the initial identification of EGFR mutations and the development of EGFR inhibitors, so that we had a way to start providing the first targeted therapy for lung cancer. In that setting, and over the last few years, the number of drug approvals for targeted therapies has just skyrocketed—and that’s been reflected in outcomes. A paper last year in the New England Journal of Medicine discussed how lung cancer deaths have sharply declined, particularly in NSCLC. And that’s in part because in more and more cases, when patients first come to us, we can do biomarker testing. Then, we can really personalize their treatment based on the therapy, whether it’s targeted or immunotherapy, that they are likely to get the most benefit from.

SCLC is an incredibly aggressive disease. In most cases, patients already have advanced metastatic cancer by the time it’s detected. For the last several decades—and still—the standard treatments are really a 1-size-fits-all approach. Unlike in NSCLC, no biomarkers have been clinically validated that would let us start thinking about personalized treatment approaches for SCLC. I think that’s really the game-changer, and why we’re so excited about having this framework where we can now say, “Here are the 4 major subtypes.” Being able to define those types really gives us a path forward for doing the hard work that comes next. In clinical trials for SCLC, especially with new agents that we’re excited about, we can look and start to identify whether certain therapies that are being tested seem to be especially active and especially beneficial for patients in 1 of these 4 groups. That really is the next step in moving toward precision oncology or a biomarker-driven approach.

EBO: Potential therapeutic targets for those 4 subtypes were also identified. How could this affect future clinical trials and drug development?

BYERS: With SCLC, because most past trials have been sort of for all comers, if it was an active drug, you might see 1 in 10 patients responding—but you never really knew who the patients were who were getting that benefit from those drugs. Something that can happen immediately in the current clinical trials that are taking all SCLC patients is that, because we’ve identified what these 4 major subtypes are—and other drug-specific biomarkers are emerging as well—we can begin testing them to find out which of those 4 groups they’re in. Then, when we get to the end of the of the study and we see, for example, a 20% response rate with a certain drug or drug combination, but half or 80% of those patients are in 1 subgroup, then we can figure out which patients are most likely to be getting a benefit from that particular therapeutic approach. Then, that lets us design the next trial to do what has gone on for the last several years in NSCLC, which is where you identify patients for a trial based on a biomarker and then treat them with that drug. You then [can hopefully] sort of flip the paradigm from a situation in which you have a minority of patients responding, to one in which, if you can identify which group of patients seems to be getting the most benefit, you hopefully get to a point where the majority of patients are having clinical benefit from a biomarker-matched treatment approach.

EBO: The analysis also showed that using a full gene panel wasn’t necessary to classify the tumors. What are the implications of those findings?

BYERS: I’m very practical about this: If you can’t do the test routinely in the clinical setting, then it’s not a useful biomarker. Fortunately, biotechnology is continuing to rapidly advance and become more sophisticated. Certainly, we can do things like liquid biopsies that we couldn’t do even a very short time ago. For us, the gene signature was really a powerful discovery tool to identify what these major subgroups were. But then it was really important to us to also develop tests that can be readily done in the clinic. That was why we worked together with our collaborators in our pathology group to develop immunohistochemistry assays. So basically the exact same way that we test for PD-L1 levels and the way we diagnose cancer, we have been working hard and sharing those assays that we’ve developed using immunohistochemistry, [so they] could be immediately used as a way to test which subgroup a patient is in. I think that can be moved forward right away. Another limitation with SCLC is that the amount of tissue that’s available from biopsies is often very small. So, at the same time, we’re looking at some of the newer technologies and ways to [test for] as many biomarkers as possible and get the best possible test [results] from the smallest amount of tissue. We’re excited about potential opportunities to develop blood-based methods to test for the subgroups, as well.

EBO: SCLC is far behind NSCLC in new treatment development, but with approvals of immunotherapies and, more recently, lusemidetin, things seem to be changing. Going forward, what therapies or combinations do you think have the most potential?

BYERS: First, a great thing about this study was that we found a drug that had activity for each of the 4 groups. So, it wasn’t just that there was 1 group that was resistant to everything. It was really that certain drugs worked for certain groups. A lot of [the research] has been on the preclinical side, with the exception of...
the immunotherapy study; we were able to validate [the results] in the clinical trial from IMpower133. But now, it’s really exciting because many of those drugs that we focused on in the preclinical work are currently in, or about to enter, clinical trials for SCLC. For example, I’m still very enthusiastic about PARP inhibitors. John Heymach, MD, PhD, [and I] originally identified PARP as being overexpressed in SCLC, and we did the first study showing that PARP inhibitors had activity in some of the preclinical models. Having a subtype that may work especially well for PARP inhibitors is [exciting].

Also, we saw in the NEUROD1 group that those SCLCs seem to be very responsive to Aurora kinase inhibitors, and those are targeted agents that are also currently in trials for SCLC. That allows another opportunity for the inflamed group. Across the board, we see that there’s certainly room for improvement in terms of responses in each of the subgroups, compared with what we have with the current standard treatment. For example, there are opportunities for thinking about novel immune approaches that might be especially effective in the inflamed group. I’m also excited about tyrosine kinase inhibitors, cell therapy, and BITE [bispecific T-cell engager] molecules—other, novel ways to engage the immune response beyond standard immune checkpoint inhibitors. These things are very exciting, and we’ll be seeing a lot going forward with the current clinical trials.

**EBO:** Can you discuss the significance of the novel fourth group identified in the research in regard to immunotherapy, which has become part of the standard of care in SCLC?

**BYERS:** One thing we did when we decided to ask the question about subgroups in SCLC is that we really took a data-driven, kind of agnostic approach. We said, “Let’s let the data tell us how many groups there are, and what the major groups are,” rather than just trying to guess, or to fit it to what we thought it might be. Because we took that approach, we have 3 “major player” groups activated by 3 different genes: ASCL1, NEUROD1, and POGE2. But the fourth group, the inflamed group—comprised of a group of tumors in which the biomarker was unclear, based on the work that had been done up to this point—was identified through this data-driven approach. That [fourth] group has such high expression of multiple immune genes and interferon signatures—all the [signs] that you’d expect from tumors that may be potentially more responsive to immunotherapy. Our hypothesis was that in this group we’d see the longer-term responses to immunotherapy.

It was really exciting to partner with some of our collaborators and look at the IMpower133 trial, in which the inflamed group made up about 18% of all the SCLC patients. And if you looked at how that group did, the addition of atezolizumab to chemotherapy essentially doubled their survival. So that really was the group who was getting the greater benefit from the addition of immunotherapy.

We’ve still got a lot of hard work to do. We can improve outcomes for patients in each of those groups through new approaches and combinations and other things to further enhance response in a more personalized way. But that was really one of the most exciting parts about the trial: finding that fourth group and being able to show that those patients did get relatively greater benefit from currently approved immunotherapy agents.

**EBO:** If the findings in regard to treatment vulnerabilities in the subtypes are verified in future research, how might they affect the overall treatment algorithm for SCLC?

**BYERS:** First of all, just like with other lung cancer patients upon diagnosis, I hope and expect that we would immediately test to determine which group their cancer was in. I expect there’ll be additional biomarkers that may be drug-specific. Beyond the 4 subtypes, I think we’ll continue to see growth in terms of [finding] new biomarkers to further refine treatment selection. Then, based on clinical trials looking at differences in terms of the benefit of specific treatments for specific groups of patients, we’ll pick the most effective treatment for that individual patient.

The current standard of care for expansive-stage SCLC—which is the majority of newly diagnosed patients—is chemotherapy with immunotherapy. The change that we may see first is that when patients have completed chemotherapy and they’re doing immunotherapy maintenance, those biomarkers could help guide us in terms of what should we combine with immunotherapy during the maintenance period to get more durable responses or to enhance the immune response. I would expect, first, to see advances or changes in how we pick therapies, and choose the most effective therapy for patients based on these subgroups. And then, ultimately, hopefully, as we have more trials and hopefully identify things that are that are particularly effective in certain subgroups, those would be brought in even earlier in the treatment. Potentially, eventually, we could replace chemotherapy with a novel combination as a targeted immune combination approach.

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The Impact of Reinsurance of Gene Therapies on Employer Financial Risk

MARC HIXSON, MBA; NEIL MINKOFF, MD; KIM GWIAZDZINSKI, MBA, RPH; AND JIM CLEMENT, MHA

Between 2013 and 2017, rising insurance premiums and administrative costs, coupled with the coverage mandates of the Affordable Care Act (ACA), drove nearly a quarter of midsize (100–499 employees) and smaller (<100 employees) employers out of the traditional (or fully funded) insurance market and into self-insured (or self-funded) arrangements. By 2017, 31% of midsize and 16% of smaller employers offered a self-funded health plan.1 For employers that have decided to go it alone, claims payouts and the risk of unanticipated losses rise in step with the cost of innovation.

Self-funded plans, authorized by the Early Retirement Income Security Act (ERISA), come in 2 varieties. In a totally self-funded plan, the employer is responsible for all insurable risk and pays claims through a third-party administrator. Totally self-funded plans are rare because of the risk of catastrophic claims. In partially self-funded plans, the employer uses a stop-loss carrier to limit claims exposure. This is called stop-loss coverage (not to be confused with reinsurance, which a secondary reinsurer provides protection for stop-loss carriers).2,3

The potential for million- and multimillion-dollar treatments over the coming decade has raised new questions about the purpose of stop loss coverage. As employers and third-party carriers wrestle with these questions, patients’ need for access to lifesaving innovation remains critical. Manufacturers whose products are at the center of this issue can help to lead a constructive discussion.

Anatomy of Stop Loss

Stop-loss coverage shields self-insured employers from individual catastrophic claims as well as overall exposure. In exchange for an annual premium, the stop-loss carrier provides the employer with protection against shock claims (high-dollar, low-frequency events like sepsis), as well as outlier cost spikes arising from cancer care, premature births, organ transplants, and other resource-intensive health events. Increasingly, complicated cases involving single high-cost drug, such as those for hemophilia, are becoming an area of concern.

Stop-loss policies usually contain 2 components: specific and aggregate coverage:2

- Specific coverage protects against claim severity for a single individual. An attachment point—essentially, an individual deductible for each member of the plan that an employer must cover before a stop-loss claim is paid—defines a dollar limit on the employer's liability for any single individual during the plan year. Any excess costs become the responsibility of the stop-loss carrier.

- Aggregate coverage provides protection against the cumulative impact of smaller claims. When an employer's total claims payments reach an aggregate attachment point, often calculated monthly, the stop-loss provider picks up all remaining costs up to the limit of the policy. Stop-loss claims paid are not included in the aggregate attachment point.

Stop-loss pricing is a complicated affair. Attachment points determine the level of risk an employer is willing to absorb and are priced on an actuary’s determination of the group’s expected losses. Policies are subject to underwriting on an annual basis. At renewal, carriers evaluate current claims data to determine whether this year’s attachment points represent a reasonable risk for the price. However, the smaller the group, the less reliable its experience for pricing purposes.4

An individual with unusually high expenses may be carved out or excluded from the plan the following year, leaving the employer to pay all claims on that individual. Alternatively, a carrier may offer a laser—a higher specific attachment point—for a beneficiary known to have a high-cost condition and whom underwriters believe is likely to breach the deductible in the coming plan year. Rather than raise the premium, the carrier adjusts the threshold for that single claimant. In some cases, a laser may be required as a condition of any coverage.5

The potential for million- and multimillion-dollar treatments over the coming decade has raised new questions about the purpose of stop loss coverage. As employers and third-party carriers wrestle with these questions, patients’ need for access to lifesaving innovation remains critical.

A laser may be many multiples of the specific attachment point. As an example, an employee undergoing cancer treatment may be lasered at $500,000, whereas the remainder of the employer’s population carries a $150,000 specific attachment point. The deductible for the employee who is lasered will be similar to what the underwriter believes the cost of her treatment will be.5 Cancer is a common condition for lasers; others are kidney failure, severe injuries, and conditions that may ultimately require an organ transplant.4

Aggregate attachment points are determined by estimating total claims expected and then adding a risk corridor—a margin of anywhere from 10% to 25% of expected claims—to account for medical inflation, fluctuations in the size of the employer’s workforce, or other unexpected circumstances.2,6 If, for instance, the underwriter expects total claims (not including those that exceed the specific deductible) to reach $4 million and the stop-loss carrier adds a 25% risk corridor, then the employer's aggregate liability will $5 million (Figure). It is rare for an employer to hit this, as it would involve a very high percent of employees hitting these limits in 1 year.

Market Trends and Dilemmas

Once the domain of large employers, self-insurance has become popular with smaller companies that seek to control expenses. In the past, the rule of thumb was that once a company offered health benefits to more than 250 beneficiaries, a transition from fully insured to self-insured status made sense. The savings on premiums, taxes, and insurers’ reserves and administrative costs outweighed the cost of claims payments, assuming the employer

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1. Early Retirement Income Security Act (ERISA)
2. Aggregate and specific attachments
3. Specific and aggregate claims
4. Aggregate and specific attachments
5. Aggregate and specific attachments
6. Aggregate and specific attachments
also had help from a stop-loss carrier with outliers.5 But today, groups as small as 100 beneficiaries are self-insuring. Why?

The ACA helped accelerate this shift. The law included new coverage mandates and administrative costs, and it required qualified health plans to cover 10 categories of essential health benefits (EHB), some of which were less essential to some employers than others. Self-insured employers are exempt from the EHB clause. Moreover, in a self-insured arrangement, the employer has access to its own claims history, which allows management to make more informed decisions about plan design.4

But where the ACA created incentives for small employers to migrate away from fully insured plans, it also created trapdoors for them to mind along the journey. The health care reform law removed annual and lifetime limits on benefits, making catastrophic claims a much greater risk for self-insured groups, especially smaller ones. For an employer with 100 covered lives, a single million-dollar claim could be greater than the sum of all other claims in a given year.7

One insurance carrier saw its number of annual claims that exceeded $1 million rise by 68% between 2013 (the year before ACA protections were implemented) and 2016, according to the Massachusetts Institute of Technology’s Center for BioMedical Innovation. The center estimates the incidence of such claimants today at 1 per 10,000 to 15,000 covered lives each year.8

With benefit limits lifted, claims in excess of $1 million were no longer rare. Stop-loss coverage became essential not only for smaller employers, but also for larger employers that once might have been able to absorb 1 or 2 million-dollar claims but now struggle with 10 or 20.9

That brings us back to innovation. Potentially curative therapies have reached the market today, and as many as 50 cell and gene therapies could receive Food and Drug Administration approval by 2030.10 Although many are for limited populations, they nonetheless contribute to the frequency of high-dollar claims. Tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta), chimeric antigen receptor (CAR) T-cell therapies for blood cancers, debuted in 2017 at list prices of $475,000 and $373,000 each for a course of treatment.11

And those don't even make the top 10 list in terms of cost (Table). Two gene therapies, onasemnogene abeparvovec (Zolgensma) and voretigene neparvovec (Luxturna), developed respectively for a rare muscular disorder and a form of blindness, rank first and third. Zolgensma will set a plan sponsor back $2.1 million; Luxturna, $850,000.12

The costs of all of these products raise the question: What is the purpose of stop-loss coverage? Is it to cover unexpected risk? Or is it to buffer an employer from the known cost of expensive therapies? For a beneficiary with a history of claims for large B-cell lymphoma, tisagenlecleucel may well be a predictable cost-in-waiting. And yet, reinsurers may not be able to plan for it because most patients with cancer are treated within a short window of diagnosis. This beneficiary may not be carved out or lasered until next year.

Stop-loss Providers Respond
In the long term, answers to questions like those above will influence how those who write stop-loss policies will approach costly new innovations. For the short term, however, many are already taking steps to limit their own exposure. At their core, each of the following short-term responses to market trends is a variation on the same concern: »
A Hypothetical Treatment for Rare Disease

When an expensive new product reaches the market, the manner in which a stop-loss carrier handles it has multiple ramifications for payers and patients. Imagine, for instance, that a rare disease affects 1 in every 75,000 children. A first-in-class, breakthrough treatment for this condition debuts with a list price of $2 million for a course of therapy. Considerations to the carrier may include:

**WHAT IS THE POPULATION FOR THIS PRODUCT?** In an employer group covering 200,000 lives, there is a likelihood of approximately 1 child needing the product. But if the condition it treats is prevalent in certain populations because of a particular genetic mutation, or some other means, then incidence in a given population may be higher. Incidence estimates would also have to consider the number of women of childbearing age covered and their genetic predisposition.

**WHAT IS THE COST TO THE EMPLOYER?** Assuming a $25,000 patient deductible and a $10,000 cap on co-insurance, the patient would normally be asked to pay $12,500 and, absent stop-loss coverage, the employer would be responsible for the balance. If the employer has a specific attachment of $10,000; however, the employer will cut its losses normally be asked to pay $12,500 and, absent stop-loss coverage, the employer would be responsible for the balance. If the employer has a specific attachment of $10,000; however, the employer will cut its losses at $137,500. These amounts do not figure in the possibility that a patient may be eligible for a manufacturer’s copayment assistance program—the existence of which may also increase utilization of the product.

**HOW DOES THE STOP-LOSS CARRIER PROTECT ITSELF?** Continuing with our example, the stop-loss carrier would pick up $1,850,000 of the cost of the beneficiary’s treatment. Whether the carrier is willing to shoulder such losses in future years depends on a number of factors, such as whether it could require certain women be tested for a relevant genetic mutation to be eligible for coverage, a laser, or to be excluded from coverage; whether to increase premiums across the population, or whether the employer moves the risk elsewhere, such as giving patients vouchers to buy coverage in the health insurance exchanges.  

as high-cost innovations serve an ever-greater number of people, stop-loss coverage becomes more expensive and includes more qualifications and lasers.

**HIGH-COST AND HIGH-RISK PATIENTS.** As stop-loss contracts are subject to underwriting on an annual basis, carriers begin to review medical and prescription drug claims data a few months before a policy will renew. The purpose of this exercise is to identify individual claimants with a high likelihood of breaching the specific deductible during the next plan year.

To avoid unwelcome coverage surprises in the next or subsequent years, employers will need data mining and analytics capabilities that enable them to take a population health management approach. This means identifying those in their workforce who are not only at high risk now but also those who may be thought of as rising risk.

**LASERS.** Beneficiaries with a history of claims for a high-cost therapy, injectable drug, or other service have long been at risk for being lasered. Now, as the cost of innovation soars to new heights, even people with a higher-than-average predisposition for a costly illness may be candidates for lasers. Because a laser can be a sweeping liability to plan assets, a self-insured employer typically can absorb only 1 or 2 such cases.

Employers should work with their third-party administrators to understand their stop-loss carriers’ own appetite for risk and whether the carrier is sensitive to a particular diagnosis, therapy, or dollar threshold. This may help the employer to identify individuals who are at risk of being lasered and proactively evaluate their eligibility for patient assistance programs on a regular basis.

**EXCEPTIONS.** If the stop-loss carrier does not offer a laser on a high-cost beneficiary, it may choose 1 of several actuarial options: build a high-cost treatment into premiums, increase the cost threshold (i.e., the specific attachment) for each beneficiary or, perhaps a worst-case scenario for the employer, exclude the individual from coverage altogether. While the ACA guarantees coverage for people with pre-existing conditions in ERISA plans, this protection is not incumbent on stop-loss carriers that back a self-funded plan.

Patient exclusions drive up the cost of claims in ERISA plans. The cumulative effect of exclusions may force employers to move back into the fully insured market, where services are more tightly managed and where they have less control over costs and less transparency of claims.

**SECONDARY REINSURERS.** Yes, stop-loss carriers themselves purchase reinsurance. It is not uncommon for carriers to transfer individual-claim risk (anywhere from $1 million for a smaller carrier to $5 million or more for a larger one) to a secondary reinsurer in exchange for a per-person, per-month premium. When this happens, a portion of an employer’s premium for stop-loss coverage becomes a pass-through expense to the employer.

Because of the increasing severity and frequency of high-cost drug claims, secondary reinsurers are beginning to exit the market. Stop-loss carriers are a safety valve for self-insured employers (and for traditional payers as well), and secondary reinsurers are their safety valve. As each valve closes, pushing risk back toward the payer, the cost of self-insuring grows, forcing the employer to consider alternatives to its current strategies for managing risk.

**MONITORING PIPELINES.** Stop-loss carriers follow manufacturers’ pipelines to identify potential new treatments, especially innovations likely to be high cost. These potential treatments are matched to individuals within the employer’s population whose medical and claims histories suggest they may be candidates for it. The stop-loss carrier’s underwriters may, in turn, set qualifications for these beneficiaries, although at times there may be no way to tell if treatment will happen in the plan year.
The uncertainty in how carriers may view and treat new products (see A Hypothetical Treatment for Rare Disease) underscores the need for manufacturers to communicate their pipelines in ways that convey meaningful value to each “customer”—not just investors, but also to employers, clinical nurse reviewers at traditional insurers, and even to stop-loss claim teams.

Where We Go From Here

Historically, stop-loss carriers have functioned as traditional insurers, using actuarial analyses to determine their potential responsibility for otherwise random risk. As the emergence of costly therapies for conditions that can be expected to occur causes stakeholders to rethink reinsurance, employers and payers may lose or have limited access to a tool that is vital to their efforts to finance health care delivery.

Failure to address this problem has multiple potential ramifications. As patients are lacerated or carved out altogether, costs rise for both plan sponsors and patients through higher premiums and cost sharing, respectively. Payers may tighten coverage policies for costly therapies, with the potential to limit or delay access to therapy. The loss of secondary reinsurers may lead to health plan consolidation and a decrease in state and regional health plans, as only the large national players will be able to absorb the risk of high-cost treatments. And self-insured employers—especially smaller ones—might find that giving beneficiaries vouchers to shop for coverage in the health exchanges is cheaper than self-insuring.

That’s not the future is grim. To the contrary, creative thinking can open several paths forward:

- **SOLICIT COOPERATION ACROSS ENTITIES.** Manufacturers will need to communicate value, ensuring that traditional and stop-loss payers have an accurate understanding of a drug’s place in therapy and which patients are appropriate beneficiaries—vouchers to shop for coverage in the health exchanges is cheaper than self-insuring.

- **CREATE A NEW BENEFIT FOR HIGH-COST THERAPIES.** Vertically integrated traditional insurers are beginning to fill the void created by stop-loss exceptions, offering protection plans that cover 1% or more specific high-cost therapies in exchange for a per-member, per-month fee. This model does not include supportive care that a member might need and leverages aggregate volume to support claims expenses. These models rely heavily on the integrated company’s data capabilities and offer a nuanced alternative to traditional stop-loss dollar limits.

- **POOL AGGREGATE RISK.** The current paradigm is for individual employers to purchase stop-loss coverage for their own work forces. As an alternative, self-insured employers may investigate whether to form or join a captive—in essence, a private insurer set up by a small employer or group of employers to pool risk—to absorb some of the shock from the self-funded plan. Doing so might mitigate the need for patient exclusions in stop-loss coverage.

- **LEVERAGE MANUFACTURER, PATIENT REGISTRY, AND CLAIMS DATA.** When it comes to rare diseases and treatments for them, manufacturers and payers have an opportunity to partner with one another by tracking patient outcomes over time and sharing de-identified data. This real-world monitoring of clinical and financial outcomes can lead to the development of realistic risk profiles and may ease barriers related to portability of coverage when a patient finds new coverage and to portability of risk for the new payer.

- **COOPERATE WITH TECHNOLOGY DEVELOPERS.** After federal incentives for providers to embrace electronic health record (EHR) systems took effect, forward-looking pharmaceutical companies began to develop digital channel strategies and formed relationships with EHR vendors. Embedding referrals to patient assistance programs into EHRs may help to reduce the likelihood that a beneficiary who is at risk of being carved out by a stop-loss provider will be denied access to an expensive therapy.

**Conclusions**

Stop-loss coverage is a key risk-mitigation component for self-funded health plans. The emergence of gene therapies and other costly one-time treatments is forcing a re-examination of what stop-loss coverage is for and what all parties can do to provide patients with access to innovative treatment, prevent plan sponsors from catastrophic costs, and avoid reinsurers from exiting the market. When all parties are engaged in the discussion, solutions “for something for everyone” are possible.

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