ONCOLOGY

PAYMENT MODELS
With No Replacement for OCM on Horizon, Oncology Practices Ask: What Now?
Gianna Melillo

IF ONCOLOGY PRACTICES expected an explanation from CMS on next steps following the imminent end of the Oncology Care Model (OCM) during Center for Medicare and Medicaid Innovation's (CMMI) announcement of a "strategic refresh" earlier this year, they may have been disappointed.1 The OCM, which began in 2016, has an anticipated performance period end date of June 2022.2 For many participating practices, what follows is in the air.

"I think a lot of us had the expectation there would be a gap, and I think the lack of hearing anything otherwise just makes it more [clear] that there will be a gap," said Stephen M. Schleicher, MD, MBA, a medical oncologist at Tennessee Oncology and medical director of value-based care at OneOncology. "I'm afraid that priority on a next-generation cancer model may be even more delayed than some of us had hoped."

As part of its strategic refresh announcement, Elizabeth Fowler, PhD, JD, deputy administrator of CMS and director of CMMI, said the center did not plan to end any models early, although objectives of the refresh will guide revisions to existing models and consideration of future models.

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PRECISION MEDICINE
The MMRF: Understanding and Sharing the Genomic Landscape of Multiple Myeloma
Maggie L. Shaw

THE MMRF CURECLOUD RESEARCH INITIATIVE, a novel direct-to-patient observational study developed by the Multiple Myeloma Research Foundation (MMRF), collects and aggregates de-identified genomic and clinical data from thousands of patients, providing each participant with a personalized genomic report based on their disease subtype, with the ultimate goal to individualize and optimize their treatment.

In the process, the initiative will create a data set that can inform treatment decisions for all patients with multiple myeloma (MM), according to Anne Quinn Young, MPH, brand president, MMRF Gathering, aggregating, and sharing the data will lead to "democratization of care," which is especially important in MM because it disproportionately affects underserved groups, Young said in an interview.

CONTINUED ON SP392 »

POLICY
Flatiron Health Leverages Expertise With Real-World Data to Examine Cancer Care Disparities
Mary Caffrey

DURING THE COVID-19 PANDEMIC, the challenge of reducing disparities in health care delivery and outcomes soared to the top of the policy agenda. It's a topic at most scientific meetings, and health plans and pharmaceutical manufacturers are building teams to address this issue.

For investigators who work with real-world evidence, health care disparities have been on the radar for some time. However, the current focus on disparities is shaping research priorities.

CONTINUED ON SP397 »
FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

BLENREP is the first and only BCMA-targeted ADC monotherapy. So you can offer your RRMM patients a different option.

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.

ADC = antibody-drug conjugate; BCMA = B-cell maturation antigen; RRMM = relapsed or refractory multiple myeloma.
IMPORTANT SAFETY INFORMATION
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 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 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 14%. 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.

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 and/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. 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.

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

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.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). 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 lymphocytosis decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

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%).

USE IN SPECIFIC POPULATIONS

Lactation: 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: Based on findings in animal studies, BLENREP may impair fertility in females and males.

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 95 patients who received BLENREP in the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

Renal or Hepatic Impairment: 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. The recommended dosage 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.
BLEREP 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 BLEREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

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

1 INDICATIONS AND USAGE

BLEREP 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).

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%), blurring of 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 KIR 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% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had full corneal epithelial healing, 28% were still on treatment, 9% were in follow-up, and 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, 86% 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 BLEREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

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) of full Prescribing Information].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLEREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].

5.2 BLEREP REMS

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

Notable requirements of the BLEREP REMS include the following:

- Prescribers must be certified through enrolling and completing training in the BLEREP REMS.
- Prescribers must counsel patients receiving BLEREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLEREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLEREP.
- Wholesalers and distributors must only distribute BLEREP to certified healthcare facilities.

Further information is available, at www.BLEREPREMS.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 thrombocytopenia 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 or 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) of full Prescribing Information].

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) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLEREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLEREP 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 BLEREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLEREP and for 4 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)].
- Thrombocytopenia [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 BLEREP 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.

Relapsed or Refractory Multiple Myeloma

The safety of BLEREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLEREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 99). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLEREP. Serious adverse reactions in ≥5% 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 (7%), 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 lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

Table 1. 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></td>
<td></td>
</tr>
<tr>
<td>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></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>20</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions*</td>
<td>21</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>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 epithelium changes with or without symptoms.

**Visual acuity changes were determined upon eye examination.

* Blurred vision included diplopia, vision blurred, 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: Albuminuria.

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-blmf, 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-blmf 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-blmf. 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.

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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 (8.3)]

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 and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and 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/1.73 m² 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 and for 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].

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) of full Prescribing Information, 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)].

BLENREP REMS:

BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia

• Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions

• Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].

• Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].

• 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 (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

Infertility

• 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 (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

For:

GlaxoSmithKline

Research Triangle Park, NC 27709
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August 2020 BRP:1BRS
©2021 GSK or licensor.
BLMADVT190001 January 2021
Produced in USA.
One thing that will ensure success in OCM.”

dispelled the idea of quick fixes, writing, “There is no fixed, not discarded. In an article earlier this year in Oncology Model, which uses a different platform.

The OCM does need work. For all it offers, the model’s payment structures were always playing catch-up with innovation. That’s a problem when gene and cell therapies are being used to treat more types of cancer.

Practices that stayed in the OCM learned by doing. Over the past year, some practices willingly embraced 2-sided risk—a move that once seemed unimaginable. Those that have succeeded—delivering better care and saving Medicare millions—say it took years of fine-tuning before practice transformation showed up on the bottom line.

A bright spot, from our perspective, is that real leadership in the OCM—and oncology reform in general—is bubbling up from the trenches as doctors, nurse navigators, and creative practice leaders find what works and share their knowledge. This happens at meetings such as the Community Oncology Alliance (COA) Payer Exchange Summit, which we cover in this issue, and at PCOC.

At these meetings, those leading the discussion of the OCM’s future are the oncologists and practice leaders we know best: our Strategic Alliance Partners (SAPs). EBO Associate Editor Kashyap Patel, MD, in his role as this year’s COA president, has called for keeping the OCM in place for now, at the same time endorsing CMS’ call to add health equity to the quality equation. Lalani Wilfong, MD, vice president of Payer Relations and Practice Transformation at McKesson Health and an EBO board member, spoke at a November 18 listening session about the technical challenges practices face in completing the OCM while launching the new mandatory Radiation Oncology Model, which uses a different platform.

Throughout the OCM’s run, our SAPs have been among those publishing commentary on the model and sharing their wisdom—including Wilfong and Patel, and leaders from The US Oncology Network, OneOncology, Northwest Medical Specialties, PLLC, and the Quality Cancer Care Alliance, among others.

The collective view of our partners is that the OCM is hard work but it’s worth it. It should be fixed, not discarded. In an article earlier this year in JCO Oncology Practice, authors from several SAPs dispelled the idea of quick fixes, writing, “There is no one thing that will ensure success in OCM.”

Sincerely,
Mike Hennessy Jr
President & CEO
Patel Receives Living the Mission Award

KASHYAP PATEL, MD, the CEO of Carolina Blood and Cancer Care Associates and associate editor of Evidence-Based Oncology™ received the 2021 Living the Mission Award from the National Community Oncology Dispensing Association (NCODA). Patel was honored during NCODA’s Fall Summit, held October 20-21 in Scottsdale, Arizona.

NCODA presents the award annually to members of the organization “who exemplify the mission and values of NCODA in its quest to advance the value of dispensing practices for oncology physicians and deliver positive outcomes through collaboration in the care of oncology patients.” According to the organization, honorees are recognized for their leadership, expertise, quality standards, best practices, and collaboration, as well as their involvement in community activities, student engagement, and volunteer activities.

Patel has served as the 2021 president of the Community Oncology Alliance and is active in multiple organizations to advance quality care in community oncology. He also serves as the co-chair of the annual meeting presented by The American Journal of Managed Care®, Patient-Centered Oncology Care®.

Congratulations, Dr Patel!

Biomarkers

Review: Era of Precision Medicine Dawning in Prostate Cancer

Brisk Tumor-Infiltrating Lymphocytes May Hold Prognostic Value in Primary Cutaneous Melanoma

Comprehensive Genomic Features, Therapeutic Biomarkers Are Identified in Clear Cell Renal Cell Carcinoma

Research Report

Surface Proteins in DLBCL Offer Therapeutic Targets

Investigators Document Muscle Loss During Immunotherapy for DLBCL

Samsung Bioepis White Paper Describes Barriers to Adoption of Biosimilars
ONE PROVEN PORTFOLIO. TWO FDA-APPROVED OPTIONS. THAT’S OUR FOUNDATION.

Only Foundation Medicine has an FDA-approved portfolio of tissue- and blood-based comprehensive genomic profiling tests. Our tests help identify treatment options across all solid tumors. FoundationOne®Liquid CDx and FoundationOne®CDx both analyze 300+ cancer related genes, report additional relevant biomarkers and genomic signatures, and offer high quality insights. Our proven portfolio allows providers to choose the most appropriate sample option, between a blood draw and a tissue biopsy, to help guide treatment strategies for advanced cancer patients.

Learn more about Foundation Medicine’s proven portfolio at foundationmedicine.com/portfolio

FoundationOne®CDx and FoundationOne®Liquid CDx are next-generation sequencing based in vitro diagnostic tests for advanced cancer patients with solid tumors and are for prescription use only. FoundationOne CDx utilizes FFPE tissue and analyzes 324 genes as well as genomic signatures. FoundationOne Liquid CDx analyzes 324 genes utilizing circulating cell-free DNA and is FDA-approved to report short variants in 311 genes. The tests are companion diagnostics to identify patients who may benefit from treatment with specific therapies in accordance with the therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the tests does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration.

Some patients may require a biopsy for testing with FoundationOne CDx when archival tissue is not available which may pose a risk. Patients who are tested with FoundationOne Liquid CDx and are negative for companion diagnostic mutations should be reflexed to tumor tissue testing and mutation status confirmed using an FDA-approved tumor tissue test, if feasible.

For the complete label, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com and www.F1LCDxLabel.com.
Objects in Motion

Truth is ever to be found in simplicity, and not in the multiplicity and confusion of things.

Sir Isaac Newton

Joseph Alvarnas, MD
EDITOR-IN-CHIEF
Spotlighting Key Therapies in the Oncology Pipeline for the First Half of 2022

MATTHEW GAVIDIA

INNOVATION IN THE ONCOLOGY drug pipeline has led to a record number of FDA approvals in recent years, as investigators and sponsors seek new treatments for the nearly 2 million cancer cases diagnosed in the United States each year. In this trend should continue, as regulators evaluate new therapies and those approved in other indications for unmet needs in the growing, aging cancer community. Below is a roundup of notable drugs in the oncology pipeline that have a Prescription Drug User Fee Act (PDUFA) date scheduled for the first half of 2022.

Ciltacabtagene Autoleucel (Cilta-cell)
Developed as a B-cell maturation antigen (BCMA)–directed chimeric antigen receptor (CAR) T-cell therapy, cilta-cell’s combined findings in its phase 1b/2 CARTITUDE-1 trial (NCT03548207) signal an exciting potential for developing treatment for the adult with heavily pretreated relapsed and/or refractory multiple myeloma (MM). Evidence shows that patients with MM have a poor prognosis if their disease progresses after 3 treatments, with a typical overall survival (OS) of less than 6 months.2

Marked by novel 2 BCMA-binding domains, Janssen’s cilta-cell was investigated among 97 patients with MM (median age, 61 years; 58.8% male) whose prior lines of therapy ranged from 3 to 18, with a median of 6 treatments. With 88% of patients identified as triple-class refractory and 42% as penta-refractory, CARTITUDE-1 findings reported at last year’s American Society of Hematology (ASH) Annual Meeting and Exposition showed that those treated with the investigational CAR T-cell therapy had a 12-month progression-free survival (PFS) of 77% (95% CI, 66%-84%) and a 12-month OS rate of 89% (95% CI, 80%-94%).3

Moreover, study participants exhibited an overall response rate (ORR) of 97% and a stringent response rate of 67%, and 93% of patients achieved minimal residual disease. Potential for administration in an outpatient setting was also noted because median onset of cytokine release syndrome (CRS), a common adverse event (AE) in CAR T-cell therapy, was 7 days after infusion, with 89% not experiencing CRS until day 4. CRS was seen in all but 5 patients, with most cases indicated as grade 1 or 2 and 99% resolving within 14 days. Neurotoxicity was reported in 21% of patients, in which 10% had neurotoxicity of grade 3 or higher. Overall, 6 individuals died due to AEs from treatment.

Following these findings, Janssen and its collaborators submitted a biologics license application (BLA) for cilta-cell in the treatment of adults with relapsed or refractory multiple myeloma. The application was accepted under priority review in May 2021. Cilta-cell was previously granted breakthrough therapy designation in December 2019 and orphan drug designation in February 2019.4

The FDA recently extended cilta-cell’s PDUFA date to February 28, 2022, citing the need for sufficient time in reviewing new information submitted following an FDA request. A November 1 statement said both collaborators had met with the FDA, with no additional clinical data having been requested.5 Additional research on cilta-cell is set to be presented at the 63rd ASH Annual Meeting and Exposition in December 2021, including the following:

- Longer-term follow-up data and new subgroup analysis results from the phase 1b/2 CARTITUDE-1 study
- Adjusted indirect comparison of CARTITUDE-1 patient outcomes relative to standard-of-care therapies in real-world clinical practice from the LocomMotion study (NCT04035226)
- First data release from cohort B and longer-term follow-up data from cohort A of the CARTITUDE-2 study (NCT04133636) in earlier lines of treatments

Tislelizumab
Tislelizumab, an anti–PD-1 immune checkpoint inhibitor, recently had its BLA accepted by the FDA for the treatment of unresectable recurrent locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior systemic therapy. ESCC is the most common type of esophageal cancer and sixth-leading cause of cancer death worldwide; right now, patients with ESCC typically have a 5-year survival rate of 19.9%.

The therapy also has potential to treat myriad oncology disease states as either a monotherapy or in combination with other drugs and is already approved in China for certain patients with non–small cell lung cancer (NSCLC), classical Hodgkin’s lymphoma, and metastatic urothelial carcinoma. Novartis’ BLA in ESCC marks the first overseas application for the drug; the application is based on findings of the phase 3 RATIONAL: 302 trial (NCT03430843) that investigated its use vs chemo-therapy as second-line treatment for advanced unresectable/metastatic ESCC. Findings presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting showed that tislelizumab met its primary end point of improvement in OS (median OS, 8.6 vs 6.3 m) and exhibited a 30% decreased risk of death (HR, 0.70; 95% CI, 0.57-0.85; P = .0001), compared with investigator-chosen standard chemo-therapy (paclitaxel, docetaxel, or irinotecan).

The treatment is designed to have reduced binding to Fc receptors, a potential mechanism of resistance associated with other PD-1 inhibitors. In preclinical studies, binding to Fcγ receptors on macrophages has been shown to compromise the antitumor activity of PD-1 antibodies through activation of antibody-dependent macrophage-mediated killing of T effector cells. However, the clinical impact of these features is not yet known.

The BLA currently has a PDUFA target action date of July 12, 2022. If approved, the drug would compete with other checkpoint inhibitors, including Bristol Myers Squibb’s (BMS) nivolumab (Opdivo) and Merck’s pembrolizumab (Keytruda), both approved as first-line treatments in combination with chemotherapy for patients with ESCC regardless of PD-L1 status.6 Novartis is also investigating tislelizumab as a monotherapy and combination therapy for other indications, including in NSCLC, gastric cancer, hepatocellular carcinoma, and nasopharyngeal carcinoma, with broad potential in several other solid tumors.7,8

The first half of 2022 promises to bring approvals for cilta-cell, a new CAR T-cell therapy in multiple myeloma; tislelizumab, an immune checkpoint inhibitor to treat esophageal squamous cell carcinoma; tebentafusp, a bispecific T-cell engager for a specific form of metastatic uveal melanoma; and pirtobrutinib, a BTK-inhibitor to treat B-cell malignancies.

Tebentafusp
As the first investigational therapy in a phase 3 trial to show a survival benefit in patients with the rare and potentially fatal metastatic uveal cancer, tebentafusp, a bispecific T-cell engager (BITE), functions by simultaneously binding to lymphocyte CD3 receptors and gp100 antigens expressed on cancer cells—a novel process of bringing T cells to tumor cells that has not been explored in prior solid tumor indications. Based on findings from the IMCgp100-202 trial (NCT03070392) presented at the American Association for Cancer Research Annual Meeting 2021,9 Immuncore’s tebentafusp was granted BLA approval with priority review by the FDA and marketing authorization by the European Medicines Agency in the treatment of patients with HLA-A*02:01–positive metastatic uveal melanoma.10

Notably, patients treated with the experimental agent over a median follow-up of 14.1 months were associated with a median OS of 21.7 months.
Among the 121 patients with CLL, SLL, or MCL who were treated with pirtobrutinib, 32% patients with MCL previously treated with covalent BTK inhibitors. The most common AEs overall included fatigue (20%), diarrhea (17%), and contu-
sion (13%), and the most common grade 3 or higher AE was neutropenia (10%).

Of the 117 patients with CLL, SLL, or MCL who responded, all but 4 remain progression-free to date. In fact, data have also shown that the ORR with pirtobrutinib increases over time, with those who had been on treatment for at least 10 months exhibiting an ORR of 86%. In addition to the phase 1/2 BRUIN trial, a series of phase 3 studies investi-
gating pirtobrutinib are planned to be initiated in 2021, including 3 in CLL and one in MCL.

New Indications for FDA-Approved Therapies

Along with the new therapies poised to enter the oncology market in 2022, there are several FDA-approved cancer therapies that may be approved for new indications.

**Pirtobrutinib**

Although no BLA has been submitted for pirtobrut-
inib, the findings of the phase 1/2 BRUIN clinical trial (NCT03740529) have shown promising efficacy and safety for Eli Lilly and Company’s investigational, highly selective, noncovalent Bruton tyrosine kinase (BTK) inhibitor in the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and other B-cell malignancies. Results published in The Lancet reported that pirtobrutinib was investigated in 323 patients with relapsed or refractory disease, including those with CLL or small lymphocytic leukemia (SLL) and mantle cell lymphoma (MCL). Wäldenström macroglob-
ilinemia, and other non-Hodgkin lymphomas. In patients with CLL/SLL, evaluated for response (n = 139), ORR was shown to be 63%; more notably, findings in those treated with a previous covalent BTK inhibitor suggest a potential opportunity to address a growing unmet need for alternative therapies. Currently, 5-year discontinuation rates with the BTK inhibitor ofibrutinib are 41% in the frontline setting and 54% for those with relapsed/refractory disease. Among the 121 patients with CLL/SLL who were treated with a previous covalent BTK inhibitor (median previous lines of treatment, 4), ORR was 62%. This comprises a 47% partial response (PR) rate and a 15% PR rate with lymphocytosis, according to dose-expansion/dose-expansion findings presented during the Society of Hematologic Oncology 2021 Annual Meeting. Moreover, similar response rates were found in patients with CLL who had previous covalent BTK inhibitor resistance (ORR, 67%) and covalent BTK inhibitor intolerance (ORR, 52%), as well as those with BTK/C481 mutations (ORR, 71%) and BTK wild-type (ORR, 66%) disease. Cases of progressive disease in CLL following administration of covalent BTK inhibitors have been found most frequently in patients with BTK/C481 mutations, which prevent covalent BTK inhibitors from achieving effective target inhibition. Further findings showed an ORR of 52% in patients with MCL previously treated with covalent BTK inhibitors. The most common AEs overall included fatigue (20%), diarrhea (17%), and contusion (13%), and the most common grade 3 or higher AE was neutropenia (10%).

**RELATIVAMIR AND NIVOLUMAB.** Another therapy combination with potential in the treatment of melanoma is BMS’ relatlimab and nivolumab. This combination recently had its BLA accepted under priority review for the treatment of adults and pediatric patients with unresectable or meta-
static disease, with a PDUFA date scheduled for March 19, 2022. Based on findings of the phase 2/3 RELATIVITY-047 trial (NCT03470922), the fixed-dose combination, administered as a single infusion, was associated with a statistically significant and clinically meaningful
IN AN IMPORTANT ADVANCE for precision medicine, the Medicare administrative contractor Palmetto GBA, through its Molecular Diagnostic Services Program (MolDX), has recently finalized a local coverage determination (LCD) for tests for minimal residual disease (MRD).1 Following the release of a draft policy in September 2020, the final LCD in MRD testing was announced November 11.

The decision, which takes effect December 26, covers the Adaptive Biotechnologies Corporation’s clonoSEQ test to detect and monitor MRD for patients with B-cell acute lymphoblastic leukemia, multiple myeloma, and chronic lymphocytic leukemia. The LCD also creates a pathway for clonoSEQ’s use in other indications.2 The LCD also covers Natera, Inc’s Signatera MRD test for several indications involving patients with solid and hematologic cancers.3

In its notice, MolDX cited National Coverage Determination 90.2, which “allows contractors to cover next-generation sequencing tests as a diagnostic laboratory test for patients with cancer in specific circumstances.” MolDX outlined 10 specific conditions that must be met for MRD tests to receive coverage; the conditions include, but are not limited to, the following:

The patient must have a personal history of cancer. The type and staging that matches the intended use of the MRD test.

The use of the test must align with guidelines from the National Comprehensive Cancer Network “or other established guidelines as a condition that requires a definitive change in patient management.”

The test is demonstrated to “identify molecular recurrence or progression” before evidence of progression is present and demonstrates “sensitivity and specificity of subsequent recurrence or progression” that is on par with radiological or other evidence of recurrence or progression.

As a comparatively new application of novel genomic technologies, MRD testing has been highly regarded for its sensitivity and specificity in allowing detection of extremely dilute tumor material or tracking the relative increase or decrease of tumor material being deposited in the blood.

Specifically, MRD testing can be leveraged to diagnose cancer progression, recurrence, or relapse before there is clinical, biological, or radiographic evidence of progression, recurrence, or relapse as well as detect tumor response to therapy by measuring the proportional changes in the amount of available tumor DNA.

“Both above uses may enable physicians to better assign risk stratification, deploy alternate treatment strategies, or preclude the use of unnecessary adjuvant therapies,” the statement from MolDX said.1 Several limitations have also been identified for MRD testing, including discordance of mutations between circulating-tumor (ct) DNA and tissue, possibility of ctDNA enrichment with therapy resistance alterations, and inability to detect a second primary tumor.

“We are pleased that MolDX finalized the LCD for next-generation sequencing…tests for MRD, solidifying patient access to the critical results that our clonoSEQ assay provides across the continuum of care,” said Lance Baldo, MD, chief medical officer of Adaptive Biotechnologies. “This LCD provides a pathway for the continued expansion of clonoSEQ into routine clinical care to benefit the more than 700,000 patients living with lymphoid malignancies in the United States. We look forward to our continued work with Medicare to help evolve coverage within this rapidly advancing field.”

“Monitoring ctDNA kinetics with Signatera can identify treatment nonresponders earlier than imaging alone and independent of other biomarkers, including PD-L1 and tumor mutational burden,” said Solomon Moshkevich, general manager of oncology for Natera. “We look forward to working with Medicare and with the oncology community to make personalized monitoring and MRD assessment accessible for cancer patients of all tumor types.”

REFERENCES

**WARNINGS AND PRECAUTIONS**

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

- **Thrombocytopenia** has been reported with NINLARO. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines. Adjust dosing as needed. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle.

- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting, were reported with NINLARO and may occasionally require the use of anti-diarrheal and antiemetic medications, and supportive care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for severe symptoms.

Please see additional Important Safety Information on the next page and accompanying Brief Summary.

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10/21 USO-IXA-0248
• **Peripheral Neuropathy** (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

• **Peripheral Edema** was reported with NINLARO. Monitor for fluid retention. Investigate for underlying causes when appropriate and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

• **Cutaneous Reactions**: Rash, most commonly maculopapular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification.

• **Thrombotic Microangiopathy**: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

• **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly during treatment and adjust dosing as needed.

• **Embryofetal Toxicity**: Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. NINLARO can cause fetal harm.

**ADVERSE REACTIONS**

The most common adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen, respectively, were diarrhea (42%, 36%), constipation (34%, 25%), thrombocytopenia (78%, 54%; pooled from adverse events and laboratory data), peripheral neuropathy (28%, 21%), nausea (26%, 21%), peripheral edema (25%, 18%), vomiting (22%, 11%), and back pain (21%, 16%). Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%).

**DRUG INTERACTIONS**: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

**SPECIAL POPULATIONS**

• **Hepatic Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.

• **Renal Impairment**: Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

• **Lactation**: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.


Please see accompanying Brief Summary on the following pages.
5.6 Thrombotic Microangiopathy: Cases, sometimes fatal, of thrombotic microangiopathy have been reported in patients treated with NINLARO. Patients treated with NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall difference in safety was observed between these two age groups. In addition, there was no overall difference in safety between younger and elderly subjects, and other reported clinical experience has not identified age to be a factor for either adverse drug reactions or drug dosages resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥ 5% of Patients with a ≥ 5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>69 (19)</td>
<td>52 (14)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>100 (28)</td>
<td>77 (21)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (42)</td>
<td>130 (36)</td>
</tr>
<tr>
<td>Constipation</td>
<td>122 (34)</td>
<td>90 (25)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>72 (20)</td>
<td>74 (21)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td>68 (19)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Musculoskeletal and connective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>74 (21)</td>
<td>57 (16)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>91 (25)</td>
<td>66 (18)</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 16.0.

Table 5 represents pooled information from adverse event and laboratory data.

Table 5: Thrombocytopenia and Neutropenia

<table>
<thead>
<tr>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>281 (78)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>240 (67)</td>
</tr>
</tbody>
</table>

Hepatic Zoster

Hepatic Zoster was reported in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider’s discretion. Patients treated in the NINLARO regimen who (Continued on next page)
received antiviral prophylaxis had a lower incidence (< 1%) of herpes zoster infection compared to patients who did not receive prophylaxis (6%).

Eye Disorders
Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 26% in patients in the NINLARO regimen and 16% of patients in the placebo regimen. The most common adverse reactions were blurred vision (6% in the NINLARO regimen and 3% in the placebo regimen), dry eye (5% in the NINLARO regimen and 1% in the placebo regimen), and conjunctivitis (6% in the NINLARO regimen and 1% in the placebo regimen). Grade 3 adverse reactions were reported in 2% of patients in the NINLARO regimen and 1% in the placebo regimen.

Adverse Events Reported Outside of the Randomized Controlled Trial

The following serious adverse reactions have each been reported at a frequency of < 1%: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inducers: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John’s Wort).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to pregnant women. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ixazomib caused embryo-fetal toxicity in pregnant rabbits at doses that were approximately 8- and 10-fold higher than the maximum recommended dose. Ixazomib caused embryo-fetal toxicity in pregnant rats at doses that were approximately 10- and 7-fold higher than the maximum recommended dose. Therefore, use NINLARO during pregnancy only if the potential benefit justifies the potential risk to the fetus. The safety and effectiveness of NINLARO have not been established in pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO. Contraception: Females: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the final dose. NINLARO can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO. Contraception: Females: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the final dose. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days after the final dose.

8.2 Lactation: Risk Summary: There are no data on the presence of ixazomib or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions from NINLARO in a breastfed infant, advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential: NINLARO can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO. Contraception: Females: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the final dose. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days after the final dose.

8.4 Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 or over, while 17% were 75 or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment: In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: Overdose, including fatal overdose, has been reported in patients taking NINLARO. Manifestations of overdose include adverse reactions reported at the recommended dosage. Serious adverse reactions reported with overdose include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death. In the event of an overdose, monitor for adverse reactions and provide appropriate supportive care. NINLARO is not dialyzable.

17 PATIENT COUNSELING INFORMATION

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

- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdosage has led to death.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥ 72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising [see Warnings and Precautions (5.1)].

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their healthcare providers if these adverse reactions persist [see Warnings and Precautions (5.2)].

Peripheral Neuropathy: Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs [see Warnings and Precautions (5.3)].

Peripheral Edema: Advise patients to contact their healthcare providers if they experience unusual swelling of their extremities or weight gain due to swelling [see Warnings and Precautions (5.4)].

Cataracts: Advise patients to contact their healthcare providers if they experience new or worsening vision [see Warnings and Precautions (5.5)].

Renal Toxicity: Advise patients to contact their healthcare providers if they experience new or worsening renal impairment [see Warnings and Precautions (5.6)].

Hepatotoxicity: Advise patients to contact their healthcare providers if they experience jaundice or right upper quadrant abdominal pain [see Warnings and Precautions (5.7)].

Other Adverse Reactions: Advise patients to contact their healthcare providers if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura [see Adverse Reactions (6.1)].

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose.

Advise women using hormonal contraceptives to also use a barrier method of contraception [see Use in Specific Populations (8.1)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose [see Use in Specific Populations (8.1)].

Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the final dose [see Use in Specific Populations (8.1)].

Other Adverse Reactions: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

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A National Perspective on the Opportunities, Challenges Facing Health Care Cost and Sustainability

MATTHEW GAVIDIA

COVID-19, RISING SPENDING, and the need to address health equity each offer challenges for the health care industry. Michael E. Chernew, PhD, co-editor in chief of The American Journal of Managed Care® and chair of the Medicare Payment Advisory Commission (MedPAC), warned in a November 10 keynote address at the National Alliance 2021 Annual Forum, a meeting of the National Alliance of Healthcare Purchaser Coalitions.

Chernew, a health care economist at Harvard Medical School, said these issues create fiscal and operational limits that will affect sustainability and the transition to value-based care.

Focusing primarily on health care spending, Chernew said “everyone wants to pay for value until they actually have to pay for value,” and that efficient delivery and pricing are key to financing and providing access to high-value care.

“We want to avoid spending on low-value services. There is a lot of waste in the system in a range of ways, and we don’t want to have people using care that they shouldn’t get or care that’s more expensive when they could get a cheaper service,” he added.

Notably, managing cost-related issues varies according to the type of coverage sector, with spending for commercial insurance shown to be growing much more rapidly than that of Medicare and Medicaid.

With prescription drug costs identified as a cost burden across all insurance types, Chernew said that health care issues specific to each sector included beneficiary growth and long-term social support for Medicaid, prices for commercial insurance, and beneficiary growth and utilization for Medicare.

Speaking on the fiscal challenges for Medicare, whose Part A trust fund is scheduled to be depleted in 2026, CMS’ Office of the Actuary estimated a 4.7% spending growth per year over the next decade, in which almost half (2.2%) is attributed to beneficiary growth and more than half to volume growth (3.6%). Moreover, these estimates indicate that Medicare price growth is scheduled to run below inflation, at ~0.7%.

“The current law is that Medicare fees for physicians (and hospitals in general) will grow [more slowly] than inflation. So the main part now of assumed Medicare cost growth going forward is an assumption about the rate of volume and intensity growth. And the way to solve the Medicare problem…is…to reduce the actual growth in volume and intensity below what the Office of the Actuary assumed in their projections.”

Chernew listed 5 specific issues affecting Medicare spending:

- Efficient pricing, including site-neutral payment, wage index, updates in recommendations on the Medicare Physician Fee Schedule, and postacute care
- Medicare Advantage
- Launch prices for drugs
- Alternative payment models (APMs)
- Safety net

Although it was designed for cost savings and is efficient in providing benefits to Medicare beneficiaries, Medicare Advantage was noted to be likely overpaid. Some health experts perceive the plan as a mechanism to compensate for the fact that the Medicare benefit package is actually not that great, said Chernew.

“When Medicare Advantage plans bid below fee-for-service (FFS) benchmarks, they have to give a lot of that back to beneficiaries in terms of transportation services, lower cost-sharing, and lower part D premiums. It’s actually quite a good program for getting people benefits, but it is more expensive than FFS,” he explained.

Delving further into the cost burden in Medicare, he noted that the current system encourages the use of high-price drugs, as issues regarding biosimilar entry and reimbursement continue to impede cost-effective competition. With payers not only financing previous drugs but also the innovation required to invent novel therapies, Chernew said that simply lowering prices is not an effective solution.

“We need to find out how to get lower prices, get people to use the right drugs, and encourage innovation, because in many clinical areas, the drugs are actually really important.”

Ultimately, curbing cost requires a look into the nuances that may raise the prices for types of care. Addressing FFS, Chernew said that paying for specific care services encourages inefficient production due to the revenue and profit tied to these wasteful options.

In adopting APMs, these models allow for the integration of more cost-effective and value-based care services, noted Chernew, while also giving the flexibility to mix and match services to produce efficient health care.

As the plethora of APMs available may create problems for care delivery or even impede commitment from health care systems, focusing on the core message of lowering cost and improving quality through fewer models was recommended to improve uptake.

“I think we will continue to move toward these APMs, because I think (those involved with) the delivery system will understand [that] if given the choice between what’s behind door number 1, which is subinflation fee increases, vs number 2, you get to own the waste. If they were really rational, they would want to own the waste….That requires a business model change, which is hard for people to conceptualize: getting paid for doing less as opposed to getting paid [for] doing more.”

Further issues regarding cost in Medicare include the safety net, which Chernew said is the biggest problem he manages at MedPAC. As COVID-19 has caused significant utilization and financial disruption that has contributed to the bankruptcy or closure of some hospitals, the “lumpy” payment system by which each hospital receives a 3% raise was noted to have a disproportionate impact on vulnerable hospitals and those serving vulnerable patients.

“Figuring out how to deal with that heterogeneity is a challenge. Defining what the safety net is, who the important providers are, how we make sure there are enough providers in the areas that we need to serve the vulnerable populations—all those things are really important.

“I think we need to build out a care system in this country that makes sure that everybody has access to high-quality care…in a way that doesn’t overpay a whole bunch of other people. And that’s kind of the core challenge that we’ve had.”

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Cancer Treatments, Orphan Drugs, Gene Therapies Represent Big Areas to Watch in Specialty Drug Pipeline

During Her October 20 Presentation at the Academy of Managed Care Pharmacy Nexus 2021 meeting, Aimee Tharaldson, PharmD, senior clinical pharmacist of emerging therapeutics at Express Scripts, highlighted the most anticipated specialty pharmacy drugs awaiting FDA approval, which include several treatments for cancer and rare diseases as well as gene therapies. Tharaldson identified the specialty medications that are expected to receive FDA approval or new indications in the next 12 months and reported on the likely effect that new specialty medications will have in the managed care market.

At the time of Tharaldson's presentation, 31 specialty drugs had been approved in 2021, with 8 more expected to be approved by the end of the year. If this schedule holds, it will rival the 39 approvals that were given in 2020.

Biosimilars
A big topic of discussion was the potential for biosimilars, which represents a $61-billion opportunity for manufacturers. By 2025, 98 patent expirations are anticipated, including those for Humira (adalimumab), Stelara (ustekinumab), Eylea (etanercept), and Prolia (denosumab).

Tharaldson mentioned 13 biosimilars that are pending approval, including some referencing Humira, Avastin (bevacizumab), Neupogen (filgrastim), Novolog (insulin aspart), Neulasta (pegfilgrastim), and Lucentis (ranibizumab).

Oncology
Tharaldson discussed how approximately 17 million Americans have a history of cancer and nearly 2 million new cases of cancer are diagnosed each year. In 2020, 19 cancer drugs were approved, which was a new record in approvals. So far, in 2021, 15 have been approved, with 2 more expected to receive approval by the end of November 2021.

Tharaldson mentioned that 6 new cancer drugs are expected to be approved during the first quarter of 2022 to treat neuroendocrine tumors, uveal melanoma, chronic myeloid leukemia, melanoma, chronic lymphocytic leukemia, and non–small cell lung cancer.

Orphan Drugs
As of October 2021, 9 of the drugs approved during the year were indicated for orphan conditions. Among all drugs currently in the specialty drug pipeline, 47% are indicated for orphan conditions, compared with 31% for oncology and 22% for other conditions.

Gene Therapies
Gene therapies involve the modification of a person's genes to treat or cure a disease. Tharaldson said that about 400 gene and cell therapies are in the pipeline and that the market is expected to generate $25 billion per year by 2034.

Nine gene therapies have been approved between 2010 and 2021, and 9 more are expected to receive approval by 2022, including Janssen's cilta-cabtagene autoleucel, which was on schedule to receive approval in late November 2021.

Inflammatory
The inflammatory pipeline currently contains 8 drugs, 4 of which have already been approved but are expected to get new indications for psoriatic arthritis, ankylosing spondylitis, Crohn disease, and alopecia areata. Additionally, the approval for the psoriasis medication bimekizumab, which was anticipated in 2021, was deferred due to the manufacturer, UCB, receiving a complete response letter from the FDA requiring them to do additional testing.

Acutic Dermatitis
Tharaldson explained that the atopic dermatitis pipeline through 2023 has 7 drugs pending approval, 4 of which will be administered orally and 3 subcutaneously.

Multiple Sclerosis
Through 2025, the multiple sclerosis space is expected to have approvals for 5 new medications, 4 of which are orally delivered Bruton tyrosine kinase inhibitors. The outlier, ublituximab, is expected to be approved in 2022 and is the only anti-CD20 monoclonal antibody currently in the pipeline.

HIV
Tharaldson said that 95% adherence is needed to maintain viral suppression of HIV, which is why the most frequently used medications rely on daily intake. However, ViiV Healthcare is looking to get an updated approval for its cabotegravir/rilpivirine combination to be administered every 2 months instead of every 1 month, which is expected in December 2021.

Of the 5 products awaiting approval, all are for injectable formulations, with the exception of islatravir by Merck, which is delivered orally and is expected to be approved in 2022.

Aimee Tharaldson, PharmD, senior clinical pharmacist of emerging therapeutics at Express Scripts, highlighted the most anticipated specialty pharmacy drugs awaiting FDA approval. These include 6 new cancer drugs, 13 biosimilars, and 13 products awaiting approval for nonalcoholic steatohepatitis, or NASH.

Nonalcoholic Steatohepatitis (NASH)
NASH is estimated to impact between 6 and 19 million Americans, according to Tharaldson, and treatment options are limited. The treatment space is expected to grow substantially in the coming years, with 13 products awaiting approval between 2023 and 2024. Eventually, the NASH therapeutic market is expected to generate $20 billion per year as the treatment space grows.

Alzheimer Disease
The Alzheimer disease pipeline currently has 5 drugs awaiting approval, with 3 anti–amyloid-beta antibodies expected to be approved in 2022 or 2023 and 2 anti-tau antibodies expected to be approved in 2024, stated Tharaldson.

Alzheimer disease is estimated to affect 6.2 million Americans. Although Aduhelm (aducanumab-avwa) was approved in June 2021, the approval has drawn a large amount of controversy; data have revealed the possibility that the drug does not work as well as previously disclosed.

Hemophilia
Tharaldson highlighted 9 drugs that are expected to receive FDA approval between 2022 and 2023: 5 are indicated for just hemophilia A, 2 for just hemophilia B, and 2 for both hemophilia types A and B. The 2 drugs indicated for both hemophilia A and B are delivered through subcutaneous injection; the others are all administered through intravenous infusion. Hemophilia A is the most common type of hemophilia, estimated to account for about 80% of hemophilia cases.
Panel: Biosimilar Acceptance May Be Greater Among Payers Than Previously Thought

Payers were found to be more accepting of biosimilars than expected, according to survey results presented during a panel discussion at the Academy of Managed Care Pharmacy’s 2021 Nexus meeting.

The panel discussed the current trajectory of biosimilar adoption, barriers to adoption, and how coverage of biosimilars is anticipated to evolve in the coming years.

Tasmina Hydery, PharmD, MBA, RCGP, assistant director of integrated delivery solutions at AmerisourceBergen/Xcenda, talked about the anticipation surrounding the launches of the 6 FDA-approved adalimumab biosimilars, which are scheduled to enter the US market in 2023, and the interchangeable formulation of Semglee (insulin glargine), the first interchangeable biosimilar to be approved in the United States.

Hydery mentioned that reactions to the potential for interchangeable biosimilars have been positive; however, states have enacted their own laws, which has caused confusion among payers, patients, and providers on whether interchangeability designations will have an impact.

“Some FDA leaders have noted that there’s potential for cost savings, there’s more competition in the marketplace, and now there’s potentially more access to affordable products. But others are speculating whether this will actually translate into uptake and how important it is to educate pharmacists about the different state laws and how pharmacies will actually operationalize the availability of the interchangeable biosimilars,” said Hydery.

Another challenge for biosimilar uptake concerns patent thickets, which Congress is working to address, according to Hydery. She said that by limiting the number of continuation and divisional patents that can be filed for a single patent and capping the number of patents that could be asserted against a biosimilar product, Congress could prevent future patent thickets.

Cate Lockhart, PhD, PharmD, MS, executive director of the Biologics and Biosimilars Collective Intelligence Consortium, delved into the existing research on coverage, adoption, and utilization patterns of biosimilars, saying that survey results show that among 17 of the largest commercial health plans in the United States, only 14% cover biosimilars as preferred products.

Lockhart also explained how the filgrastim biosimilar Zaxio (filgrastim-sndz) is listed as a preferred product on coverage plans 51% of the time, a figure much higher than the national average (32% and 3%, respectively). Lockhart said that by limiting the number of continuation and divisional patents that can be filed for a single patent and capping the number of patents that could be asserted against a biosimilar product, Congress could prevent future patent thickets.

Lockhart mentioned that 35% of payers are continuing to cover all biosimilars, according to Jennifer Snow, MPH, vice president of reimbursement policy insights at AmerisourceBergen/Xcenda. Health plans (48%) and pharmacy benefit managers (22%) were most likely to cover all biosimilars whereas 100% of integrated delivery networks surveyed said they cover only some biosimilars.

Overall, Snow said that 59% of payers agreed that biosimilars have provided their organization with meaningful cost savings. Most surveyed payers said that they contract with biosimilar manufacturers for select biosimilars and that they would cover the biosimilar for the same indications as the reference product (75% and 55% respectively), regardless of whether the indications were approved by the FDA.

Snow proclaimed that the statistics that surprised her most were that 96% of the surveyed payers agreed that biosimilars are safe and effective for treatment-naive patients and that 92% agreed that switching to a biosimilar from a reference product was safe and effective. Cost savings were also cited as the most important factor driving the adoption of biosimilars; 65% of payers ranked it as their top influencing factor, followed by 27% who chose interchangeability status as their top influencing factor.

Lockhart noted Kaiser Permanente’s success in achieving substantial biosimilar uptake, achieving a 95% utilization rate for filgrastim-sndz and 80% rate for infliximab-dyyb, both much higher than the national average (32% and 3%, respectively). Lockhart said they were able to achieve such numbers by adopting the biosimilars shortly after they received FDA approval.

Finally, Lockhart explained that despite biosimilar adoption having a slow start, the United States is starting to see increased utilization, with shorter lag times between approval and launch. Additionally, many managed care settings are seeing success by implementing strategies to encourage biosimilar use; they anticipate biosimilars covered by pharmacy benefits and are identifying potential formulary strategies.

“There’s a lot of hope and a lot of people who I think are really invested in doing this, because we want patients to get access to the medications they need at a cost they can afford. And we’ve seen some successes with that,” said Lockhart.

Simplifying the Complexity of Value-Based Contracting: Present, Future Implications in Specialty Pharmacy

The current integration and future implications of value-based contracting (VBC) in specialty pharmacy signal a shift for payers, providers, and the pharmaceutical industry, and stakeholders must strategically position themselves to excel in a changing market, according to panelists in a session at the Asembia 2021 Specialty Pharmacy Summit in Las Vegas.

Noting that VBC will be an essential pillar in specialty pharmacy within the next 4 years, moderator Burt Zweigenhaft, PhD, DLitt, managing partner, Upstream Partners, opened the discussion by introducing the speakers on the panel and asking them how they would define VBC:

- Jeff Berkowitz, JD, chief executive officer, Real Endpoints
- Todd Grisco, vice president, Patient Value & Access, Takeda Oncology
- Kjel Johnson, PharmD, vice president, Specialty and Client Solutions, CVS Health
- Steven Peskin, MD, MBA, executive medical director, Population Health & Transformation, Horizon Blue Cross Blue Shield of New Jersey
- Michael Lynch, CPA, MBA, executive director, Oncology Market Access, Bayer

Although definitions of VBC vary across the health care system, Berkowitz explained that the essentials involve a performance-based reimbursement agreement between a payer and a pharmaceutical company that deals with pricing or reimbursement issues that are tied to the value of potential outcomes.

“You can have a lot of different ways of doing that, but the broadest is that you want to improve quality across the health care system with the drug that you’re delivering, with the potential to lower overall costs,” he added.
Opening the scope of VBC to quality of care improvement in addition to cost, there remain several challenges that continue to impede the optimization of these agreements—specifically, internal alignment on market access and risk sharing, and transparency and trust when working with payers.

In mirroring Bayer’s VBC framework around clinical trials, which did not require contracts with payers and pharmacy benefit managers, Lynch discussed how manufacturing these contracts warranted a top-down approach that was of value to manufacturers, patients, payers, and providers. Although the approach is seemingly complex, the simple effort of beginning these discussions was highlighted by Lynch. “I think as you go into these, you’ll hit hurdles with one customer type or another customer type, but the idea is if you don’t start small and you don’t start early, then you won’t have that muscle memory. When it gets more challenging, you won’t have that experience you’ll be able to rely on.”

From a pharmaceutical perspective, these agreements come with risk, but they also serve as an opportunity to get either preferred product placement or to differentiate one’s product from the competition. Manufacturers can also address often burdensome prior authorizations with these agreements.

In fact, Grisco noted that Takeda Oncology’s approach to VBC revolves around making their drugs more attractive as first-line therapies by reducing some of the uncertainty that payers and providers may have in utilizing their product.

Noting that their therapies for epidermal growth factor receptor–mutated non–small cell lung cancer are effective but not efficacious for everyone due to toxicity, Takeda constructed a program focused on continuation of therapy to address those uncertainties of effectiveness and tolerability early in treatment.

“For those patients who discontinued within the first 2 months, we’re providing a very significant rebate back to our payer partners to reduce that uncertainty,” said Grisco.

Ultimately, engaging in these conversations with payers and providers is warranted to optimize the full capabilities of VBC.

“Across the board, whether it’s on the provider side, understanding it at the payer side, or the pharma side, we really have an evolution of skill sets that is needed to be able to have a much more coordinated, sophisticated conversation around delivering, and going at risk together, for a greater quality outcome at a potentially lower cost,” said Berkowitz.

In concluding, panelists provided several thoughts on the future of VBC and its growing importance in specialty pharmacy.

“Probably hundreds of VBCs are in effect today. So, they’re here, but they’re just not as effective as they need to be to be widely adopted,” said Grisco.

“The other thing is, we’re going to need fundamental changes in infrastructure to really enable VBCs to become core to a market access strategy, to a product’s commercialization strategy.... the whole world doesn’t have to go to VBCs, but there will be a subset of high-cost, potentially lower-utilization products that are really going to benefit, and that will take special changes.”

Berkowitz added that while he doesn’t expect structural changes when it comes to VBCs, the evolving capabilities of operating systems and potential transparency of derived data regarding the benefits of value-based care delivery could help drive these agreements further.
By Lauren Clampet)

The care management infrastructure has led to a host of savings initiatives, including Texas Oncology's gold carding program, which allows physicians with good track records to reduce delays when they adhere to 6 specific pathways regimens.

**Two Models at Once.** Diaz presented information from Blue Ridge Cancer Care, which participates in 2 governmental value programs: the OCM and a Virginia Medicaid episode-of-care pilot. The practice also takes part in the Oncology Medical Home through the American Society of Clinical Oncology. “They attempt to lower costs for all payers as result,” Diaz said. “This is all being accomplished with transparency and closer collaboration with hospice entities and attention to the well-being of patients.”

**Reducing Inpatient Stays.** Wilfong presented information from the Center for Cancer and Blood Disorders, based in Fort Worth, Texas, showing the results of an effort for the practice to gain real-time notice when a patient visited the ED. This effort allowed the practice to intervene and reduce hospital stays, with a dispatch system allowing patients to get more direct assistance at home. “They’ve done a lot of great work in this space,” Wilfong said.

The Oncology Network, with 14 practices in the OCM, has a total of 18 practices participating in 49 commercial value-based contracts across 24 programs. One of these practices, Minnesota Oncology, is involved in 14 different value-based programs, plus the Merit-based Incentive Payment System. Drilling into the data allowed OHC Specialists in Cancer and Blood Disorders of Ohio to uncover the mystery behind midday ED visits. Patient satisfaction responses showed that people could not get through on the practice’s phone system—or were not receiving returned phone calls—and were heading to the ED despite instructions to contact the practice. Fixing the communications issue allowed the practice to cut down on their patients’ unnecessary ED visits.

**Reducing Administrative Burdens.** Wilfong presented data on Texas Oncology, which is pursuing direct employer arrangements and has seen a reduction of $139.5 million in drug costs through use of biosimilars and a bone health initiative. Additionally, Texas Oncology’s gold carding program, a prior authorization initiative under a new state law, allows physicians with good track records to reduce delays when they adhere to 6 specific pathways regimens.

“Hopefully, that [initiative] will expand,” Wilfong said. It grew out of discussions in which payers and providers agreed that some standard, evidence-based regimens shouldn’t require prior authorization. “Everybody would agree that these things are beneficial for patients—so let’s reduce some administrative burden on the practice and the payer to move things forward,” explained Wilfong.

**Evolving From the OCM.** Diaz then discussed his own practice, Florida Cancer Specialists, in which more than 70% of the lives are being managed in a value-based model.

“A lot of this evolved from participating in the OCM,” Diaz said, but the lessons of earning shared saving and reducing unplanned admissions and ED visits have migrated beyond Medicare to commercial and employer-based contracts, allowing the practice to control increasing cancer care costs.

*“As you can see, we have] a whole list of different things where I think we’ve been able to accomplish significant milestones, especially with the OCM,” said Diaz, pointing to 5 consecutive years of shared savings and other milestones. The care management infrastructure has led to a host of savings initiatives, “whether it’s 24/7 nurse on call, standardized protocol-driven symptom management, social and financial support for patients, [or] survivorship programs.” The overview, Diaz said, shows how efforts to “increase value with transparency” and work with employers can help patients “improve their journey while reducing everyone’s costs.”

“All of this tied together helps us take better care of our patients,” Diaz concluded.

**Covering Key Cancer Services Before Deductible Would Help Close Gaps, Fendrick Says**

IT’S BEEN 20 YEARS since Mark Fendrick, MD, heard his mother’s observation about one of his studies: “I can’t believe you had to spend a million dollars to show that if we make people pay more for something, they will buy less of it.”

Evidence that patients with high out-of-pocket costs will avoid screenings and preventive care is the foundation of Fendrick’s mission to change the quality equation in health care. The idea that payers should make it easy to catch cancers early or treat chronic diseases, called value-based insurance design (V-BID), now informs Medicare, commercial, and employer-funded plans.

The experience of COVID-19—in which making vaccines free of cost to users accelerated their uptake—has only bolstered the idea that removing barriers to high-value services brings them to more people.

But Fendrick, the director of the University of Michigan’s V-BID Center, told the Community Oncology Alliance (COA) Payer Exchange Summit that much more work remains. Today’s focus on equity in care aligns with what Fendrick and co-authors found in 2008, when they showed how increased patient cost sharing widened socioeconomic disparities in health care.

Capping or eliminating out-of-pocket costs for more cancer services will lead to more early diagnoses and treatment, when survival is more likely, Fendrick said. Changes in the Affordable Care Act (ACA) removed co-payments for basic cancer screenings, he noted, but cost barriers still keep many from getting a diagnosis.

Whenever there is less access to evidence-based diagnostic tests and therapies, “the result is more morbidity and mortality,” Fendrick pointed out. “It’s not only very sad to me that communities of color have lower rates of access to the things that we know work, but that they also, paradoxically, have increased utilization of [therapies] that we’re trying to eliminate—those that [lack] evidence to improve patient-centered outcomes,” he said.

Fendrick, who is co-editor-in-chief of *The American Journal of Managed Care* and a board member of *Evidence-Based Oncology*, said that he once worried more about co-payments and coinsurance, but today his top concern is the annual deductible that keeps patients from following up on a troublesome screening, or causes some to stop taking cancer drugs. This “January effect” is now recognized in Medicare, he said. Cancer foundations see a jump in applications early each calendar year, and patients who are in the midst of treatment must regroup to find a way to make another large payment.

Deductibles have gone from “practically nothing” to reach a point, Fendrick said, where “more than 80% of Americans with good insurance have a deductible. The average deductible is more than $1000. And this flies in the face of a Federal Reserve study showing that 40% of Americans don’t have $400 in a bank.”

It’s “completely irrational,” Fendrick continued, to find patients having bake sales or online fundraising campaigns to treat a tumor based on a specific outcome.
marker, because of the “blunt instrument of health care cost for patients, who are asked to pay more and more out of pocket for services, regardless of whether they are life-saving or potentially harmful.”

**REDIRECTING HEALTH CARE SPENDING.** US health care spending, which reached $3.8 billion in 2019,1 would be adequate if those dollars were spent the right way, Fendrick said. Instead of continuing to spend more, health systems must eliminate wasteful and harmful spending and redirect dollars to high-value services. Cancer care has a particularly high stake in this shift, he said.

“The move into cost containment will only intensify given the exciting, rapid pace of oncological advances—not just the translational science and therapeutics, but also our ability to potentially deliver care in ways that we couldn’t even have dreamed of a decade or two ago,” Fendrick said.

The US health system was making progress in shifting spending to preventive screenings when COVID-19 hit, and is just now “creeping back to where we were at baseline,” Fendrick explained.

How can care be reallocated? Alternative payment models are just one way, and Fendrick said COA has been a leader through its work with the American Society of Clinical Oncology on the Oncology Medical Home and other efforts. Leveraging technology—including electronic health records, wearables, and virtual medicine—can “make it easier for consumers to access evidence-based care, but also make it harder for them to get care that will not make them healthier,” he noted.

**FINDING SOLUTIONS.** The ACA provision that required preventive services to be covered 100% now extends to more than 100 services, Fendrick said, and evidence shows that individuals at the low end of the socioeconomic scale have benefited most. Any shift in recommendations from the US Preventive Services Task Force—whose judgments drive which services must be covered—can have huge effects on reducing disparities. As an example, Fendrick pointed to changes that will cover screenings for colorectal cancer starting at age 45 years; this may extend screening to 20 million more Americans.

But gaps still exist. Notably, if a screening points to a problem that requires a follow-up diagnostic test, the second test often is not covered or eliminated from a deductible. The too-frequent result: Patients are aware they may have a cancer but cannot afford to have that diagnosis confirmed.

Fendrick had previously advocated for a change in the tax code that would allow certain lifesaving drugs and services—such as insulin—to be excluded from health costs that are subject to an annual deductible. The “spirit” of this provision, he said, “was that when people started a process for, [let’s say], cervical cancer screening or colorectal cancer screening, they would get coverage for the entire screening process.”

Fendrick is working with cancer advocacy groups to engage government leaders to extend coverage to follow-up at-home colorectal screenings, mammograms, Pap smears, and low-dose CT scans in lung cancer. California and Oregon have passed laws requiring that a follow-up colonoscopy be covered 100%. What’s more, Fendrick said, the complaint that companies will raise prices on screenings if payers are forced to cover them has not been borne out.

These concepts are making their way into Medicare Advantage modeling and into the “refresh” of payment reforms from the Center for Medicare and Medicaid Innovation, to include areas such as food insecurity and transportation. Drug provisions were contained in the Senior Savings Plan model1 that took effect in January 2021, Fendrick said, and adding oncology drugs to the model could be a game-changer.

Bipartisan legislation endorsing this idea is currently pending in Congress, Fendrick added. Fendrick was surprised how quickly employers embraced this idea: He said he would have been “happy with 5% of plans or employers picking up this rule,” but to date, almost 50% of the largest employers and 30% of smaller employers have updated coverage.

“If we could get oncology services on that list, I believe that public and private employers would change their benefit design to make those high-value oncology services pre-deductible. And that would be a win for everyone,” Fendrick said, “but especially for those patient populations who are socioeconomically challenged or for the communities of color that we worry most about.”

From the perspective of health plans or pharmaceutical companies, out-of-pocket costs for cancer drugs might cover a small piece of total price, “but they’re a very, very important piece, and the piece that patients care about the most,” emphasized Fendrick. “The growrooms in the house to have to make decisions about what things should actually cost, but the burden of their inability to decide what prices should be should not fall onto our patients.”

**REFERENCES**


A FOUNDATION in MM maintenance therapy post auto-HSCT

Lenalidomide (REVLIMID)
- The ONLY National Comprehensive Cancer Network® (NCCN®) Category 1 preferred maintenance therapy post auto-HSCT
- The ONLY FDA-approved maintenance therapy post auto-HSCT
- The #1 prescribed maintenance therapy post auto-HSCT

Indications
REVLIMID® (lenalidomide) is indicated as maintenance therapy in adult patients with multiple myeloma (MM) following autologous hematopoietic stem cell transplantation (auto-HSCT). REVLIMID® is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

REVLIMID® is only available through a restricted distribution program called the Lenalidomide REMS program.

Selected Safety Information: Boxed WARNINGS

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

See the next spread and Brief Summary for complete Boxed WARNINGS.

EMBRYO-FETAL TOXICITY
- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.
- Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.
- REVLIMID is available only through a restricted distribution program called the Lenalidomide REMS program.

HEMATOLOGIC TOXICITY
- REVLIMID can cause significant neutropenia and thrombocytopenia.

VENOUS AND ARTERIAL THROMBOEMBOLISM
- Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving REVLIMID with dexamethasone. Anti-thrombotic prophylaxis is recommended.

CONTRAINDICATIONS
Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

Please see Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
CALGB (STUDY 1)
5.7-year median PFS with REVLIMID Maintenance

CALGB PFS Events: REVLIMID = 97/231 (42%), Placebo = 116/229 (51%)
IFM PFS Events: REVLIMID = 191/307 (62%), Placebo = 248/307 (81%)

3.8-YEAR INCREASE IN MEDIAN PFS VS PLACEBO (UPDATED ANALYSIS: MARCH 2015)

REVLIMID (n=231) Placebo (n=229) HR 0.38 (95% CI 0.28, 0.50)

IFM (Study 2): 1.9-year advantage in median PFS vs placebo

Median PFS: 3.9 years with REVLIMID Maintenance (95% CI 3.3, 4.7) (n=307) vs 2.0 years with placebo (95% CI 1.8, 2.3) (n=307) (HR 0.53 [95% CI 0.44, 0.64])

Trial design: CALGB (Study 1) and IFM (Study 2) were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies in newly diagnosed patients 18-70 years (CALGB) and <65 years at diagnosis (IFM) who received auto-HSCT following induction therapy, which must have occurred within 12 months. Patients were randomized 1:1 to receive REVLIMID or placebo maintenance 90-100 days (CALGB) or within 6 months (IFM) post auto-HSCT. Patients were required to achieve at least stable disease following hematologic recovery and CrCl ≥30 mL/min. The primary endpoint for both studies was PFS, based on assessment by investigator, and was defined from randomization to the date of progression or death, whichever occurred first. In both studies, the starting dose of REVLIMID was 10 mg once daily for repeated 28-day cycles. After 3 months, a dose increase to 15 mg once daily occurred in 135 patients (68%) in CALGB, and 183 patients (66%) in IFM. The dose was reduced, interrupted, and/or discontinued as needed to manage toxicity. Patients were treated until disease progression, unacceptable toxicity, or patient withdrawal for any reason. At a preplanned interim analysis, the primary endpoint of PFS was met and both studies were unblinded, and patients continued to be followed as before. Patients in the placebo arm of CALGB were allowed to cross over to receive REVLIMID before disease progression; patients in the IFM study were not recommended to cross over. In IFM, REVLIMID was stopped at the recommendation of the Data Monitoring Committee in January 2011.

*See full NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for further detail about recommended therapies.
*Claims data 07/2018-06/2021. Source: PrecisionIQ Data © 2021, IntrinsiQ Specialty Solutions, Inc. All rights reserved.
†Claim analysis, March 2015. Based on intent-to-treat (ITT) population. auto-HSCT, autologous hematopoietic stem cell transplantation; CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; IFM, Intergroupe Francophone du Myelome; MM, multiple myeloma; NE, not evaluable; PFS, progression-free survival.
Indications

REVLIMID® (lenalidomide) is indicated as maintenance therapy in adult patients with multiple myeloma (MM) following autologous hematopoietic stem cell transplantation (auto-HSCT). REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials. REVLIMID is only available through a restricted distribution program, Lenalidomide REMS.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity
Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the Lenalidomide REMS program. Information about the Lenalidomide REMS program is available at www.cellgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)
REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous and Arterial Thromboembolism
REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient’s underlying risks.

CONTRAINDICATIONS

Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: See Boxed WARNINGS
- Females of Reproductive Potential: See Boxed WARNINGS.
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
Important Safety Information (continued)

**Lenalidomide REMS Program:** See Boxed WARNINGS: Prescribers and pharmacies must be certified with the Lenalidomide REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

**Hematologic Toxicity:** REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. Patients may require a dose interruption and/or dose reduction. **MM:** Monitor complete blood counts in patients taking REVLIMID + dexamethasone or REVLIMID as maintenance therapy, every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter.

**Venous and Arterial Thromboembolism:** See Boxed WARNINGS: Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVLIMID. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended and the regimen should be based on the patient's underlying risks. Erythropoietin-stimulating agents (ESAs) and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision.

**Increased Mortality in Patients With CLL:** In a clinical trial in the first-line treatment of patients with CLL, single-agent REVLIMID therapy increased the risk of death as compared to single-agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in the REVLIMID arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

**Second Primary Malignancies (SPM):** In clinical trials in patients with MM receiving REVLIMID and in patients with FL or MZL receiving REVLIMID + rituximab therapy, an increase of hematologic plus solid tumor SPM, notably AML, have been observed. In patients with MM, MDS was also observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment.

**Increased Mortality With Pembrolizumab:** In clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

**Severe Cutaneous Reactions:** Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

**Tumor Lysis Syndrome (TLS):** Fatal instances of TLS have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

**Tumor Flare Reaction (TFR):** TFR has occurred during investigational use of REVLIMID for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion.

**Impaired Stem Cell Mobilization:** A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

**Thyroid Disorders:** Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before starting REVLIMID treatment and during therapy.

**Early Mortality in Patients With MCL:** In another MCL study, there was an increase in early deaths (within 20 weeks); 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥10 x 10^9/L).

**Hypersensitivity:** Hypersensitivity including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for these reactions.
ADVERSE REACTIONS

Multiple Myeloma

• Maintenance Therapy Post Auto-HSCT: The most frequently reported Grade 3 or 4 reactions in ≥20% (REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm.

• The most frequently reported adverse reactions in ≥20% (REVLIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 32%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (4%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (54%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 20%).

DRUG INTERACTIONS

Periodically monitor digoxin plasma levels due to increased Cmax and AUC with concomitant REVLIMID therapy. Patients taking concomitant therapies such as ESAs or estrogen-containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

USE IN SPECIFIC POPULATIONS

• PREGNANCY: See Boxed WARNINGS: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

• LACTATION: There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.

• RENAL IMPAIRMENT: Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis.


Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

REVLIMID (lenalidomide) during pregnancy. Lenalidomide, a thalidomide analog, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryolethal death. In females of reproductive potential, obtain 1 negative pregnancy test before starting REVLIMID® treatment. Females of reproductive potential must use 2 methods of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment (see Warnings and Precautions, and Medication Guide (57) in full Prescribing Information). To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the Lenalidomide REMS program. Information about the Lenalidomide REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-866-423-5430.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on Therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose information and/or reduction. Patients may require use of blood product support and/or growth factors (see Dosage and Administration)."
Pharmacies must be certified with the

Patients must sign a Patient-Physician agreement form and comply with the REMS requirements.

should have their complete blood counts assessed periodically as described below

with use of concomitant medication that may increase risk of bleeding. Patients taking REVLIMID

REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with

Because of the embryo-fetal risk

fetus must not be exposed to REVLIMID.

discontinuation of the drug because the blood might be given to a pregnant female patient whose

while taking REVLIMID (lenalidomide) and for up to 4 weeks after discontinuing REVLIMID, even

In clinical trials in patients with MM receiving REVLIMID, an increase of hematologic plus solid

Second Primary Malignancies

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and

Increased Mortality in Patients with CLL

[see Drug Interactions]

Symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of

The median time to first thrombosis event was 4.3 months in the combined Rd Continuous and

in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious

The patients at risk of TLS are those with high tumor burden prior to treatment. Monitor patients

Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has

for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline

REVLIMID arm versus 7.1% in the control arm. On exploratory multivariate analysis, risk factors

Tumor flare reaction (TFR) has occurred during investigational use of REVLIMID for CLL and lymphoma, and is characterized by rapid lymph node and/or organ enlargement. TFR is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Tumor flare reaction (TFR) has occurred during investigational use of REVLIMID for CLL, and is characterized by rapid lymph node and/or organ enlargement. TFR is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Curvature fluctuation in the rate of risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving REVLIMID

In patients receiving REVLIMID (lenalidomide) maintenance therapy following high dose intravenous melphalan and auto-HSCT, hematologic SPM occurred in 7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor including squamous cell carcinoma and basal cell carcinoma SPM was 14.9%, compared to 8.8% in patients receiving placebo with a median follow-up of 13.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.9% of patients receiving REVLIMID maintenance, compared to 2.9% in the placebo arm.

In patients with relapsed or refractory MM treated with REVLIMID/dexamethasone, the incidence of hematologic plus solid tumor (including squamous cell carcinoma and basal cell carcinoma) SPM was 2.4% versus 0.6% in the dexamethasone alone arm. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.1% of patients receiving REVLIMID/dexamethasone, compared to 0.6% in the dexamethasone alone arm.

Patients who received REVLIMID-containing therapy during disease progression did not show a higher incidence of invasive SPM than patients treated in the front-line REVLIMID-containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

Increased Mortality in Patients with CLL

Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatis), eosinophilia, fever, and/or lymphomatisos with systemic complications such as hepatic, neurologic, pneumonic, myocardiac, and/or periarticular. These events can be fatal. Patients with a prior history of Grade 4 or more severe cutaneous reactions associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or DRESS. [see Doseage and Administration].

Tumor Lysis Syndrome

Focal lesions of tumor lysis syndrome (TLS) have been reported during treatment with REVLIMID.

The risk of TLS is those with high tumor burden prior to treatment. Monitor patients at risk of death and take appropriate preventive approaches. In the AUMEN trial in FL or MCL patients, TLS occurred in 2 patients (1.1%) in the REVLIMID/bisulfate arm. TLS occurred in 1 patient (0.5%) in the Placebo arm during the REVLIMID/bisulfate induction period; the event was a serious, Grade 3 adverse reaction.

Tumor flare reaction (TFR) has occurred during investigational use of REVLIMID for CLL and lymphoma, and is characterized by rapid lymph node and/or organ enlargement. TFR is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Tumor flare reaction (TFR) has occurred during investigational use of REVLIMID for CLL, and is characterized by rapid lymph node and/or organ enlargement. TFR is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (≤4 cycles) with REVLIMID has been reported in patients who are auto-HCT candidates, referred to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a REVLIMID-containing treatment or for whom inadequate numbers of CD34+ cells were collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CSK inhibitor may be considered.

Thyroid Disorders

Both hyperthyroidism and hypothyroidism have been reported [see Adverse Reactions]. Measure thyroid function before start of REVLIMID treatment and during therapy.

Early Mortality in Patients with MCL

In another MCL study, there was an increase in early deaths within 20 weeks, 12.6% in the REVLIMID arm versus 7.1% in the control arm. On exploratory multivariate analysis, risk factors for early deaths include high tumor burden, MPN score at diagnosis, and high WBC at baseline (>10 x 10^9/L).

Hypersensitivity

Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for angioedema and anaphylaxis [see Doseage and Administration].
ADVERSE REACTIONS

The following clinically significant adverse reactions are described in detail in other sections of the prescribing information:

- Embryo-Fetal Toxicity [see Boxed Warning, Warnings and Precautions]
- Hematologic Toxicity [see Boxed Warning, Warnings and Precautions]
- Increased Mortality in Patients with CLL [see Warnings and Precautions]
- Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analog and Dexamethasone [see Warnings and Precautions]
- Hepatotoxicity [see Warnings and Precautions]
- Severe Cutaneous Reactions [see Warnings and Precautions]
- Tumor Lysis Syndrome [see Warnings and Precautions]
- Impaired Stem Cell Mobilization [see Warnings and Precautions]
- Thrombosis [see Warnings and Precautions]
- Early Mortality in Patients with MCL [see Warnings and Precautions]
- Hypersensitivity [see Warnings and Precautions]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs or to the rates observed in practice.

Table 3: All Adverse Reactions in ≥5% and Grade 3/4 Adverse Reactions in ≥1% of Patients with MM in the REVLIMID (lenalidomide) Vs Placebo Arms*
and AUC\textsubscript{inf/uni} were increased by 14%. Periodically monitor digoxin plasma levels, in accordance with

Sepsis: Bacterial sepsis, Pneumococcal sepsis, Sepsis, Septic shock, Staphylococcal sepsis

Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis

Digoxin

Stevens-Johnson Syndrome, toxic epidermal

Pneumonitis

syndrome, tumor flare reaction

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Angioedema, anaphylaxis, acute graft-versus-host disease (following

Endocrine disorders:

[see Warnings and Precautions].

population of uncertain size, it is not always possible to reliably estimate their frequency or establish

Postmarketing Experience

The following adverse drug reactions have been reported from the worldwide post-marketing experience with REVLIMID (lenalidomide). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [see Warnings and Precautions].

Endocrine disorders: Hypothyroidism, hyperthyroidism

Respiratory, thoracic and mediastinal disorders: Aspiration

Respiratory, gastrointestinal disorders: Diarrhea

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)

DRUG INTERACTIONS

Digoxin

When digoxin co-administration was with multiple doses of REVLIMID (10 mg/day) the digoxin C\text{max} and AUC\text{max} were increased by 14%. Periodically monitor digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, during administration of REVLIMID.

Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thromboembolic events, such as estrogen containing contraceptives, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID [see Warnings and Precautions].

Warfarin

Co-administration of multiple doses of REVLIMID (10 mg/day) with a single dose of warfarin (25 mg) had no effect on the pharmacokinetics of lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between lenalidomide and warfarin. Close monitoring of PT and INR is recommended in patients with warfarin taking concurrent warfarin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. REVLIMID is not indicated to use in pregnancy; see Warnings and Precautions.

Risk Summary

Based on the mechanism of action [see Clinical Pharmacology (12.1) in Full Prescribing Information] and findings from animal studies [see Data], REVLIMID can cause embryo-fetal harm when administered to a pregnant female animal, prenatally during pregnancy. [See Boxed Warning, Contraindications, and Use in Specific Populations].

REVLIMID is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as aneuploidy (abnormality of karyotype), phocomelia (short limbs), hypoplasia of the bones, absence of bones, extramedullary hematopoiesis (including

anemia, microcytosis, small or absent external auditory canals), facial palsy, eye abnormalities

(anophthalmos, microphthalmos), and congenital heart defects. Abnormality of face, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40%-50% of infants.

Lenalidomide caused thalidomide-like limb defects in monkey offspring. Lenalidomide crossed the placenta after administration to pregnant rabbits and pregnant rats. [see Data] If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to REVLIMID (lenalidomide) to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-422-0436. 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, death, or other adverse outcomes. The estimated background risk in the U.S. general population of major birth defects 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

In an embryo-fetal development toxicology study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkey at the lowest dose was 1.7 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 350 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rodent model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.

Following daily oral administration of lenalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma lenalidomide concentrations were approximately 20-40% of the maternal plasma. Following a single oral dose to pregnant rats, lenalidomide was detected in fetal plasma and tissues; concentrations of radioactivity in fetal tissues were generally lower than those in maternal tissues. These data indicated that lenalidomide crossed the placenta.

Lactation

Risk Summary

There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed child, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing children from REVLIMID, advise women not to breastfeed during treatment with REVLIMID.

Females and Males of Reproductive Potential

Pregnancy Testing

REVLIMID can cause fetal harm when administered during pregnancy [see Use in Specific Populations]. Verify the pregnancy status of females of reproductive potential prior to initiating REVLIMID therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, dose interruptions and for at least 4 weeks after completing therapy.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use.
Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even when there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Advise females to use a latex or synthetic condom during any sexual contact with males while taking REVLIMID and for up to 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even when there has been a history of infertility, unless due to hysterectomy. Males must comply with the contraception requirements (see Use in Specific Populations).

Instruct patient to immediately stop taking REVLIMID and contact her healthcare provider if she becomes pregnant while taking this drug, if she misses her menstrual period, or if she feels any signs and symptoms of these reactions. Advise patients to seek emergency medical attention for signs or symptoms of these reactions. Advise patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation. Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation.

Instruct patients that REVLIMID had increased mortality in patients with CLL and serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure (see Warnings and Precautions). Instruct patients to read the FDA-approved Patient labeling (Medication Guide). Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms suggestive of these events for evaluation (see Warnings and Precautions).

Inform patients that REVLIMID is only available through a restricted program called the Lenalidomide REMS program (see Warnings and Precautions).

Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia (seeWARNINGS and PRECAUTIONS). Inform patients of the potential risk of developing second primary malignancies during treatment with REVLIMID (see WARNINGS and PRECAUTIONS). Inform patients of the potential risk of tumor flare syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation (see WARNINGS and PRECAUTIONS).

Inform patients that REVLIMID was not mutagenic in the bacterial reverse mutation assay (Ames test) and did not induce reverse mutation in the Chinese Hamster Ovary (CHO) chromosome assay (see NONCLINICAL TOXICOLOGY). Inform patients that REVLIMID is contraindicated in pregnancy (see WARNINGS and PRECAUTIONS). Instruct patients to use 2 different forms of contraception including at least 1 highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, implant), or partner’s vasectomy and a barrier method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions, and for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even when there has been a history of infertility, unless due to hysterectomy. Males must comply with the contraception requirements (see Use in Specific Populations).

Inform patients that REVLIMID is only available through a restricted program called the Lenalidomide REMS program (see WARNINGS and PRECAUTIONS). Inform patients of the potential risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the Lenalidomide REMS program (see WARNINGS and PRECAUTIONS). Inform patients of the risk of thrombosis including DVT, PE, MI, and stroke and to report immediately any signs and symptoms of these reactions for evaluation (see WARNINGS and PRECAUTIONS). Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia (see WARNINGS and PRECAUTIONS) and carciogenicity studies with lenalidomide have not been conducted. Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms suggestive of these events for evaluation (see WARNINGS and PRECAUTIONS). Inform patients of the potential risk of severe skin reactions such as SJS, TEN, and DRESS and to report any signs and symptoms associated with these reactions to their healthcare provider for evaluation (see WARNINGS and PRECAUTIONS).

Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation (see WARNINGS and PRECAUTIONS). Inform patients of the potential risk of severe skin reactions such as SJS, TEN, and DRESS and to report any signs and symptoms associated with these reactions to their healthcare provider for evaluation (see WARNINGS and PRECAUTIONS).

Inform patients of the potential risk of hepatic toxicity, including hepatic failure and death, and to report any signs and symptoms suggestive of these events for evaluation (see WARNINGS and PRECAUTIONS). Inform patients of the potential risk of severe skin reactions such as SJS, TEN, and DRESS and to report any signs and symptoms associated with these reactions to their healthcare provider for evaluation (see WARNINGS and PRECAUTIONS).

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FDA Extends Review for Pacritinib for Treatment of Myelofibrosis With Severe Thrombocytopenia

ON NOVEMBER 30, the FDA extended the review period for pacritinib, a novel therapy to treat adult patients with intermediate- or high-risk primary or secondary myelofibrosis with severe thrombocytopenia. The Prescription Drug User Fee Act (PDUFA) action date was extended by 3 months to February 28, 2022, according to a statement from CTI BioPharma Corp.1

The FDA had previously granted priority review for the new drug application (NDA) for patients with myelofibrosis, with a PDUFA date of November 30. During discussions for the drug's label, the agency requested additional data, which CTI BioPharma's statement said was submitted on November 24. According to CTI BioPharma, the FDA stated that the submission constituted a "major amendment," triggering the extension to allow for additional review.

In its statement, CTI BioPharma said the company was not aware of any major deficiencies in the application.

"We are committed to providing [a new treatment option for] patients [with] cytopenic myelofibrosis as soon as possible and are confident in pacritinib’s potential to establish a new standard of care."

—Adam R. Craig, MD, PhD, president and CEO, CTI BioPharma

"CTI is continuing to engage collaboratively and constructively with the FDA during review of our NDA," Adam R. Craig, MD, PhD, president and CEO of CTI BioPharma, said in the statement. "We are committed to providing [a new treatment option for] patients [with] cytopenic myelofibrosis as soon as possible and are confident in pacritinib's potential to establish a new standard of care."

Pacritinib, an oral kinase inhibitor with specificity for JAK2, IRAK1, and CSF1R, had been given priority review based on the results from a pair of phase 3 trials, PERSIST-2 (NCT02055781) and PERSIST-1 (NCT01773187), as well as an earlier study that examined the effectiveness of pacritinib in patients with severe thrombocytopenia. 2

PERSIST-2 involved 311 patients and showed that pacritinib 200 mg taken twice daily was significantly more effective than the best available therapies, including ruxolitinib. Of note, a reduction in spleen volume of at least 35% was seen in 29% of those patients compared with just 3% of those taking the best available therapy.3

In PERSIST-1, investigators found that pacritinib was well tolerated. Patients taking it experienced significant spleen volume reduction and reduced myelofibrosis symptoms. The most common grade 3/4 adverse effects through week 24 of pacritinib treatment were anemia (17%), thrombocytopenia (12%), and diarrhea (5%).4

REFERENCES


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The Myriad Ways ctDNA Analysis Using Liquid Biopsy Can Be Applied in NSCLC

A NEW REVIEW OF THE EVIDENCE spotlights the myriad clinical ways that analysis of circulating tumor DNA (ctDNA) using liquid biopsy can be used in patients with non–small cell lung cancer (NSCLC), delving into the advantages and limitations with certain applications.

The review, published in *Current Treatment Options in Oncology*, focused on the clinical applications and the potential use of ctDNA as well as where research on ctDNA applications should be targeted.

"Specifically, the analysis of ctDNA has shown tremendous advantages in the management of lung cancer patients, enabling for noninvasive biomarker testing, tumor response to treatment monitoring, early detection of resistance mutations, the study of clonal evolution, and early detection of molecular relapse or residual disease," wrote the authors.

Lung cancer is the leading cause of cancer-related deaths, and NSCLC accounts for 85% of lung cancer cases. NSCLC is often diagnosed at an advanced stage and carries a 5-year survival rate of about 5%. Biomarker testing was developed to be a crucial part of ensuring adequate management for patients with lung cancer.

Circulating tumor DNA (ctDNA) can be used to select patients for clinical trials, and its measures can serve as trial end points because they can be reached sooner than survival time end points. According to the authors, ctDNA can also aid in detecting immune checkpoints that are known biomarkers of non–small cell lung cancer, including tumor mutational burden.

However, tissue-based biomarker testing can be challenging in patients with lung cancer, as the anatomical location of the tumor may limit the ability to access tissue to test for eligibility for targeted therapies. Additionally, the growing number of biomarkers that have been associated with NSCLC means that it may be necessary to obtain multiple biopsies to conduct several analyses, which is not always possible. At the time of disease progression, providers may want to know the molecular profile of a tumor in order to tailor therapeutic regimens. Liquid biopsy can serve as an avenue to avoid such limitations.

Most noninvasive biomarker tests using liquid biopsies are based on quantitative polymerase chain reaction (QPCR); digital PCR (dPCR); beads, emulsion, amplification, and magnets (BEAMing); or next-generation sequencing (NGS) technology. QPCR tests can lack the level of sensitivity needed to detect genetic mutations. Two of the benefits of NGS analysis are that it allows a larger number of mutations to be tested for simultaneously, compared with dPCR or BEAMing; and that it may provide valuable insight into ALK-positive patients with NSCLC after treatment failure.

The authors noted that ctDNA can be used for selecting patients for clinical trials, and its measures can serve as trial end points because they can be reached sooner than survival time end points. ctDNA can also aid in detecting immune checkpoints that are known biomarkers of NSCLC, including tumor mutational burden.

Research results have shown that the amount of ctDNA observed correlates with tumor bulk and can be used to determine treatment outcomes and to quantify targetable mutations in EGFR-positive patients with NSCLC. Although longitudinal ctDNA quantification is not yet standard practice, evidence increasingly demonstrates that the amount of ctDNA has prognostic significance.

ctDNA analyses can serve as a tool for early detection of resistance mutations, especially T790M mutations, which can be effectively identified in plasma collected from patients with advanced lung cancer several months prior to clinical progression. However, there is still a lack of clinical trials examining whether a change of therapy is needed upon molecular progression rather than clinical progression.

"Intratumor heterogeneity is a key factor underlying treatment failure. It is important to recognize that the advent of liquid biopsies has improved our understanding of tumor evolution under the course of treatment," the authors wrote.

Liquid biopsy technology can also detect residual disease after receiving local treatment during the early stages of several cancer types. Additionally, liquid biopsies through NGS can aid in the reliable detection of minimal residual disease (MRD) in patients with lung cancer.

"While the use of ctDNA for MRD detection appears promising, whether ctDNA detection is reliable enough to determine subsequent treatments has not been proven. Likewise, the interpretation of undetectable ctDNA levels remains unclear. In this way, clinical trials addressing these issues are of particular interest," the authors noted.

Although liquid biopsies are a promising approach for cancer screening, the authors said that they may not be powerful enough yet to accurately detect early-stage lung cancer in patients and that technical improvements are needed to implement ctDNA NGS profiling as an effective screening tool.

REFERENCE

Liver Cancer Is Rising in Rural Parts of the United States

A RECENT STUDY FOUND that the incidence of hepatocellular carcinoma (HCC) is slowing in urban areas but rising in rural ones. The study, from the University of Southern California (USC) Norris Comprehensive Cancer Center, part of Keck Medicine of USC, found that the incidence of the cancer is rising at a rate of 5.7% annually in rural areas and approaching the rates seen in urban areas.

The study examined data from 1995 to 2016. The researchers also discovered that certain urban subgroups experienced declining incidence rates of HCC starting in 2013, including both men and women, younger individuals aged 40 to 59 years, Asian Pacific Islander individuals, and people who live in the Western United States. No rural subgroups experienced a clear decline, even as rates of other cancers—including lung, breast, and colorectal cancers—are falling for those populations.

"Considering that 1 in 5 Americans live in a rural community, this study suggests that HCC is a critical underrecognized public health issue affecting rural Americans," said Kali Zhou, MD, MAS, in a statement.

Liver Cancer is the most common form of liver cancer and the fastest-growing cause of cancer-related deaths in the United States. Historically, the rates of HCC have been lower in rural areas than urban.
The study examined HCC trends across rural and urban communities over the past 20 years for which data are available, using the North American Association of Central Cancer Registries database; this covers 93% of the United States and satisfactorily represents the rural parts of the country.

The researchers tracked new cases per year for both geographic groups and found that of the more than 310,000 total new cases of HCC, 85% were diagnosed in urban and 15% in rural areas. While the average rate of new cases was still lower in rural areas compared with urban ones over the entire 20 years, cases increased at a higher rate per year in rural areas.

The rates of increase were similar for the 2 groups from 1995 to 2009. But in 2009, the pace of new HCC cases in urban America began to slow down, with a peak around 2014, with no corresponding slowing in rural America.

By 2016, this meant that the number of cases increased 218% from 1995 in rural settings, compared with 118% in urban ones.

The study did not examine all the potential reasons for the rise in new HCC cases in rural areas, but Zhou pointed to the prevalence of obesity and alcohol use in those areas as one possible explanation.

In addition, rural residents may lack the health care access as well as preventive cancer care that is available to city residents.

Zhou’s previous research showed that people living in rural parts of the country are also more likely to have a late-stage liver cancer diagnosis and worse survival rates than those in urban communities. ✪

REFERENCES

BIOMARKERS

Review: Era of Precision Medicine Dawning in Prostate Cancer

THE USE OF PROGNOSTIC and predictive molecular factors is bringing a new era of prostate cancer management into focus, according to a new report.

In a review article published in the journal Cancers, investigators outlined the role of molecular biomarkers and the current state of precision therapy for prostate cancer.

Corresponding author Pasquale Rescigno, PhD, head of the Interdisciplinary Group for Translational Research and Clinical Trials, GU cancers, at the Candidolo Cancer Institute in Italy, and colleagues explained that even with new precision medicine advances, the histopathological exam—including an evaluation of the cytological and architectural features of prostate cancer—remains “the cornerstone” of prostate cancer definition.

“Nevertheless, in the era of precision oncology, stratification of metastatic prostate cancer patients through molecular testing has gained a prominent role, even in the attempt of tackling resistance to approved drugs, which remains a key issue and is ultimately responsible for patients’ death,” they wrote.

Rescigno and colleagues began their review by outlining a number of predictive molecular factors that have been the subject of recent investigations, including androgen receptor alterations, loss of phosphatase and TET3 (PTEN) homologue, homologous recombination deficiency, mismatch repair deficiency (MMRd), and tumor microenvironment modifications. Those biomarkers have been linked to prognostic consequences, such as shorter overall survival and response to particular therapies, in various studies.

“Overall, the discovery of biologically distinct subtypes has revolutionized the historical assumption that prostate cancer is a homogenous disease with an indolent behavior,” they said. “There are indeed molecular characteristics that can significantly differentiate prostate cancers between patients and within the same patient over time.”

For instance, the authors said patients with androgen receptor alterations tend to have poor survival and are less likely to respond to hormonal agents. Patients with PTEN loss have poor survival but may respond to AKT inhibitors. Patients with MMRd have shorter overall survival, but may respond to PD-1 inhibitors, the investigators noted.

Still, Rescigno and co-authors added that the studies identifying these biomarkers utilized different methodologies and platforms, and thus it is important that the findings are taken in the context of the particular methods and tissues used.

The investigators next turned to tissue specimens, asserting that they remain “crucial” to formulating a final diagnosis, even in an age when biomarker-specific screenings are available.

The authors said that while it is not yet clear which biomedical specimens are best to test, tissue samples give “the exquisite advantage to perform complementary analysis to genomic sequencing, such as immunohistochemical and [tumor microenvironment] studies.”

Plasma or blood derivatives have advantages, too, including ease of collection and the availability of serial specimen collection.

“Preservation of archival tissue, feasibility of fresh tissue biopsy, and adequate tumor fraction in plasma remain the big limitations of these tests,” they added.

For now, Rescigno and colleagues said, there is no unique test or tissue that can provide all of the necessary information to fully represent a patient’s disease biology. Absent that, they said both tumor and blood should be used to study predictive and prognostic factors in metastatic castration-resistant prostate cancers, and to investigate new mechanisms of resistance to approved treatments. ✪

REFERENCE

Brisk Tumor-Infiltrating Lymphocytes May Hold Prognostic Value in Primary Cutaneous Melanoma

TUMOR-INFLTRATING LYMPHOCYTES (TILs) are a known and important biomarker for monitoring immune therapy response in patients with melanoma, but research has been lacking regarding their potential function as a prognostic factor. Results of a large study published in JAMA Network Open suggest that TILs categorized as “brisk” could be an independent prognostic factor for overall survival (OS) in melanoma.

TILs are reliable as a biomarker, but past research has produced varied results on their value in prognosis for cutaneous melanoma; cutaneous melanoma is the most aggressive form of melanoma, which is the most common form of skin cancer after basal cell carcinoma. In melanoma, TILs are classified as absent, present, nonbrisk (infiltrating focally, not along the entire base of the tumor), or brisk (infiltrating the entire tumor or entire base of the tumor). One barrier to large-cohort studies on TILs in melanoma is that manual review and aggregation of medical records is a labor-intensive undertaking. The current study aimed to gauge the prognostic significance of TILs in the largest cohort to date of patients with cutaneous melanoma that was established using natural language processing (NLP) algorithms.

Researchers identified patients with primary cutaneous melanoma in the Brigham and Women’s Hospital pathology laboratory information system between June 1, 2004, and December 31, 2019. They used NLP to identify »
patients whose records included primary invasive melanomas with TIL grades assessed and vertical growth phase documentation. Then, data on 7 characteristics were extracted and normalized into groups. These factors were TIL grade, Breslow thickness, mitotic rate, ulceration, histologic regression, microsatellites, and vascular or lymphatic invasion.

The pathology reports identified by the NLP were linked to patients’ electronic health record data and to Massachusetts death certificate files from 2004 to 2019, allowing researchers to gather patient demographic information and death information to calculate OS.

In total, 14,436 patients with cutaneous melanoma were identified, and a cohort of 2624 patients had vertical growth phase melanoma with TIL status scored. The cohort was 55.7% male and the patients’ median age was 61 years (interquartile range, 50–72). Median follow-up was 3.1 years.

Of the 2624 patients, 434 (16.5%) had disease classified as absent TILs, 1916 (73%) had nonbrisk TILs, and 274 (10.4%) had brisk TILs. For patients with absent TILs, the 5-year survival rate was 71.0% (95% CI, 65.5%-76.9%). Patients with nonbrisk TILs had a 73.8% (95% CI, 71.1%-76.5%) 5-year survival rate, and those with brisk TILs had an 85.2% 5-year survival rate (95% CI, 80.0%-90.7%).

In the overall cohort, the 5-year survival rate was 74.3% (95% CI, 72.1%-76.5%). Brisk TILs were identified as an independent prognostic factor associated with improved OS (adjusted HR, 0.63; 95% CI, 0.42-0.95; P = .03). Those patients had a 14.2% OS improvement at the 5-year mark compared with those classified as having absent TILs. Nonbrisk TILs were not associated with an OS improvement compared with the absence of TILs (adjusted HR, 0.87; 95% CI, 0.68-1.11; P = .25).

Overall, patients who were younger, were female, and had lower Breslow thickness, lower mitotic rate, brisk TILs, absence of ulceration, absence of microscopic satellites, and absence of vascular or lymphatic invasion had improved OS, which is consistent with results of previous studies.

One study takeaway was the effectiveness of utilizing NLP to establish large cohorts with detailed histopathologic features for survival analysis. In regard to TILs, the data provide evidence that brisk TILs can be a prognostic factor for OS in primary cutaneous melanoma.

The authors concluded, “Based on our findings, we suggest that TIL grade be included in future AJCC staging revisions and routinely incorporated in a standardized manner into primary cutaneous melanoma pathology reports.”

REFERENCE

Comprehensive Genomic Features, Therapeutic Biomarkers Identified in Clear Cell Renal Cell Carcinoma

IN A RECENT STUDY, investigators reported the comprehensive genomic features of patients in China with clear cell renal cell carcinoma (ccRCC), which detailed the relationship between immunotherapy biomarkers and gene alterations. The analysis was published in Frontiers in Oncology.

“This is the first large-scale comprehensive genomic analysis for Chinese ccRCC patients, and these results might provide a better understanding of molecular features in Chinese ccRCC patients, which can lead to an improvement in the personalized treatment for these patients,” wrote the investigators.

cRCRC is the most common subtype of RCC, accounting for 70% to 85% of RCC cases, and is almost uniformly lethal and is considered critical. cRCC often lacks sensitivity to radiation and chemotherapy and many efforts are being made to establish a biomarker-oriented therapy.

Some therapies that target VEGF have greatly improved the prognosis of patients with ccRCC. Additionally, the use of an immune checkpoint inhibitor, either alone or in combination with other medications, may be a potential therapeutic strategy for patients with ccRCC.

Although some studies have reported on the genomic landscape of ccRCC, most previous data had been collected from patients from Western countries or had focused on how gene alterations can help determine disease prognosis. Because of this, the genomic landscape in Chinese patients with ccRCC has remained in need of further investigation.

“Revealing comprehensive genomic features is of great importance for understanding ccRCC and developing new therapeutic lines for patients with ccRCC,” the investigators said.

The investigators analyzed genomic profiling of DNA from Chinese patients with ccRCC who had undergone next-generation sequencing (NGS) between January 2017 and March 2020. In total, 880 patients with ccRCC and NGS data were included in the analysis.

Immunohistochemistry staining for PD-L1 expression was also conducted for 460 of those patients. PD-L1 expression is associated with improved overall response rates and longer progression-free survival in patients with metastatic RCC who are being administered immunotherapy.

Among the patients, 95.8% harbored at least 1 pathogenic mutation, with somatic alterations for VHL being the most commonly detected mutation among the samples (59.7%). Mutations in PBRM1 were detected in 18.0% of samples and SETD2 alterations were identified in 12.2% of samples. BAP1 alterations were found in 10.2% of samples and TP53 mutations were found in 9.4%.

When comparing the results with The Center Genome Atlas database, the investigators found a higher mutation frequencies of VHL (59.6% vs 59.7%; P < .001) and of TP53 (3.5% vs 9.4%; P < .001) among the Chinese cohort. Additionally, the Chinese cohort had a lower mutation frequency of PBRM1 than the database (18.0% vs 31.0%; P < .001).

VHL is a tumor suppressor gene that plays a prominent role in cellular oxygen sensing of ccRCC as well as the tumorigenesis that is associated with the disease. Inactivation of VHL is not associated with response to anti-VEGF receptor inhibitors, but it may help providers predict the effectiveness of HIF-2 inhibitors in ccRCC.

Of the patients who were evaluated for expression of PD-L1, 139 (30.2%) were positive for PD-L1 expression. Five (0.7%) patients were classified as microsatellite instability–high. Moreover, 5.9% (n = 52) of the patients were identified to carry pathogenic or likely pathogenic germline mutations for 22 cancer predisposition genes.

The retrospective nature of the analysis was listed as a study limitation, because it prevented the investigators from eliminating a potential selection bias. Another limitation involved the lack of data on the cancer subtypes, treatment histories, and survival outcomes of the patients.

“Thus, the effect of the biomarkers on treatment decisions and its correlation with survival outcomes need to be further confirmed in further studies,” the investigators suggested.

REFERENCE

Continued on SP380
# Fulphila® Product Highlights

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Fulphila® (pegfilgrastim-jmdb) injection</th>
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<td><strong>WAC price</strong></td>
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Available in Full Line and Specialty Channels

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Not Made With Natural Rubber Latex
Surface Proteins in DLBCL Offer Therapeutic Targets

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) has a complicated development pattern that is based on genetic alterations of tumor cells, the tumor microenvironment (TME), and tumor cell ability to evade attack by the immune system. However, recent insights into genetic alterations have been a key and progression in DLBCL. For example, reduced expression of major histocompatibility complex proteins resulting from genetic mutations plays “a key role in the immune escape of DLBCL,” according to the article’s author, Daisuke Ennishi, MD, PhD, of the British Columbia Cancer Centre for Lymphoid Cancer, in Canada.

The author noted that DLBCL is the most common malignant lymphoma, and that altered immune recognition “is deeply involved in tumor development and progression in DLBCL.” For example, reduced expression of major histocompatibility complex proteins resulting from genetic mutations plays “a key role in the immune escape of DLBCL.” Ennishi wrote, further observing that the host immune system is, therefore, an attractive therapeutic target in DLBCL.

The Role of the TME in Immune Escape

Ennishi cited large-scale genetic analyses that established new molecular classifications of DLBCL based on genetic abnormalities associated with prognosis. The identification of these genetic subtypes “can serve as a foothold for personalized medicine for DLBCL,” he wrote. However, the clinical implications of these genetic classifications on future immunotherapies may be limited because “the correlation between the genetic subtypes and TME composition remains unclear.”

According to the author, features of the TME differ among lymphoma types, and notably, “in DLBCL, disrupted cross talk between lymphoma cells and the microenvironment plays a role in the ability of lymphoma cells to escape immune surveillance of the host.”

Phagocytosis is induced by exposure to the phospholipid called phosphatidylserine (PS), a component of the cell membrane. It has a role in cell cycle signaling in relation to apoptosis, or programmed cell death. PS on the cell membrane surface induces phagocytosis, so its presence on the cell surface is an essential element to apoptosis. Investigators have found that transmembrane protein 30A (TMEM30A) moves PS inside the plasma membrane, which thwarts the phagocytosis process of absorption. Ennishi noted that investigators have promoted the elimination of cancer cells in mice by blocking the action of TMEM30A.

These and other findings prompted Ennishi to write that “TMEM30A is one of the main players regulating the ‘eat me’ signal that promotes phagocytosis of macrophages.”

He also addressed TMEM30A gene mutations, which he said occur specifically in aggressive B-cell lymphomas. Studies by the author’s research group confirmed that loss of TMEM30A function promotes phagocytosis of DLBCL cells.

Ennishi also cited a study of signal regulatory protein alpha (SIRPα), “another ‘don’t eat me’ signal that suppresses phagocytosis,” and noted that this analysis helped to confirm that TMEM30A can help “predict the therapeutic response to macrophage checkpoint inhibitors.”

Phagocytosis-Related Signals

In addition, clinical studies have investigated inhibition of either CD47 or SIRPα in lymphomas as well as other cancers. Inhibition of the CD47-SIRPα axis aims to diminish the “don’t eat me” signal, potentially leading to enhanced phagocytosis.

In particular, Ennishi cited a small study that found “significant efficacy” with no severe toxicity using CD47 blockade in combination with rituximab in patients with relapsed and refractory DLBCL or follicular lymphoma with resistance to immune chemotherapy. The author added that a phase 2 trial seeking to validate these initial findings is ongoing.

According to the author, “recent biological insights regarding immune evasion by lymphomas have enabled the development of multiple promising immunotherapeutic strategies,” including blockade of CD47. Future therapeutic strategies could target TMEM30A function to enhance the “eat me” signal, potentially facilitating recognition and phagocytosis of DLBCL cells by host macrophages.

Investigators Document Muscle Loss During Immunochemotherapy for DLBCL

IN A RETROSPECTIVE STUDY of patients (N = 104) with newly diagnosed diffuse large B-cell lymphoma (DLBCL) with unfavorable disease features who were treated with a standard immunochemotherapy combination, approximately half experienced muscle loss. However, the authors of the study said the observed muscle loss was “detrimental only if very pronounced.”

In the study, investigators sought to understand how treatments for curable lymphoma affect the musculoskeletal system. They based their observations on measurable changes in the psoas, which is a flexor muscle extending from the lower back to the femur. “Factors that affect muscle loss are mostly related to immunochemotherapy and not disease features prior to therapy per se,” they concluded.

The investigators evaluated muscle loss in patients who received a combination treatment composed of etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, doxorubicin hydrochloride, and rituximab (R-DA-EPOCH). The standard of care for DLBCL is the combination therapy rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, or R-CHOP, and with this, DLBCL is “curable in a majority of newly diagnosed patients,” the authors wrote. However, they said, “a substantial proportion” of patients with DLBCL who have aggressive disease or poor prognostic disease features “might benefit from more intensive therapeutic approaches.”

Previous studies have reported improved outcomes with the R-DA-EPOCH regimen in these patients.

The authors noted that sarcopenia (muscle loss) or cancer-induced cachexia (weight loss, muscle wasting) at baseline have been associated with poorer outcomes in patients with various cancers, including non-Hodgkin lymphoma, and skeletal muscle loss during chemotherapy has been associated with negative prognosis in gastrointestinal cancers.

To the authors’ knowledge, their study is the first to assess muscle mass dynamics during immunochemotherapy and prognostic associations in patients with lymphoid malignancies.

Investigators assessed the effect of R-DA-EPOCH immunochemotherapy on skeletal muscle mass by measuring psoas muscle area (PMA) in patients who had available baseline and end-of-treatment CT scans.

The study included patients with unfavorable prognostic features who were treated with R-DA-EPOCH between 2005 and 2019. Unfavorable prognostic features were defined as “a very high proliferative index Ki-67+ ≥ 80% and/or International Prognostic Index (IPI) ≥ 2 points.” Ki-67 is a marker that is strongly associated with tumor cell proliferation and IPI helps to predict outcomes in patients with cancer.
“Small but Significant” Muscle Mass Loss
The authors reported that more than half (57.7%) of patients experienced muscle mass loss, and the mean loss was 5%. Median psoas area measurement was 1238 mm$^2$ at baseline and 1099 mm$^2$ at the end of treatment, “with a small but significant decline during the immunochemotherapy period.”

In their multivariate model, investigators identified the following as contributors to psoas muscle mass loss: higher body surface area (odds ratio (OR), 17.98 for each 1 m$^2$), the number of cycles with required dose reduction (OR, 2.86, for each additional cycle), and worse response to therapy (OR, 3.09, for each response category increment).

They theorized that because R-DA-EPOCH is dosed according to body surface area, the association between body surface area and muscle loss could be “a consequence of higher delivered absolute drug doses.” Further, the number of cycles with required dose reduction could indicate “poor immunochemotherapy tolerance” or “weaker hematopoietic reserve” (bodily ability to produce blood cells), both of which could be important predictors of psoas muscle loss/improvement, they said.

Pronounced Muscle Loss and Survival
Median overall survival (OS) and progression-free survival (PFS) were not reached over the median 46-month follow-up of the study. The investigators found that PMA loss of 21% or greater, which occurred in 24% of patients, was associated with significantly worse OS and PFS.

These associations amounted to a significant, approximately 3-fold increase in the risk of death or progression after adjustment for age, sex, IPI score, and response to treatment. Lack of response to treatment (progressive or stable disease vs partial or complete remission) was also associated with poorer OS and PFS.

Also, the authors reported that baseline PMA parameters characteristic of more aggressive tumor behavior, body mass index, age, and gender did not predict loss of muscle mass during immunochemotherapy, based on study findings. They concluded that “muscle mass loss occurs in approximately half of R-DA-EPOCH-treated [patients with] newly diagnosed DLBCL with unfavorable disease features, and if pronounced, this is associated with worse clinical outcomes independent of achieved response to therapy.” Because they found “profound negative prognostic implications” with pronounced muscle loss, “a question emerges [of] whether active strategies aimed at muscle mass improvement, like physiotherapy and intensive nutritional support, might improve outcomes in this subgroup of patients.”

REFERENCE

Samsung Bioepis White Paper Describes Barriers to Adoption of Biosimilars

A WHITE PAPER FROM SAMSUNG BIOEPIS and Organon takes aim at misconceptions about biosimilars and industry practices that hinder their adoption. “The companies held 3 virtual panel sessions with doctors, nurses, pharmacists, policy experts, and patient advocates. Authors of the paper hold up Cleveland Clinic as a model of a health system that has achieved success in converting patients to biosimilars from reference products.

Cleveland Clinic was held up as an example of a health care institution that has had a high degree of success converting patients to biosimilars. Key to the success of Cleveland Clinic’s program, the authors explain, was educating stakeholders and setting up direct communications so that patients and providers could learn what they needed to know about biosimilars.

Some of those stakeholders were nurses, who were given specific training so that they could “reassure patients about the quality of care they would be receiving and answer any questions patients might have.”

In the broader health care community, “many physicians still lack confidence in biosimilars,” the authors wrote. In oncology, biosimilars have been embraced by physicians and patients, but in gastroenterology, there are lingering concerns about whether these agents will serve patients as well as their reference products.

“Many gastroenterologists who prescribe biologics for their patients with inflammatory bowel disease are concerned about biosimilar safety, immunogenicity, and indication extrapolation,” the authors wrote.

Kaiser Permanente
Another health care institution that has successfully transitioned patients to biosimilars is Kaiser Permanente, authors of the white paper said.

“Kaiser’s approach starts with a rigorous review of available biosimilar evidence, including data from manufacturers, FDA approvals, and real-world data from countries where biosimilars have already launched,” they wrote. Kaiser Permanente got biosimilars into circulation by building physician confidence, a strategy that a Samsung Bioepis executive has previously said should be employed more widely.

Having these data on hand is critical to informing physicians and other stakeholders so they can more readily embrace biosimilars, the authors wrote. However, those informational materials need to be digestible. “A gastroenterologist participating on the panel who has published on the merits of biosimilars in treating inflammatory conditions shared that many physicians are too busy to study in-depth clinical trial data and would prefer to receive easy digestible educational materials demonstrating a biosimilar’s safety, equivalence, and cost savings,” the authors wrote.

Samsung Bioepis has developed and gained regulatory approval for multiple biosimilar versions of reference products, and it relies on Organon for assistance with marketing these products. Some of Samsung Bioepis’ biosimilars include etanercept (autoimmune), infliximab (immunosuppressive), adalimumab (autoimmune), and other products. The company has a robust pipeline of biosimilars in development, including adalimumab (ophthalmology), denosumab (endocrinology), ustekinumab (immunology), and eculizumab (hematology) candidates.

REFERENCES
INDICATIONS
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:
• In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
• In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
• In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
• In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
• As monotherapy in patients who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

Systemic Reactions
In a pooled safety population of 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.6%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (86%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients. Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5.5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.
**DARZALEX FASPRO**: For a strong start to their treatment journey

- **3 to 5 minute administration**
  - Subcutaneous injection is substantially faster than intravenous daratumumab.2,3

The recommended dose of DARZALEX FASPRO® is 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously over 3 to 5 minutes. DARZALEX FASPRO® is for subcutaneous use only. Do not administer intravenously.

See the Dosage and Administration section of the Prescribing Information for dosing considerations and dosing schedules for approved regimens.

See Important Safety Information below for hypersensitivity and administration reactions, pre-medication and post-medication requirements, and other important considerations for use of DARZALEX FASPRO®.

Get the latest data and information at darzalexhcp.com/faspro

Contact your Oncology Specialist to learn more about DARZALEX FASPRO®

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**Efficacy consistent with intravenous daratumumab**

- **DARZALEX FASPRO®** demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients.
  - ORR was 41% (95% CI: 35%, 47%) for DARZALEX FASPRO® (n=263) and 39% (95% CI: 31%, 43%) for intravenous daratumumab (n=259).
  - Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥2 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent.
  - In a single arm of a multicohort, open-label study, DARZALEX FASPRO® with lenalidomide and dexamethasone (DRd) was evaluated in 65 patients with multiple myeloma who had received ≥3 prior lines of multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%).

- In a single arm of a multicohort, open-label trial, DARZALEX FASPRO® with bortezomib, melphalan, and prednisone (DVMp) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for transplant. The ORR was 86% (95% CI: 78%, 93%).

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX FASPRO®.

**Fewer systemic ARRs vs intravenous daratumumab**

- Nearly 3x reduction in systemic administration-related reactions (ARRs) with DARZALEX FASPRO® vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZALEX FASPRO® had systemic ARRs of any grade vs 34% with intravenous daratumumab).2

- Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. See Important Safety Information for more details.

For intravenous daratumumab, median duration of id mg/kg infusion for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.

In clinical trials of DARZALEX FASPRO®, DARZALEX (daratumumab), and the Prescribing Information for DARZALEX®, the term “fusion reactions” was used instead of “systemic administration-related reactions.”

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**Neutropenia**

Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO® until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

**Thrombocytopenia**

Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO® until recovery of platelets.

**Embryo-Fetal Toxicity**

Based on the mechanism of action, DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO® and for 3 months after the last dose.

The combination of DARZALEX FASPRO® with lenalidomide, thalidomide, or pomalidomide is contraindicated in pregnant women because lenalidomide, thalidomide, and pomalidomide may cause birth defects and death of the unborn baby. Refer to the lenalidomide, thalidomide, or pomalidomide prescribing information on use during pregnancy.

**Interference With Serological Testing**

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX FASPRO®.

**Embryo-Fetal Toxicity**

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO®-treated patients with IgG kappa myeloma protein.

**ADVERSE REACTIONS**

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥50% for any combination) include fatigue, nausea, diarrhea, dyspepsia, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematologic laboratory abnormalities (≥40%) with DARZALEX FASPRO® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

**Please see accompanying full Prescribing Information.**

- cp:143279v4

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

Multiple Myeloma

DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:

• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

• in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.

• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.

• in combination with bortezomib, thalidomide, and dexamethasone in patients who have received at least one prior therapy.

• in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy.

• in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy.

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur

with the formulation [see Warnings and Precautions Adverse Reactions].

Limitations of Use

The determination of a patient’s ABO and Rh blood type are not impacted by daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References (150)]. The interference with serological testing for greater than one year.

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

• Hypersensitivity and Other Administration Reactions

• Systemic Reactions

• Local Reactions

• Neutropenia

• Neutropenia

• Neutropenia

• Neutropenia

• Neutropenia

• Neutropenia

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Severe or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone [see Adverse Reactions]. Serious cardiac disorders occurred in 18% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Ddaratumumab may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of neutrophils.

Neurotoxins

Daaratumumab may increase neurotoxicity induced by background therapy [see Adverse Reactions].

Monitor complete blood counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Adverse pregnancy outcomes have been observed. DARZALEX FASPRO in combination with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD138 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References (150)]. The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO [see Dosage and Administration (2.1) in Full Prescribing Information].

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein [see Drug Interactions]. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO–treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

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

• Hypersensitivity and Other Administration Reactions [see Warnings and Precautions].

• Cardiovascular Toxicity in Patients with Light Chain (AL) Amyloidosis [see Warnings and Precautions].

• Neutropenia [see Warnings and Precautions].

• Thrombocytopenia [see Warnings and Precautions].

Clinical Trials Experience

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

Newly Diagnosed Multiple Myeloma

In combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO in combination with bortezomb, melphalan and prednisone was evaluated in a single-arm cohort of PLEIADEs [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 8 months or longer and 19% were exposed for greater than one year.
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection is indicated for the treatment of relapsed or refractory multiple myeloma in patients who have received at least two prior therapies, including lenalidomide and dexamethasone (see Clinical Studies (14.2) in Full Prescribing Information).

In combination with lenalidomide and dexamethasone, DARZALEX FASPRO® was evaluated in a single-arm cohort of PLEIADES (see Clinical Studies (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO® with Bortezomib, Melphalan and Prednisone (DARZALEX FASPRO®-VMP) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO®. Serious adverse reactions in <5% of patients included pneumonia, influenza, and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO®. Serious adverse reactions in <5% of patients included pneumonia, influenza, and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Peritoneal discontinuation of DARZALEX FASPRO® due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO®. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO® in more than one patient were pneumonia and anemia.

Dose reductions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO®. Adverse reactions requiring dosage interruption in <5% of patients included hypotension, nasal congestion, and dyspnea.

Dose interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO®. Adverse reactions requiring dosage interruption in <5% of patients included hypotension, nasal congestion, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO® in PLEIADES.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (DARZALEX FASPRO®-VMP) in PLEIADES

Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (DARZALEX FASPRO®-Rd) in PLEIADES

Table 4: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO®-Rd) in PLEIADES

Table 5: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO®-Rd) in PLEIADES
Table 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
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<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

- Fatigue includes asthenia, and fatigue.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
- Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
- Bronchitis includes bronchitis, and bronchitis viral.
- Dryness includes dryness, and dryness excretional.
- Cough includes cough, and productive cough.
- Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain
- Nervous system disorders: dizziness, headache, paresthesia
- Skin and subcutaneous tissue disorders: rash, pruritus
- Gastrointestinal disorders: abdominal pain
- Infections: influenza, sepsis, herpes zoster
- Metabolism and nutrition disorders: decreased appetite
- Cardiac disorders: atrial fibrillation
- General disorders and administration site conditions: chills, infusion reaction, injection site reaction
- Vascular disorders: hypertension, hypotension

Table 4: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone*</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>66</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>83</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

- Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

In combination with Pomalidomide and Dexamethasone

The safety of DARZALEX FASPRO with pomalidomide and dexamethasone compared to pomalidomide and dexamethasone (Pd) in patients who had received at least one prior line of therapy with lenalidomide and a proteasome inhibitor (P) was evaluated in APOLLO (see Clinical Studies (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity in combination with pomalidomide and dexamethasone (n=180) or pomalidomide and dexamethasone (n=150). Among patients receiving DARZALEX FASPRO-Pd, 71% were exposed for 6 months or longer and 50% were exposed for greater than one year.

Serious adverse reactions occurred in 50% of patients who received DARZALEX FASPRO-Pd. The most frequent serious adverse reactions in <5% of patients who received DARZALEX FASPRO-Pd were pneumonia (15%) and lower respiratory tract infection (12%). Fatal adverse reactions occurred in 7% of patients who received DARZALEX FASPRO-Pd.

Permanent treatment discontinuation due to an adverse reaction occurred in 2% of patients who received DARZALEX FASPRO-Pd. No adverse reactions resulting in permanent discontinuation occurred in more than 1 patient.

The most common adverse reactions (≥20%) were fatigue, pneumonia, upper respiratory tract infection, and diarrhea.

Table 5 summarizes the adverse reactions in patients who received DARZALEX FASPRO in APOLLO.

Table 5: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DARZALEX FASPRO-Pd Arm in APOLLO

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO-Pd (N=149)</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
<th>DARZALEX FASPRO-Pd (N=150)</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>46</td>
<td>13</td>
<td>9%</td>
<td>39</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>38</td>
<td>23</td>
<td>27</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>36</td>
<td>1%</td>
<td>22</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>5%</td>
<td>14</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Key: Pd=pomalidomide-dexamethasone
- Fatigue includes asthenia, and fatigue.
- Edema peripheral includes edema, edema peripheral and peripheral swelling.
- Pneumonia includes atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia respiratory syncytial viral.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cough includes cough, and productive cough.
- Only grade 3 adverse reactions occurred.
- Grade 5 adverse reactions occurred, n=3 (2.0%) in the DARZALEX FASPRO-Pd arm and n=2 (1.3%) in the Pd arm.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with pomalidomide and dexamethasone included:

- Metabolism and nutrition disorders: hypocalcemia, hypokalemia, decreased appetite, dehydration
- Nervous system disorders: peripheral sensory neuropathy, syncope, headache, paresthesia, dizziness
- Musculoskeletal and connective tissue disorders: muscle spasms, musculoskeletal chest pain, arthralgia
- Psychiatric disorders: insomnia
- Gastrointestinal disorders: nausea, abdominal pain, vomiting
- Skin and subcutaneous tissue disorders: rash, pruritus
- Cardiac disorders: atrial fibrillation
- General disorders and administration site conditions: infusion reactions, chills, injection site reaction
- Infections: urinary tract infection, influenza, hepatitis B reactivation, herpes zoster, sepsis
- Venous disorders: hypertension, hypotension

Table 6 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in APOLLO.

Table 6: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO-Pd or Pd in APOLLO

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO-Pd#</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
<th>DARZALEX FASPRO-Pd#</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased neutrophils</td>
<td>97</td>
<td>84</td>
<td>84</td>
<td>96</td>
<td>82</td>
<td>40</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
<td>58</td>
<td>93</td>
<td>79</td>
<td>3%</td>
<td>33</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>51</td>
<td>16</td>
<td>57</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: Pd=pomalidomide-dexamethasone
- Denominator is based on number of patients with a baseline and post-baseline laboratory value for each laboratory test: N=148 for DARZALEX FASPRO-Pd and N=149 for Pd.
**DARZALEX FASPRO®** (daratumumab and hyaluronidase-fihi) injection

**Monotherapy**

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA [see Clinical Trials (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 18 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than one patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 7 summarizes the adverse reactions in COLUMBA.

### Table 7: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24%</td>
<td>1%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>13%</td>
<td>24%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Chills</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6%</td>
<td>11%</td>
</tr>
</tbody>
</table>

### Infections

- Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, sinusitis, rhinovirus infection, sinuitis, and upper respiratory tract infection.

### Gastrointestinal disorders

- Diarrhea includes acute diarrhoea, diarrhea, and pseudomembranous colitis.

### General disorders and administration site conditions

- Fatigue includes asthenia, and fatigue.

### Musculoskeletal and connective tissue disorders

- Back pain includes acute low back pain, back pain, and acute back pain.

### Respiratory, thoracic and mediastinal disorders

- Cough includes cough, productive cough.

### Other Adverse Reactions

- Fatigue includes asthenia, and fatigue.

- Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, sinusitis, rhinovirus infection, sinuitis, and upper respiratory tract infection.

- Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.

- Nausea includes nausea and vomiting.

- Fatigue includes asthma, and fatigue.

- Infusion reactions includes terms determined by investigators to be related to infusion.

- Cough includes cough, and productive cough.

- Dyspnea includes dyspnea, and dyspnea exertional.

- Grade 5 adverse reactions occurred.

### Clinically relevant adverse reactions in >10% of patients who received DARZALEX FASPRO included:

- General disorders and administration site conditions: injection site reaction, peripheral edema

- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, muscle spasm

- Gastrointestinal disorders: constipation, vomiting, abdominal pain

- Metabolism and nutrition disorders: decreased appetite, hyperglycemia, hypocalcemia, dehydration

- Psychiatric disorders: insomnia

- Vascular disorders: hypertension, hypotension

- Nervous system disorders: dizziness, peripheral sensory neuropathy, paresthesia

- Infections: bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B virus reactivation

- Skin and subcutaneous tissue disorders: pruritus, rash

- Cardiac disorders: atrial fibrillation

- Respiratory, thoracic and mediastinal disorders: pulmonary edema

---

**DARZALEX FASPRO®** (daratumumab and hyaluronidase-fihi) injection

### Table 8: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPROa</th>
<th>Intravenous Daratumumaba</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>Grades 3-4 (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>59%</td>
<td>56%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>55%</td>
<td>43%</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>42%</td>
<td>45%</td>
</tr>
</tbody>
</table>

### In Combination with Bortezomib, Cyclophosphamide and Dexamethasone

The safety of DARZALEX FASPRO with bortezomib, cyclophosphamide and dexamethasone (DARZALEX FASPRO-VCd) was evaluated in ANDROMEDA [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity or for a maximum of 2 years. Among patients who received DARZALEX FASPRO-VCd, 74% were exposed for 6 months or longer and 32% were exposed for greater than one year.

Serious adverse reactions occurred in 43% of patients who received DARZALEX FASPRO in combination with VCd. Serious adverse reactions that occurred in at least 5% of patients in the DARZALEX FASPRO-VCd arm were pneumonia (9%), cardiac failure (9%), and sepsis (5%). Fatal adverse reactions occurred in 11% of patients. Fatal adverse reactions that occurred in more than one patient included cardiac arrest (4%), sudden death (3%), cardiac failure (3%), and sepsis (1%).

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 5% of patients. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia, sepsis, and cardiac failure.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 36% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 9 below summarizes the adverse reactions in patients who received DARZALEX FASPRO in ANDROMEDA.

### Table 9: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (DARZALEX FASPRO-VCd) with a Difference Between Arms of >5% Compared to VCd in ANDROMEDA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO-VCd (N=180)</th>
<th>VCd (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>45%</td>
<td>21%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38%</td>
<td>20%</td>
</tr>
<tr>
<td>Constipation</td>
<td>34%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Cough</td>
<td>20%</td>
<td>11%</td>
</tr>
</tbody>
</table>
DRUG INTERACTIONS
Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)
Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References). Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/Rh-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
Daratumumab can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigens CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk.

Animal reproduction studies have not been conducted.
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 outcomes. 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. The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematological evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (mouse). No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose. There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed or refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=154). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Use in Specific Populations

Of the 198 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, anemia, pneumonia and hypotenion.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itching, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see Warnings and Precautions].

Cardiac Toxicity

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program [see Use in Specific Populations].

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

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With No Replacement for OCM on Horizon, Oncology Practices Ask: What Now?

GIANNA MELILLO

CONTINUED FROM COVER

The new approach will also focus on a “streamlined portfolio of models,” as the previous volume led to confusion among participating practices. “In addition to reducing overlap, we also want our models to be simpler and easier to participate in, with less administrative burden,” Fowler said. CMS declined to comment directly for this article. A spokesperson said there is likely to be some gap between the end of OCM and the start of any potential oncology model.

Uncertainty Grows

This raises a myriad of challenges and questions for those enrolled in OCM who have complied with data reporting and operational requirements for the past 5 years. When it launched, OCM was to expire in 2021, but due to the pandemic, a proposed successor model called Oncology Care First was shelved.

“It actually feels more like a void than merely a potential gap in the comprehensive care that a lot of patients are now receiving and benefiting from under this model,” said Karen L. van Caulil, PhD, president and CEO of the Florida Alliance for Healthcare Value.

Intended to increase value-based care in the oncology field, OCM provides participants with monthly enhanced oncology services (MEOS) payments in addition to regular fee-for-service Medicare payments. Whether practices will receive bridge payments to continue funding services such as navigators and 24/7 record access until a new model is implemented remains to be seen.

“What do you do when you don’t have those payments anymore?” asked Schleicher. “We’re lucky Tennessee Oncology is very large, and we will continue to provide high-quality care that we’ve learned to do through OCM. But if you’re a small practice, I worry, are practices going to have to revert back to the old ways of doing things where they don’t have support from Medicare along the way?”

Amid this uncertainty, the Community Oncology Alliance (COA) called on CMMI to extend OCM through December 31, 2022. However, in a letter sent November 16, the group cited the investment that practices have made in the model, along with the effect the model has had on patient care. COA also argued that some negative reviews of OCM, notably the Abt Associates’ evaluation, failed to capture later data that show practices became better at implementing the model over time.

“The millions of dollars of taxpayers’ money invested in the OCM and the dramatic successes of many independent community oncology practices participating in the OCM in enhancing patient cancer care while lowering treatment costs should be clear reasons why the OCM should not be trashed, but refined and reenvisioned based on what is working,” the letter stated. COA strongly endorsed CMMI’s call to focus on health equity and 24/7 record access until a new model is implemented.

This move received support from the Florida Alliance for Healthcare Value. “We think that’s a very reasonable and appropriate request by COA,” rather than to just completely stop the program entirely,” said van Caulil.

Higher quality, more coordinated care at the same or lower cost than Medicare, was the primary target of OCM; the voluntary model also allowed practices to opt into 1- or 2-sided risk.

Absence of OCM raises regulatory compliance issues as well. Once the model ends, the possibility is raised that by default, OCM practices would be governed by other elements of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Under MACRA, if practices were enrolled in an alternative payment model (APM), they did not have to abide by the Merit-Based Incentive Payment System (MIPS). “But if OCM expires and practices find themselves no longer enrolled in an APM, it is unclear if that fact compels MIPS participation.”

Challenges in OCM

Despite mixed reports of success with the model, various shortcomings hindered efficient implementation and participation for some practices and ought to be addressed in future iterations, experts argued.

“What do you do when you don’t have those payments anymore? We’re lucky Tennessee Oncology is very large, and we will continue to provide high-quality care that we’ve learned to do through the [Oncology Care Model]. But if you’re a small practice, I worry, are practices going to have to revert to the old ways of doing things?”

—Stephen M. Schleicher, MD, MBA, medical oncologist, Tennessee Oncology; medical director of value-based care, OneOncology

Because of OCM’s structure, participation in the model could disincentivize providing care for underserved communities or high-risk patients. Despite meeting reporting requirements and following guidelines, practices serving populations with baseline poor health would necessarily have increased risks of worse overall outcomes compared with practices serving healthier populations. A paper presented at the 2021 meeting of the American Society of Clinical Oncology found, for example, that high-risk patients were, on average, $21,500 over target when undergoing autologous stem cell transplant, even with risk adjustment for this procedure.

“Provider exposure to risk in the OCM is highly sensitive to factors at the cancer and patient level,” wrote the authors, who called for models that “model risk in more clinically granular ways.”

In their strategic refresh, CMMI acknowledged this problem, which was also apparent in earlier additional models.

“My vision for the future of the agency, our programs, and the people we serve is straightforward: that CMS serve the public as a trusted partner and steward, dedicated to advancing health equity, expanding coverage, and improving health outcomes,” said CMS Administrator Chiquita Brooks-LaSure during the refresh announcement.

Among lessons learned listed in an accompanying CMMI white paper, the center stressed that moving forward, health equity will...
be embedded into every model. This step was seen by many as encouraging.2

“So far, models have focused on cost, quality, and patient experience,” said Kashyap Patel, MD, CEO of the Carolina Blood and Cancer Care Associates, associate editor of Evidence-Based Oncology3, and president of COA.

But rising treatment costs in the oncology space also posed a challenge to practices. OCM includes a reimbursement system based on a snapshot of time to calculate reimbursement rates for oncology treatments. Over the years as new, more expensive treatments were developed and approved, they were, at times, not accurately captured by the model. The model was so ill-equipped to handle major innovations that CMMI initially did not even include chimeric antigen receptor T-cell therapy in the cost-of-care calculations.4

Cancer is a multifaceted disease with numerous variations, types, and mutations. This heterogeneity complicates standardization of care—a key component of other, more streamlined payment models. CMMI plans to begin the Radiation Oncology (RO) Model in January 2022,2 a start date the American Society for Radiation Oncology has deemed “extremely challenging,” due in part to recently permitted cuts in Medicare fee schedules.10

The RO Model “tests whether prospective, site-neutral, modality-agnostic, episode-based payments to physician group practices, hospital outpatient departments, and freestanding radiation therapy centers for radiotherapy episodes of care [reduce] Medicare expenditures while preserving or enhancing the quality of care for Medicare beneficiaries.”11

Under this model, there are limited options for treatment, and its mandatory nature encourages uniformity across practices. However, compulsory participation brings along its own challenges.

It is unclear if OCM’s successor will be mandatory. Although this change would remove selection bias when it comes to covering certain patient populations, a mandatory model would also impose onerous data-reporting requirements on smaller practices with less resources and manpower, adding to compliance hurdles.

On the flipside, voluntary models allow practices to simply drop out at the first hint of a bleak financial forecast, limiting the quality and quantity of data produced by model participation. During OCM’s 5-year implementation, changing conditions required by CMS and a lag in outcome reports meant practices were unable to implement successful practices in a timely fashion.

Looking Ahead

Moving forward, CMMI plans to increase stakeholder perspectives and feedback on model successes and challenges via listening sessions hosted throughout the year—the first of which took place on November 18.

During this session, Lalan Wilfong, MD, vice president of care relations and practice transformation at McKesson and a medical oncologist and hematologist at Texas Oncology, laid out some complications of OCM and subsequent RO Model participation.

Wilfong discussed how these practices will have to submit data for the mandatory RO Model through a different platform than that used for OCM. This inconsistency presents a hurdle for practices as it took some years to optimize data reporting procedures to minimize compliance burdens.

With a new data reporting format under the RO Model, “it feels like we have to start over again,” Wilfong said. But improved alignment from CMMI in the future may help alleviate these challenges and enable model participation, he added.

Touching on the heterogeneity of cancer care, Wilfong explained how historical benchmarks may not accurately reflect the current care provided. For example, at the start of the OCM, lung cancer care was “very simple in the management at that time,” but over the past few years, has seen “tremendous innovation.”

“My care paths for patients with lung cancer are very complex now, where they used to be pretty simple, with very different costs and outcomes and toxicities that we manage,” Wilfong said. Putting appropriate benchmarks in place for oncology patients that reflect the changing nature of the treatment landscape will help encourage rural and smaller practices to participate in future models.

Although this session was broad in scope, in upcoming discussions stakeholders may be eager to know whether practices that invested in models and reported success will be recognized in future or replacement models.

“If you want to continue to garner enthusiasm for participating in APMs and get people excited about it, there needs to be some recognition of groups that did double down on OCM—the first of its type—and especially the ones that are taking 2-sided risk,” said Schleicher. “It is frustrating for us in that boat who made all these large practice- transformation efforts, and hired new teams, and invested in analytics, and have been messaging to everybody around us how important this is to then feel like the rug got ripped from below us.”

Before practices invest in infrastructure and change how they operate in preparation for the next model, the concern is they participate for a few years, the model ends, and what comes next is unknown, he explained.

Overall, Schleicher does not think OCM was a failure and hopes it doesn’t get remembered as such, stressing the model resulted in improved care and cost savings for Tennessee Oncology.

Using MEOS payments, the practice was able to better reach rural patients and help them navigate a complex care journey by creating a new health care infrastructure that incorporates care coordination and data analytics. Performing well in OCM also enabled the practice to take on major goals of accountable care organizations, including keeping patients out of hospitals and improving end-of-life care.

In fact, as EBO went to press, Tennessee Oncology received word that for the period spanning the second half of 2019 and the first half of 2020, the community practice received a 100% quality score under the model, for metrics that include patient pain, depression assessment and management, reduction in emergency department visits, and appropriate use of hospice.

Tennessee Oncology also saved Medicare $5 million during this period, according to an emailed news release.11

Schleicher aims to continue these efforts even after OCM ends. “It’s the right thing to do for patients…. I think OCM was a success for groups like us,” he said. “We learned how to provide better care, and we couldn’t have done that without this model.”

Hayden E. Klein contributed to this report.

References


11. Tennessee Oncology receives perfect quality score while saving Medicare $5 million during the last year of the Oncology Care Model. News release sent November 16, 2021, via e-mail.
The MMRF: Understanding and Sharing the Genomic Landscape of Multiple Myeloma

MAGGIE L. SHAW

CONTINUED FROM COVER

Precision Medicine and Multiple Myeloma

Precision medicine focuses on individualizing treatment by patient and disease state. It is personalized medicine, with a goal to protect each patient’s health by considering the factors that influence that individual. It is individualized specialized treatment.

Per the Precision Medicine Initiative, it is “an innovative approach that takes into account individual differences in people’s genes, environments, and lifestyles, giving medical professionals the resources they need to target the specific treatments of the illnesses we encounter.”

The CDC calls these disease risks “unique,” noting that such an approach can “better predict, prevent, treat, and manage disease.” Methods of doing this include gathering a family disease history, using genomic sequencing, and screening for possible inheritable conditions, such as mutations (eg, BRCA1, BRCA2 or conditions (eg, Lynch syndrome) that predispose some to certain cancers.2

Overall, the process facilitates a more accurate forecast on the success of potential strategies for specialized care, which is in stark contrast to a more generalized approach, and when considering contributions from such digital health tools as wearable devices and remote monitoring, the American Medical Association highlights progress in disease prevention and treatment effectiveness.2

In MM—an extremely heterogeneous cancer of plasma cells, considered by many to be a chronic condition because it is incurable—the accumulation of abnormal antibodies in the bone marrow interferes with healthy blood cell production, crowding them out and leading to bone pain, mental confusion, and leg weakness/numbness, among other symptoms, as well as low levels of several important blood components: white blood cells, red blood cells, and platelets.11

“When I started in myeloma almost a quarter of a century ago, what you have to realize is the treatment back then for patients was still this drug called melphalan, which was developed in the 1960s,” said Daniel Auclair, PhD, chief scientific officer at the MMRF, in an interview with Evidence-Based Oncology.2

The MMRF: From Drug Development to Data Generation

That quarter century ago was 1996, a full 2 years before Kathy Giusti and her twin sister Karen Andrews founded the MMRF following Giusti’s 1996 MM diagnosis and, soon thereafter, frustration at the lack of effective treatments that could extend a patient’s life beyond the average 3 years between diagnosis and death.11 At first, the MMRF purely funded research grants, including those for novel immune approaches, Auclair stated, “but very early on we realized that in order to make a difference for our patients, we needed to do much more than that. We needed to not only fund some of the research but get intimately involved in the research itself.”

That goal first manifested as the Multiple Myeloma Research Consortium (MMRC), founded in 2004, which has since conducted 89 clinical trials. “Basically, most drugs approved in MM were tested through this clinical consortium,” Auclair said.

While the MMRC was getting off the ground, so, too, was what would become known as The Cancer Genome Atlas (TCGA) at the National Cancer Institute, under the direction of Eric S. Lander, PhD, AR, then at the Broad Institute in Massachusetts. Herculean efforts on the part of TCGA resulted in molecularly characterizing more than 20,000 samples for 33 cancer types over 12 years.12 Noting that 15% of Black individuals at higher risk for MM or with a first-degree relative with a blood cancer who were screened have been found to have a myeloma precursor condition, Auclair underscored the importance of early detection and that this could be as simple as a blood test to detect the antibody monoclonal immunoglobulin M protein, “a very beautiful biomarker,” he said, and one that is often used as an indicator of disease extent and possible progression.11 “But we just don’t do it,” he said.

MM was not among the 25 cancers the soon-to-be TCGA had determined to survey. This omission spurred the MMRF to genetically characterize the disease and come up with a long-awaited genomic blueprint by 2009 by incorporating data from several hundred patients who had newly diagnosed or relapsed disease. In total, 6 MM subtypes were identified through those efforts, as were never-before-seen genetic alterations, which helped fuel the MMRF’s efforts to get at the root causes of MM.

The MMRF has since expanded its efforts to defeat MM on several fronts, each of which has incorporated extensive patient data and follow-up, research, and clinical trial work.

In 2011, the CoMMpass Study was initiated, which expanded upon the MMRC’s groundwork by gathering information on close to 1200 patients aged 27 to 93 years—846 from the United States, 172 from Italy, 93 from Spain, and 32 from Canada—from 76 worldwide sites and following up with them on a biannual basis for at least 8 years. With the data it gathered and interpreted through the study, the MMRF has been able to report on what regimens work in what line—from first through fourth—and to what degree, as well as for how long a patient was on a certain combination treatment.16

Patient data have also enabled the MMRF to double its innovative results seen with CoMMpass and identify an astounding 12 subtypes of MM via RNA sequencing. “These subtypes can be related back to DNA alterations, some of which are actionable, meaning there is a therapy available to target and treat that alteration,” the MMRF notes.16

In addition, the CoMMpass findings themselves have given rise to the MMRF’s newest study, MyDRUG (Myeloma - Developing Regimens Using Genomics), which is investigating regimens of drugs—proven effective and already approved to treat other cancers—that specifically target the genetic mutations in each MM subtype.16,17 This study aims to be effective on 2 fronts: hastening the treatment testing process and streamlining the matching of patient to effective regimen.17

“My father always said that there isn’t a coin so thin that it doesn’t have 2 sides to it. There’s the genomic blueprint of the cancer and then there’s how the immune system reacts to it, is influenced by, changes, and responds to treatment,” Auclair added. “When novel immune agents entered the field of myeloma in 2015, we were able to see long remissions; not only responses, but good response and remission. So that told us that immune approaches are the way of the future. That is why we’ve been investing more in this area.”

A Multipronged Approach

cureCloud is that “more,” and through this new initiative launched in July 2020,10 the MMRF is hoping to deploy its
CoMMpass findings to the masses—thousands of patients far beyond the 1200 of CoMMpass—with next-generation sequencing (NGS) technology, starting with direct outreach to a potential 5000 patients that it hopes results in treatments for all of them.19

Thinking outside the box through CureCloud—yet building on knowledge gained through CoMMpass—the MMRF is using a multipronged approach to advance precision medicine for patients by consolidating all of the information in one place that they can access with their physicians to inform treatment decisions. For patients, this involves enabling consent online (smartphones can be used), including the release of their medical record, which brings a phlebotomist to their home for a liquid biopsy blood draw, which in turn leads to a personalized genomic report containing information on their variation of MM along with clinical trials focused on their subtype. Clinicians approve each patient’s free liquid biopsy orders and review the personalized genomic report with them to determine the optimal course of action, adding to their MM treatment knowledge with each new participant in CureCloud20,21 and by making that data available to all patients and doctors.

Genetic sequencing of those blood samples comes next, through the use of an NGS assay that looks at the 70 most relevant genes in MM, Auclair said, by capturing the DNA that MM cells release into the blood through apoptosis. Molecular pathologists look over these sequencing reports and approve the findings before passing them on to the treating clinicians and the patients, the latter of whom receive a report they can more readily understand.

“We felt very strongly that for all the patients have given, for all their altruism, we wanted to give something actionable back,” Young said in an interview with Evidence-Based Oncology22. “The exciting technology allowed us to work toward democratization of care, which is especially important in a disease like multiple myeloma, which disproportionately affects traditionally underserved populations.”

For example, Black Americans receive a diagnosis of MM at twice the rate of White Americans and are younger when they receive that diagnosis,22,23 and per 100,000 individuals, non-Hispanic Whites have been shown to have a higher incidence rate than Asian and Hispanics outpace Whites.2 In addition, other Americans tend to shoulder a disproportionate burden of MM diagnoses, with the median age of diagnosis ranging from late 60s to early 70s.24

Bringing Greater Diversity to Enrollment

Speaking to how CureCloud aims to balance patient diversity and disease diversity, Young told of how past MMRF work keeps paying it forward. Those working on CureCloud have consulted with the MMRC and CoMMpass sites that have found success at enrolling diverse patient populations in their studies for help in devising plans to ensure at least 20% of CureCloud patients are Black.

“We asked them, ‘How can we help you make sure that we do the same with CureCloud, that 20% of the 5000 patients are Black?’—because 20% of myeloma patients are Black,” she said. “We’re also working with health systems,” she noted, one of which is Ochsner, for whom over 40% of their patients with myeloma are Black.

The outreach doesn’t stop there, however. In fact, it is constantly evolving, and the MMRF continues to evaluate its efforts by looking at the data that come in to see where refinement is needed—to uncover goals that are not being met and to come up with new strategies to ensure they are.

Young also shone a spotlight on 4 of the sites that are MMRC participants—Winship Cancer Institute at Emory University/Medical Center in Atlanta, Georgia; Icahn School of Medicine at Mount Sinai in New York City; Karmanos Cancer Center at Wayne State University in Detroit, Michigan; and Siteman Cancer Center at Washington University in St. Louis—noting their good relationships with their surrounding communities foster collaboration.

“CureCloud helped us better understand where we were falling short in reaching patients directly,” she emphasized. “That made us decide to supplement the marketing we were already doing to our patient database with consulting with those sites that have already been successful at patient engagement with more diverse or underserved communities.”

“We have drugs approved in MM that have not been extensively tested in certain populations. Some drugs that were approved in myeloma didn’t even have 1% of African American participants in the registration studies,” Auclair added. “We’ve learned that we need to reach them where they are, because direct-to-patient contact doesn’t always work for underserved communities.

Especially if patients aren’t able to be seen at some of the biggest centers, where sequencing is more common, the report they get from CureCloud could open up treatment options “they didn’t know about before,” Young continued.

“There are different ways to do research, there are different ways to do science, and efforts direct to patients, like CureCloud, using a lot of technology, a lot of telemedicine, are truly the future for our patients,” Auclair said.

Even with the extensive knowledge that has now been gained through the MMRC, CoMMpass, and CureCloud—along with the treasure trove of genomic data gained—there are still gaps in the precision space for MM because of the heterogeneous nature of this chronic disease. A cure remains out of reach, at least for now.

Although the trials the MMRF has conducted through the MMRC and its partners have led to an average overall survival of 5 to 7 years following an MM diagnosis for approximately 75% of patients, with transplant and standard-of-care treatment—and to a median overall survival of 9 to 10 years in 25% of patients—the majority do not reach the 3-year mark after treatment initiation because of disease relapse while on treatment, the MMRF experts said. Three areas in this regard that continue to benefit from the ongoing research conducted by the MMRC are early-stage disease, prevention of upfront/high-risk disease, and relapsed/refractory disease.

“We’re addressing each of these groups with potentially transformative agents,” Young pointed out. “We’re not here to do trials that are just for publication; we are here to make a difference in those populations, to extend progression-free survival and, ultimately, extend survival.”

A Resource for All Cancers

When asked if they are already thinking beyond CureCloud, not just for MM but for how the MMRF’s efforts could expand to push progress in other hematological disorders, Auclair and Young emphasized how the MMRF’s collective efforts aim to open a path to precision medicine, not just for all blood cancers but for all cancers in clinical immune genomic precision medicine.

Ultimately, a cure will only come from this kind of precision medicine approach, they said, with the next frontier in MM being to intercept the disease early—so patients don’t have to face worse outcomes from an advanced-stage diagnosis—by combining real-world data collection and 21st-century technology, by translating research efforts to the clinic, and by making a difference with actionable information from the patients themselves. »

FIGURE. Highlights of the MMRF Roadmap to Genomic Landscape Success
REFERENCES

CLINICAL PATHWAYS
Boston Medical Center’s Shah: Nonclinical Factors Can Drive Value Equation in Multiple Myeloma

MARY CAFFREY AND MAGGIE L. SHAW

BHAVESH SHAH, RPH, BCOP, is associate chief pharmacy officer for specialty and hematology pharmacy at Boston Medical Center (BMC); he joined the staff more than 21 years ago. Evidence-based Oncology” (EBO) spoke with Shah about several current issues in multiple myeloma, including the use of anti-CD38 agents and risk stratification of patients.

EBO: In the context of multiple myeloma, what is risk and how are patients stratified by risk?

SHAH: Just to kind of level-set for myeloma, there are approximately 28 FDA-approved treatments on the market.1 Regarding risk, risk is mainly defined as progression of disease, and multiple factors determine the risk of progression that a patient may have. Practicing as long as I have in oncology, [I’ve seen] a revision of the International Staging System that combines all the elements that capture risk of progression, such as tumor burden and the biology of the disease, which is essentially the presence of high-risk cell genomic abnormalities. Then, of course, you have elevated lactate dehydrogenase. This essentially captures all the elements used to quantify risk of progression for a patient.

Now, in the current landscape of myeloma treatment, we have a new risk factor: minimal residual disease–positive disease. This has really been incorporated outside of clinical trials now, and many providers and experts look at that in quantifying risk of progression.

EBO: In your experience, how are anti-CD38 agents being used in high-risk patients?

SHAH: If you ask me and then you ask 10 other pharmacists, you’ll get probably 11 different answers. Essentially, you have your standard-risk and your high-risk myeloma patients. In those with standard risk, the therapy for many centers is still VRD [bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone] for 3 or 4 cycles. And the management of these patients depends on whether they are transplant candidates. With high-risk disease, you still have VRD, or now you have a quadruple therapy approach that is reserved for your higher-risk patients—your double-hit/ triple-hit myeloma patients. I think there’s still controversy around that, where providers are not using quadruple therapy for all of their patients with high risk. I think they’re being very selective...
because we’re still waiting for overall survival data. We have so many active agents in myeloma, so these providers may be asking, do we really need to use all 4 agents up front? It’s really a controversy.

In regard to anti-CD38, for both standard-risk and high-risk patients, more and more are getting an anti-CD38-based regimen. There may be differences in practice, some providers still use VRD in that setting, too, and it’s appropriate to do so.

So, providers have multiple options. DRRD [dara-tumumab, lenalidomide, and dexamethasone] has been well established in high-risk patients. More and more we are seeing anti-CD38, but not a quadruple regimen, being utilized for high-risk and standard-risk disease.

**EBO**: How are clinical pathways developed and used in multiple myeloma at BMC?

**SHAH**: There is often confusion about pathways. Some pathways are purchased from an organization, like a vendor that makes pathways, and then some pathways you create through your electronic medical record (EMR) in your institution.

We have our pathways incorporated into our EMR, which essentially drives prescribing. How are they developed? The process is essentially based on national guidelines and expert provider feedback and formulary. Once a drug is on formulary, those pathways are built based on the opinions of our internal experts, who weigh in about what regimens they want to be incorporated in that pathway for first-line, second-line, third-line therapy, etc. Of course, in myeloma, you have Nth-line of pathways, so it varies institution to institution. Most institutions have homegrown pathways, developed internally.

**EBO**: Where do anti-CD38 agents fit into pathways at your institution?

**SHAH**: Two anti-CD38 molecules are on the market: isatuximab and daratumumab. We don’t have isatux-imab on our pathways at all, but that doesn’t mean a prescriber can’t order it. Essentially, subcutaneous [sub-Q] and intravenous [IV] daratumumab are the drugs on most of the regimens that we built out in our pathways, because daratumumab sub-Q brings a pretty huge efficiency component.

I think you’ll see this situation across the country; at just about every single institution, there are constraints in managing the number of patients they have on a daily basis and the number of infusions they require. Everybody’s at capacity, so having a drug that can eliminate approximately 90 minutes from a patient’s infusion time [helps a lot]. You can imagine how many myeloma patients we treat on a weekly basis who are on anti-CD38 agents.

We published a paper in Blood last year about this: It actually showed that in the small number of our patients we analyzed who we had converted from IV utilization, we were able to save about 130 hours of chair time and nursing time per week. And if you analyzed those numbers, it was more than 1000 hours in nursing and chair time, which can be a significant efficiency benefit for an institution or a clinic that is struggling with chair capacity and infusion capacity.

Essentially, that’s the main reason we have that anti-CD38 on our pathway. However, that doesn’t mean that a patient who actually does not want to get sub-Q cannot get IV—that’s definitely allowed…It’s a patient choice. We do allow that.

Then, there’s some favorability from a cost perspective, depending on weight of the patient. With [sub-Q] daratumumab, it’s a flat dose vs isatuximab IV and daratumumab IV, which are both milligram-per-kilogram-based dosing. You do end up having a higher cost with the sub-Q [version], but I think that based on the needs of the clinic, we’re able to justify that higher cost of the drug itself.

**EBO**: When a conflict arises between the institution pathway and the payer pathway, how does your institution resolve it?

**SHAH**: We have not come across too many payers who have [an] overly restricted myeloma formulary, because myeloma is such a fast-paced disease in terms of change in treatment landscape. Payers are now more aware of combinations and are used to seeing combination therapy, so we haven’t seen roadblocks from payers who say that they prefer lenalidomide over pomalidomide, lenalidomide over bortezomib, or daratumumab over isatuximab.

We haven’t seen any type of pathways restrictions from payers on myeloma-specific drugs. Even if a provider wanted to use pomalidomide instead of lenalidomide for a VRD-based regimen, no restrictions from payers, that I’m aware of, basically require [a patient] to fail or be refractory or relapsed after lenalidomide to be on pomalidomide.

**EBO**: How does the presence of renal impairment impact treatment decisions in multiple myeloma, particularly with anti-CD38 therapy?

**SHAH**: I think anti-CD38 molecules are definitely kidney friendly vs some of the other myeloma agents. However, I think [other] very good agents also work pretty well and are safe when it comes to the renal toxicity perspective. Bortezomib and CyBoRd [cyclophosphamide, bortezomib, and dexamethasone] have been around for a very long time. Even when you have a patient with acute nephrotoxicity, or renal failure, there’s still significant benefit in response or time to response, whether they used bortezomib or CyBoRd or an antiCD38 agent.

Obviously, lenalidomide is a drug that’s not preferred in patients with renal failure, so I think that would drive a provider [with such a patient] to maybe use an anti-CD38 mixed with bortezomib or a proteasome inhibitor vs a lenalidomide combination. However, there’s no preference of anti-CD38 over a proteasome inhibitor for patients with renal dysfunction. I think that they’re equally efficacious in providing the response that you need in those patients who present with renal failure or other renal complications.

**EBO**: Can you share anything else about the criteria your institution uses to evaluate which patients would be eligible for quadruplet therapy?

**SHAH**: I think high risk is probably the biggest [criterion]. I don’t think that a provider would ever use a quadruplet therapy for somebody with standard risk. And even with high risk, I think there is still hesitation in doing that for everybody. We still need more long-term data, or overall survival data, before everybody starts using quadruplet therapy.

**EBO**: Has prior authorization from payers been a barrier to the use of quadruplet therapy?

**SHAH**: No, we have not run into any issues with prior authorization with quadruplet therapy.

**EBO**: What are some of the nonclinical value considerations you evaluate in the use of anti-CD38 therapy (eg, cost, patient support programs)?

**SHAH**: [Again], the patient satisfaction component is something that we consider from a nonclinical value consideration. A patient having to spend hours in a chair for an infusion vs getting a sub-Q shot and being able to go home—that’s a huge value driver, a nonclinical value driver that needs to be taken into consideration.

There’s also cost. We know that many times patients with Medicare will have a very high co-pay for an oral drug, whereas they will not have a high co-pay for an IV drug, so I think patient affordability also sometimes needs to be taken into consideration. And I would also say that most manufacturers have a very robust patient assistance program. I think challenges [emerge] when [patients are on] oral drugs and they have Medicare and there’s not adequate funding to support them.

Obviously, sometimes the income criteria are also not in favor of the patient. For instance, think about somebody who has an $80,000 household income. That may be the income criteria, so they have a $2000 co-pay, but just because they have that income doesn’t mean that they can [actually] afford that $2000 co-pay on a monthly basis.

Essentially, those are the main nonvalue considerations that need to be considered.

Then, of course, think about logistics for patients—for example, transportation issues. Especially during the height of the COVID-19 pandemic, I think there was more favorability of using an all-oral regimen—such as ixazomib, lenalidomide, or pomalidomide. And dexamethasone-based regimens were more frequently utilized vs the IV [drugs], where you have to come in to the clinic every week or every 2 weeks, depending on the regimen. So, those considerations definitely tie into efficiency also, because oral-based regimens, even more than a sub-Q regimen, can also help with efficiency.

**REFERENCES**

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Flatiron Health is well known for its digital products that help community oncology practices collect and analyze data, provide insights for patient care, and promote clinical trial participation. Today, Flatiron is expanding its footprint in health equity and disparities research, with both community and academic partners.

A team from Flatiron Health recently published data first presented at the American Society of Clinical Oncology (ASCO),1 which highlighted how Medicaid expansion under the Affordable Care Act (ACA) has narrowed the gap between Black and White patients in receiving timely care for cancer. Results were published in the July issue of The American Journal of Managed Care (AJMC).2

The study covered 30,310 patients, including 12.3% who were documented as Black. Investigators found that, in states without Medicaid expansion, Black patients were less likely to receive timely treatment than White patients—43.7% of the Black patients started systemic first-line therapy within 30 days of diagnosis, compared with 48.4% of White patients (adjusted difference, –4.8 percentage points (PP); P<.001). In states with Medicaid expansion, this gap closed to the point where there was no significant difference (49.7% vs 50.5%; adjusted difference, –0.8 PP; P=.605).3

In an interview with Evidence-Based Oncology4 (EBO), Flatiron Health’s Kathleen Maignan, MSN, NP; and Blythe Adamson, PhD, MPH, discussed the AJMC study, what the data have continued to show, and Flatiron’s research plans. Maignan is an oncology nurse practitioner who served as senior clinical director of Research Oncology at the time of this interview. She is now the Medical Affairs executive director at Genentech. Adamson is a principal quantitative scientist at Flatiron Health and the lead author of the study that appeared in AJMC.5

**EBO:** Your study covered a period from 2011 through January of 2019. Have you continued to look at these data in period since the study ended? Have the patterns you observed continued?

**KATHLEEN MAIGNAN:** Absolutely. We continue to track our data longitudinally, so there's never going to be a pause in investigating. But what we're dealing with now—in the treatment landscape in 2021 versus what we encountered pre-pandemic—is very different. It's difficult to draw any early conclusions.

For example, we collaborated on a study led by investigators at the University of Pennsylvania—one of our academic partners—and this study was presented at ASCO during the 2021 meeting.1 It looked at the impact of COVID-19 on time-to-treatment initiation of systemic therapy for patients with advanced cancers. Surprisingly, at a national level, we did not find evidence to suggest that the COVID-19 pandemic was associated with longer time to starting systemic treatment. That might seem counter-intuitive, but one explanation could be that fewer patients were diagnosed with advanced cancer during that period and that some patients potentially delayed surveillance follow-up visits. The smaller volume of patients may have been able to access timely care despite pandemic-related health care disruptions. Compared with previous years, it’s hard to compare this using the metric of time-to-treatment initiation, but that’s something we’re going to look at very closely in the years to come—I would even say the months to come, as this is all in near real time.

**EBO:** Blythe, did you want to add anything?

**BLYTHE ADAMSON:** I’m really proud of the work evolving and all the research questions being responsive to the policy dilemmas we’re seeing today.

**EBO:** The phenomenon of fewer patients seeking cancer care has occurred alongside huge drops in screening, so I presume you’re looking at that as well?

**MAIGNAN:** Absolutely. The drop in screening [documented by others] was quite alarming in the beginning of the pandemic. We’re starting to see those numbers pick up, but it’s something we’re keeping a very close eye on throughout the progression of the pandemic, as it’s still ongoing.

“When we first presented these results in 2019, there was a lot of pushback from oncologists who had never seen methods like this used before....When we think about designing effective health care policy, it would be very difficult for us to run a randomized experiment to test the effect.”

—Blythe Adamson, PhD, MPH, principal quantitative scientist, Flatiron Health

**EBO:** As Medicaid expansion has unfolded, I’ve been interested in differences between states that adopted expansion at different points in time. In addition to the overall natural experiment, I’m wondering if you’ve seen differences in the data between the states that expanded right away vs those, such as Louisiana, that expanded later in the process. Has this phenomenon had any effect on the data that is noteworthy?

**ADAMSON:** That’s such an interesting research question. It’s not one we were able to answer with this study. We would probably want to design an entirely new study. You would have to create a whole new hypothesis to be able to test and answer that one, but it brings up an interesting point in thinking about regional differences and how treatment patterns differ between states. As I brainstorm, how [I would] design a research study to test the hypothesis you’re describing, and try to unpack and explore what the confounders might be, I think about representativeness. One thing I’ve been learning a lot lately is that, even across the United States, treatment patterns can vary from the West Coast to the East Coast. Even sequences of treatments can differ within the United States and outside the United States. So, while I wasn’t able to look specifically into the early vs late adopters [of Medicaid expansion], considerations I would think an academic partner might be interested in doing a study like that would be adding in attributes of individual states and even using methods, [such as] instrumental variables, that might be able to help guide based on what the types of policy decisions or treatment patterns...»
those individual states have made in the past and how that might have influenced the time at which they adopted [expansion] early vs late. But it’s an interesting research question.

EBO: Kathleen, did you want to add anything?

MAIGNAN: Blythe hit it on the head. It’s one of the things we were curious about when developing the study. But again, over time, we could start to think of new methods to do that.

ADAMSON: A parallel of why I think it’s important for researchers to figure out how to untangle policy effects for early vs late adopting states [involves] what we’ve seen was important at the beginning of COVID-19. With lockdown policies, masking policies, or closures of bars and restaurants, [there were] states that were early adopting states vs late adopting states. Untangling what the characteristics of those individual states were that led to those decisions—and the timing of those decisions—is important to be able to understand the causal effect of that policy on the outcomes that were achieved.

EBO: You’ve brought up the issue of regional differences. Obviously, that’s been a standout phenomenon of the whole Medicaid expansion experience. As you know, most of the states that have not expanded are in the South. Unfortunately, [these states] have a lot of the population that is most in need. Knowing that this area is where Medicaid expansion has not happened, I’m wondering whether you’ve had any engagement with state policymakers or any legislators in the states that have not expanded, and what those discussions have been like?

ADAMSON: It’s been one of my original intentions in designing this study that it would be useful for policymakers, not just to describe health disparities, but also to evaluate the effectiveness of [Medicaid expansion]. I’m delighted to report that these research findings have been cited in policy briefs for legislators across the country. It was cited in ASCO’s position statement on block grants in Medicaid and legislators across the country. It was cited in ASCO’s position statement on block grants in Medicaid and their impact on cancer care. This is exactly why this type of research is critical for informing policy.

EBO: So, your conclusion is that the use of clinical data during routine care can allow for real-time evaluation of health care policy. Since your study appeared, we’ve had CMS announce a “refresh” of the work on payment models undertaken by the Center for Medicare and Medicaid Innovation (CMMI). If you’ve had time to review the CMMI proposal, what can we expect? Can we anticipate that the use of real-world evidence on disparities will be used by CMMI? To create the successor to the Oncology Care Model (OCM)?

MAIGNAN: We absolutely hope so. We’re early adopters, in that Flatiron is an early adopter of unlocking the use of real-world data and generating real-world evidence for cancer care and research. If you look at everything we know about how drugs work, we’re getting most of that information from clinical trials. We understand that is the gold standard for medical evidence about efficacy, but there are relatively few patients in trials that represent the totality of the patients we see in our network. In clinical trials, patients tend to be younger, they are better educated, they’re less diverse, [and] they have fewer comorbidities than the overall cancer patient population. So, when you look at a field, such as oncology, where it’s becoming increasingly specialized, we need the ability to use real-world data and real-world evidence to investigate things that are critically important to life after OCM.

The OCM expires in 2022, and we know there will probably be a gap. So there is a sense of urgency, especially given the treatment landscape. Novel therapies tend to be incredibly expensive. We have the opportunity to look at outcomes, using patients in our database who are adopting some of these early novel therapies to ask, are they even more effective than what’s available? Are they more effective than what’s been traditionally available in the market? Can we compare them with traditional chemotherapy or immunotherapies? Is it worth the extra expense of those novel therapies? We don’t know that until we can look at those outcomes across a broader population.

We are also thinking about different care settings. As we have seen with COVID-19 and the explosion of the use of telehealth, I don’t think that’s a genie that’s ever going to go back in the bottle. Although we may not see telehealth continue at the level we saw during lockdown, we know this is something we’re going to start to integrate into everyday care and management of oncology patients. So what is the impact? That’s something we can see in real time or near real time, and that will be critically important to building that next model beyond OCM.

EBO: Since the start of the ACA, given the decisions by different states whether to adopt Medicaid expansion, I’ve wondered when we would see results that show the differences in the health of different state populations who are entering the Medicare population. Would we see differences in population health from expansion vs noneexpansion states? For example, would we see different percentages of patients who had regular cancer screenings vs those that did not? Are these the kind of studies you’ll be examining in the future? How can real-world data help in this regard?

ADAMSON: This is such an important research question. It’s not one my team is currently answering. Right now, there could be an opportunity for an academic research partner to answer this with Flatiron data. One of the specific challenges of designing a study like that and understanding, “Is the population entering Medicare healthier?” is that we would hope that, among populations with cancer, who are close to aging into Medicare, if they were receiving poor-quality care and had limited access to treatments, they might die before they even are able to age into Medicare. If they received high-quality care and had great access to life-extending treatments, then we would expect more people to be alive to age into Medicare, which is good.

It would require a thoughtful study because, if you just simply looked at the health of people entering Medicare, you might think a sicker population over time meant people were less and less healthy, when really, your pool of people was actually getting larger because you’ve kept more people alive to be able to enter Medicare. I would invite any of our academic partners to think through the best way to answer that because that all of us have an investment in a healthy Medicare population and want everyone to be able to reach that point, with all the investments made in preventing severe illness.

EBO: We talked earlier about the ongoing issues with cancer screening. Are there any other issues related to the deferral of cancer screening that you’ll be examining?

ADAMSON: There are studies going on right now, within Flatiron and with our partnerships with academic researchers, particularly related to the impact of COVID-19—including the impact it’s made on cancer screening visits. We have more work coming out soon on the substitution of in-person office visits with telemedicine visits, which has been an incredible gift that I hope we continue to see going forward.

MAIGNAN: When we think about ongoing work in this area, obviously, the pandemic has highlighted alarming disparities in health outcomes across all types of underrepresented groups. What we know is that race alone can’t tell the full story. Among the things we’ve been working on in this past year is not just our ability to capture race data, but look beyond that—to investigate what are better ways to look at socioeconomic status, understand relevant social determinants of health, and build an index using Flatiron data? How do we improve capture of our insurance variables? How do we increase the representation of patients on Medicare or Medicaid? How can we better standardize our race data? Again, this is one of the great advantages of working with a very recent data set where we can be flexible and improve on those variables and our ability to tell those stories in almost real time.

EBO: Finally, we wanted to discuss whether there’s a growing appreciation for the importance of natural experiments. And is there greater acceptance of natural experiments in health care since you published your study?

ADAMSON: It was very affirming that, just recently, the Nobel [Memorial] Prize in Economic Sciences has been awarded to 3 professors for the development of the methods we were able to use and deploy in our ACA study. When we first presented these results in 2019, there was a lot of pushback from oncologists who had never seen methods like this used before. In medicine, we have the privilege of designing randomized controlled trials that are excellent at helping us understand the cause and effect to evaluate things, such as [therapeutic] treatments. But when we think about designing effective health care policy, it would be very difficult to run a randomized experiment to test the effect. Although the approach we used has been used for decades within the field of economics, it was much more
unfamiliar to oncologists [at the time]. I was grateful for the patients, providers, and cancer community members who took the time to understand the methods and approach used to understand the effect on racial disparities.

**EBO:** You’re referring, in part, to the work of David Card and Alan Krueger, and the work on the minimum wage they did at Princeton University.

(Editor’s Note: Card, now at the University of California, Berkeley, and Krueger, who remained at Princeton University and died in 2019, showed that a minimum wage increase in New Jersey in 1992 did not lead to job losses. Until then, it was assumed that raising the minimum wage would cause job losses.)

**ADAMSON:** Yes! In economics, natural experiments have been an incredible tool that’s been essential for us to understand things, [such as] the effect of minimum wage, immigration, or adding an extra year of education for someone. Those are things that would be very difficult to do a randomized control trial for. I’m really grateful for all the oncology community [for having] the patience, curiosity, and willingness to learn of a study design that they had not been familiar with. I’m happy to see there is willingness to learn of a study design that they had not been familiar with. I’m happy to see there is willingness to learn of a study design that they had not been familiar with. I’m happy to see there is willingness to learn of a study design that they had not been familiar with. I’m happy to see there is willingness to learn of a study design that they had not been familiar with.

**MAIGNAN:**: One thing I always come back to when we start thinking about disparities work—there’s a James Baldwin quote we anchor to: “Not everything that is faced can be changed, but nothing can be changed until it is faced.” And [although] we’re not in the hospital daily, [and I’m] not at the frontlines the same way I used to be, as a nurse practitioner. Just being able to tell the story is so vitally important to making real change.

**ADAMSON:**: There’s one more thing I would add. One of the spillover gifts of the research we’re discussing today is that the response from Flatiron as a company has been incredibly encouraging. The investments they’re making now in health equity and health disparities research is just astounding to me. We are currently recruiting for a head of health equity and disparities research to help us build a productive and transformative scientific data-driven agenda, and Kathleen has been one of the essential leaders within Flatiron for this type of research and building this program. So I’m really grateful [for] her and hope that we are able to really identify a talented [investigator] to join us.

**MAIGNAN:**: In the meantime, we are actively supporting investigators who are working on disparities research. We have a joint grant-making program with the American Cancer Society. We’re now in our third year, which is exciting. We also awarded 2 health equity and health disparity grants to [investigators] within our academic network, so we’re excited to bring new talent on board so we can keep this energy going.

**REFERENCES**


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