PATIENT EXPERIENCE

Building a Patient-Centered Cancer Center From the Ground Up

Mary Caffrey

From left, RWJBarnabas Health’s Barry Ostrowsky, Sheryl and Jack Morris, and Rutgers CINJ Director Steven K. Libutti, MD, FACS, at the June 24 groundbreaking in New Brunswick, NJ.

FOR GENERATIONS, PEOPLE IN New Jersey who received a diagnosis of cancer spoke of “going into the city” for treatment.

In the northern counties, that meant New York City; further south, it meant a trip into Philadelphia. But over the past decade, the state with the fifth-highest rate of cancer incidence has invested in keeping patients closer to home, supported by evidence that travel not only exacts a toll on patients and affects outcomes, but it may also lead to longer hospital stays.1-4

Now, Rutgers Cancer Institute of New Jersey (CINJ), the state’s only National Cancer Institute–designated Comprehensive Center, is raising the stakes.6 On June 24, New Jersey Governor Phil Murphy and a “who’s who” of the state’s health care community seized the opportunity between the state surpassing a COVID-19 vaccination goal and dealing with the Delta variant to break ground on a $750 million, 12-story building, to be known as the Jack and Sheryl Morris Cancer Center.6 This new facility was borne of a partnership between Rutgers CINJ and RWJBarnabas Health, which operates 11 acute-care hospitals across a region that is home to 5 million people.11

Busy Times at FDA

Regulators come through with a groundbreaking approval in mebectimibnib for a rare type of non–small cell lung cancer and a pair of new indications in zanubrutinib, SP274-SP275.

Conference Coverage: ESMO

Dr David S. Hong:
We Are Learning Every Day About Cellular Therapies

Maggie L. Shaw

GAVO-CEL (GAVOCABTAGENE AUTOLEUCEL; TCR® Therapeutics) is currently being investigated for use against mesothelioma overexpression in 4 types of solid-tumor cancers: malignant mesothelioma, ovarian cancer, cholangiocarcinoma, and non–small cell lung cancer (NSCLC). Data, first presented at this year’s American Association of Cancer Research (AACR) annual meeting, showed a single intravenous (IV) infusion of the engineered cellular therapy produced a 100% disease control rate (DCR) and 61% target lesion regression rate (TLR) in 7 evaluable patients: 6 with malignant mesothelioma and 1, ovarian cancer.1

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INDICATIONS AND USAGE
PEMAZYRE is the first FDA-approved therapy for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The major efficacy outcomes were evaluated in 107 patients with an FGFR2 fusion or non-fusion rearrangement in a multicenter, open-label, single-arm study of 146 total patients with locally advanced unresectable or metastatic cholangiocarcinoma who had received ≥1 previous line of systemic therapy.

Patients receiving PEMAZYRE achieved durable responses
Median DoR was 9.1 months
Patients with DoR:
- ≥6 months: 63% (n=24)
- ≥12 months: 18% (n=7)

Molecular profiling is necessary to detect FGFR2 fusions or rearrangements
A next-generation sequencing assay, such as FoundationOne® CDx, meets the following criteria to detect FGFR2 fusions:• Specifically detects FGFR2 fusions (distinct from FGFR2 mutations)
• Detects FGFR2 fusions with a wide range of fusion partners (whether known or unknown)

Learn more about testing and treating your appropriate patients.
Visit hcp.PEMAZYRE.com

IMPORTANT SAFETY INFORMATION
Ocular Toxicity
Retinal Pigment Epithelial Detachment (RPED): PEMAZYRE can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with PEMAZYRE is unknown.

Clinical response rates of PEMAZYRE

ORR: the primary endpoint

2.8% CR
33% PR
36% ORR
(95% CI, 27%–45%)

Efficacy evaluable population (N=107)
Note: Data are from IRC per RECIST v1.1, and CR and PR are confirmed.

*Determined by a clinical trial assay performed at a central laboratory.

1Patients received PEMAZYRE in 21-day cycles at a dosage of 13.5 mg orally once daily for 14 consecutive days, followed by 7 days off therapy, until disease progression or unacceptable toxicity occurred. The major efficacy outcome measures were ORR and DoR, as determined by IRC according to RECIST v1.1.

10 CI, confidence interval; DoR, duration of response; IRC, independent review committee; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Among 466 patients who received PEMAZYRE across clinical trials, RPED occurred in 8% of patients, including Grade 3–4 RPED in 0.6%. The median time to first onset of RPED was 82 days. RPED led to dose interruption of PEMAZYRE in 1.7% of patients, and dose reduction and permanent discontinuation in 0.4% and in 0.4% of patients, respectively. RPED resolved continued
or improved to Grade 1 levels in 87.5% of patients who required dosage modification of PEMAZYRE for RPED. Perform a comprehensive ophthalmological examination including OCT prior to initiation of PEMAZYRE and every 2 months for the first 6 months and every 3 months thereafter during treatment. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of PEMAZYRE. Modify the dose or permanently discontinue PEMAZYRE as recommended in the prescribing information for PEMAZYRE.

Dry Eye: Among 466 patients who received PEMAZYRE across clinical trials, dry eye occurred in 27% of patients, including Grade 3–4 in 0.6% of patients. Treat patients with ocular demulcents as needed.

Hyperphosphatemia and Soft Tissue Mineralization

PEMAZYRE can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of PEMAZYRE. Among 466 patients who received PEMAZYRE across clinical trials, hyperphosphatemia was reported in 92% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1–189). Phosphate lowering therapy was required in 29% of patients receiving PEMAZYRE.

Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is >5.5 mg/dL. For serum phosphate levels >7 mg/dL, initiate phosphate lowering therapy and withhold, reduce the dose, or permanently discontinue PEMAZYRE based on duration and severity of hyperphosphatemia as recommended in the prescribing information.

Embryo–Fetal Toxicity

Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Oral administration of pemigatinib to pregnant rats during the period of organogenesis caused fetal malformations, fetal growth retardation, and embryo–fetal death at maternal exposures lower than the human exposure based on area under the curve (AUC) at the clinical dose of 13.5 mg.

Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with PEMAZYRE and for 1 week after the final dose.

Adverse Reactions

Serious adverse reactions occurred in 45% of patients receiving PEMAZYRE. Serious adverse reactions in ≥2% of patients who received PEMAZYRE included abdominal pain, pyrexia, cholangitis, pleural effusion, acute kidney injury, cholangitis infective, failure to thrive, hypercalcemia, hyponatremia, small intestinal obstruction, and urinary tract infection. Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received PEMAZYRE. Adverse reactions requiring permanent discontinuation in ≥1% of patients included intestinal obstruction and acute kidney injury. Dosage interruptions due to an adverse reaction occurred in 43% of patients who received PEMAZYRE. Adverse reactions requiring dosage interruption in ≥1% of patients included stomatitis, palmar-plantar erythrodysesthesia syndrome, arthralgia, fatigue, abdominal pain, AST increased, anemia, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophosphatemia, back pain, pain in extremity, syncope, acute kidney injury, onychomadesis, and hypotension.

Dose reductions due to an adverse reaction occurred in 14% of patients who received PEMAZYRE. Adverse reactions requiring dosage reductions in ≥1% of patients who received PEMAZYRE included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, anemia, and onychomadesis.

Clinically relevant adverse reactions occurring in ≤10% of patients included fractures (2.1%). In all patients treated with pemigatinib, 1.3% experienced pathologic fractures (which included patients with and without cholangiocarcinoma [N=468]). Soft tissue mineralization, including cutaneous calcification, calcinosis, and non-uremic calciphylaxis associated with hyperphosphatemia were observed with PEMAZYRE treatment.

Within the first 21-day cycle of PEMAZYRE dosing, serum creatinine increased (mean increase of 0.2 mg/dL) and reached steady state by Day 8, and then decreased during the 7 days off therapy. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed. The most common adverse reactions (incidence ≥20%) were hyperphosphatemia (60%), alopecia (49%), diarrhea (47%), nail toxicity (43%), fatigue (42%), dysgeusia (40%), nausea (40%), constipation (35%), stomatitis (35%), eye dryness (35%), dry mouth (34%), decreased appetite (33%), vomiting (27%), arthralgia (25%), abdominal pain (23%), hypophosphatemia (23%), back pain (20%), and dry skin (20%).

Drug Interactions

Avoid concomitant use of strong and moderate CYP3A inhibitors with PEMAZYRE. Reduce the dose of PEMAZYRE if concomitant use with a strong or moderate CYP3A inhibitor cannot be avoided. Avoid concomitant use of strong and moderate CYP3A inducers with PEMAZYRE.

Special Populations

Advise lactating women not to breastfeed during treatment with PEMAZYRE and for 1 week after the final dose. Reduce the recommended dose of PEMAZYRE for patients with severe renal impairment as described in the prescribing information.

Reduce the recommended dose of PEMAZYRE for patients with severe hepatic impairment as described in the prescribing information.

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

References:

Pemazyre (pemigatinib) tablets

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BRIEF SUMMARY: For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE PEMAZYRE is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test [see Dosage and Administration (2.1) in Full Prescribing Information]. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14.1) in Full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Ocular Toxicity Retinal Pigment Epithelial Detachment (RPED) PEMAZYRE can cause RPED, which may cause symptoms such as blurred vision, visual floaters, or photopsia. Clinical trials of PEMAZYRE did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED; therefore, the incidence of asymptomatic RPED with PEMAZYRE is unknown. Among 466 patients who received PEMAZYRE across clinical trials, RPED occurred in 6% of patients, including Grade 3–4 RPED in 0.6%. The median time to first onset of RPED was 62 days. RPED led to dose interruption of PEMAZYRE in 1.7% of patients, and dose reduction and permanent discontinuation in 0.4% and in 0.4% of patients, respectively. RPED resolved or improved to Grade 1 levels in 85.5% of patients who required dosage modification of PEMAZYRE for RPED. Perform a comprehensive ophthalmological examination including OCT prior to initiation of PEMAZYRE and every 2 months for the first 6 months and every 3 months thereafter during treatment. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of PEMAZYRE. Modify the dose or permanently discontinue PEMAZYRE as recommended [see Dosage and Administration (2.3) in Full Prescribing Information]. Dry Eye Among 466 patients who received PEMAZYRE across clinical trials, dry eye occurred in 27% of patients, including Grade 3–4 in 0.6% of patients. Treat patients with ocular demulcants as needed.

Hyperphosphatemia and Soft Tissue Mineralization PEMAZYRE can cause hyperphosphatemia leading to soft tissue mineralization, cutaneous calcification, calcinosis, and non-uremic calciphylaxis. Increases in phosphate levels are a pharmacodynamic effect of PEMAZYRE [see Clinical Pharmacology (12.2) in Full Prescribing Information]. Among 466 patients who received PEMAZYRE across clinical trials, hyperphosphatemia was reported in 92% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 9 days (range 1-169). Phosphate lowering therapy was required in 29% of patients receiving PEMAZYRE. Monitor for hyperphosphatemia and initiate a low phosphate diet when serum phosphate level is ≥ 5.5 mg/dL. For serum phosphate levels > 7 mg/dL, initiate phosphate lowering therapy and withhold, reduce the dose, or permanently discontinue PEMAZYRE based on duration and severity of hyperphosphatemia [see Dosage and Administration (2.3) in Full Prescribing Information].

Embryo-Fetal Toxicity Based on findings in an animal study and its mechanism of action, PEMAZYRE can cause fetal harm when administered to a pregnant woman. Oral administration of pemigatinib to pregnant rats during the period of organogenesis resulted in 100% embryofetal fractures (2.1%). In all patients treated with pemigatinib, 1.3% experienced mortality due to post-implantation loss at doses ≥ 0.3 mg/kg. Doses ≥ 0.3 mg/kg in all studies had a statistically significant increase in stillbirths observed at doses ≥ 0.3 mg/kg and a statistically significant increase in early embryonic mortality at doses ≥ 0.6 mg/kg. Doses ≥ 0.6 mg/kg had a statistically significant increase in fetal fractures at doses ≥ 0.9 mg/kg.

Hepatic Impairment Patients with mild (total bilirubin > upper limit of normal [ULN] to 1.5 × ULN or ALT > 1.5 × ULN) or moderate (total bilirubin > 1.5 × ULN or ALT > 3 × ULN) hepatic impairment did not require dosage adjustment in clinical trials. However, patients with hepatic impairment should be closely monitored for increased adverse reactions due to PEMAZYRE treatment.

Reproductive Potential Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the final dose. Advise females who are pregnant or breast-feeding to avoid concomitant PEMAZYRE use and to use birth control methods with a high degree of reliability while taking PEMAZYRE and for 1 week after the final dose [see Use in Specific Populations (8.1, 8.3) in Full Prescribing Information].

ADVERSE REACTIONS The following adverse reactions are discussed elsewhere in the labeling: Ocular Toxicity [see Warnings and Precautions (5.1) in Full Prescribing Information], Hyperphosphatemia and Soft Tissue Mineralization [see Warnings and Precautions (5.2) in Full Prescribing Information].

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of PEMAZYRE was evaluated in FIGHT-202, which included 146 patients with previously treated, locally advanced or metastatic cholangiocarcinoma [see Clinical Studies (14.1) in Full Prescribing Information]. Patients were treated orally with PEMAZYRE 13.5 mg once daily for 14 days on followed by 7 days off therapy until disease progression or unacceptable toxicity. The median duration of treatment was 181 days (range: 7 to 730 days). The median age of PEMAZYRE-treated patients was 59 years (range 26–78), 58% were females, and 71% were White. Serious adverse reactions occurred in PEMAZYRE. Serious adverse reactions in ≥ 2% of patients who received PEMAZYRE included abdominal pain, pyrexia, cholangitis, pleural effusion, acute kidney injury, cholangitis infective, failure to thrive, hypercalcemia, hyponatremia, small intestinal obstruction, and urinary tract infection. Fatal adverse reactions occurred in 4.1% of patients, including failure to thrive, bile duct obstruction, cholangitis, sepsis, and pleural effusion. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received PEMAZYRE. Adverse reactions requiring permanent discontinuation in ≥ 1% of patients included intestinal obstruction and acute kidney injury. Dosage interruptions due to an adverse reaction occurred in 43% of patients who received PEMAZYRE. Adverse reactions requiring dosage interruption in ≥ 1% of patients included stomatitis, palmar-plantar erythrodysesthesia syndrome, arthralgia, fatigue, abdominal pain, AST increased, asthenia, pyrexia, ALT increased, cholangitis, small intestinal obstruction, alkaline phosphatase increased, diarrhea, hyperbilirubinemia, electrocardiogram QT prolonged, decreased appetite, dehydration, hypercalcemia, hyperphosphatemia, hypophysiph phosphatemia, back pain, pain in extremity, syncope, acute kidney injury, onychomadesis, and hypotension. Dose reductions due to an adverse reaction occurred in 14% of patients who received PEMAZYRE. Adverse reactions requiring dosage reductions in ≥ 1% of patients who received PEMAZYRE included stomatitis, arthralgia, palmar-plantar erythrodysesthesia syndrome, asthenia, and onychomadesis. Table 1 summarizes the adverse reactions in FIGHT-202. Table 2 summarizes laboratory abnormalities in FIGHT-202.

Table 1: Adverse Reactions (≥ 15%) in Patients Receiving PEMAZYRE in FIGHT-202

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PEMAZYRE N=146</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>60</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>33</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>23</td>
</tr>
<tr>
<td>Dehydration</td>
<td>15</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>49</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>43</td>
</tr>
<tr>
<td>Dry skin</td>
<td>20</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>15</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
</tr>
<tr>
<td>Nausea</td>
<td>40</td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>35</td>
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<tr>
<td>Dry mouth</td>
<td>34</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
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<tr>
<td><strong>General disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>42</td>
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<tr>
<td>Edema peripheral</td>
<td>18</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>40</td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
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<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>35</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>25</td>
</tr>
<tr>
<td>Back pain</td>
<td>20</td>
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<tr>
<td>Pain in extremity</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 1 continued above.
**Table 1 continued.**

<table>
<thead>
<tr>
<th>PEMAZYRE N=146</th>
<th>All Grades* (%)</th>
<th>Grades ≥ 3 (%)</th>
</tr>
</thead>
</table>

### Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades* (%)</th>
<th>Grades ≥ 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>16</td>
<td>2.7</td>
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</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades* (%)</th>
<th>Grades ≥ 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>16</td>
<td>2.1</td>
</tr>
</tbody>
</table>

### Adverse Reactions in Clinical Trials

- **Hyperphosphatemia and Soft Tissue Mineralization**
- **Weight loss**
- **Decreased appetite**
- **Hypophosphatemia**
- **Fatigue**
- **Nail toxicity**
- **Increased alkaline phosphatase**
- **Increased phosphate**
- **Increased creatinine**
- **Increased urate**
- **Decreased sodium**
- **Increased calcium**
- **Increased AST**
- **Increased bilirubin**
- **Decreased potassium**
- **Increased alkaline phosphatase**
- **Increased creatinine**

### Adverse Reaction Rates

The table above provides a summary of adverse reactions observed in clinical trials of PEMAZYRE. The rates are shown as percentages of patients who experienced the reactions. The table includes hematological reactions, hepatic reactions, metabolic and nutritional disorders, gastrointestinal reactions, dermatological reactions, musculoskeletal and connective tissue disorders, infections and infestations, and other adverse drug reactions.

- **Hematology**
  - Decreased hemoglobin: 43%
  - Decreased lymphocytes: 36%
  - Decreased platelets: 28%
  - Increased leukocytes: 27%
  - Decreased leukocytes: 18%

- **Chemistry**
  - Increased phosphate: 94%
  - Decreased phosphate: 68%
  - Increased alanine aminotransferase: 43%
  - Increased aspartate aminotransferase: 43%
  - Increased calcium: 43%
  - Increased alkaline phosphatase: 41%
  - Increased creatinine: 41%
  - Decreased sodium: 39%
  - Increased glucose: 36%
  - Decreased albumin: 34%
  - Increased urea: 30%
  - Increased bilirubin: 26%
  - Decreased potassium: 26%
  - Increased calcium: 17%
  - Increased potassium: 12%
  - Decreased glucose: 11%

### Other Adverse Reactions

- **Musculoskeletal and connective tissue disorders**
- **Metabolism and nutrition disorders**
- **Infections and infestations**
- **Other adverse drug reactions**

### Clinical Pharmacology

- **Clinical Pharmacology**
- **Dosage and Administration**
- **Warnings and Precautions**
- **Use in Specific Populations**
- **Clinical Studies**

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With Immuno-oncology, Are Payers the Main Barrier to Access?

THIS ISSUE of Evidence-Based Oncology™ features important conversations regarding access to immuno-oncology. Amiktig Mehta, MD, of the University of Alabama at Birmingham, suggests that payer delays are part of the calculation when physicians make treatment decisions for patients with diffuse large B-cell lymphoma (DLBCL). For some of these patients, chimeric antigen receptor (CAR) T-cell therapy can work wonders, but not if the rapid disease progression that is a hallmark of DLBCL occurs before payers clear a treatment plan.

Mehta’s observations match results from a survey by the Association of Community Cancer Centers (ACCC), which revealed reimbursement problems for immuno-oncology (IO) agents that are used off label. Collecting patient-reported outcomes, and having access to clinical trials investigating IO therapies also presented issues. Further, medical oncologists reported challenges with having information available on IO treatments, and nurse managers said they had to prioritize finding time to work directly with payers to explain the unique aspects of IO therapies.

Delays in payer approval for expensive drugs are expected when therapies are new, but we are well past the infancy stage for modern IO therapies, a decade after ipilimumab received approval. More than 60 agents have been approved, and hundreds of trials are studying the use of CAR T-cell therapy in cancer care. Yet a gulf exists between what is happening in clinical trials and in some practices. Fortunately, the explosion of telemedicine can connect the best experts with local physicians almost anywhere—and this should give payers the assurances they need to green light the use of IO.

Challenges with prior authorization and payer barriers to immunotherapy generally and CAR T-cell specifically merit attention, given the disparities in cancer outcomes that every major cancer care organization has noted in the past year. The ACCC study said the challenges with payer approval for IO could be due to the increased availability of IO therapies in community cancer programs. This shift, the survey report found, “has engendered a tremendous learning curve in oncology. Remarkably, the world of IO is shifting once again in ways that will demand ongoing education to ensure providers stay on the cutting edge of care.” (See SP277)

Ironically, Mehta, who leads an academic oncology program, said payers would be wise to make approvals more seamless at the community level. Mehta says part of his role at UAB is acting as a resource for community oncologists, to extend the reach of the academic center to rural areas so patients don’t have to travel long distances for care. But that doesn’t work if reimbursement at the local level remains a challenge.

“We have very limited time for factors like insurance approval and for doing some of the testing before pursuing CAR T.” Mehta said. He feels the next frontier in this life-saving treatment is, “How can we make it universal?”

Sincerely,
Mike Hennessy Sr
CHAIRMAN AND FOUNDER
A survey by the Association of Community Cancer Centers said prior authorization issues with immuno-oncology (IO) could be connected to the proliferation of IO in community practices.
The Way Up

AS WE LIVE THROUGH these strange, tragic, extraordinary times, the phrase, “Trust the science” has become a mantra. The ubiquity of this phrase, with its intertwined messages of implosion and admonition, reflect the evolution of the power of social media and messaging driven by an infinitely expanding cyberspace universe. For all the silly ways in which this message has been communicated in a time when 30-second TikTok videos represent the level of discourse, there is value in acknowledging the power of science to unlock the unknown—and there is transformative value in that knowledge. Over the course of my career, progress in understanding the genetic, genomic, and epigenetic underpinnings of cancer, as well as our growing understanding of the role of the immune system in eradicating cancer cells, has unleashed a wealth of innovative and effective anti-cancer treatments. The last 2 American Cancer Society (ACS) Cancer Statistics reports demonstrated the greatest decrements in cancer mortality ever reported. In reality, the aforementioned advances in science are leading to improved survival outcomes for patients with cancer. Not all Americans, however, realize these benefits. While it is reasonable to “Trust the science,” we need to do much more. This includes the creation of better systems of ensuring that this care is equitably available to all who need it, when they need it. Moreover, we need to ensure that the barriers of geography, distance, poverty, scientific literacy, and other social determinants of health impede equitable access to this level of care innovation. At this year’s Patient Centered Oncology Care® (PCOC) conference, presented by The American Journal of Managed Care®, we heard about both advances in the science of care and exciting new models for ensuring that the life-saving benefits of cancer care advances are better realized by more patients and families. Throughout the two-day conference we heard from speakers and panelists who, while noting the growing impact of precision medicine, also described the ways in which underserved populations remained underserved. These gaps in care include access to clinical trials, trial design that fails to incorporate the needs of a diverse population, biospecimen banking practices that failed to include sufficient human diversity for the creating of new genomic analytics, the challenges of improving health literacy, and limited patient access to the requisite care expertise. Beyond the science, we need better care models that more accessible and sustainable for the underserved; we also need more effective reimbursement models that incentivize more patient access and align with greater investment into holistic and humanized care delivery. Moreover, if we are to achieve better patient outcomes and ensure more equitable patient access, our system will need to grow beyond its current “bricks and mortar” mindset. During the PCOC meeting our discussions embraced that creative challenge and described the ways in which wearable devices, the Internet of Things, and more effective use of artificial intelligence tools to create more powerful means of engaging patients and their communities in the support of life-saving cancer care.

This year’s PCOC meeting marked a shift in our thinking. Beyond reviewing the extraordinary assets of cancer science and technology, which we have discussed for the past decade, this year began a reconsideration of the types of systems that we will need to build to find the way up beyond the limitations of our current care delivery models. As the ACS data show, the life dividend of getting better care to the millions of patients who fail to benefit fully from our current cancer care revolution is enormous. The shift toward an equitable realization of the culminated fruits of our scientific endeavors is where we venture forth toward the challenge of making the science a reality for those who need it most.
# Fulphila® Product Highlights

<table>
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<tr>
<th><strong>Product Name</strong></th>
<th><strong>WAC price</strong></th>
<th><strong>NDC</strong></th>
<th><strong>Billing Code</strong></th>
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<tbody>
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<td>Fulphila® (pegfilgrastim–jmdb) injection</td>
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Conversations on CAR T:
UAB’s Mehta Discusses Opportunities and Challenges

MARY CAFFREY

MEHTA: If you look at CAR T treatment, it is one of the best for relapsed diffuse large B-cell lymphoma (DLBCL)—it has definitively changed the treatment paradigm. If patients have the first relapse—whether [they are] transplant eligible or not or...high-dose chemotherapy eligible or not, based on their comorbidities and performance status—once they cross the second-line therapy and the third-line therapy everybody looks at the care team: are all patients able to go to CAR T? The answer is no. There are a variety of reasons, including the distance from the academic center, because most CAR T treatments are offered at academic centers or large community-based practices. So if the doctor’s practice is in rural Alabama, the patient must travel all the way to the academic center to get CAR T therapy. That’s one factor.

Another is insurance—it’s a big challenge. The third is that this disease is aggressive; patients progress very fast. We have very limited time for factors like insurance approval and for doing some of the testing before pursuing CAR T, or for the case-based agreement that the institutions have to do with the insurance company. These are all limiting factors for offering this life-saving treatment for patients.”

—Amritkumar Mehta, MD,
University of Alabama at Birmingham

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So how can we make it universal? That was my concept—whether we can bring it to the community centers, where we can have a concept of a formal partnership in which academia can create teams that...offer treatment locally or closest to the patient, or whether we can have off-the-shelf CAR T, where the patients don’t have to wait for the preparation time, which ranges from 2 weeks to 6 weeks depending on which product you’re using.

Also, off-the-shelf CAR T reduces the preparation time as well as availability. So, if I...have a patient who has to go for a treatment, I say, “Well, I’m going to prescribe this, which will be available next week,” compared to 6 weeks from now. Those factors will make this treatment universal.

Other subtle factors that come in are to do with biomarkers, such as a biomarker-driven prediction as to whether this patient will develop toxicities like cytokine release syndrome or neurotoxicity, or whether this patient will respond or not. That way we can predict the outcome of not only the toxicity but also the efficacy of treatment.

MEHTA: At the American Society of Clinical Oncology there were a few phase 1 studies published, and they are being expanded. At the [December American Society of Hematology] meeting we’ll have further updates. There are a few therapies—I would put them in the cellular therapy category—and one is definitely CAR T. A second is CAR-NK (natural killer), where we are transfecting these NK cells. The third emerging therapy is activated NK cells...and they are being combined with other CD-20– or CD-19–directed therapies to see how the outcomes are. The activated NK and T-cell therapies have been used in Epstein-Barr virus (EBV)-driven lymphomas and EBV-driven malignancies before. So it’s not just CAR T, but we are also looking at other ways to expand the cellular therapy offering to lymphoma patients. It will be very exciting in the next 3 to 5 years when we might have some of this approved.

These treatments do come with adverse effects, so if you have allogenic cellular therapy—just like allogenic transplant—we may have to look at the additional toxicities in terms of graft-vs-host disease. Apart from the toxicities that we see with autologous CAR T cells, where the patient’s T cells are transfected..., there could be an added adverse effect of graft-vs-host disease, which may have a longer or shorter duration.

MEHTA: We still don’t have any biomarkers, but there are some indirect indicators that we can discuss. One of them is how bulky the disease is, whether the patient’s lactate dehydrogenase is elevated right from the beginning or whether the patient has elevated ferritin or C-reactive protein levels. That can tell us that these patients may develop more cytokine release syndrome or the neurotoxicity syndrome. Hopefully, in a couple of years, we might have a predictive index to tell us “this patient could develop cytokine release syndrome” or “the patient will have higher chances compared with other patients.”

Why is this important? Of course, it is very important for the safety of the patients. But another aspect is very key, which many
of the patients might be interested in, especially at institutions such as mine where we have rolled out an outpatient CAR T program. We want to make sure that those who are outpatients are at low risk of developing cytokine release syndrome and the neurotoxicity. If we can manage them as outpatients, the patient doesn’t have to go in the hospital for 7 to 10 days. Why is it critical at this point? Because of the COVID-19 pandemic. As you know, the Delta variant cases are rapidly rising; hospital beds are full with those patients. Therefore if I have to plan for a CAR T patient, and if I say I need 7 to 10 days for an inpatient bed, the hospital administration will look at me and say, “You know, it may not be possible.”

So if we can avoid those kinds of challenges, based on predictive markers that show a patient is low risk, we can treat a patient as an outpatient instead of admitting him. The other factor from a payer perspective is whether there is a change in the incentive model. With outpatient regimens and treatments they’re paid differently compared to inpatient, and most of the inpatient regimens, as you know, are way more expensive for both the hospital and the payer. If you have a predictive marker and an index that can say this patient is low risk, and we can treat them on an outpatient basis, there may be a huge difference in finances compared with a patient who is treated as an inpatient. So those factors are very critical. And I am very positive that based on the markers we’re looking at we will come up with some type of index in the next couple of years.

**EBO:** Speaking of COVID-19, how are you handling patients with DLBCL and vaccination? Have you developed a set of protocols in terms of timing, vaccination, and treatment?

**MEHTA:** For most of my patients on therapy, I ask them to get vaccinated. If you look at the recent CDC recommendations, they’re suggesting a booster for immunocompromised patients. If I’m starting any patient on new treatment, I’m highly recommending that they get the vaccine before they start the treatment. They’re immunocompetent right now, so they can impart an immune response. That way they are protected. As with other immunocompetent people, if they’re on the therapy and they have not received the vaccine, I asked them to get vaccinated at the earliest opportunity. And that can happen during the time where their counts are coming up so that they can get the vaccine. But I do know that if they’re on the treatment, or within a few months after completion of treatment, they may not have the immune response needed. So there is a time that I suggest they get the booster when they finish the therapy. My arbitrary timeline is around 4 to 6 months. Once they finish the chemotherapy, 4 to 6 months out, I ask them to get a booster dose or the vaccine.

Many times I am asked whether that decision is based on the antibody titers. We don’t have any data yet. What is the cutoff? I don’t even know whether there is a certified test available on which we can base a decision that says, “Your titer level is this high, that’s why you don’t need a booster,” or “This is low; you need a booster.” We don’t have that kind of flowchart yet from the CDC. But I hope we get guidance in the future.

**EBO:** I was going to ask whether you test for antibodies but it sounds as though it’s all still too new. We’ll just have to wait.

**MEHTA:** So far, the information we have is that the cancer patient undergoing treatment for patients with lymphoma and chronic lymphocytic leukemia (CLL), either on or off treatment, are not importing the immune response like immunocompetent people. So that’s [one reason] that I still ask my patients to practice masking and social distancing. Because even though they are vaccinated—and either they recently finished treatment or they are on treatment—CLL itself makes you immunocompromised. You should not be that confident that [you say], “Yes, I’ve got a vaccine and I can take off my mask.” For their protection, I highly recommend that they put on a mask, especially in crowded places like churches or malls.

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**Conversations on CAR T: Study of Checkpoint Inhibitors After Transplant Bolsters Case for CAR T, Skarbnik Says**

**MARY CAFFREY**

**THE SECOND OF Evidence-Based Oncology**’s summer interviews with experts on diffuse large B-cell lymphoma (DLBCL) is with Alan Skarbnik, MD, director of the Lymphoma and Chronic Lymphocytic Leukemia (CLL) program and director of the Experimental Therapeutic and Immune Effector Cell Program at Novant Health Cancer Institute in Charlotte, North Carolina.

In May, Skarbnik was lead author of an article on phase 1b results on safety and clinical effects of combining checkpoint inhibition therapy (ipilimumab and nivolumab) after autologous stem cell transplant (ASCT) for patients with high-risk DLBCL, mature T-cell lymphoma, and multiple myeloma. Although the cohorts were small and Skarbnik describes the findings as “hypothesis driving,” progression-free survival (PFS) and overall survival (OS) at 18 months post-ASCT were highest in the primary refractory DLBCL cohorts, at 85% and 100%, respectively. In relapsed DLBCL, the results were not as promising; PFS was 28.6% and OS was 57.1%.1

As Skarbnik explains, the phase 1b study (NCT02681302) was planned before the first chimeric antigen receptor (CAR) T-cell therapies were approved—but it informs the bottom line being reported today: immunotherapy approaches in primary refractory DLBCL may be superior to cytotoxic chemotherapy with transplant.

This interview has been edited for length and clarity.

**EBO:** In May, you published results involving the use of combined checkpoint inhibitors following ASCT in DLBCL and other conditions. Can you discuss the overall findings?

**SKARBNIK:** The study first [sought] to evaluate the safety of this approach, using combined checkpoint inhibitors, nivolumab and ipilimumab, immediately following autologous stem cell transplantation. That combination had not been used before in that specific setting, and we wanted to evaluate whether it was safe and feasible. »
The second end point investigated outcomes, particularly in terms of PFS and OS. For patients with high-risk, multiple hematologic malignancies, there were different cohorts. We had 1 cohort for patients with primary refractory DLBCL and a cohort for patients who had early relapse DLBCL within the first year after frontline treatment.

We had 2 cohorts for T-cell lymphoma: 1 for advanced stage frontline consolidation, the other for relapse or refractory peripheral T-cell lymphoma. We excluded ALK-positive anaplastic large cell lymphoma from this cohort because we know they have better outcomes. Then we had 2 myeloma cohorts: 1 for high-risk multiple myeloma by cyto-genetics as frontline consolidation and the other for myeloma that relapsed within 3 years of an up-front transplant—so [this would] be a second transplant with the checkpoint inhibitor consolidation.

In this study, we did not identify any new safety signals, when compared with previous studies—these drugs are largely used in solid tumors—for lung, for renal cancer and melanoma. The adverse effects [AEs] were largely immune-related and were treated with steroids. We saw more cytopenias with these agents than in other settings, but cytopenias are very common following transplantation, so there’s a confounding factor.

**EBO:** What about efficacy in DLBCL? What differences did you observe?

**SKARBNIK:** Efficacy seems to be largely dependent on the disease state we used it for; this is a phase 1 study, and is mainly hypothesis driving. Cohorts had small numbers; each cohort had 7 patients, except for the T-cell cohorts, that were closed early due to slow accrual. The cohort of primary refractory DLBCL had 7 patients. Most of them were not in complete remission after 2nd line therapy before undergoing transplant. Patients were allowed enrollment in the trial with active disease as long as there was no progression through the previous line of salvage therapy. We allowed for stable disease or partial responses to the most recent salvage therapy. Most of the patients had a partial response in that cohort, and all the patients presented with complete response after transplant and checkpoint inhibitor consolidation.

Of the 7 patients, only 1 patient presented progression of disease in a small lymph node. The patient was treated with radiation therapy and rituximab, entered remission again and is still in remission. All other patients remain progression and disease free, and it’s been over 3 years of follow-up. This is a disease state where the median overall survival after transplant is close to 14 months. Again, it’s hard to compare different trials, particularly in a very small population. But it raises a question: Is it a reasonable and efficacious approach? It will take a larger trial to confirm that.

However, in the cohort of patients with DLBCL that achieved a complete remission and then presented relapse within the first year—which was the second cohort of DLBCL—we didn’t see similar outcomes. At 18 months, the PFS was 28.6% and OS was 57%. So there’s a potentially different efficacy signal there. We’re not sure why that happened. It could be because there were small numbers and this difference is random. It could be that there are actual biological differences in the disease states. What we tried to accomplish with this approach was to skew the post-transplant immune reconstitution toward an effector phenotype rather than a tolerance phenotype, by using checkpoint inhibitors. Usually, after autologous stem cell transplantation the first immune cells to recover are regulatory T cells, which may hinder an effective immune response against cancer. By using this combination, we tried to flip that and increase the T effector component to allow for an anti-cancer immunologic effect. We observed differences in the immunologic profiles between the two DLBCL cohorts, using this approach. In the primary refractory DLBCL cohort, the regulatory T-cells remained low for 18 weeks following transplantation, with a corresponding early increase in the effector T-cell population. In the early-relapsed DLBCL cohort, there was no significant decrease in the regulatory T-cell component and the effector T-cells remained low until 12 weeks post transplant. These differences may explain the contrasting outcomes between these two cohorts.

**EBO:** Even if it’s small numbers, though, you’ve simultaneously addressed all the big issues that come up in DBLCL. Patients relapse—and what is the right therapy once the relapse happens? What’s the right sequence when there are so many choices? Once there is a transplant, what comes next? You’ve looked at a lot of those challenges.

**SKARBNIK:** Yes, we did. Let me remind you that when the study was written and started, CAR T cells weren’t approved. We started writing the study in 2015, and the study started in 2016 before the commercial approval of CAR T cells. I think what’s clear to the lymphoma community is that for patients who present primary refractory disease and/or early relapse of disease—especially within the first 6 to 12 months following frontline therapy—chemotherapy is not the answer. The disease has shown its face and it doesn’t generally respond to more chemotherapy. It’s different than a disease that comes 2 years later or even more than a year later, where you do have still a chance to salvage those patients and then consolidate with autologous stem cell transplantation. We know that stem cell transplantation on its own is basically very high-dose chemotherapy—the stem cell transplant is a rescue for the myelotoxicity that the chemotherapy causes, There’s a minimal immunologic effect for a very short period after recovery, but that’s it.

We’ve seen with the CAR T experience—there have been press releases, but we don’t have all the data yet—that in 2 trials [NCT03391466; NCT03575351] comparing chemotherapy and transplantation vs CAR T [3] in the second-line setting for patients with primary refractory [and] early relapse disease [that] there’s superiority in terms of both OS and PFS in the CAR T patients.

The experience in the past show that it’s very hard to treat primary refractory DLBCL. The option we had before was to take the patient to transplant with potential residual disease after salvage, and those are the patients who generally end up presenting a relapse. So, the idea of the [phase 1] trial was to shift that perspective and include some immunotherapy in the fold to improve on efficacy. It is a different process, but to some extent it is the same idea behind CAR T-cell therapy—using an immunologic approach rather than a purely cytotoxic chemotheraphy approach.

As of today, we don’t yet know what’s the ideal process for treating these patients. Fortunately, we have more options coming on board. There are bispecifc antibiotics that are being studied for DLBCL. I think they are going to have a very strong place in the treatment of patients with refractory or early relapse disease. We need to go beyond cytotoxic chemotherapy for primary refractory disease, and evaluate immunotheraphy beyond rituximab.

**EBO:** In terms of the approach [in this study], you’ve tried some of the more standard immunotherapy—you’ve had CAR T come online, we’ve had [taxis- tama] come online. Would you try these therapies?

**SKARBNIK:** I’m a big fan of CAR T cells. I think CAR T cells in the second-line setting may be very reasonable; there’s a good rationale for that but we need to wait for the complete dataset from the studies comparing CAR T with autologous stem cell transplant in second line to draw conclusions. It seems that the earlier you use these therapies, when you have less T cell exhaustion, they may be more effective in driving responses. Once patients have seen 3 or 4 lines of chemotherapy, T cells are likely to be more exhausted.

In terms of logistics, CAR T cell therapy is certainly easier than this approach that we studied. First, there’s the transplant and then there are almost 6 months of consolidation with immunotherapy using an intensive schedule. There are new agents coming on board. Tafasitamab is approved; we have loncastuximab tesirine approved, which is an antibody-drug conjugate that also targets CD19. We do have CAR T, which is likely to come to second line in the very near future, and have the bispecific [antibodies], with ongoing studies for DLBCL. Again, I think the point to make is that an immunologic approach for primary refractory or early relapsed DLBCL seems more promising than the traditional cytotoxic chemotherapy approach with stem cell transplant.

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The Promise of Liquid Biopsies for Cancer Diagnosis

LIZ KWO, MD, MBA, MPH; AND JENNA ARONSON

IN RECENT YEARS, the clinical development of liquid biopsies for cancer, a revolutionary screening tool, has created great optimism. The discovery of circulating tumor cells (CTCs) during an autopsy more than 150 years ago1,2 was followed by the discovery of other significant circulating cancer elements, such as cell-free DNA (cfDNA)3 and finally circulating tumor DNA (ctDNA)4,5.

Defined as a test to search for cancer cells or pieces of DNA from tumor cells in a blood sample,6 liquid biopsies can serve a variety of purposes, including:

- diagnosing cancers earlier than traditional means such as radiology or imaging
- customizing treatment for detected diseases through genotyping
- identifying mechanisms of resistance to therapies
- measuring minimal residual disease or remaining disease after treatment
- assessing for cancer relapse or resistance to administered treatment

Although standard tissue biopsies generally involve invasive procedures to detect a tumor, liquid biopsies are performed on peripheral blood which is easy to access, allowing for more widespread use, particularly in patients who cannot have surgery. As a result, the use of liquid biopsies can reduce the time to treatment based on tumor detection, improve the efficiency of medical staff and resources, and can be used to screen more diseases. Liquid biopsies can also avoid some of the potential complications of traditional biopsies, including risk of tumor spread, injury to surrounding tissue, or severe bleeding.

Many tumors display regional heterogeneity (diverse tumor cells) that can limit the ability of a single, tissue-based biopsy to access the full molecular profile of the tumor. In contrast, liquid biopsies may detect tumor DNA shed from numerous sites within the tumor and thus provide a more comprehensive genomic picture. In so doing, the clinicians can be more informed in the use of molecularly targeted therapies. Similarly, liquid biopsies may bring a more efficient and innovative method to select patients for clinical trials, as the broader analysis of mutations can help guide appropriate therapy. Liquid biopsies can also be used for patient segmentation or inclusion and for patient monitoring.

Level of Use and Estimates Regarding Adoption

Some research reports say that the liquid biopsy market will be valued in at $6 billion by 2030.7 The United States is currently in the lead for development due to higher per capita health care expenditures and the awareness of improved early cancer detection benefits.

Liquid biopsies have been used for diagnosing non–small cell lung cancer (NSCLC)8 and screening or as a companion diagnostic (a test that indicates a patient could benefit from a specific therapy) for other types of cancers such as gastrointestinal, colorectal, breast, prostate, and ovarian cancer.

When used as a cancer detection tool for segments of the general population, there is speculation that liquid biopsies may improve the outcomes of diagnosis. Evidence shows that a more realistic approach is to use this screening technique on high-risk patients who have a personal or family history of cancer.9 Currently, liquid biopsies are most commonly used as a complementary technique to standard tissue biopsies, primarily in academic centers and procedures in community practices. Standard tissue biopsies are still the mainstay for cancer diagnosis, but for those patients who are unable to undergo or whose tumors are not amenable to invasive biopsies, liquid biopsies hold promise.

Challenges Faced by Clinical Adoption of Liquid Biopsy

Although more and more molecular diagnostic tests are being performed, they still must reach 2 important milestones: development of standards for their adoption and clinical validation. In addition, a few areas include10,11:

- complex biological data need to be developed and validated in studies that can generate clinically useful outcomes in order to trigger appropriate treatment decisions
- the deeper understanding of cancer biology and biomarkers, otherwise risks for false-negative or false-positive results of liquid biopsies are possible
- the number of liquid biopsy tests or methods that have received regulatory approval is low compared to the pool of tests developed by various companies10
- uncertainty or limitation of procedure reimbursement12

A review by Douglas et al that appeared in Journal of the National Comprehensive Cancer Network13 highlights some fragmented reimbursement approaches by payers but also provides a comprehensive view for companies that are looking for cancer detection solutions.

How Can Liquid Biopsy Move Forward?

In 2020, the FDA approved FoundationOne Liquid CDx designed by Foundation Medicine, which can detect alterations in all solid tumors with specific diagnostics.14 Analyzing more than 300 genes and their signatures, this sequencing test can be used to guide therapy selection and clinical trial options for patients. Also in 2020, the FDA approved another next-generation sequencing (NGS) test, Guardant360 CDx, which is able to detect EGFR mutations in cfDNA of some patients affected by NSCLC.15

However, before liquid biopsies can become an integrated part of regular oncologic practices, physician education is key to ensure that they understand the utility and limitations of liquid biopsies. This type of education enables clinicians to have a comprehensive understanding of how to implement utilize this technology most meaningfully for their patients.

In this next year, data from prospective studies must show that liquid biopsies deliver benefits to patients beyond being non-invasive, such as increasing quality-adjusted life-years. A number of companies have taken steps to make the widespread adoption of liquid biopsies a reality. In 2016, the cancer diagnostics company GRAIL became an important name in biotech. With $100 million in funding from its parent company, Illumina, and another $2 billion raised from private funding sources, GRAIL has set a bold objective to improve patient outcomes through early detection of cancer.16,17 It has combined data science and the most advanced genetic sequencing technologies to detect cancer. Illumina agreed to bring GRAIL back into its umbrella by purchasing it for $8 billion. »
As Evidence-Based Oncology\textsuperscript{®} went to press, New York state regulators approved GRAIL’s multicancer screening test, Galleri, meaning it has achieved one of the most rigorous validation standards in the country for a laboratory developed test; the test is already available to some health systems.\textsuperscript{16,17}

Conclusions
Large scale adoption of liquid biopsy screening tools will require further clinical evidence of clear benefits to patients and reductions in medical costs. The high complexity and diversity of coverage structures, especially in the private sector, will require clear guidelines regarding how test outcomes will affect clinical decision-making by providers. Ultimately, the future of liquid biopsy has the potential to increase diagnostic options and personalized care. ●

AUTHOR INFORMATION
Liz Koc, MHA, MBA, IPA, is a faculty lecturer at Harvard Medical School and physician entrepreneur. Jenna Aronson is a PhD candidate at MIT.

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Abstract at ASCO Quality Shows Rapid Uptake of NGS Testing Across OneOncology

AJMC\textsuperscript{®} Staff

AN ABSTRACT INVOLVING real-world data presented at the 2021 American Society of Clinical Oncology Quality Care Symposium tracked the uptake of next-generation sequencing (NGS) by 4 practices in the OneOncology network and compared usage with data from a national database. The study examined NGS testing patterns for advanced non–small cell lung cancer (NSCLC) and metastatic breast cancer at OneOncology practices that use Flatiron’s OncoEMR electronic health record. The abstract was presented September 25 by authors from OneOncology and Genentech, a member of the Roche Group, which acquired Flatiron Health in 2018. (The authors presented a second abstract on biomarker testing.) “Biomarker and next-generation sequencing are the backbone of personalized treatments in oncology,” Lee Schwartzberg, MD, OneOncology’s chief medical officer and senior author on both abstracts, said in a statement. “Understanding current testing patterns and strategies to increase their uptake is a vital component to bring precision medicine to oncology practices across the country. These research presentations identify an important baseline for how the physicians on the OneOncology platform are bringing advanced diagnostics to their clinic and how we can improve future utilization.”

Data from the 4 OneOncology sites were collected from January 2015 to May 2020 and compared with de-identified patient data in the Flatiron national database. According to investigators, across the OneOncology sites, 2045 of 3221 patients with advanced NSCLC (63%) received NGS with or without other genetic profile testing compared with 13,681 of 29,572 (46%) in the Flatiron NSCLC database. In mBC, 513 of 1295 (40%) got NGS at the OneOncology sites compared with 2458 of 12,175 (20%) in the Flatiron database.

Data showed the dramatic uptake of NGS across the 5-year period, both at OneOncology and nationwide; NGS was used in 41% of the patients with NSCLC diagnosed at the 4 sites in 2015 compared with 72% by 2020; NGS was used in 22% of cases in the national database in 2015 and 40% by 2020.

The gap between OneOncology and the national database was wider in mBC: Uptake of NGS shifted from 42% to 53% over the study period at OneOncology and 17% to 27% across the database. Testing rates were highest for patients with BRCA and HER2. In advanced NSCLC, the median time from diagnosis to NGS testing in OneOncology was 33 days vs 32 days for the Flatiron database, for mBC, it was 70 days for OneOncology vs 188 days in the database. The study authors observed that patients in the OneOncology sites were slightly younger and slightly more likely to have commercial insurance than those in the national database. ●

REFERENCE
Consumer Data Transparency Is More Important Than Ever as the Battle Against COVID-19 Rages On

SCOTT PALMER, MBA

IT’S WELL KNOWN AMONG economists and health care leaders alike that health care spending in the United States remains incredibly high and continues to grow rapidly. US health care spending is projected to grow at an average annual rate of 5.4% over the next decade, outspending all other nations in health care as a percentage of gross domestic product. Yet when it comes to understanding the details of what we’re spending money on and providing patients with information about their share of costs to help them make value-based decisions in their health care, the answers are much less clear. There may be a lot of disparate data out there about factors influencing costs, but there is much less “actionable information” that patients or providers can use to inform care decisions and try to keep expenses lower where possible.

Even though health care is one of our most essential needs, the health industry’s pricing and patient expected contributions are often cloaked in secrecy. Rates negotiated between providers and insurers have traditionally been conducted behind closed doors. Currently, there is little public information to explain the wide variability in the prices for services, ranging from simple blood tests to complex surgeries, often those delivered in the same city by similar providers for the same payer. Also, patients who are out-of-network may face surprise bills and cash pay patients often pay off a percentage of unreasonable standard charges that do not reflect market rates.

CMS implemented the Hospital Price Transparency final rule to improve price transparency, which went into effect on January 1 of this year. Among many things, the rule required hospitals to post clear, accessible pricing information online about the items and services they provide. However, by July, it was clear that many hospitals were choosing to remain noncompliant, and an executive order and proposed rule for penalties were issued to add teeth to the new regulations. Even with efforts to strengthen the rule, the requirements still only fall on certain parts of the health care industry, providing a limited view of what other options consumers might have when identifying the highest quality care at the best value.

Outpatient surgery has taken on an increasingly important role in the context of the larger health system, particularly as the nation continues to battle the effects of COVID-19 on hospital intensive care unit and staff capacity. Although ambulatory surgery centers (ASCs) are currently exempt from the federal rule on price transparency, many states are implementing their own regulations for price transparency in these settings. For example, Indiana enacted a series of laws in 2020 that require ASCs to provide a good faith estimate of the cost of health care services. These requirements are good news not only for patients so they can be informed consumers but also for ASCs that can more clearly demonstrate their value and become even more attractive as a preferred site of service for specific procedures.

The growing reliance on ASC services as a cost-effective and safe alternative to the hospital setting should encourage facilities to evaluate how to preemptively offer solutions for price transparency at the consumer level that align with and support the newly established regulations on the hospital side.

For this data to benefit patients and providers, the pricing and payment “menu” must be upfront and accessible. Health care facilities need to try to replicate how costs for services are communicated in other businesses. For example, car repair services or home remodeling companies do a diagnostic and develop a game plan for service and provide a clear cost estimate to the customer before they start working. Of course, there may be factors that cause adjustments, but the up-front information is organized in a way that consumers can easily compare similar services across potential contractors.

Many surgical business offices do attempt to calculate and communicate patient responsibility in advance. This is challenging because the data sources are not readily available or always reliable. To achieve the high level of accuracy needed, surgery centers should adopt technology to calculate and communicate costs while avoiding information overload that could lead to patient misunderstandings of which information is relevant. The benefits of the right technology include improved staff efficiency, shifting dollars from post care to preserve, compliance with state and federal laws, improved patient and surgeon satisfaction, and helping to drive the health care cost trajectory down by fostering competition, which will ultimately benefit the surgery center.

New pending regulatory requirements on price transparency will help push this transformation and culture change faster. In the context of COVID-19, we can expect case-type assignments and resource allocations between hospitals and ASCs to be more fluid than we have seen before. Before federal requirements catch up, taking steps to track and make price information available in the ASC setting will only further boost the industry’s reputation, demonstrate regulatory compliance, and make it easy to participate in the greater national move toward consumer transparency.

AUTHOR INFORMATION
Scott Palmer, MBA, is senior vice president of business development of HST Pathways, a leader in cloud-based end-to-end technology solutions for outpatient surgery centers. Palmer was the founder and CEO of Clariti Health, which in June merged with HST Pathways.

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Addressing Polypharmacy and PIMs in Geriatric Patients With Cancer

GIANNA MELILLO

IN A NARRATIVE REVIEW published in *Journal of Geriatric Oncology,* investigators outlined available studies assessing the effects of interventions aimed at reducing the burden of polypharmacy and potentially inappropriate medications (PIMs) among older adults with cancer.

Based on their analyses, investigators concluded that implementing services to address polypharmacy and PIMs in both acute and ambulatory settings can help identify drug-related problems (DRPs) and mitigate adverse effects. In addition, applying more than 1 polypharmacy assessment tool increases the capability to identify more PIMs and increases the ability for interventions.

Polypharmacy is defined as the concurrent use of 5 or more medications. It predominately affects adults 65 years and older, the review’s authors explained. PIMs can fall under the category of polypharmacy and include medications that interact with other medications and/or disease states. PIMs also may lack evidence-based indications and may have treatment risks that outweigh benefits.

“Although” older adults comprise 14.9% of the United States population, they account for 34% of prescription medications and 30% of over-the-counter (OTC) medications, the authors wrote. Compounding this issue, older adults with cancer are at a higher risk of polypharmacy due to the accumulation of other comorbidities requiring treatments. It is estimated that 8% to 84% of older adults with cancer deal with polypharmacy and 11% to 63% take PIMs.

“Addressing polypharmacy, PIMs, and other DRPs can be challenging not only because of the number of medications used but also because of the multi-layered process of managing many comorbidities between specialists, primary care physicians, and allied health professionals,” the authors wrote.

Two recently published meta-analyses1,2 have shown polypharmacy is associated with chemotherapy-related adverse events (AEs), postoperative complications, functional impairment, and shortened survival. In addition, PIMs and polypharmacy have been linked with reduced quality of life.

However, because older patients are more likely to have comorbidities and functional impairment to begin with, confounding may have been present in some studies. Analyses also have yet to establish a cause-and-effect relationship between polypharmacy/PIMs and poor outcomes, warranting more intervention-based research.

A lack of definitive recommendations from national and international guidelines regarding the optimal strategy for implementing interventions can make addressing these issues challenging.

“No single assessment tool comprehensively addresses all DRPs, including polypharmacy or PIM use, so the best practice recommendations are to apply them in combination,” the authors noted. These can include Beers Criteria, Medication Adherence Index, or Screening Tool to Alert Doctors to Right Treatment/Screening Tool of Older Person’s Prescriptions. These tools have some weaknesses when applied to older patients with cancer. For example, they may not account for OTC medications or herbal supplements that patients take.

According to authors, the ultimate goal when using these tools is to identify and discontinue unnecessary medications or those that pose greater risks than benefits to the patients. So as to not abruptly stop medications and risk withdrawal or resurgence of an underlying illness, providers can deprescribe medications.

“The high degree of pharmacist-driven interventions reported in the literature opens a window of opportunity to expand [clinical pharmacy services] into diverse practice settings to optimize outcomes for older adults with cancer.” —*Journal of Geriatric Oncology*

“Deprescribing systematically facilitates medication discontinuation by slowly tapering and continuously reassessing to reduce any potential harms from stopping treatment,” they explained. To assist providers, several international guidelines exist, including the comprehensive geriatric assessment (CGA) and the comprehensive medication review (CMR).

However, no universal recommendation exists as to which provider (eg, clinical pharmacist, nurse, physician, geriatrician, oncologist) is best suited to address the issue of polypharmacy.

Results of several interventional studies show that despite the pivotal role oncologists play in older patients’ care, “these physicians lack the time and resources to provide formal guidance on adjusting therapy after DRPs hinder interventions in practice,” the authors wrote.

The incorporation of polypharmacy and PIM assessment tools into clinical practice may help providers better identify and manage DRPs, but these can be difficult to implement. Abbreviated assessment tools have been studied for this purpose, although they may not be sufficient when used alone.

An additional analysis found that a pharmacist-led CMR carried out with multiple assessment tools was highly effective in identifying PIMs, “although data regarding modifications of therapy [were] unreported,” the authors wrote. Enhanced communication of CGA and CMR results between the patient and care teams could also assist in deprescribing.

Investigators underscored the need for an interprofessional team with expertise in each assessment domain, combining the knowledge of oncologists, geriatricians, nurses, and pharmacists to mitigate polypharmacy and PIMs outcomes.

Overall, given all the limitations present in the analyses included in the review, the authors noted the critical need for additional literature assessing interventions in these patients.

“Future investigators should consider the development of a polypharmacy and PIM assessment tool that is specific to older adults with cancer as their medication care varies greatly from the average older adult without cancer, as does their prognosis and performance status,” they wrote.

“The high degree of pharmacist-driven interventions reported in the literature opens a window of opportunity to expand [clinical pharmacy services] into diverse practice settings to optimize outcomes for older adults with cancer,” the authors concluded.

**REFERENCES**


**THE AMERICAN JOURNAL OF ACCOUNTABLE CARE**

Coordination Without Consolidation? Options for ACOs

Read more at: https://doi.org/10.37765/ajac.2021.88748
Specialty Therapies Offering Incremental Benefit Shouldn’t Be Added to Clinical Pathways, Hertler Says

DENISE MYSHKO

ONCOLOGY DRUG COSTS have climbed rapidly, but price increases do not always align with the value the drugs offer, according to Andrew Hertler, MD, chief medical officer of New Century Health, a specialty care management company focused on oncology and cardiology in Brea, California.

The value of new oncology therapies comes from increasing survival and improving the quality of life for patients, but new therapies may provide only incremental benefit that comes with a high price tag, he said in a recent interview. “In 2020 alone, the average prices of new drugs coming to market [were] between $100,000 and $200,000 a year, with some drugs costing as much as $400,000 for an individual dose,” Hertler said.

“Realistically, there has to be a consensus solution for these high costs,” he added. “What we can do as physicians is to follow the clinical pathways for any clinical situation for what is the highest-value drug. To me, if a drug just isn’t that good, we shouldn’t use it. We routinely see approved drugs with 1.4 months to 1.6 months’ improvement in progression-free survival. For marginal drugs, we don’t have to put them on our pathways.”

“The newest innovations, the chimeric antigen receptor (CAR) T-cell therapies, have an even higher price tag, especially when considering the total cost of patient care. In fact, the total cost of administering CAR T-cell therapies averaged more than $700,000 and, in some cases, exceeded $1 million, even though the wholesale acquisition cost of the treatment is $373,000, according to data from a recent real-world study from Prime Therapeutics in Eagan, Minnesota.”

Over 2.5 years, Prime Therapeutics’ investigators looked at 74 members of Blue Cross Blue Shield plans who received Novartis’ tisagenlecleucel (Kymriah) or Kite Pharma’s axicabtagene ciloleucel (Yescarta) for the treatment of B-cell lymphoma.

The cost of CAR T-cell medication alone was $527,000 on average, which was 74% of the total cost during the initial treatment period. However, 12% of patients with post–CAR T-cell events incurred more than $1 million for their total cost of care, including drug and other costs, such as those for infusion center visits or transplants.

A 2018 Institute for Clinical and Economic Review (ICER) report estimated the cost-effectiveness of the 2 CAR T-cell therapies in B-cell cancers and suggested the therapies are priced in alignment with their clinical value, despite their high cost.

The cost-effectiveness of both CAR T-cell therapies fell near or within commonly cited thresholds of $100,000 to $150,000 per quality-adjusted life years, according to the report. Because ICER’s study estimated only total treatment cost, Prime’s real-world evidence is another barometer to consider when evaluating whether CAR T cells’ pricing is in line with value.

A version of this article first appeared in Formulary Watch.

REFERENCES

See our Exclusive Coverage of the European Society for Medical Oncology. Read more at: https://bit.ly/3Ac95f0
Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

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

• The first-line treatment of patients with non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic

• The treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate

• The treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation

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

**Warnings and Precautions (cont’d)**

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

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

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

**Immune-mediated pneumonitis:** LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Immune-mediated colitis:** LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/ PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Immune-mediated hepatitis:** LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN.

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

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

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

- **Adrenal insufficiency:** LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

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

Warnings and Precautions (cont’d)

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

Immune-mediated endocrinopathies: (cont’d)

- **Hypophysitis:** LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

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

- **Thyroiditis:** Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

- **Hyperthyroidism:** Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hyperthyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

- **Hypothyroidism:** Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

- **Type 1 diabetes mellitus, which can present with diabetic ketoacidosis:** Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/ PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

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

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

Warnings and Precautions (cont’d)

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

Other immune-mediated adverse reactions: (cont’d)

- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **Endocrine:** Hypoparathyroidism
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash, and dyspnea. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Complications of allogeneic HSCT

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

Embryo-fetal toxicity

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

Adverse Reactions

- In the pooled safety analysis of 810 patients, the most common adverse reactions (≥15%) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea
- In the pooled safety analysis of 810 patients, the most common Grade 3-4 laboratory abnormalities (≥2%) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia

Use in Specific Populations

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

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

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; PD-L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.

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

**Brief Summary of Prescribing Information**

**INDICATIONS AND USAGE**

**1.1 Basal Cell Carcinoma**

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

**1.2 Basal Cell Carcinoma**

LIBTAYO is indicated for the treatment of patients:
- with locally advanced basal cell carcinoma (sACB) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

**1.3 Non-Small Cell Lung Cancer**

LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-1 expression (Tumor Proportion Score (TPS) ≥ 50%) as determined by an FDA-approved test (see Dosage and Administration (2.1) in the full prescribing information), with no EGFR, ALK or ROS1 alterations, and is:
- locally advanced where patients are not candidates for surgical resection or definitive chemoradia or
- metastatic.

**4 CONTRAINDICATIONS**

- None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Severe and Fatal Immunemediated Adverse Reactions**

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with or without endocrinopathy. Hypophysitis can follow hyperthyroidism. Immune-mediated hypophysitis can present with clinical symptoms of diabetes insipidus as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Type 1 Diabetes Melitus, which can present with diabetic ketoacidosis.

- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Type 1 diabetes melitus occurred in 0.1% (18/180) of patients, including Grade 4 (0.1%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes melitus. Type 1 diabetes melitus led to withholding of LIBTAYO in 0.1% of patients.

**Immune-mediated Nephritis with Renal Dysfunction**

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

Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.1% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 86% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for nephritis, 2 reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

**Immune-mediated Dermatologic Adverse Reactions**

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and Lyell’s Disease (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with other PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reinstituted LIBTAYO after symptom improvement; of these 43% (5/7) had recurrence of the dermatologic adverse reaction.

**Other Immune-mediated Adverse Reactions**

Adverse reactions may occur at any time during treatment with LIBTAYO. In Study 1620, the most common (> 1%) of all non-gynecologic serious (≥30%) and fatal (≥10%) adverse events were:

- Hypothyroidism
- Hypophysitis
- Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. No patient discontinued treatment due to hypophysitis. Hypophysitis occurred in 50% of the 20 patients. Of the 4 patients in whom LIBTAYO was withheld for hypophysitis, 2 reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of hypophysitis.

**6 ADVERSE REACTIONS**

**6.1 General**

The following table presents the adverse reactions that occurred in ≥1% of patients receiving LIBTAYO, including fatal (≥0.1%), Grade 4 (0.1%) and Grade 3 (0.6%) adverse reactions. Adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. **Table 2** summarizes the adverse reactions that occurred in ≥1% of patients receiving LIBTAYO.

**6.2 Adverse Reactions Associated with Systemic Corticosteroids or Other Immunosuppressants**

**6.2.1 Adverse Reactions Associated with Systemic Corticosteroids or Other Immunosuppressants**

**6.2.1.1 Adrenal Insufficiency**

LIBTAYO can cause severe or fatal adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate systemic replacement with hydrocortisone or other mineralocorticoids as clinically indicated. Withhold LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 0.1% patient. LIBTAYO was not withhold or permanently discontinued due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 87% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

**6.2.1.2 Hypophysitis**

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with or without endocrinopathy. Immune-mediated hypophysitis can follow hyperthyroidism. Immune-mediated hypophysitis can present with clinical symptoms of diabetes insipidus as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis had not resolved in any patient at the time of data cutoff.

**6.3 Other Adverse Reactions**

**6.3.1 Adverse Reactions Associated with Systemic Corticosteroids or Other Immunosuppressants**

**6.3.1.1 Adrenal Insufficiency**

LIBTAYO can cause severe or fatal adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate systemic replacement with hydrocortisone or other mineralocorticoids as clinically indicated. Withhold LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 0.1% patient. LIBTAYO was not withheld or permanently discontinued due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 87% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.
6 ADVERSE REACTIONS

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

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 350 patients with NSCLC (Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=185), 3 mg/kg every 3 weeks (n=120) or 350 mg every 3 weeks (n=53), or other doses (n=33; 1 mg/kg every 2 weeks; 10 mg/kg every 2 weeks; 200 mg/kg every 4 weeks). Among the 810 patients, 57% were exposed for ≥6 months and 20% were exposed for >12 months. In this pooled safety population, the most common adverse reactions (≥15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hypothyroidism, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Cutaneous Squamous Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 (see Clinical Studies (14.1) in the full prescribing information). Of these 219 patients, 131 had mCSCC (nodal or distal) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=13), 30 mg/kg every 3 weeks (n=2), or other doses (n=20; 1 mg/kg every 2 weeks; 10 mg/kg every 2 weeks; 200 mg/kg every 4 weeks). Among the 810 patients, 57% were exposed for >6 months and 20% were exposed for >12 months. In this pooled safety population, the most common adverse reactions (≥15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hypothyroidism, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

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

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

Toxicity graded per NCI CITCA v. 4.0.1.

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

Basal Cell Carcinoma (BCC)

The safety of LIBTAYO was evaluated in 132 patients with advanced BCC (mBCC N=44, laBCC N=88) in an open-label, single-arm trial (Study 1620) (see Clinical Studies (14.2) in the full prescribing information). Patients received LIBTAYO 350 mg every 3 weeks as an intravenous infusion for up to 93 weeks or until disease progression or unacceptable toxicity. The median duration of exposure was 42 weeks (range, 2.1 weeks to 93 weeks).

The safety population characteristics were: median age of 68 years (38 to 99 years), 87% male, 74% White, and European Cooperative Oncology Group (ECOG) performance score (ECOG) performance score (PS) of 0 (44%) and 1 (56%). Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia.

Permanent discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, paniostitis, rash maculopapular, pruritus, and confinement state.

The most common (≥20%) adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3 or 4 adverse reactions (≥2%) were cellulitis, anemia, hypothyroidism, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcaemia. The most common (≥4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hypothyroidism, and hyperkalemia.

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>General and Administration Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**a.** Composite term includes fatigue and anemia

**b.** Composite term includes rash, and musculoskeletal pain

**c.** Composite term includes pruritus and pruritus urticaria

**d.** Composite term includes diarrhea and colitis

**e.** Composite term includes cough and upper airway cough syndrome

**Footnote:**

- **a.** Composite term includes fatigue, anemia, and malaise
- **b.** Composite term includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain
- **c.** Composite term includes rash, musculoskeletal pain, rash, dermatitis acroainitis, erythema, rash-pruritic, dermatitis bullous, dysproteic exema, pemphigoid, rash erythematous, and urticaria
- **d.** Composite term includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection
- **e.** Composite term includes dyspnea and dyspnea exertion
- **f.** Composite term includes hypertension and hypertensive crisis
6.2 Immunogenicity

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

Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Lactation

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

8.4 Pediatric Use

Pediatric Use

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

8.5 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 218 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 122 patients with BCG who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.6 Pregnancy

Pregnancy

Animal studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1-PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss. Therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1-PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action which likely leads to immune-mediated toxicity, patients with NSCLC should only be considered for treatment with LIBTAYO if they are not pregnant or breastfeeding.

8.7 Lactation

Lactation

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

8.8 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

8.9 Pediatric Use

Pediatric Use

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

8.10 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 218 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 122 patients with BCG who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.11 Fertility

Fertility

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

8.12 Pregnancy

Pregnancy

Animal studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1-PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1-PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action which likely leads to immune-mediated toxicity, patients with NSCLC should only be considered for treatment with LIBTAYO if they are not pregnant or breastfeeding.

8.13 Lactation

Lactation

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effect on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.
Lurbinectedin Plus Doxorubicin Misses OS End Point in Relapsed SCLC, But Shows Superior Safety vs SOC

COURTNEY MARABELLA

THE COMBINATION OF LURBINECTIDIN (Zepzelca) and doxorubicin produced comparable efficacy to that of standard-of-care (SOC) vincristine, cyclophosphamide, and doxorubicin (CAV) or topotecan in patients with relapsed small cell lung cancer (SCLC), missing the primary end point of the phase 3 ATLANTIS trial (NCT02566993). However, the doublet did showcase a superior safety and tolerability profile.

Results were presented September 10 during the International Association for the Study of Lung Cancer 2021 World Conference on Lung Cancer. They showed that the median overall survival (OS) in the investigative and control arms was 8.6 months (95% CI, 7.1-9.4) and 7.6 months (95% CI, 6.6-8.2), respectively, in the intent-to-treat population (HR, 0.967; 95% CI, 0.815-1.148; P = .7032). The mean OS in these arms was 10.6 months and 9.9 months, respectively.

“We did not see a [significant] improvement in efficacy, and the trial did not meet the primary end point; however, we did confirm the safety profile of lurbinectedin, even when adding doxorubicin,” lead study author Luis Paz-Ares, MD, PhD, chair of the Medical Oncology Department at the Hospital Universitario 12 de Octubre, associate professor at the Universidad Complutense, and head of the Lung Cancer Unit at the National Oncology Research Center, all in Madrid, Spain, said during a press briefing. “Lurbinectedin [was more tolerable], particularly in terms of myelosuppression, than SOC. More importantly, new combinations of lurbinectedin and other cytotoxic agents are currently being explored in this setting.”

SCLC is the most aggressive form of lung cancer and mostly occurs in smokers, according to Paz-Ares. Additionally, although the disease has proved to be sensitive to chemotherapy and radiation, responses are short and those who relapse have a survival of just 6 to 8 months. Much has been learned about the biology of the disease, but treatment options remain limited, Paz-Ares added.

In June 2020, the FDA approved single-agent lurbinectedin for use in the treatment of adult patients with metastatic SCLC with disease progression following platinum-based chemotherapy, at a dose of 3.2 mg/m² every 3 weeks. The regulatory decision was based on results from a phase 2 basket trial (NCT02454972), in which the agent elicited higher response rates in those who were platinum sensitive and had a chemotherapy-free interval (CTFI) of 90 days or more compared with those who were platinum resistant and had a CTFI of less than 90 days; these rates were 45.0% and 22.2%, respectively.

A phase 1 dose-escalation study (NCT01970540) was conducted to investigate lurbinectedin in combination with doxorubicin, based on synergistic activity observed in in vitro assays. Results showed that the combination elicited an overall response rate (ORR) of 36%, a median progression-free survival (PFS) of 3.3 months, and a median OS of 7.6 months in patients with second-line SCLC. When excluding patients with refractory disease with a CTFI of 30 days or less, the ORR achieved with the regimen was 46%, the median PFS was 5.1 months, and the median OS was 10.2 months. “These results were promising compared with historical data for topotecan and CAV,” Paz-Ares noted.

Based on results from this study, it was determined that the recommended dosing for the regimen in the second-line setting is 40 mg/m² of doxorubicin and 2.0 mg/m² of lurbinectedin to be given on day 1 of every 3-week cycle. Investigators launched ATLANTIS to examine the combination vs SOC in a phase 3 setting.

To be eligible for enrollment, patients had to have a confirmed diagnosis of SCLC and have received 1 prior line of chemotherapy. Additionally, patients needed to have an ECOG performance status of 2 or less and measurable disease per RECIST criteria. Those with a CTFI of less than 30 days were excluded.

A total of 613 patients were randomized 1:1 to receive either lurbinectedin plus doxorubicin at the recommended dose, topotecan at a dose of 1.5 mg/m² on days 1 to 5 of every 3-week cycle, or CAV on day 1 of every 3-week cycle. Primary prophylaxis with granulocyte colony-stimulating factor was mandatory for both arms. Patients received treatment until progressive disease or intolerable toxicity.

Patients were stratified by ECOG performance status (0 vs a 1), CTFI (a 180, 179-190, < 90), central nervous system involvement (yes vs no), prior treatment with PD-1/L1/PD-1 agents (yes vs no), and investigator preference for the control arm.

The primary end point of the study was OS.

Additional data showed that the median PFS, as assessed by an independent review committee, was 4.0 months in both the investigative arm (95% CI, 2.8-4.2) and the control arm (95% CI, 3.0-4.1; HR, 0.831; 95% CI, 0.693-0.966; P = .0437). Additionally, PFS rate at 6 months was 31.3% (95% CI, 25.8%-36.9%) in the investigative arm vs 24.4% (95% CI, 19.1%-30.1%) in the control arm. At 12 months, these rates were 10.8% (95% CI, 7.1%-15.3%; P = .00851) and 4.4% (95% CI, 2.1%-6.1%; P = .0129), respectively.

Regarding safety, treatment-related adverse effects (TRAEs) of any grade were reported in 88.4% of patients in the investigative arm (n = 303) and 92.0% of those in the control arm (n = 289). Notably, lower rates of grade 3 or greater TRAEs were reported in the lurbinectedin arm vs the control arm, at 47.2% and 75.4%, respectively. Moreover, lower rates of grade 4 TRAEs were reported with lurbinectedin vs SOC (16.2% and 54.7%, respectively), grade 3 or higher serious AEs (12.5% vs 28.7%), treatment discontinuation associated with AEs (7.6% vs 15.6%), and deaths associated with AEs (0.3% vs 3.5%).

Additionally, lower rates of grade 3 or higher hematologic AEs were reported in the investigative arm vs the control arm, including anemia (14.5% vs 31.1%), neutropenia (37.0% vs 69.2%), and thrombocytopenia (13.9% vs 31.1%). The most frequently reported grade 3 or higher nonhematologic AE was fatigue; this was experienced by 8.6% of patients in the investigative arm and 10.7% of patients in the control arm.

Despite the findings, lurbinectedin may remain part of the National Comprehensive Cancer Network clinical guidelines, according to the committee chair for the SCLC guidelines. In a recent interview, Apraj Kishor Ganti, MD, professor of internal medicine in the Division of Oncology & Hematology at the Fred & Pamela Buffett Cancer Center at the University of Nebraska Medical Center in Omaha, discussed that possibility, after Jazz Pharmaceuticals had announced the ATLANTIS trial failed to meet its primary end point.

“We will evaluate that data and compare [them] with the data that we already have, knowing that those trials are not directly comparable, because the doses were low and for cytotoxic chemotherapy drugs, we know that those matter to a certain extent,” Ganti said. “But if the data do not show that there was a significant detriment to lurbinectedin, we may elect to keep it on the guidelines.”

“What I’m telling you right now is my personal opinion,” he continued. “We may elect to keep it just to allow patients to have another option.”

A version of this article originally appeared on OncLive.com. Mary Caffrey contributed to this report.

REFERENCES
Mobocertinib Approved in EGFR Exon 20 Insertion+ NSCLC

ON SEPTEMBER 15, 2021, the FDA granted approval to mobocertinib (Exkivity; Takeda), a first-in-class oral tyrosine kinase inhibitor (TKI) for locally advanced or metastatic non–small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations. The therapy is approved for adult patients whose disease has progressed on platinum-based chemotherapy.

Mutations will be detected with Thermo Fisher Scientific’s Oncomine Dx Target Test, which was simultaneously approved as a next-generation sequencing companion diagnostic, according to a news release from Takeda announcing the approvals.¹

NSCLC accounts for 85% of the 1.8 million new cases of lung cancer diagnosed each year worldwide, according to the World Health Organization. Patients with EGFR exon 20 insertion–positive NSCLC make up approximately 1% to 2% of patients with NSCLC and have lacked treatment options.²

Approval of mobocertinib is based on phase 1/2 data presented during the 2021 meeting of the American Society of Clinical Oncology that showed an overall response rate of 28% and a median duration of response of 17.5 months. Mobocertinib showed a median overall survival of 24 months in patients with platinum-based chemotherapy.³

Common adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. ⁴

REFERENCES

Zanubrutinib Gains Accelerated Approval in R/R Marginal Zone Lymphoma

ZANUBRUTINIB, A SECOND-GENERATION selective inhibitor of Bruton tyrosine kinase (BTK), received accelerated approval September 15, 2021, for adult patients with relapsed or refractory (R/R) marginal zone lymphoma (MZL) who have received at least 1 anti-CD20–based treatment.

BeiGene, which sells zanubrutinib as Brukinsa, announced the approval in a statement. This is the third approval for zanubrutinib.¹

The FDA’s action was based on overall response rate (ORR) as seen in updated phase 2 results for the MAGNOLIA trial (NCT03846427), which were presented during the European Hematology Association (EHA) 2021 Virtual Congress in June.² Continued approval will depend on how zanubrutinib performs in a phase 3 trial.

“We are excited about the FDA’s approval for [zanubrutinib] in patients with previously treated marginal zone lymphoma, a significant milestone that was made possible by the diligent BeiGene team, the dedicated investigators, and the participating patients and their families,” Jane Huang, MD, chief medical officer for hematology at BeiGene, said in the news release.³

The MAGNOLIA trial results provided additional evidence that the selective design of Brukinsa can be translated to improved treatment outcomes for these patients.”

Stephen Opat, MBBS, FRACP, FRCPA, director of clinical hematology at Monash University in Melbourne, Australia, and lead principal investigator for MAGNOLIA, explained that BTK plays a critical role in B-cell receptor signaling, which drives the development of MZL. In the trial, zanubrutinib was well tolerated, he said, with a low rate of discontinuation due to adverse events (AEs).

MAGNOLIA is a single-arm, multicenter phase 2 study of adults with R/R MZL who were treated with at least 1 prior line of therapy, including at least 1 CD20-directed regimen. Patients were treated with 160 mg of zanubrutinib twice daily until disease progression or unacceptable toxicity. The primary end point was ORR as determined by an independent review committee. Secondary end points include ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), and safety.

Results presented at EHA were from the 68 patients enrolled and treated, with a median age of 70, including 28% who were at least 75 years old. MZL subtypes seen in the study included 38% of patients with extranodal MZL, 38% nodal, 18% splenic, and 6% indeterminate. Patients in the study had received a median of 2 prior therapies, and 32% had disease that was refractory to their last therapy. Data showed:

• Patients were exposed to the drug for a median of 59.1 (range, 3.7–84.1) weeks; 66 patients could be evaluated for the drug’s efficacy.
• At a median follow-up of 15.5 (range, 1.6–21.7) months, investigator-assessed ORR, including complete response (CR) and partial
response (PR), was 74%; this included 24 CRs, 50% PRs, and 17% with stable disease.  
• Responses were observed in all subtypes, with an ORR of 68% in extranodal, 84% in nodal, 75% in splenic, and 50% in indeterminate subtypes; the CR rate was 36% for extranodal MZL, 20% for nodal, 8% for splenic, and 25% for indeterminate subtype.  
• Median DOR and PFS were not reached; at 15 months, PFS was 68% and the 12-month DOR was 81%.  

Of the 66 patients who could be evaluated, 28 (42%) stopped treatments, including 20 due to disease progression, 1 who withdrew consent, and 3 who required prohibited medications. Four stopped treatment due to AEs, including 2 who had COVID-19 pneumonia. 1 patient who had a heart attack, and 1 who had pyrexia attributed to disease transformation.  

The most common (≥10%) treatment-emergent AEs reported were diarrhea (22%), bruising (21%), constipation (15%), pyrexia (13%), abdominal pain (12%), upper respiratory tract infection (12%), back pain (10%), and nausea (10%). Most AEs were grade 1 or 2.  

REFERENCES  

FDA Approves Zanubrutinib in Adults With Waldenström Macroglobulinemia

THE FDA HAS APPROVED ZANUBRUTINIB (Brukinsa) for the treatment of adults with Waldenström macroglobulinemia (WM), a rare type of lymphoma.  

The September 1 approval was based on results from the phase 3 ASPEN trial, which compared zanubrutinib against ibrutinib (Imbruvica) in patients with WM. Results were published in Blood in October 2020.  

Both agents are Bruton tyrosine kinase (BTK) inhibitors. However, as a next-generation BTK inhibitor, zanubrutinib is more targeted, which reduces toxicity while improving outcomes, explained Peter Hillmen, PhD, MB ChB, professor at the University of Leeds and honorary consultant hematologist at Leeds Teaching Hospitals NHS Trust, United Kingdom, when he presented results of zanubrutinib at the European Hematology Association (EHA) 2021 Virtual Congress in June.  

“The ASPEN trial provided compelling evidence that Brukinsa is a highly active BTK inhibitor in Waldenström macroglobulinemia and, compared to the first-generation BTK inhibitor, showed improved tolerability across a number of clinically important side effects,” Steven Treon, MD, PhD, director of the Bing Center for Waldenström’s Macroglobulinemia Research at the Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School, Boston, Massachusetts, said in a statement. “The approval of Brukinsa provides an important new option for targeted therapy in Waldenström macroglobulinemia.”  

The primary end point of ASPEN was very good partial response (VGPR) in the intention-to-treat population. For zanubrutinib, the VGPR rate was 28% compared with 19% for ibrutinib, based on the modified Sixth International Workshop on Waldenström Macroglobulinemia (IWWM-6).  

Using IWWM-6 criteria, the response rate of partial response or better was 78% for zanubrutinib vs 78% for ibrutinib (95% CI, 68%-85% vs 95% CI, 68%-86%). At 12 months, the event-free duration of response was 94% for zanubrutinib compared with 88% for ibrutinib (95% CI, 86%-98% vs 95% CI, 77%-94%).  

The most common adverse events (AEs) occurring in at least 20% of the safety population of 779 patients were decreased neutrophil count, upper respiratory tract infection, decreased platelet count, rash, hemorrhage, musculoskeletal pain, decreased hemoglobin, bruising, diarrhea, pneumonia, and cough.  

The study results showed that 23% of patients on ibrutinib required dose reductions for AEs vs 14% of patients on zanubrutinib. In addition, the zanubrutinib group had lower incidence and severity of most toxicities associated with BTK inhibitors compared with ibrutinib.  

“The approval of Brukinsa in Waldenström macroglobulinemia, which is the second therapy approved specifically for the treatment of this rare type of lymphoma, is positive news for patients,” said Pete DeNardis, MBA, chair of the board at the International Waldenström Macroglobulinemia Foundation.  

“Expanded treatment options offer new hope for those living with this disease and can potentially improve patient experience, especially oral therapies that can be given as a single agent.”  

At EHA2021, additional research on zanubrutinib in WM found that:  

• Compared with dexamethasone–rituximab–cyclophosphamide (DRC) and bendamustine–rituximab (BR), zanubrutinib had significantly longer 12- and 24-month progression-free survival and overall survival.  
• Zanubrutinib had a higher incidence of neutropenia vs DR but a lower incidence vs BR.  
• Zanubrutinib is cost-effective vs ibrutinib based on life-years, quality-adjusted life-years, and treatment costs. Zanubrutinib reduced the cost of disease management by $2935 and other direct costs by $2964 vs ibrutinib.  

Zanubrutinib is already approved in the United States for adults with mantle cell lymphoma. It is under investigation in the MAGNOLIA trial for marginal zone lymphoma and the ALPINE study for relapsed/refractory chronic lymphocytic leukemia and small lymphocytic leukemia.  

REFERENCES  

Genomic Complexity Is Linked With Poor Outcomes in DLBCL

A NEW ANALYSIS OF PATIENTS with diffuse large B-cell lymphoma (DLBCL) suggests genomic complexity is associated with a poor prognosis and poor response to standard immunochemotherapy.  

The report, published in the journal Oncoimmunology, gives new context to the different treatment responses seen in DLBCL, the most common type of non-Hodgkin lymphoma.  

Corresponding author Hua You, PhD, of Guangzhou Medical University, in China, and Duke University, in the United States, and colleagues explained that tumor mutational burden (TMB) has increasingly become an important biomarker in understanding treatment responses, but hematological malignancies tend to have lower TMBs compared with solid tumors. DLBCL has relatively high TMB for a hematological malignancy, and it also has low response rates to immune checkpoint inhibitors.  

You and colleagues sought to better understand the clinical implications of TMB in this cancer type, so they conducted an analysis of 275 genes that are commonly mutated in patients with hematologic cancers.  

The investigators recruited 424 patients with DLBCL who had undergone standard immunochemotherapy. Patients with primary cutaneous DLBCL, T-cell lymphomas, and angioimmunoblastic T-cell lymphomas were excluded from the analysis.  

The investigators divided the 424 patients into two groups based on TMB: high TMB (≥63 mutations per megabase) and low TMB (<63 mutations per megabase). They found that patients with high TMB were more likely to have poor clinical outcomes compared with those with low TMB.  

The report is the first to show that DLBCL patients with high TMB have poor clinical outcomes, according to the investigators.  

“Further study is warranted to determine the clinical implications of TMB in DLBCL,” they wrote.
primary mediastinal large B-cell lymphoma, and primary central nervous system lymphoma were excluded.

Patient samples underwent fluorescent multiplex immunohistochemistry and NGS targeted toward the commonly mutated set of genes.

The analysis elucidated a number of patterns. They found that patients with nonsynonymous mutations in KMT2D and TP53 were more likely to have higher levels of nonsynonymous mutations.

The investigators further showed that in patients with germinal center B-cell-like (GCB) DLBCL who had wild-type TP53, a high mutation number correlated with significantly poorer clinical outcomes.

"In correlating NGS mutation numbers to clinical outcome, we found that only in patients with wild-type (WT) TP53, and more particularly in the GCB subtype with WT-TP53, significantly poorer survival was associated with high numbers of nonsynonymous mutations (with all cutoffs ranged from >4 to >23) and [mutated] genes (with all cutoffs ranged from >4 to >18)," You and colleagues wrote.

More broadly, the investigators said a high number of mutations were linked with lower PD-1 expression in T cells and PD-L1 expression in macrophages, “suggesting a positive role” of high mutation numbers in immune responses. To validate their data, the investigators used a publicly available data set of 304 patients with DLBCL who had undergone whole-exome sequencing as part of research at Harvard University. That analysis confirmed that KMT2D mutations were associated with high genomic complexity, which in turn was associated with poorer survival rates.

"Together, these results suggest that KMT2D inactivation or epigenetic dys-regulation has a role in driving DLBCL genomic instability and that genomic complexity has adverse impact on clinical outcome in DLBCL patients with wild-type TP53 treated with standard immunochemotherapy," they said.

The findings could help pave the way for more precise therapeutic decisions for patients with DLBCL, although the investigators said further research is needed for that to become a reality. "Further studies elucidating the oncogenic and neoantigen roles of DLBCL mutations in DLBCL patients are needed, as well as the therapeutic implications of genetic and immune biomarkers," the investigators said.

REFERENCE

High-Dose Methotrexate Is Effective in Preventing Isolated CNS Relapse in Diffuse Large B-Cell Lymphoma

HIGH-DOSE METHOTREXATE (HDMTX) may reduce risk of isolated central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL), according to study findings published in *Blood Cancer Journal*. Occurring in 1% to 14% of patients with DLBCL, CNS relapse is associated with significant risk of mortality, as prognosis for survival ranges from 2 to 5 months. For those at high risk, investigators note that guidelines have recommended systemic high-dose methotrexate as a preventive measure, although evidence has been limited to small retrospective studies, with some studies demonstrating no benefit on curbing CNS involvement.

"The potential for high-dose methotrexate to be associated with significant toxicity and delays of R-CHOP chemotherapy which may compromise systemic control, further evaluation of the role of HDMTX in mitigating the risk of CNS recurrence is warranted," the investigators said. R-CHOP refers to the combination of rituximab (Rituxan), cyclophosphamide, doxorubicin hydrochloride (Hydroxydaunomycin), vincristine sulfate (Oncovin), and prednisone.

Seeking to further investigate the preventive efficacy of high-dose methotrexate on CNS relapse in patients with DLBCL, they conducted a retrospective study of 226 patients with newly diagnosed DLBCL and high-risk CNS International Prognostic Index score treated with R-CHOP.

Participants were evaluated for isolated CNS relapse, concomitant CNS and systemic relapse, systemic relapse, and survival outcomes. A total of 66 patients were administered prophylactic HDMTX at a dosage of greater than or equal to 3 g/m² in 81% of cycles, in which this trend tended to be younger, have more extranodal involvement, and have lymphoma involving the breast.

Across a median follow-up of 20 months overall (range, 10 months to 8 years), 24 isolated CNS relapses, 10 concomitant CNS-systemic relapses, and 43 systemic relapses were identified.

Compared with patients given standard R-CHOP chemotherapy, those administered HDMTX were associated with significantly lower 3-year risk of isolated CNS relapse (14.6% vs 3.1%; P = .032). Furthermore, among propensity score-matched patients (n = 102), HDMTX was associated with a significant 94% lower risk of isolated CNS relapse than the control group (HR, 0.06; 95% CI, 0.004–0.946; P = .046).

Conversely, concomitant CNS-systemic relapse rates and systemic relapse rates were not significantly different between both groups. For survival, 3-year progression-free survival (PFS) and overall survival (OS) rates were improved in patients given HDMTX compared with R-CHOP chemotherapy, but multivariable analysis findings were also not significant (PFS: 66% vs 58%; P = .05; OS: 69.1% vs 63.2%; P = .07).

HDMTX was indicated to be well tolerated with manageable toxicities when given at a dose of 3 g/m² by day 3 of R-CHOP chemotherapy.

"Our study suggests that effective prophylaxis against isolated CNS relapse can be provided with high-dose methotrexate in a high-risk cohort, possibly by treating occult microscopic disease or preventing dissemination during primary therapy," the investigators concluded. "Further investigation is necessary to better define the group of patients who will benefit from high-dose methotrexate prophylaxis, and the optimal dose and timing, while minimizing potential toxicities."

REFERENCE

Review Determines Cost-effectiveness of Precision Diagnostic Testing in NSCLC

A SYSTEMATIC REVIEW of available literature was conducted to determine the cost-effectiveness of precision diagnostic testing (PDT) for precision medicine in non–small cell lung cancer (NSCLC).

The analysis included 64 cost-effectiveness analysis scenarios across more than 30 studies between 2009 and 2019, approximately half (53%) of which determined PDT to be cost-effective. When the researchers compared PDT-guided therapy with a treat-all-patients approach, all tested scenarios suggested that PDT was cost-effective.

Among the scenarios were those that compared therapy guided by PDT with nonguided therapy (*EGFR*- and PD-L1-guided treatment), those that compared PDT-guided therapy with chemotherapy alone (anaplastic lymphoma kinase-, *EGFR*-, and PD-L1-guided treatment), and those that compared PDT-guided treatment with chemotherapy alone while varying the PDT approach.

The life-years gained or quality-adjusted life-years gained with *EGFR*-directed therapy were more pronounced in Asian studies compared with North Amer-
MHC-II May Be Predictor of Immunotherapy Response in HR+, Triple-Negative Breast Cancers

A BIOMARKER USED TO PREDICT response to immunotherapy for patients with melanoma could also prove useful in patients with breast cancer, suggests new research, which showed that major histocompatibility complex class II (MHC-II) protein may be a predictor of response for 2 types of breast cancer, including a particularly difficult-to-treat form of the disease.

Samples from hundreds of patients with breast cancer were analyzed, and investigators found that MHC-II was expressed in 15% of primary triple-negative breast cancer (TNBC) samples and 19% of hormone receptor-positive (HR+) samples.

“These findings are particularly exciting for us, because if validated, they could provide a way to personalize therapy for breast cancer patients,” senior investigator Justin Balko, PharmD, PhD, associate professor of medicine and pathology, microbiology, and immunology at Vanderbilt University Medical Center, said in a statement. “So far, the typical biomarkers like PD-L1 expression and the numbers of immune cells in the tumor have not done a good job of identifying patients who need immunotherapy.”

The investigators believe the tissue-based study is the first to demonstrate the potential use of MHC-II as a predictor of immunotherapy response in these patients. If further studies prove MHC-II to be a reliable marker for response to immunotherapy, testing for the molecule could help determine which patients do not need to receive immunotherapy, preventing possible treatment complications and added costs, the investigators explained.

Throughout their assessment, the investigators found that the presence of MHC-II on the tumor cells was predictive of response to durvalumab (Imfinzi) in combination with neoadjuvant chemotherapy (NAC) and pembrolizumab (Keytruda) in combination with NAC. Notably, it was not predictive of response to NAC alone.

“The predefined cut point of 5% used in melanoma proved to be useful for breast cancer in the neoadjuvant setting,” the investigators wrote. “In the KEYNOTE-522 study, the addition of pembrolizumab to NAC yielded an improvement in [pathologic complete response (pCR)] rate from 54.9% to 68.9%, or a 14% change, while in the IMPassion031 trial, the addition of atezolizumab [Tecentriq] improved pCR rates from 41% to 58%, or a 17% change. Thus, in a biomarker assessment of immunotherapy benefit in a single-arm trial, approximately 20% to 30% of responding patients should be identified by the biomarker (sensitivity), while most biomarker-negative patients should be predicted to have PD (specificity). The 5% cut point approximated these sensitivity and specificity values.”

“These findings are particularly exciting for us because if validated, they could provide a better way to personalize therapy for breast cancer patients.”

—Justin Balko, PharmD, PhD, Vanderbilt University Medical Center

With MHC-II having shown predictive benefit in melanoma, Hodgkin lymphoma, and now potentially breast cancer, the investigators suggest the molecule could prove to be a pan-cancer biomarker for predicting response to immunotherapies.

REFERENCE

MANAGED CARE UPDATES

ACCC Survey Reveals Biggest Challenges and Concerns Regarding IO Therapies

DESPITE THE COVID-19 PANDEMIC, there was a 22% increase in the amount of actively investigated immuno-oncology (IO) agents since 2019, according to an annual report from the Association of Community Cancer Centers (ACCC).

The 2020 IO Census Survey invited respondents to share their thoughts on barriers to IO treatments, top priorities, and difficulties with providing and managing treatment regimens for patients that arose during the pandemic. “Remarkably, the world of IO is shifting once again in ways that will demand ongoing education to ensure providers stay on the cutting edge of care,” the authors wrote.

Immunotherapies have the potential to improve patient outcomes by allowing them to continue to live their daily lives thanks to short treatment durations. The development of new IO therapies has grown significantly since 2011 and by August 2020, there were 4720 IO agents and 504 targets being investigated in more than 6000 ongoing clinical trials.

Currently, there are more than 60 approved IO therapy indications and more than 800 trials that are evaluating the effects of chimeric antigen receptor T-cell...
Disparities Persist in the Long Term for 5-Year AYA Survivors of Hodgkin Lymphoma

DECADES AFTER ADOLESCENTS and young adults (AYAs) survive Hodgkin lymphoma (HL), racial, ethnic, and socioeconomic status (SES) disparities continue to exist, according to a study published in Cancer Epidemiology, Biomarkers & Prevention.

Previous studies have focused on early survival, but this new study looked at 5-year survivors with an extended follow-up for up to 30 years. The overall cancer incidence in AYAs is increasing, but so are the cure rates, and there is growing research on the long-term mortality outcomes among these survivors.

“As the AYA cancer survivor population continues to grow, more data are needed on long-term outcomes, specifically factors associated with inferior long-term survival,” the investigators explained.

They characterized long-term mortality patterns using data from the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2011. The analysis included 15,899 patients with HL who survived 5 years after their initial diagnosis.

The median age of diagnosis was 27 years, and the follow-up after 5-year survival was 9.4 years. The overall mortality rate was 11%, but the rate varied widely depending on when an individual received their diagnosis: 30% in the 1980s, 13% in the 1990s, and 5% in the 2000s.

Half of the cohort was female; 10%, non-Hispanic Black; 12%, Hispanic; 4%, were non-Hispanic Asian or Pacific Islander; and 74%, non-Hispanic White. Non-Hispanic Black survivors had worse long-term survival compared with non-Hispanic White survivors. Their survival rate was 66% that of non-Hispanic White survivors.

Although all groups saw an improvement in survival from the 1980s to the 2000s, non-Hispanic White survivors who received their diagnosis in the 2000s had survival times almost 3 times as long as those who received their diagnosis in the 1980s. In comparison, non-Hispanic Black and Hispanic survivors with a diagnosis in the 2000s had survival times that were nearly twice the survival time as those with a diagnosis in the 1980s.

“Structural racism is also likely to be contributing to the persistent racial/ethnic disparities seen in the current study, particularly as it relates to health care access and SES disparities,” the investigators wrote. As SES declined, so did survival time. Each additional unit increase on the count of socioeconomic deprivation index, in which a higher value indicates lower SES, was associated with an 8% reduction in survival time. However, only survivors who received a diagnosis in the 1980s had a difference in long-term survival by SES level. There were no significant differences for survivors who received diagnoses in the 1990s or 2000s.

The researchers also found the following:

- Each additional year of age at diagnosis was associated with a 4% reduction in survival time.
- Rurality had no significant effect on long-term survival.
- Female survivors had a significantly longer survival time. Male had a survival rate that was only 68% of females’ survival time.
- Survival for both male and survivors improved over time.
- High stage at diagnosis was associated with worse long-term survival.

Treatment-related modifications have benefited the overall HL population and led to improved outcomes, but there needs to be a better understanding of why racial, ethnic, SES, and sex disparities persist in the long term, the investigators said.

“With improved cure rates for AYAs with HL, additional attention is needed to improve long-term outcomes for specific high-risk populations,” they wrote.
CONSIDERATIONS FOR PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

PSMA: A POTENTIAL PHENOTYPIC BIOMARKER IN PROSTATE CANCER

PSMA may bring the potential of phenotypic precision medicine to the mCRPC population

• Highly expressed in >80% of men with advanced prostate cancer
• Can be detected noninvasively by PSMA-targeted PET/CT imaging, which has shown high sensitivity and specificity in detecting tumor lesions
• Is a potential therapeutic target associated with oncogenic signaling pathways that promote cell proliferation, cell survival, and angiogenesis

*Clinical significance has not been established and research is ongoing.

References

BIO Attorneys Address Patent Thicket Misconceptions

TONY HAGEN

PATENTS PROTECT intellectual property rights, especially in the realm of biologics, but is the level of patenting and patent litigation excessive and obstructive?

Two members of the Biotechnology Innovation Organization (BIO), a large trade group of pharmaceutical companies, argue that this is not the case. Basing their arguments in part on recent research into biosimilar litigation, Hans Sauer, deputy general counsel, and Melissa Brand, former assistant general counsel for Intellectual Property, contend that patents in general are not holding up biosimilar competition (FIGURE).

There are 2 primary reasons for this, they argue. First, in the majority of biosimilar patent litigations, the number of patents under contention is relatively small, according to their research. Second, there are many different types of patents, and of these, only a handful may represent roadblocks that could lead to litigation or costly settlements.

There have been some high-profile litigations since the first US biosimilar was approved in 2015 (Zarxio), but since that time, 30 biosimilars have been approved and 21 have been marketed, or "launched." Patent portfolios for 2 originator drugs in particular, adalimumab (Humira; AbbVie) and etanercept (Enbrel; Amgen), have stalled the marketing of 9 biosimilars of these agents. "One thing that characterizes this debate is that it's very anecdotal," Sauer said in an interview with The Center for Biosimilars®. "Discussions about patenting practices in the biologics space and how they affect biosimilar market entry usually focus on 1 drug for the most part, and we know which one that is." Sauer was referring to Humira, which has at least 136 patents on adalimumab.¹ These have played a role in stalling competition until 2023 in the US market and enabled AbbVie to generate over $170 billion in Humira revenues worldwide.² This product is very much the exception, Sauer and Brand said. Not counting ongoing US market exclusivity for Humira and the etanercept originator, 21 biosimilars have launched referencing 8 other originator products.³ And for 20 of these biosimilars, the median time to launch post approval was 6.2 months vs 13 to 14 months for generics approved between 2010 and 2014, according to BIO research. "What we thought would be healthy for this debate was to look at what we know from the empirical literature about these patterns, and it paints a picture that I think is somewhere in between different narratives that we're hearing," Sauer said.

The Truth About Patent Thickets

It may be true that large "patent thickets" protect the innovations that went into developing and producing some of these originator biologics, but only select patents play a significant role in determining whether a competitor can bring a biosimilar to market, Brand said. "The size of a patent portfolio doesn't mean that those are the patents that actually matter for resolving disputes between an innovator and a biosimilar company," she said. "Actually, if you look at the Humira litigations, there were only 18 patents asserted and litigated," out of as many as 60 AbbVie identified as potentially being infringed. "The average number of patents asserted in any [Biologics Price Competition and Innovation Act] litigation was 12, and that is not out of line when you talk about other complex patent technological cases," Brand said.

A launch half a year after FDA approval is not bad, Sauer and Brand said. "It's not like these products are getting approved and just sitting there. They're actually launching pretty quickly, and they're launching 'at risk,'" meaning there is a chance of further litigation with the originator company once the biosimilars are on the market, Brand said. This suggests confidence on the part of biosimilar companies that the patents are not the obstacles they are made out to be.

Of course, these data exclude anomalies that would skew the averages quite a bit. For example, there are 6 biosimilars approved for adalimumab in the United States, and these were approved from September 2016 to July 2020, and none of them will come to market until 2023 according to settlements with AbbVie. For the earliest approved of these biosimilars, that represents a 7-year delay from FDA approval.

In the case of etanercept, an Amgen product, 2 biosimilars were approved, one in 2016 and the other in 2019, and yet no launch date has been announced for either. Both have faced patent litigation from Amgen.

FIGURE. Biosimilar Patent Litigation Often Does Not Delay Product Launch

- Roughly 75% of approved US biosimilars were litigated. In most cases, the originator company sought damages but not to prevent biosimilar launch.
- From 2014 to 2020, 9 of 28 approved biosimilars (32%) were launched “at risk,” meaning patent disputes had not been resolved by that time.
- Historically, just 1% of generics have been launched at risk.
- Most PTAB challenges to originator company patents (90%) are filed before a biosimilar company files a biosimilar approval application.
- Most (80%) of these challenges concern method of use (indication) and drug product (formulation) patents.
- At the BPCIA stage, most litigated patents (59%) concern manufacturing process.

Source: Biotechnology Innovation Organization
BPCIA, Biologics Price Competition and Innovation Act; PTAB, Patent Trial and Appeal Board.
According to BIO, 59% of patents “asserted” by originator companies in litigation are manufacturing process patents, 23% have to do with product indications, and 9% with formulation, according to BIO research. “There’s this notion that there are these giant patent portfolios out there that people can’t get through. That doesn’t really align with the fact that biosimilar companies are launching at risk. If they had this overwhelming fear that they’re going to get sued on all these patents, they probably wouldn’t be doing that,” Brand said.

Strength of Patent Protection Varies by Patent Type
When it comes to patent litigation and biosimilars, the type of patent warrants close inspection, according to Sauer and Brand. Some patents constitute bigger obstacles than others, said Sauer. In the portfolio of patents amassed by biologics originator companies, the “vast majority of these are manufacturing patents, about 75% of them,” Brand said. “It’s a little bit different when you’re talking about a manufacturing patent as opposed to a composition patent. If it’s a patent on the molecule, it’s usually thought that it’s harder to get around that type of patent.”

Manufacturing technology is not that restrictive. There are alternatives to using the most modern processes or equipment, or a resourceful company can simply design around a manufacturing innovation that is not available for licensing, Sauer and Brand said.

According to BIO, across 28 patent litigations involving 21 biosimilars, 125 patents were asserted by originator companies, meaning that of all the patents identified as being potentially infringed by the proposed biosimilar, just 125 were the subject of litigation. Of those, about 63% were asserted more than once.

“Most manufacturers, if they were pressed, would say, ‘We have a lot of patents around this technology, but which ones are going to be relevant? We’ll only know once we see the biosimilar and once we understand how the biosimilar is proposed to be made,’ ” Sauer said.

Does Patent Portfolio Size Matter?
“Regarding the size of a patent portfolio, it’s hard to say how relevant that is,” he added. “What matters is how many patents cover whatever the biosimilar entrant might want to do.”

A common complaint about originator companies is their tendency to continue filing for patent protections long after their biologics have been approved by the FDA. The patents they acquire for an individual product can be separated into “patent families” and may concern manufacturing processes, dosing regimens, or formulations, among others. Effectively, they add to the cost and complexity of bringing a biosimilar to market.

About 70% of patents that have been asserted in biosimilar litigation were filed after the originator product was approved for marketing, according to BIO. Most of the patent applications filed after the originator product approval concerned manufacturing technology (76% vs 53% filed prior to FDA approval). In second place were indication patents (21% vs 19% filed prior to FDA approval). Formulation and composition patent filings after originator approval each amount to 1% of total patent filings vs 15% and 13%, respectively, before approval.

“From the perspective of the biosimilar maker, maybe the thing that’s most important to them is to have advance notice of the kinds of patents they may be dealing with when they still have flexibility to design their manufacturing processes,” Sauer said. Almost half of the biosimilars currently on the market launched “at risk” of litigation over alleged patent infringements, but none of those ended up being taken off the market, Sauer said. At some point the biosimilar developer is going to take a calculated risk to get the biosimilar onto market based on their own assessment of what the costs from failed litigation might be vs the revenue potential, he said. One of the things that Brand has noticed from her research is that many litigations are about compensation and not about blocking market entry. “There were very few instances of anybody moving for an injunction” to stop a biosimilar from being marketed, she said. “That might tell you something about the patents that are being litigated as well.”

An originator company that wants to defend against potential biosimilar competition will want to spend its legal dollars wisely, Sauer and Brand said. In AbbVie’s court cases over the originator product Humira (adalimumab), the number of patents litigated, or “asserted,” are a fraction of the patents that AbbVie has implied might be infringed by biosimilar competition.

REFERENCES

O C T O B E R  2 0 2 1  |  A J M C . C O M  |  S P 2 8 1
Building a Patient-Centered Cancer Center From the Ground Up

MARY CAFFREY

Continued From Cover

Libutti arrived after a period of transition following 2012 legislation that overhauled higher education governance and made the institute part of Rutgers University. At the time, restructuring was controversial, and some faculty left. Then part of the Robert Wood Johnson Medical School, CINJ already was producing world-class scientific results and collaborating with the state’s pharmaceutical sector on clinical trials.

Four years after Libutti’s arrival, predictions that reorganization could help make Rutgers CINJ a “powerhouse” appear to be coming true. Libutti has expanded the reach of the National Cancer Institute designation to cover the entire state as he has laid the groundwork for greater integration between the research and clinical programs and construction of a cancer center designed with patient experience as the focal point.

Patient experience is not a buzzword. Consumers increasingly select where they receive care based on experience ratings and patient reviews, and CMS’ patient experience ratings also factor into reimbursement. Therefore, getting patients to stay in New Jersey for cancer care is not enough, Libutti said.

When a patient arrives at Rutgers CINJ, every phase of treatment—including survivorship care—should be delivered seamlessly, he said. All treatment soon will be offered under one roof, without the need to cross town or change services. A bridge will connect the existing cancer center and hospital to the new pavilion. The relationship with the state’s largest health system will mean better coordination during emergencies, he continued.

“Having an integrated oncology service line across the many hospitals and facilities of RWJBarnabas Health (will mean) that even if a patient needs that kind of additional care, such as a visit to an emergency room hopefully they’re no more than 15 or 20 minutes away,” he said. “And now, you’re showing up in an emergency room in New Jersey. As is often the case, when there’s a side effect, if it’s a Saturday or it’s 10 o’clock on a Friday night, tracking down your physician or your records at a distant place is a challenge.”

Doctors, Patients Give Input Into Design

Designed by HOK Healthcare, the Jack and Sheryl Morris Cancer Center will cover 310,000 square feet and have 84 infusion bays, which will increase capacity by one-third; the number of examination rooms will double to 74. There will be 96 inpatient beds on 3 floors, a dedicated floor for surgical and procedure rooms, wet-lab spaces for 10 research teams, and faculty offices. Advanced radiology services, diagnostic laboratories and equipment, a pharmacy, outpatient urgent care, and inpatient support spaces will be available in 1 location. Libutti is excited that existing services, such as a weekly tumor board that has met for years, will be able to better coordinate with other activities.

“The way I like to describe it is, rather than the patients going from doctor to doctor in a linear fashion, I think of the patient in the center of the lazy Susan [turntable] with all the physicians and necessary activities they have to undergo to get to a good diagnosis or to follow along during their care sort of circling around them,” he said. “And the patient is really the centerpiece of our care paradigm.”

Libutti worked closely with the developer, New Brunswick Development Corporation (DEVCO). Led by its president, Christopher J. Paladino, and its executive vice president, Sarah F. Clarke, DEVCO has reshaped the area in and around Rutgers’ New Brunswick campus, adding structures that include the honors college, New Brunswick’s performing arts center, and a hotel and conference center. The cancer center will stand out in the New Brunswick skyline and feature both indoor and outdoor common areas.

In an interview, Paladino said, “We’re really focused on making sure the public spaces are inviting, [that] they’re warm…. As Dr Libutti described it, he wants the building to give everyone who walks in a virtual hug.”

The public might overlook the 25-foot-deep basement or the pavilion’s self-contained power plant, but these features will be achievements on their own. Clarke explained how sequencing will allow use of the garage to store materials as the tower is built. The deep basement will allow radiology services to be housed safely below ground; an earlier concept would have required above-ground concrete reinforcement. To avoid a feeling of darkness, the building will have a 4-story lobby that extends underground to allow natural light into the space.

Every project DEVCO completes offers insight into how people move through spaces, Paladino said. To design a cancer center, Libutti and the development team went straight to the sources as they conducted charrettes that included physicians of different specialties, nurses, support staff, former patients, and caregivers. The groups initially received an early design overview from the architect, and then they went to work with markers and Post-It notes in hand.

“The natural thing was for this to turn into a ‘bitch’ session,” Paladino said, “but it very quickly became a ‘what if?’ session.” Paladino estimated that approximately 50 modifications came from this process, allowing the development team to catch problems early on. For example, Clarke has the gift of being able to identify materials that won’t last and finding aesthetically pleasing substitutes.

Paladino credits Libutti for his attention to the infusion center design, which went through multiple revisions until the team achieved the right balance of “privacy and openness.”

Paladino brings personal experience to this project. His wife was treated for breast cancer many years ago, and the atmosphere of an infusion center remains familiar. “You get used to seeing certain people on your schedule. There was some level of camaraderie.” But on other days, patients don’t want company; rather than hanging curtains to give patients privacy, the Rutgers team decided that half walls with glass doors that open and close would be built.

As the pavilion rises, the team that will work in the new center continues to grow. Several high-profile hires have been announced, including Missak Haigenz Jr. MD, as chief of thoracic medical oncology and of head and neck medical oncology and clinical director for oncology integration; the latter role involves promoting patient safety and efficiency and improving value-based care, including screening and preventive services.

This integration will build upon what Libutti says is the center’s the team-based approach. “We have multidisciplinary teams focused on breast cancer, lung cancer, colon cancer, pancreas cancer, etc.,” he said. “In terms of other specialists that are necessary in the context of caring for these patients, whether it be the appropriate diagnosis or providing supportive care, we have experts from a variety of disciplines, whether it be gastroenterologists, pathologists, or radiologists that all work together with our teams. That’s happening now and will continue to happen in the new cancer center.”

The Evidence for Staying Close to Home

From the groundbreaking to the visit with Libutti, the phrase repeated is, “Cancer doesn’t travel well.” The aim to keep patients “15 to 20 minutes” from home is not arbitrary. Some patients will still seek cancer management in medical centers with greater fame in New York City, even though the burdens of travel are being recognized in the literature. Longer travel times to a cancer center also may pose unanticipated consequences for payers:

• For patients with pancreatic cancer, traveling more than 12.5 miles after surgery has been associated with worse overall survival.
• Longer travel distance and insurance status helped determine which patients being treated for breast cancer were more likely to have contralateral prophylactic mastectomy;
Black and Hispanic patients were at particular risk.  
  • In a study of Medicare beneficiaries given a diagnosis of cancer, Medicare spending was 14% higher and patient cost responsibility was 10% greater among those traveling longer than 1 hour to a cancer center than for those having a travel time of 30 minutes or less. Shorter travel times were related to higher hospitalization rates in the initial management stage, whereas longer travel times were related to a greater likelihood of hospitalization at the end of life.  
  • Studies of patients with colorectal cancer and of surgery for prostate cancer found that longer travel times were associated with longer hospital stays.  

Libutti said the issue of what excess travel does to patients with cancer is an area ripe for further study. “First off, there’s the expense….for chemotherapy or radiation therapy, these are multiple visits a week and, certainly, many times per month in terms of travel,” he said. “That’s an expense not only in dollar expense for the travel itself, but time away from family, time away from work—you have a support system that’s critically important as you’re going through a cancer diagnosis. And that support system is turned upside down or at least on its side when you have to get your care at a distance.”  

The realization that some patients from New Jersey need to drive 2 hours each way to New York City for every cancer treatment became real for Paladino and his wife when a traffic accident turned their typical 40-minute ride from their home outside Princeton into a trek spanning more than 2 hours.  

As they reached valet parking for the appointment, Paladino said, he related his wife’s saying, “Just imagine if we had to do that every time.” And that really struck home with me.”

**REFERENCES**
All of this points to the need to reduce disparities, and quickly. But how? The ASCO authors found plenty of inertia in health care. Evidence-Based Oncology® gathered input from a group of health care leaders, from within and beyond the cancer community, and asked: How can we cancer disparities be reduced now? Specifically, the leaders were asked to discuss ideas that could be put into action in a 2-year time frame.

Reduce disparities by leveraging lessons of telemedicine
AccessHope is a program that allows patients and community oncologists to tap into the expertise of City of Hope, often through electronic sharing of records so the patient does not have to travel.11 Todd M. Sachs, MD, called for increased education within the care delivery system, especially for patients. "That means getting out to various people where they live, where they work, where they spend their time," he explained.

The increased use of telemedicine could also reduce disparities—COVID-19 revealed the potential for technology, Sachs noted. "We started to get to where people live, where they are," he said.

Since the pandemic began, hospitals have developed better protocols to ensure safety, Sachs said, but the risk is that the advantages seen with telemedicine could be lost. "I don't want us to lose all that we gained by using telemedicine," he said. With AccessHope, "we're providing this high level of expertise and knowledge from physicians in Los Angeles to people who may not live in Los Angeles proper, who may live in South Dakota in a very rural area, or in Kansas in a rural area and are not able to be treated at a national cancer institute," he said.

Technology is also important for sharing information and key to improving quality, another way to reduce disparities in cancer care. "Cancer is different. In the world of cancer, there's so much change for the better," Sachs said. "New treatments, new therapies, new protocols, new research—if you're an oncologist today and you're trying to remember and learn and read all of those changes for over 100 types of cancer, it's too hard to do."

Finally, he said, "we need people to go in and get their preventive care. That would be a big win, and that can happen, ASAP. We don't have to wait 2 years for that."

"There's still a lot of bias that's involved in offering or not offering patients clinical trials, and we need to get training programs into the community to make sure that people understand their biases, so that we can mitigate those biases so that everyone is offered the opportunity to participate."

—Randall A. Oyer, MD, Medical Director, Oncology Program, Penn Medicine Lancaster General Health

The idea, he continued, is this: "As long as 1 person in that exam room knows the best treatment, that's fine—even if that's the patient."

Patient education is important, West said, but it can't consume all of a physician's time. West emphasized, however, that "if you make that information available to patients, they can be unbelievably laserlike-focused on finding the best information available anywhere."

Include the family health expert in all key discussions
Mesa emphasized the importance of working to achieve more effective and equitable clinical trial access as a means of improving health care access and quality. He brought attention to the need for...
inclusive research. “The key goal is, do the innovations going on in your clinical trials reflect the people in your city and region, I mean—the people you’re serving?” We all recognize that there’s tremendous diversity within diversity."

In addition to having representative demographics in a trial, Mesa also pointed out the need to understand the diversity found within diverse groups, saying, “We clearly have learned and are studying the great differences among even Latino populations. There are differences between individuals who have migrated from Mexico recently (and) individuals who are of Mexican heritage, but their families have been in the states for a long period of time; individuals from the Caribbean, people like me who are Cuban, (or individuals from) South America. So, there’s a lot of diversity, and there’s diversity as it relates to genetics, culture, and other parts.”

Those who run clinical trials must also address “logistics, access, sometimes transportation, sometimes other barriers,” he said. “The intensity of participating in the trial, in terms of time away from work” can affect who ends up participating, Mesa explained. If the trial schedule “makes it much more difficult to be able to leave work, to be allowed to leave work, or to not paid for leaving work, that can really influence things,” he said.

Another focus of Mesa’s is improving health literacy and trust in patient communities. One method Mesa said has been helpful with patients with cancer in south Texas is to include the family health expert in key discussions. This could be a family member employed in health care, anyone “from a phlebotomist at a local hospital to a phar- macy technician at CVS, or a physician or a nurse,” he said. This is a person the family trusts to discuss treatment options, including clinical trials.

SACHIN H. JAIN, MD, MBA, FACP
President and CEO, SCAN Group and SCAN Health Plan
Long Beach, California

Uncover barriers to care and underlying causes to health issues
Sachin H. Jain, MD, MBA, FACP, is a pioneer at finding the root causes of why individuals use too much unnecessary health care—such as hospitalizations—and coming up with better ways to pay for care individuals really need. Before the COVID-19 pandemic, when he worked for CareMore, Jain created programs to treat loneliness as a health issue.14

These days, he’s taking on homelessness by working on a payment model to address a crisis that has exploded in California,15 where he’s been based since 2015.

“We have a lot of unnecessary health care utilization that’s driven by poorly managed chronic disease. And if you actually apply that frame to multiple different populations, you find key areas where you can improve health care outcomes and reduce overall health care spending and utilization.”

—Sachin H. Jain, MD, MBA, FACP, President and CEO, SCAN Group and SCAN Health Plan

Doing so requires moving away from a fee-for-service model. “We actually have lots of data on who the so-called rising-risk or high-risk patients are, but the capacity in the health care system to actually act on those high-risk or rising-risk patients is low because of how we pay for care—and because of how we actually structured and organized care delivery. Because we largely have a fee-for-service chassis, we mostly take care of people when they have problems, as opposed to paying significantly for upstream management and prevention.”

When asked how soon this move away from fee-for-service care delivery could be applied, Jain said, “I see medical groups in California—and, really, all over the country—that are starting to embrace this way of thinking about patient care. And they’re changing how they work as a result of changes and how they’ve decided to get paid by third-party payers.”

Jain warns that the transition brings a measure of risk. “There is an opportunity to simultaneously improve the quality of care, but there’s also potential an erosion of the quality of care if we don’t manage that carefully,” he said.

Conclusion
Discussions with each expert confirmed that the United States still has a long way to go to achieve equity in health care. Hospitals, health care systems, and clinical trials have not fully addressed the historic barriers to access or the social factors that produce uneven outcomes. Yet, as the interviews showed, solutions are possible. Each one proposed ideas based on concrete and successful plans that have been implemented, including strategies the interviewees had used in their own fields. Although the pandemic has raised the visibility of how unequally health care is delivered, it has also been a catalyst for many providers to offer increasingly creative solutions that more effectively address disparities. As such, it is important to seize this moment and move forward with a renewed sense of urgency so that the momentum can lead to effective and sustainable transformation of how care is delivered. 

REFERENCES
Dr David S. Hong: We Are Learning Every Day About Cellular Therapies

MAGGIE L. SHAW

CONTINUED FROM COVER

In an update presented at European Society for Medical Oncology 2021 Congress, from the phase 1/2 dose-escalation trial examining gavo-cel, data were presented on 17 patients evaluated for safety—12 with malignant mesothelioma, 4 with ovarian cancer, and 1 with cholangiocarcinoma—all of whom again received a single IV gavo-cel infusion (16 patients were evaluated for efficacy). Results were still robust for both measures, but lower: 92% and 24%, respectively.¹

In an interview with Evidence-Based Oncology™ (EBO), lead author David S. Hong, MD, professor and deputy director, Department of Investigational Cancer Therapeutics, and associate vice president of clinical research, The University of Texas MD Anderson Cancer Center, discussed these newest data, why mesothelin is such an attractive target for precision treatment, and next steps in the gavo-cel investigation.

This interview has been edited slightly for conciseness and clarity.

EBO: Phase 1 data on gavo-cel were presented in April at the AACR annual meeting. With this interim update of phase 1/2 data presented at ESMO Congress 2021, will you tell us about the dose-escalation results you have seen and how they build on previous findings?

HONG: A couple of things. This is an expansion of what we presented in April—we now have 16 evaluable patients on the trial—at that time, the overall response rate was about 50%. The overall investigator response rate now, by the independent group, is around 38% have a confirmed response rate. So, some difference. We expect that there's going to be some decrease in the actual response rate as you expand these studies, but still a very robust response rate in this really heavily pretreated patient population of mesothelioma, ovarian cancer, and cholangiocarcinoma. The overall toxicity profile has not really significantly changed from what we saw in April. Overall, it's a very encouraging study. We'll see as we go into the expansion, and see more patients, if we can maintain that really robust response rate. We're really encouraged by that.

EBO: Can you explain the process behind delivering gavo-cel, particularly the use of an antimesothelin antibody lentiviral vector, as well as why lentiviral vectors are an appropriate vehicle for anticancer gene therapies?

HONG: I think mesothelin is a unique target. There are very few antigens that you can target, independent of human leukocyte antigens, that are, to a large extent, expressed on tumors and have very or limited expression on normal tissue. We know that mesothelin is highly expressed, obviously in malignant mesothelioma, but it's also expressed in a number of very common tumor types: NSCLC, cholangiocarcinoma, and ovarian cancer. Even to some extent, pancreatic cancer. So I think that was the reason that they used mesothelin as a target.

Gavo-cel is a unique platform. CAR Ts [chimeric antigen receptor T cells], in and of themselves, have not shown a whole lot of activity in solid tumors. We obviously know the success of CD19-based cellular therapies and CAR T in lymphomas and leukemias, but if you look at some of the cellular therapies that have been in existence for many, many years, CAR Ts have not been gangbusters. There's not an approved cellular therapy right now in solid tumors. But TCRs [T-cell receptors] seem to have more robust activity in solid tumors, and there's a lot of different reasons for that.

Gavo-cel—and TCR Therapeutics—is trying to take the advantage of TCRs, relatives of CAR Ts. They reengineer these T cells, really to bind the epsilon chain of these TCR receptors that then can be called HLA independent yet bind mesothelin, which is damaged and obviously that is overexpressed in a lot of tumors.

Why lentiviral vectors? I think, to a large extent, partly because that technology has probably been validated most with many of the different ways that we are constructing these platforms with these cellular therapies. That's been just the most straightforward way to do it. I know there are other technologies trying to look at that, but I think that's to a large extent why that's been implemented: because it's been something that's been proven.

EBO: Is overexpression of mesothelin the singular fact that that contributes to gavo-cel's success against solid tumor or are there other reasons?

HONG: There's a threshold we have to meet for these patients to be on the trial. The numbers are small—16 evaluable patients. The analysis that we've done so far, it's too early for us to tell if you have 100% mesothelin expression, you're going to have a better response than if you had 30% mesothelin expression, for example. That makes sense. But there have been other cellular therapies, other than mesothelin, where the nuances of whether a patient responds, based upon antigen expression, really hasn't panned out. I suspect there are lots of different variables that we're still trying to figure out, whether it's overexpression level, whether these cells persist in the body.

There are probably other factors that we haven't identified that may kind of tweak which patients may actually benefit vs not. I do think that we will figure those things out, that those things will eventually emerge, and maybe even to the point where TCR or any other companies that decide to move into larger phase 3 trials, we'll figure that out. But right now it's not really clear whether or not just expression in itself is the main driver for response.

EBO: How does lymphodepletion contribute to precision oncology treatment success?

HONG: In general, we use lymphodepletion just like we use an autologous bone marrow transplantation: to allow for continued survival in that host body. This trial is interesting. The FDA required the first patient to not get lymphodepletion as we were escalating. And then following that, after a period of time the following patients had to be lymphodepleted. Interestingly enough, we saw some tumor regression independent of lymphodepletion. Clearly, those patients who had had lymphodepletion responded well, and that's probably because the cells were able to evade the natural immune system better with lymphodepletion and were able to persist in the body longer because of lymphodepletion. That's the primary reason why we do lymphodepletion, in general.

EBO: These data also address an additional indication for gavo-cel, in cholangiocarcinoma. What do the 3 solid tumor cancer types...
for which use of gavo-cell is being investigated—mesothelioma and ovarian cancer, as well—have in common that make them appropriate targets for treatment with gavo-cell.

HONG: They all expressed mesothelin. Obviously, mesothelioma is highly expressed in mesothelioma. Interestingly enough, also in ovarian cancer and cholangiocarcinoma—not to the extent that mesothelioma patients have it, but a fairly high percentage of ovarian cancer and cholangiocarcinoma patients have high expression of mesothelin. So that’s to a large extent why we chose those patients. There’s a prescreening process that occurs with all of these patients, and the reason we narrowed this is so that we’re not prescreening 1000 patients and you get 1 patient out of it. You want to prescreen patients that you think are going to have high expression of mesothelin. So that’s why we chose ovarian, cholangiocarcinoma, and mesotheliomas.

EBO: Do patients need to have exhausted all previous treatment options or could gavo-cell eventually be a first-line choice?

HONG: That’s a question that is hard to answer right now. I think, in general, patients who have had less prior therapies will eventually do better with immunotherapy. We know that with checkpoint inhibitors. I think that may pan out for other cellular therapies, too, whether gavo-cell or other patients. Just how drug development works, as you all know, these patients have frontline options that we know have survival benefit; particularly in many of these types of tumors, it’s standard chemotherapy. My guess is that if gavo-cell continues to show this robust response, it’s a high indication that it will likely work in the refractory setting and there’s a good chance it will work as you go up the lines of prior therapy, where at some point we may be able to compare this with standard line therapy.

“My guess is that if gavo-cell continues to show this robust response, it’s a high indication that it will likely work in the refractory setting and there’s a good chance it will work as you go up the lines of prior therapy, where at some point we may be able to compare this with standard line therapy.”
—David S. Hong, MD, The University of Texas MD Anderson Cancer Center

EBO: Will you be looking at gavo-cell in a larger cohort?

HONG: We’re almost at the recommended phase 2 dose. I think we’re going to launch, once we do expansion, an amend to this as a phase 2 portion in each of these different tumor types. There are a number of other combinations that we’re going to look at down the line, whether it’s with checkpoint inhibitors or with other possible combinations that hopefully would augment these cells. I’m sure we’re going to try to present something next year, maybe an update to this, but also maybe share additional data on combinations.

I just want to say that cellular therapy in solid tumors is an exciting area that is eventually going to emerge, like checkpoint inhibitors in solid tumors. The technologies still have a long way to go, but I think what’s exciting is these technologies can be tweaked. We are learning every day. Every patient we put on we try to understand why that patient responded vs not, why those patients have certain toxicities vs not. And I think we’ll learn.

Also, just the people I’ve met, not only at TCR2, but other companies, they are just brilliant. I take care of the patients and help design the clinical trials, but the people who actually developed this technology are some of the brightest people I’ve met. I’m optimistic that we will find that fact these kinds of platforms and these cellular therapies will work in patients and in our cancer patients. And hopefully we’ll be able to scale it so that community physicians and other physicians can give it just like I give it in MD Anderson.

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