In some situations, I’ll have insurance approval within 48 hours….And then there’s other carriers who literally make patients jump through hoops. I think that’s inappropriate for an approved therapy.

Michael R. Bishop, MD
University of Chicago

I think it’s inevitable that [CAR T-cell therapy in second-line] will become the standard of care.

Laurie H. Sehn, MD, MPH
University of British Columbia

As the audience would know, BTK [Bruton tyrosine kinase] inhibitors are associated with atrial fibrillation, and it is very reassuring to see a phase 3 study where the atrial fibrillation rate in the BTK arm is the same as a comparator arm.

Constantine Tam, MBBS, MD
MacCallum Cancer Centre

HIGHLIGHTS FROM THE MEETING

• CAR T IN SECOND LINE FOR LBCL: AXI-CEL IS “NEW STANDARD” WHILE LISO-CEL OFFERS “BREAKTHROUGH,” SP11, SP19.

• POLARIX: A CHEMOTHERAPY STANDARD GETS AN UPDATE IN DLBCL, SP21.

• SEQUOIA: ZANUBRUTINIB DELIVERS FOR TREATMENT-NAÏVE PATIENTS WITH CLL/SLL, SP22.

• LEUKEMIA & LYMPHOMA SOCIETY STUDY FINDS THIRD mRNA VACCINE MAKES A DIFFERENCE FOR PATIENTS WITH BLOOD CANCER, SP28.

• LOCATION, LOCATION, LOCATION: WHERE CLINICAL TRIALS ENROLL PATIENTS AFFECTS DIVERSITY, SP36.

• AN INTERNATIONAL PANEL EXAMINES THE USE OF REAL-WORLD EVIDENCE, SP47-SP48.
LIBTAYO®
(cemiplimab-rwlc)
Injection 350 mg

LIBTAYO works with the immune system to help treat the following types of cancer:

- 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

- For the treatment of patients with metastatic BCC (mBCC) previously treated with an HHI or for whom an HHI is not appropriate. The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit

- 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

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.
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 21% 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 reinstituted 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.
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 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 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–Barre 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.

- **Systemic lupus erythematosus** (SLE). Withhold for severe or fatal SLE and permanently discontinue for Grade 4 SLE. 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.

- **Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection**

- **Pancreatitis** to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

- **Hepatitis** to include increases in liver function test results

- **Renal failure**

- **Hypoglycemia**

- **Diabetes mellitus**

- **Cytopenias**

- **Hypothyroidism**

- **Hyperthyroidism**

- **Hypophysitis**

- **Panniculitis**

- **Drug reaction with eosinophilia and systemic symptoms (DRESS)**

- **Transaminitis**

- **Neutropenia**

- **Lymphadenopathy**

- **Leukopenia**

- **Anemia**

- **Neutropenia**

- **Pancytopenia**

- **Paresthesia**

- **Neurotoxicity**

- **Hypocalcemia**

- **Hypomagnesemia**

- **Hypophosphatemia**

- **Acute renal failure**

- **Chronic renal failure**

- **Hematuria**

- **Hematoma**

- **Nephrotic syndrome**

- **Hemolysis**

- **Obstructive jaundice**

- **Acute liver failure**

- **Acute liver injury**

- **Acute hepatic necrosis**

- **Drug-induced liver injury (DILI)**

- **Sarcoidosis**

- **Nephritis**

- **Hepatitis**

- **Pericarditis**

- **Myocarditis**

- **Cardiac arrest**

- **Myasthenia gravis**

- **Guillain–Barre syndrome**

- **Pancreatitis**

- **Acute respiratory distress syndrome (ARDS)**

- **Pneumonitis**

- **Diabetes mellitus**

- **Insulin-dependent diabetes mellitus**

- **Type 1 diabetes mellitus**

- **Type 2 diabetes mellitus**

- **Hyperglycemia**

- **Hypoglycemia**

- **Hypothyroidism**

- **Hyperthyroidism**

- **Thyroid disorders**

- **Hypophysitis**

- **Hypopituitarism**

- **Hypothyroidism**

- **Hyperthyroidism**

- **Thyroid disorders**

- **Hypophysitis**

- **Hypopituitarism**
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.

Reference: 1. LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing
information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.

©2021 Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.
All rights reserved. LIB.21.05.0007 08/2021

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 350 mg
LIBTAYO® (cemiplimab-rxkz), injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Cutaneous Squamous Cell Carcinoma

LIBTAYO® is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mSCC) or locally advanced SCC (lSCC) 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 (lBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
- with metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for the mBCC indication may be contingent upon verification and description of clinical benefit.

1.3 Non-Small Cell Lung Cancer (NSCLC)

LIBTAYO® is indicated for 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 (see Dosage and Administration (2.2) in the full prescribing information).

1.4 Hypophysitis

Hypophysitis 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 LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

2.1 Adverse Reactions

Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) adverse reactions. Patients treated with LIBTAYO due to hypophysitis had not reached a median duration of treatment with LIBTAYO in 1 (0.1%) patient. 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 hypothyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

Thyroiditis: Thyroiditis occurred in 0.8% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 1 (0.1%) patient.

Systemic corticosteroids were required in 3.8% (31/810) of patients with hypothyroidism. Hypothyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hypothyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

Thyroiditis: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (0.8%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. 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.

Hypothyroidism: Hypothyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.5%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hypothyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (31/810) of patients with hypothyroidism. Hypothyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hypothyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

Hypothyroidism: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (0.8%) adverse reactions. No patient discontinued treatment due to hypothyroidism. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. Thyroiditis had not resolved in any patient at the time of data cutoff.

Two patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hypothyroidism.

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent.

TABLE 2: Adverse Reactions in ≥10% of Patients

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

TABLE 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥10% of Patients

Table 3 summarizes the laboratory abnormalities that worsened from baseline to Grade 3 or 4 in ≥10% of patients.

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

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-L1-PD-1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6. ADVERSE REACTIONS

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

- Severe and Fetal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Immuno-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allelic Loss [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 multicenter study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 194 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=225), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 37% were exposed for ≥ 26 months and 25% 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, hypoglycemia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.


<table>
<thead>
<tr>
<th>Table 2: Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Abnormality</strong></td>
</tr>
<tr>
<td>Chemistry</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
</tr>
<tr>
<td>Increased ALT</td>
</tr>
<tr>
<td>Hematology</td>
</tr>
<tr>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Electrolytes</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
</tr>
<tr>
<td>Hypocalcemia</td>
</tr>
</tbody>
</table>

Toxicity grade per NCI CTCAE v. 4.03

- Grade 1: 0-19%
- Grade 2: 20-49%
- Grade 3: 50-99%
- Grade 4: >100%

The safety of LIBTAYO was evaluated in 132 patients with advanced BCC (mBCC N=48, laBCC N=84) in one open-label, single-arm trial (Study 1620) [see Clinical Studies (14.2) in the full prescribing information].

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

- Complications of Allelic Loss
- Immuno-Related Reactions
- Severe and Fetal Immune-Mediated Adverse Reactions

Table 4 summarizes 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 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

- **Chemistry**: Increased aspartate aminotransferase (2%), increased ALT (2%), lymphopenia (9%), anemia (5%), hypokalemia (4%), hypocalcemia (2%).
- **Hematology**: Lymphopenia (9%) and anemia (5%).
- **Electrolytes**: Hypokalemia (4%) and hypocalcemia (2%).

Adverse Reactions LIBTAYO

<table>
<thead>
<tr>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility</td>
<td>49</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>33</td>
</tr>
<tr>
<td>Respiratory system disorders</td>
<td>22</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>20</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>14</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>13</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>12</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>11</td>
</tr>
</tbody>
</table>

Adverse Reactions in a 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>34</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td>31</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td>24</td>
</tr>
<tr>
<td>Arthritis</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory</td>
<td>14</td>
</tr>
<tr>
<td>Hematologic</td>
<td>11</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>10</td>
</tr>
<tr>
<td>Endocrine</td>
<td>10</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td>10</td>
</tr>
</tbody>
</table>

Adverse Reactions LIBTAYO

- **Fertility**: 49 (3.8%)
- **Musculoskeletal and Connective Tissue Disorders**: 33 (1.5%)
- **Respiratory System Disorders**: 22 (0.8%)
- **Skin and Subcutaneous Tissue Disorders**: 20 (0.8%)
- **Metabolism and Nutrition Disorders**: 14 (1.5%)
- **Blood and Lymphatic System Disorders**: 13 (0.8%)
- **Nervous System Disorders**: 12 (1.5%)
- **Endocrine Disorders**: 11 (2.3%)
- **Vascular Disorders**: 11 (4.5%)

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

- Grade 1: 0-19%
- Grade 2: 20-49%
- Grade 3: 50-99%
- Grade 4: >100%

The most common Grade 3 or 4 adverse reactions (≥2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hypoglycemia, and visual impairment. The most common (>3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia.
Table 6:  Adverse Reactions in at least 2% of patients receiving LIBTAYO.

Adverse Reactions

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>3.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.5</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v. 4.03
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 (see Clinical Studies (4.9) in the full prescribing information). Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus carboplatin or gemcitabine plus carboplatin or carboplatin or pemetrexed plus carboplatin or carboplatin followed by optional pembrolizumab maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥6 months and 22% were exposed for ≥12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years); 44% of patients 65 or older; 88% male; 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (9%) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in all 2 patients were pneumonitis, pneumonia, and hemorrhage.

Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 6 summarizes the adverse reactions that occurred in ≥10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

Table 6:  Adverse Reactions in at least 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO (n=355)</th>
<th>Chemotherapy (n=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03
a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, rash pain, spinal pain, and musculoskeletal stiffness.
b. Rash is a composite term that includes rash, dermatitis, urticaria, rash maculo-papular, erythema, rash erythematous, rash pustular, psoriasis, autommune dermatitis, dermatitis acriform, dermatitis alergic, dermatitis annularis, dermatitis herpetiform, drug eruption, dystrophic eczema, lichen planus, and skin reaction.
c. Fatigue is a composite term that includes fatigue, anemia, and myalgia.
d. Pneumonia is a composite term that includes atypical pneumonia, bacterial pneumonia, lower respiratory tract infection, lung abscesses, paracarcinomatous pneumonia, pneumonia, pneumonia bacterial, and pneumonia loboplastia.
e. Cough is a composite term that includes cough and productive cough.

Table 7:  Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in at least 1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO (n=355)</th>
<th>Chemotherapy (n=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.7</td>
<td>16</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v. 4.03
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

6.2 Immunogenicity

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

Anti-drug antibodies (ADA) were tested in 623 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADA was 3.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responders. 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 increased 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-L1 PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfed 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)].

Females

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 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 219 patients with mNSCLC or lNSCLC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 45% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

REGENERON | SANOFI GENZYME © 2021 Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. All rights reserved. LIB.21.06.0103 07/21

EBO_01_2023_ConferenceRecap_Regeneron_Libtayo.indd 8 1/10/23 1:07 PM
IN MEMORIAM | Michael J. Hennessy Sr, 1960-2021

Mike Hennessy Sr, the beloved chairman and founder of MJH Life Sciences™ and an innovative leader in medical communications, died November 21, 2021.

Through acquisitions and organic growth, Hennessy built MJH Life Sciences™ into the largest independently owned medical communications company in North America. He was also deeply committed to improving the lives of patients with cancer, active in state and national politics, and, above all, devoted to his family.

Hennessy started his career in medical publishing as a sales trainee. He launched Multimedia Healthcare in 1993 and built a portfolio of award-winning clinical journals. In 2001, Multimedia Healthcare was acquired at about the same time that Hennessy was pioneering a new approach to print and digital publishing with Intellisphere, which is now part of MJH Life Sciences™.

Hennessy added many companies and capabilities to MJH Life Sciences™ through a series of strategic acquisitions. In 2004, he acquired Healthcare Research Analytics and in 2005, ArcMeda Educators. Subsequent acquisitions included PharmacyTimes® and The American Journal of Managed Care®, Physicians’ Education Resource®, a continuing medical education company; and, in 2019, the health care and industry sciences divisions of UBM Medica. That acquisition almost doubled the size of the company and elevated it to being the largest independently owned medical communications company in North America.

Hennessy also worked tirelessly on behalf of patients with cancer. As a complement to the company’s OncLive® platform, he developed the Giants of Cancer Care® awards. He acquired the CURE Media Group in 2014, which was followed by the purchase of the Chemotherapy Foundation Symposium.

In 2019, Hennessy became chairman of MJH Life Sciences™ and named his son, Mike Hennessy Jr, to assume the leadership role of the organization. Under Mike Jr’s leadership, the company has enhanced its global potential by entering into a long-term partnership with BDJ Capital Partners in November 2021.

Hennessy’s counsel and insight were sought by many organizations, including his alma mater, Rider University, where he served on the board of trustees and was elected to the executive committee.

His true passion was his relationship with his wife, Patrice “Patti” Hennessy. After they met in college, Hennessy devoted his life to Patti and his family, raising 4 wonderful children: Shannon, Ashley, Mike Jr, and Chris. Hennessy was Patti’s rock as she bravely battled cancer for almost 10 years until her death in January 2020. Hennessy recently honored Patti by making a donation to Rider University: The Mike & Patti Hennessy Science and Technology Center is scheduled to be completed this year.

Hennessy’s legacy and “family first” mantra will live on through his children, their spouses, and his 10 grandchildren. He will be greatly missed by his family, friends, and MJH Life Sciences™ family.
SP9 IN MEMORIAM
Michael J. Hennessy Sr, 1960-2021

SP11-SP20 CAR T-CELL THERAPY
Bishop: Isis-Cell Results Highlight Importance of Time to Infusion
CLINICAL SPOTLIGHT: Frederick Locke, MD, on Real-World Implications of ZUMA-7
Findings in Relapsed/Refractory LBCL

CLINICAL SPOTLIGHT: Satvaa Neelapu, MD: Axi-Cell Highly Effective as First-line Option in High-Risk Large B-Cell Lymphoma
Liso-Cell Offers “Breakthrough” in Second-Line Treatment of LBCL, Kamdar Says

CLINICAL SPOTLIGHT Andre Goy, MD, on Predictive Biomarker Use for CAR T-Cell Therapy Response in Patients With Large B-Cell Lymphoma

SP21-SP30 LEUKEMIA & LYMPHOMA
POLARIX: Upgrading R-CHOP, Replacing Vincristine With Polatuzumab Vedotin, Improves Progression-Free Survival
SEQUOIA: At 26 Months, Zanubrutinib Prolongs PFS 58% Over Bendamustine + Rituximab in Patients With Treatment-Naive CLL/SLL

CLINICAL SPOTLIGHT: Constantine S. Tam, MBBS, MD, Touts Outcomes of Zanubrutinib vs Bendamustine/Rituximab Therapy in CLL/SLL

Sequencing helps some patients with blood cancer produce antibodies for first time
Findings show need for earlier conversations about end-of-life care with patients who have high-risk AML

CLINICAL SPOTLIGHT: Elizabeth L. Budde, MD, PhD: Mosunetuzumab is effective, well tolerated in R/R follicular lymphoma

SP31-SP34 MULTIPLE MYELOMA
Sub-Q Isatuximab Combo Offers Safety, Efficacy Profile Comparable With Phase 3 Results in IV Formulation
Phase 1/2 Trial Results Underscore Teclistamab’s Efficacy in RRMM
iStopMM: Investigators From Iceland Report First Results of Population-Based Screening for Multiple Myeloma

CLINICAL SPOTLIGHT: Mark Wildgust, PhD, Reviews Key Cilla-Cel Research Presented at ASH 2021

SP35-SP37 DISPARITIES IN CARE
Racial Disparities Are Seen in Survival Among Pediatric Patients With Acute Lymphoblastic Leukemia

CLINICAL SPOTLIGHT: Lori Muffly, MD, MS, Spotlights Disparities in Clinical Trial Enrollment, Patient Outcomes in Pediatric ALL
Most Medicare Beneficiaries With CLL Diagnosis Don’t Get Therapy, Claims Analysis Finds

SP47-SP48 REAL WORLD EVIDENCE
Collecting Real-World Data in Hematologic Malignancies, at Home and Abroad

SP49-SP51 RESEARCH FROM OUR PARTNERS
ACCC Presents Survey Responses on Adoption of Bispecific Antibodies

ACCC Presents Survey Responses on Adoption of Bispecific Antibodies

The US Oncology Network
Blue Ridge Cancer Care’s Goldschmidt Presents Data on Managing Hematologic Events

Florida Cancer Specialists
Patel Leads Dose Escalation Study of PRMT5 Inhibitor

© 2022 by Managed Care & Healthcare Communications, LLC. All rights reserved. Visit ajmc.com/subscribe for subscription information. Copyright © 2022 by Managed Care & Healthcare Communications, LLC. www.ajmc.com • Printed on acid-free paper.
ZUMA-7: Axi-Cel in Second Line Is the “New Standard” in R/R LBCL, Locke Says

MARY CAFFREY

COMING INTO the 2021 American Society of Hematology (ASH) Meeting & Exposition, Gilead Sciences had already announced that axicabtagene ciloleucel (axi-cel), sold as Yescarta, offered an event-free survival (EFS) rate more than 60% higher than that of the current second-line standard of care (SOC) for patients whose initial treatment for large B-cell lymphoma (LBCL) failed or whose cancer returned within a year.¹

For Frederick L. Locke, MD, of Moffitt Cancer Center in Tampa, the lead study author of the phase 3 ZUMA-7 trial that studied the use of axi-cel in these patients,² the question was: What now?

The answer is clear, he said. Axi-cel, with years of data behind it, will quickly become the new SOC for these patients. “ZUMA-7 met its primary EFS end point, demonstrating statistically significant and clinically meaningful improvement in efficacy with axi-cel vs second-line SOC in relapsed/refractory [R/R] LBCL,” Locke said during the ASH plenary session. “Results from the ZUMA-7 trial herald a paradigm shift: Axi-cel should be used as a first-line treatment, now follow axi-cel?”

Locke presented the data for ZUMA-7 to a large crowd, many of whom had heard the main data points but had other questions—for instance, if patients treated with axi-cel in the second-line setting fail, what happens next? Could autologous stem cell transplant (ASCT), which has been the second-line SOC treatment, now follow axi-cel?

“We don’t know what the appropriate therapy would be for a patient in the third line if they receive CAR [chimeric antigen receptor] T-cell therapy in the second line,” Locke said during a press briefing held prior to the plenary session. “We don’t understand [whether] the resistance mechanisms overlap.... I think that will be an area of intense study in the years to come.” He said that in ZUMA-7, patients could go on to transplant if they progressed after receiving axi-cel; 19 patients did so, and 9 are still alive.

And in response to a question, Locke acknowledged that minority patients had been underrepresented in ZUMA-7; across the conference, there were discussions of how to make these expensive therapies available to all patients, regardless of socioeconomic status.

DIFFERENCES WITH TRANSFORM. Axi-cel reached the market in the fall of 2017, within months of the approval of the first CAR T-cell therapy, and it is now approved for several types of R/R LBCL.¹ Clinicians have become much better at managing the most significant adverse events (AEs) arising from cytokine release syndrome (CRS), which occurs as the customized therapy attacks the cancer within the patient’s body.

ZUMA-7 has an important difference from TRANSFORM, which studied lisocabtagene maraleucel (liso-cel) in LBCL. Patients in ZUMA-7 were given corticosteroids only, not chemotherapy, prior to axi-cel treatment. “By giving CAR T-cell therapy as an earlier line of treatment, we are able to reduce the amount of chemotherapy patients are exposed to and get them quickly to a definitive therapy that can eradicate lymphoma for many years, if not forever, without a stem cell transplant,” Locke said.

But, some oncologists wondered, will bridging therapy be given in a real-world setting?

Locke told Evidence-Based Oncology³ that this may occur, but the point of ZUMA-7 is that axi-cel can be manufactured quickly and patients can avoid added chemotherapy, which appears to have contributed to the study’s positive findings (see Clinical Spotlight, SP13).

ADVANTAGES OF AXI-CEL. As City of Hope’s Alex F. Herrera, MD, noted in his plenary introduction, the question of using CAR T-cell therapy generally and axi-cel specifically arose quickly after clinicians saw its success in the third-line setting.

Locke noted that ZUMA-7 produced an advantage that is also seen with TRANSFORM: When the SOC for second-line R/R LBCL is salvage chemotherapy followed by a high-dose therapy and ASCT, the challenge is getting patients to the point of receiving the transplant in the first place. In ZUMA-7, 94% of those randomized to receive axi-cel were infused with treatment, while only 36% in the SOC group received a transplant.

“ZUMA-7 met its primary [event-free survival] end point, demonstrating statistically significant and clinically meaningful improvement in efficacy with axi-cel vs second-line [standard of care] in relapsed/refractory large B-cell lymphoma.”

—Frederick L. Locke, MD, vice chair, Department of Blood and Marrow Transplant and Cellular Immunotherapy; program co-leader, immuno-oncology; Moffitt Cancer Center, Tampa, Florida

Results from ZUMA-7 showed the following:

• After a median follow-up of 24.9 months, the median EFS was 8.3 months (95% CI, 4.5-15.8) for patients treated with axi-cel compared with 2.0 months (95% CI, 1.6-2.8) for those who received SOC (HR, 0.398; 95% CI, 0.308-0.514; P < .0001).

• The objective response rate was 83% for axi-cel vs 50% for SOC (odds ratio, 5.31; 95% CI, 3.1-8.9; P < .0001).

• Median overall survival, evaluated as a preplanned interim analysis, favored axi-cel over SOC but did not yet meet statistical significance (not reached vs 35.1 months; HR, 0.730; P = .027). Although the study did not include a crossover design, patients who failed on SOC and later received axi-cel could be confounding these results, Locke said.

• Grade 3 or higher neurologic events occurred in 21% of the axi-cel group and 1% of the SOC group; common symptoms included tremor (26% vs 1%), confusion (24% vs 2%), and aphasia (21% vs 0%); all were treated with corticosteroids. Median time to onset was 7 days with axi-cel and 23 days with SOC; median duration was 9 days vs 23 days.

• Grade 3 or higher CRS was seen in 6% of axi-cel patients; CRS was managed with tocilizumab (65%), corticosteroids (24%), and vasopressors (6%).

• Other grade 3 or higher AEs occurred in 91% of the axi-cel group vs 83% of the SOC group. Most common were neutropenia (69% vs 41%), anemia (30% vs 39%), and leukopenia (29% vs 22%)."
• The axi-cel arm had 1 treatment-related death; the SOC group had 2.
• Axi-cel was superior to SOC across key subgroups, including those younger and older than 65 years, patients whose first-line therapy failed, and those whose relapsed within the first year after their first therapy succeeded.

A separate abstract presented during the ASH meeting found that patients in ZUMA-7 who received axi-cel reported superior quality-of-life outcomes than those who received SOC. “The superior clinical outcomes and patient experience with axi-cel over SOC should help inform treatment choices in second-line R/R LBCL,” the authors wrote. •

REFERENCES

Bishop: Tisa-Cel Results Highlight Importance of Time to Infusion

MARY CAFFREY

AT THE 2021 American Society of Hematology (ASH) Meeting & Exposition, a major phase 3 study using chimeric antigen receptor (CAR) T-cell therapy in second-line treatment of aggressive B-cell lymphoma failed to yield positive results. But it’s this trial, the BELINDA study, that may help inform clinicians about the importance of infusing patients quickly, according to the lead investigator.

BELINDA, presented in ASH’s late-breaking session, found that tisagenlecleucel (tisa-cel) had no advantage in event-free survival over standard of care for patients. However, Michael R. Bishop, MD, of the University of Chicago, said it still represents a landmark study that offers many important take-aways, particularly regarding trial design.

Tisa-cel, sold as Kyrbria by Novartis, represented an historic breakthrough when it was approved in August 2017. Thus, the news that BELINDA failed to meet its end point—unlike ZUMA-7—was extremely disappointing, Bishop acknowledged in a press briefing.

Could he explain the apparent lack of benefit? “It’s an extremely important question. And if I’m completely honest, I lay awake at night thinking about it,” Bishop said.

He went through possible explanations for gap in results between the 2 trials, starting with their definitions of event-free survival. But the more important differences, he said, have to do with BELINDA’s near doubling in the mean number of days between the time patients were randomized and when they were infused with modified T-cells.

ZUMA-7 did not allow for bridging chemotherapy, only steroids. BELINDA did allow for chemotherapy, Bishop said. Sometimes patients had 2 rounds of bridging chemotherapy. As a result, the median time to infusion for BELINDA with tisa-cel was 52 days. With ZUMA-7 and axi-cel, Locke reported the median time was 27 days.

“There’s a number of variables that affected that,” Bishop said. “And we think this long infusion time, where you have an extremely progressive disease going on, did not permit the potential benefits of tisagenlecleucel. We hope that people will learn from that in the designing of future trials.”

The median time to infusion in BELINDA was 52 days, compared with 27 days in ZUMA-7. “There’s a number of variables that affected that. And we think this long infusion time, where you have an extremely progressive disease going on did not permit the potential benefits of tisagenlecleucel.” —Michael R. Bishop, MD, University of Chicago

But if the ZUMA-7 findings mean that second-line CAR T-cell therapy could soon be approved by FDA, what can be done to ensure patients are infused in a timely manner? Evidence-Based Oncology (EBO) asked Bishop to comment on this, given that the approval of 1 or more CAR T-cell therapies in the second-line setting could open the door to many more patients being eligible for treatment.

Bishop acknowledged that some patients and institutions still have challenges dealing with payers when administering CAR T-cell therapy in the third-line setting, 4 years after tisa-cel’s approval.

“I think it’s quite variable, relative to insurance approval,” he said. “In some situations, I’ll have insurance approval within 48 hours. It really depends upon the carrier. And then there’s other carriers who literally make patients jump through hoops. I think that’s inappropriate for an approved therapy, and especially when you have exactly that—a life-threatening situation. Time is of the essence, and getting that approval and moving forward is very, very important.”

Other oncologists have told EBO that payers delays have caused patients to miss the window of opportunity for CAR T-cell therapy. Bishop said in a real-world setting, multiple factors come into play, and payer delays are not helpful.

“Sometimes you can’t wait to get some chemotherapy before [patients] get referred to the [cancer] center,” he said. “And I think that’s also going to be our challenge among physicians who treat lymphoma on a regular basis, especially this patient population.” •

REFERENCE
**LOCKE:** Can anything more be done to identify which patients are the best candidates for CAR T-cell therapy generally and axi-cel specifically?

**EBO:** Can you discuss future studies that will be needed to address how to treat patients after second-line therapy?

**LOCKE:** The [design of the] trial we conducted, ZUMA-7, was to randomize [patients to] CAR T in the second line or to the current standard of care, which is multiagent chemotherapy followed by autologous stem cell transplant for those who respond.

What we don’t know is how to manage patients [afterward if they do] get CAR T-cell therapy in the second line. What treatment should they receive? Should they get chemotherapy and auto transplant if they respond, or should they get other therapies, novel agents? I think that will be an area of intense study over the next several years.

**REFERENCE**

WHEN NAVIGATING THE DIFFICULTIES OF MULTIPLE MYELOMA IN THE REAL WORLD, YOU NEED DURABLE STRENGTH

THE NINLARO® (ixazomib) REGIMEN* OFFERS EXTENDED EFFICACY AND MANAGEABLE TOLERABILITY†

The NINLARO regimen extended median PFS by ~6 months vs the Rd regimen.* Median PFS: 20.6 vs 14.7 months for the NINLARO and Rd regimens, respectively; HR=0.74 (95% CI, 0.59-0.94); P=0.012.1,4

Continuous treatment with a proteasome inhibitor (PI)-based regimen is associated with clinical benefits in multiple myeloma.1,7,8

*The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The Rd regimen included placebo+lenalidomide+dexamethasone.

†TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral PI) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.1,9

NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

Please see additional Important Safety Information on the next page and accompanying Brief Summary.
• Peripheral Neuropathy (predominantly sensory) was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Monitor patients for symptoms of peripheral neuropathy and adjust dosing as needed.

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

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

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

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

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

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

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

SPECIAL POPULATIONS
• Hepatic Impairment: Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
• Renal Impairment: Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.
• Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.


Please see accompanying Brief Summary on the following pages.
1 INDICATION
NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

5 WARNINGS AND PRECAUTIONS
5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤ 10,000/mm³ during treatment. Less than 1% of patients in both regimens had a platelet count ≤ 5000/mm³ during treatment. Discontinuations due to thrombocytopenia were similar in both regimens (< 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen discontinued one or more of the three drugs). The rate of platelet transfusions was 6% in the NINLARO regimen and 5% in the placebo regimen. Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting, have been reported with NINLARO, occasionally requiring use of anti diarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 42% of patients in the NINLARO regimen and 36% in the placebo regimen, constipation in 34% and 25%, respectively, nausea in 26% and 21%, respectively, and vomiting in 22% and 11%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (16% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (8% in the NINLARO regimen and 5% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens; there were no Grade 4 or serious adverse reactions. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 25% and 18% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (16% in the NINLARO regimen and 13% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 4% in the placebo regimen). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. There was no Grade 4 peripheral edema reported. There were no discontinuations reported due to peripheral edema. Evaluate for underlying causes and provide supportive care as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 19% of patients in the NINLARO regimen and 11% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (10% in the NINLARO regimen and 7% in the placebo regimen) or Grade 2 (6% in the NINLARO regimen and 3% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 1% of patients in the placebo regimen. There were no Grade 4 or serious adverse reactions of rash reported. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in < 1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

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

5.7 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatits cholestatic and hepatotoxicity have each been reported in < 1% of patients treated with NINLARO. Events of liver impairment have been reported (6% in the NINLARO regimen and 5% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animal studies. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose.

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 safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=360) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=360). The most frequently reported adverse reactions (≥ 20%) in the NINLARO regimen and greater than the placebo regimen were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhea (2%). For each adverse reaction, one or more of the three drugs was discontinued in ≤ 1% of patients in the NINLARO regimen.

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

<table>
<thead>
<tr>
<th></th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>All N (%)</td>
<td>All Grade 3 N (%)</td>
<td>All Grade 3 and Grade 4 N (%)</td>
</tr>
<tr>
<td>Infections and infestations Upper respiratory tract infection</td>
<td>69 (19) 1 (&lt; 1)</td>
<td>52 (14) 2 (&lt; 1)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>100 (28) 7 (2)</td>
<td>77 (21) 7 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>151 (42) 22 (6)</td>
<td>130 (36) 8 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>122 (34) 1 (&lt; 1)</td>
<td>90 (25) 1 (&lt; 1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>70 (26) 6 (2)</td>
<td>74 (21) 6 (2)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders Rash</td>
<td>68 (19) 9 (3)</td>
<td>38 (11) 2 (&lt; 1)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders Back pain</td>
<td>74 (21) 2 (&lt; 1)</td>
<td>57 (16) 9 (3)</td>
</tr>
<tr>
<td>General disorders and administration site conditions Edema peripheral</td>
<td>91 (25) 8 (2)</td>
<td>66 (18) 4 (1)</td>
</tr>
</tbody>
</table>

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

*Represents a pooling of preferred terms.

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

Table 5: Thrombocytopenia and Neutropenia

<table>
<thead>
<tr>
<th></th>
<th>NINLARO + Lenalidomide and Dexamethasone N=360</th>
<th>Placebo + Lenalidomide and Dexamethasone N=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>All N (%)</td>
<td>All Grade 3 N (%)</td>
<td>All Grade 3 and Grade 4 N (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>281 (78) 93 (26)</td>
<td>196 (54) 39 (11)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>240 (67) 93 (26)</td>
<td>239 (68) 107 (30)</td>
</tr>
</tbody>
</table>

Herpes Zoster
Herpes zoster was reported in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider’s discretion. Patients treated in the NINLARO regimen who (Continued on next page)
Brief Summary (cont’d)

received antiviral prophylaxis had a lower incidence (< 1%) of herpes zoster infection compared to patients who did not receive prophylaxis (6%).

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

Adverse Reactions Reported Outside of the Randomized Controlled Trial

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, there is a recognized background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. Animal Data: In an embryo-fetal development study in pregnant rabbits there were increases in fetal skeletal variations/anomalies (caudal vertebrae, number of lumbar vertebrae, and full supernumerary ribs) at doses that were also maternally toxic (≥ 0.3 mg/kg). Exposures in the rabbit at 0.3 mg/kg were 1.9 times the clinical time averaged exposures at the recommended dose of 4 mg. In a rat dose range-finding embryo-fetal development study, at doses that were maternally toxic, there were decreases in fetal weights, a trend towards decreased fetal viability, and increased post-implantation losses at 0.6 mg/kg. Exposures in rats at the dose of 0.6 mg/kg was 2.5 times the clinical time averaged exposures at the recommended dose of 4 mg.

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

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

Advis e females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the final dose. Advise women using hormonal contraceptives to also use a barrier method of contraception [see Use in Specific Populations (8.1)].

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

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

10 Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

Please see all Prescribing information for NINLARO at NINLAROhcp.com. All trademarks are the property of their respective owners. ©2021 Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. All rights reserved.

APRIL 2021 USO-IXA-0139
Sattva S. Neelapu, MD, Says Axi-Cel Highly Effective as First-line Option in High-Risk Large B-Cell Lymphoma

Produced by Matthew Gavidia

Neelapu is the lead author of “Primary Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-cel) as First-line Therapy in Patients With High-Risk Large B-cell Lymphoma (LBCL),” an abstract presented at ASH 2021.

Evidence-Based Oncology (EBO): Your results for axi-cel in the first-line setting demonstrate 91% overall survival at 12 months in a high-risk population. Can you discuss how this compared with the use of axi-cel in the original ZUMA study?

Neelapu: In the ZUMA-1 study, we observed at the 2-year time point that more than 50% of the patients were still alive, and long-term durability of responses had been observed in about 40% of the patients; these patients are likely cured. In fact, at this meeting, we [presented] an update on the 5-year analysis of the ZUMA-1 study; we found that at least 43% of the patients were still alive at 5 years.

In the ZUMA-12 study, we observed a very high overall response rate and a complete response rate of 78% in a very refractory patient population, where 40% of them [were] actually having progressive disease to first-line therapy after 2 cycles of chemotherapy.

So, in this patient population after a median follow-up of 16 months, we found that 73% of patients still remain in remission and 91% are still alive. This compares quite favorably with historical data in high-risk patients with LBCL where they have refractory disease to primary first-line therapy and outcomes were very poor. In fact, at the 2-year time point, only about 10% of these patients are alive.

So, even though this is not a randomized study, the data from this ZUMA-12 study indicate that axi-cel looks highly promising and is highly effective in the first-line setting in these patients.

EBO: Did any particular patient subgroups have superior responses?

Neelapu: We looked at a number of different standard prognostic subgroups in these patients. We found consistent response rates, as well as duration of response, across the various prognostic subgroups, including patients around age 65 years, patients who had high [International Prognostic Index scores], and patients who had double- or triple-hit lymphoma.

In addition, patients who had refractory disease to first-line therapy also had outcomes comparable with those of patients who were chemosensitive. So far, we have not been able to identify a subgroup that performed less well compared with the overall patient population.

EBO: Some of the more anticipated results at the ASH meeting involved phase 3 results for different CAR T-cell therapies in the second-line setting in LBCL, and your results are already moving ahead to the first-line setting. What do you think the timeline will be for use of axi-cel in earlier settings?

Neelapu: I think from the 3 randomized trials [presented at] ASH comparing CAR T-cell therapy head-to-head with stem cell transplant in patients with LBCL in the second-line setting, at least 2 of the trials are reported to be positive, with a durability of response in the 40%-to-45% range at 1 to 2 years after follow-up.

So, we expect this therapy to be approved in the second-line setting in the near future, probably within the first half of [2022] by the FDA, but eventually I think CAR T-cell therapy can be moved to the first-line setting, based on the data from the ZUMA-12 study. Ultimately, we will need a randomized study to compare [CAR T-cell therapy] head-to-head with standard-of-care chemoimmunotherapy in the first-line setting.

In the first-line setting in the ZUMA-12 study, we also compared the phenotype of these CAR T-cell products with that of the ZUMA-1 study, where CAR T-cell therapy was evaluated in the third-line setting and beyond. We found a higher frequency of CCR7-positive, CD45RA-positive T cells in the ZUMA-12 patients compared with ZUMA-1; this was associated with a greater CAR T-cell expansion and greater clinical efficacy.

So, to us, that suggests that the T-cell fitness could be better as we move CAR T-cell therapy to earlier lines, and that yields a better CAR T-cell product and better clinical outcomes for these patients. That provides further rationale to evaluate CAR T-cell therapy in earlier lines as opposed to waiting until a patient fails multiple lines of therapy.

Reference
Liso-Cel Offers “Breakthrough” in Second-line Treatment of LBCL, Kamdar Says

MARY CAFFREY

THE ANTI–CD-19 THERAPY lisoctagene maraleucel (liso-cel) offered significant benefits over standard of care (SOC) when given to patients whose large B-cell lymphoma (LBCL) returned or failed to respond (R/R) to the first treatment after 12 months, according to interim findings of the randomized phase 3 TRANSFORM study.1

“This is a breakthrough therapy which has shown superiority over SOC in terms of efficacy with an extremely favorable safety profile,” said Manali Kamdar, MD, of the University of Colorado, who presented the TRANSFORM results during the 2021 American Society of Hematology (ASH) Meeting & Exposition. “We are excited about the potential of this study to change the existing standard of care in these high-risk patients.”

All signs point to liso-cel and another chimeric antigen receptor (CAR) T-cell therapy, axicabtagene ciloleucel (axi-cel), becoming the new SOC options for second-line treatment of patients with LBCL, given the results for liso-cel and those for the phase 3 ZUMA-7 trial.2 Both trials were highlighted at a press briefing to open the ASH meeting; ZUMA-7 later headlined the ASH plenary session (see SP11).

Press briefing moderator Laurie H. Sehn, MD, MPH, a hematologist-oncologist at the British Columbia Cancer Centre for Lymphoid Cancer at the University of British Columbia, called both sets of results “remarkable” and said they would be welcomed by clinicians who feel limited by the current SOC.

“I think it’s inevitable that this will become the standard of care,” she said.

Liso-cel, sold as Breyanzi by Bristol Myers Squibb, was approved in 2021 for adults who have failed on 2 prior treatments for LBCL based on results of the TRANSCEND-NHL study.3 Investigators have reported that its manufacturing process, which results in an equal balance of CD8+ and CD4+ CAR T cells, makes the product capable with SOC, and some patients were able to receive the CAR T-cell therapy in an outpatient setting. Although the well-known effects associated with CAR T-cell therapy of cytokine release syndrome (CRS) and neurological toxicity were seen, there were no grade 4 or 5 neurological events. No deaths were attributable to liso-cel treatment.

Investigators reported no new liso-cel safety signals when giving the treatment in the second-line setting. Roughly half (49%) of those receiving liso-cel had some level of CRS, with 37% reporting grade 1 and 11% grade 2; one patient reported grade 3 effects that started on day 9 after treatment and resolved in 2 days. Patients with CRS were treated with tocilizumab (24%) and corticosteroids (17%). The most common treatment-emergent adverse events were cytopenias, which were reported in 43% of patients.

FINDINGS ARE LOGICAL. “For somebody who has to treat patients with LBCL like I do, it’s incredibly frustrating when patients have failed frontline therapy,” she said. For patients such as those in TRANSFORM and ZUMA-7, who are especially high risk—Sehn called them “the worst of the worst”—the current approach calls for doubling down with higher doses of chemotherapy. Patients continue to fail, she said.

“So, it’s not surprising that coming in [to the second-line setting] with a novel approach and a cellular therapy that has proven curative capacity [in the] third-line setting, you may have outperformed in with more chemotherapy,” Sehn said.

The word that comes to mind, she said, is that the findings are “logical.”

REFERENCES


LISO-CEL OFFERS “BREAKTHROUGH” IN SECOND-LINE TREATMENT OF LBCL, KAMDAR SAYS
Andre H. Goy, MD, on Predictive Biomarker Use for CAR T-Cell Therapy Response in Patients With Large B-Cell Lymphoma

Produced by Matthew Gavidia

A MAJORITY OF CLINICAL prognostic features associated with poor response to chemotherapy in patients with diffuse large B-cell lymphoma did not seem to apply to chimeric antigen receptor (CAR) T-cell therapy, in which response to CAR T was shown to depend more on T-cell fitness and prior lines of therapy, said Andre H. Goy, MD, physician in chief, Hackensack Meridian Health Oncology Transformation Service; chairman and chief physician officer, John Theurer Cancer Center; and professor of oncology at Hackensack Meridian School of Medicine. Goy is a coauthor of “Impact of Molecular Features of Diffuse Large B-Cell Lymphoma on Treatment Outcomes With Anti-CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy,” an abstract presented at the 2021 American Society of Hematology (ASH) Meeting & Exposition. The abstract aligns with other presentations at ASH, including results of the ZUMA-7 study (NCT033914-75), which discusses using the CA, T-cell therapy axicabtagene ciloleucel (axi-cel® Yescarta) earlier in the course of treatment for diffuse large B-cell lymphoma.

EVIDENCE-BASED ONCOLOGY™ (EBO): In findings discussed in this abstract, the varied responses to CAR T-cell therapy based on predictive biomarkers show that some patients will have a strong response to CAR T-cell therapy after a poor response. How is this information useful to both clinicians and payers?

GOY: As we talk about how to make a patient benefit more from axi-cel in relapsed/refractory large B-cell lymphoma, [we] allude to the fact that we can predict a signature that the patient will do well. 

I will just summarize that the standard clinical prognostic features such as primary refractory; multiple lines of therapy; and, more importantly, highly proliferative disease—K7 [keratin 7], double-hit, double-expression lymphoma, TPS3—all of these very poor prognostic features for chemotherapy—activated B-cell [ABC] worse than germinal center B-cell [GCB]—all of these features are not really applying to CAR T-cell.

The abstract we’re referring to, [number] 165, was a multicenter retrospective analysis of a patient with large B-cell lymphoma who had received CAR T-cell [therapy], looking at comprehensive signatures to see if we can identify markers. As I mentioned, the standard prognostic features did not apply in CAR T, so patients still responded. Patients who had highly expressive, mutated BCL2 seemed to have a worse outcome, whereas [those with] MYD88, for example, had a better outcome. This is really starting to scratch the surface of these biomarkers, and the take-home message is that, again, the prognostic features that are very well established in chemoimmunotherapy do not apply typically in CAR T-cell therapy.

Looking at the microenvironment, we had some hint or so from the study that obviously—which we know already from studying the mechanism of resistance of CAR T cells—microenvironment is going to be very important and T-cell fitness. And, as I mentioned, that’s why it’s important to bring in CAR T-cell therapy earlier in the journey of the patient [who had] fewer prior lines of therapy.

EBO: Would you discuss the findings showing that predictive biomarkers of response to traditional chemoimmunotherapy and cellular immunotherapy are distinct?

GOY: The typical prognostic factors of chemoimmunotherapy, such as ABC worse than GCB; K7; double-hit, double-expressor, high-grade lymphoma; TP53, etc—all these are markers of poor outcome for chemoimmunotherapy. They do not seem to apply with cellular immunotherapy, which makes sense. This is absolutely not the same mechanism.

What matters likely more, again, is the T-cell fitness and making sure that we bring this therapy before patients have received multiple lines of therapy. And the number of lines of therapy is not because a disease becomes more refractory to CAR T, necessarily—it’s because T cells get exposed to more lines of therapy, and, therefore, we have less expansion and less functional T cells when it comes to use of the CAR T-cell therapy and manufacturing those T cells.

REFERENCE


**POLARIX: Upgrading R-CHOP, Replacing Vincristine With Polatuzumab Vedotin, Improves Progression-Free Survival in DLBCL**

MARY CAFFREY

---

**THE CLASSIC CHEMOTHERAPY** regimen known as R-CHOP may get an upgrade for patients who are newly diagnosed with diffuse large B-cell lymphoma (DLBCL), based on study results that showed replacing an old therapy, vincristine, with polatuzumab vedotin (Polivy) improved progression-free survival (PFS) by 27%.

The findings, from the phase 3 POLARIX trial, were presented in the late-breaking session of the 2021 American Society of Hematology (ASH) Meeting & Exposition in Atlanta, with sessions also available online. Results were simultaneously published in the *New England Journal of Medicine.*

In POLARIX, an international team of investigators set out to find a better first-line treatment for DLBCL than the combination of rituximab, cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin), and prednisone (R-CHOP) that has long been the default option. Although this combination cures 60% of patients, 40% see their cancer progress and may require salvage therapy and autologous stem cell transplant.

“*This is the first randomized phase 3 study that has shown a benefit in patients with first-line [diffuse large B-cell lymphoma]. It shows that it is possible to significantly reduce disease progression, including in patients with difficult-to-treat subtypes.*” —Gilles Salles, MD, PhD, chief, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York City

Polatuzumab vedotin is an antibody-drug conjugate that targets CD79b, which is expressed on the surface of malignant B cells; it received accelerated approval in 2019 in combination with bendamustine and rituximab to treat relapsed or refractory DLBCL. It is made by Genentech, which previously announced the topline results of POLARIX.

Vincristine is a widely used chemotherapy that blocks cell division. However, an important challenge with this drug is that it has been in short supply: Some longtime manufacturers have stopped producing it.

In a press briefing before the late-breaking session, study coauthor Gilles Salles, MD, PhD, said there have been many attempts over the 20 years that R-CHOP has been used to modify the combination to boost its success rate, but none have panned out until now.

Although POLARIX found no significant difference in complete response rates or overall survival (OS) at the 2-year mark, patients who took the new combination were less likely to need additional treatment compared with those taking the usual regimen.

“This is the first randomized phase 3 study that has shown a benefit in patients with first-line DLBCL. It shows that it is possible to significantly reduce disease progression, including in patients with difficult-to-treat subtypes,” Salles said. “I think this could be a practice-changing result.”

**Study Design and Results**

Investigators randomized 879 patients aged 18 to 80 years, with 440 assigned to the polatuzumab regimen (called pola-R-CHP) and 439 to R-CHOP. Both groups received 6 cycles of their respective regimen plus 2 cycles of rituximab alone.

The primary end point was investigator-assessed progression-free survival. Secondary end points included OS and safety. After a median follow-up of 28.2 months, the percentage of patients surviving without progression was significantly higher in the pola-R-CHP group than in the R-CHOP group:

- PFS for pola-R-CHP was 76.7% (95% CI, 72.7%-80.8%) vs 70.2% for R-CHOP (95% CI, 65.8%-74.6%) at 2 years; stratified HR for progression, relapse, or death was 0.73 by Cox regression (95% CI, 0.57-0.95; *P*= .02).
- The complete response rate was similar with pola-R-CHP vs R-CHOP (78.0% vs 74.0%; *P*= .16); however, disease-free survival responses point to a more durable response with pola-R-CHP than with R-CHOP (HR, 0.70; 95% CI, 0.50-0.98), according to the ASH abstract.
- OS at 2 years did not differ significantly between the groups: 88.7% (95% CI, 85.7%-91.6%) in the pola-R-CHP group vs 88.6% (95% CI, 85.6%-91.6%) in the R-CHOP group; HR for death, 0.94 (95% CI, 0.65-1.37; *P*= .75).
- The 2 groups had similar safety profiles.

Salles said the POLARIX investigators will keep following participants to learn more about long-term responses and outcomes. They also want to learn more about patient subgroups, to understand whether tumor biology contributes to the different responses to initial treatment. Better first-line treatment for DLBCL may give patients hope and time, as much as ASH 2021 focused on moving chimeric antigen receptor T-cell therapy into earlier lines of treatment in LBCL.

“It is quite satisfying that we were able to improve outcomes without significantly impairing patients’ quality of life,” said Salles.

**References**

ZANUBRUTINIB, A NEXT-GENERATION Bruton tyrosine kinase (BTK) inhibitor, produced prolonged progression-free survival (PFS) compared with a combination of bendamustine and rituximab (BR) among treatment-naive patients with chronic lymphocytic leukemia/small cell lymphocytic lymphoma (CLL/SLL), according to new trial results presented during the 2021 American Society of Hematology Meeting & Exposition, held in Atlanta and online.1

Constantine Tam, MBBS, MD, of the Peter MacCallum Cancer Centre in Melbourne, Australia, outlined interim phase 3 findings from 2 arms of the SEQUOIA trial. He presented remotely, but beyond the masks, the ASH session on CLL looked like a scene from before the pandemic, with attendees filling most of the chairs or standing in the small space at the rear of the meeting room. The results from SEQUOIA came last, and Tam began with background on the transformation of CLL treatment with the rise of B-cell receptor signaling inhibitors, notably the BTK inhibitors zanubrutinib and acalabrutinib.

Tam said that 2 large head-to-head randomized trials have shown that zanubrutinib has a reduced risk of adverse events (AEs) compared with the first-generation BTK inhibitor ibrutinib, which is approved to treat CLL. BTK inhibitors generally are associated with atrial fibrillation (AF), but this has been reduced with zanubrutinib compared with ibrutinib. In SEQUOIA, 3.3% of patients in the zanubrutinib arm had an AF of any grade, vs 2.6% in the comparator arm.

Four Arms of SEQUOIA
Tam explained that the SEQUOIA trial has 4 arms, and that he was presenting interim results from arm A and arm B, both of which are from cohort 1, in which patients are without deletion (17p) [del(17p)]. Cohort 2, with arm C and arm D, has patients with del(17p). All patients had untreated CLL/SLL, and Tam said 80% are older than 65 years, with an mean age of 70 years.

In arm A, patients received zanubrutinib 160 mg until disease progression, intolerable toxicity, or the end of the study. In arm B, patients received bendamustine 90 mg/m² on days 1 and 2, then rituximab 375 mg/m² for the first cycle, followed by 500 mg/m² for cycles 2 to 6.

From October 31, 2017, to July 22, 2019, 479 patients who met criteria for arms A and B were randomized for zanubrutinib (241 patients) or the combination of bendamustine and rituximab (238 patients). Unmutated immunoglobulin heavy chain variable (IGHV) was present in 53.4% vs 52.4% of patients, respectively, and del(17p) was present in 17.8% vs 19.3%.

Males made up the majority of both arm A (63.9%) and arm B (60.5%). In both arms, most patients were from Europe, with 72.2% in Arm A and 72.3% in Arm B; 14.1% and 11.8%, respectively, were from North America, and 13.7% and 16.0% were from Asia/Pacific.

At median follow-up of 26.2 months, PFS as determined by an independent review committee (IRC), which was the primary end point, significantly favored zanubrutinib (HR, 0.42; 95% CI, 0.28-0.63; P < .0001).

Secondary end points included safety assessments. The most common AEs besides AF included hypertension of any grade, 14.2% for zanubrutinib vs 10.6% for BR; infection of any grade and grade 3 or higher, 62.1% and 16.3%, respectively, for zanubrutinib, vs 55.9% and 18.9% for BR; and neutropenia of any grade and grade 3 or higher, 15.8% and 11.7% for zanubrutinib vs 56.8% and 51.1% for BR. Other secondary end points included:

- Estimated 24-month PFS: by IRC, 85.5% with zanubrutinib (95% CI, 80.1%-89.6%) vs 55% vs 5% for BR (95% CI, 62.4%-73.5%)
- Objective response rate: by IRC, 94.6% (95% CI, 91.0%- 97.1%) with zanubrutinib vs 85.3% with BR (95% CI, 80.1%-89.5%). Complete response rate: 6.6% with zanubrutinib vs 15.1% with BR
- Estimated 24-month overall survival (OS): 94.3% (95% CI, 90.4%-96.7%) with zanubrutinib vs 94.6% (95% CI, 90.6%-96.9%) with BR

Reporting OS is challenging, Tam explained, because patients in arm B who progressed were permitted to cross over to receive zanubrutinib; 15 patients did this and improved on the therapy. Thus, zanubrutinib’s advantage in OS might be impossible to know. In response to a question, he said, “We do know [zanubrutinib] is very reliable as a second-line agent….so there’s no reason to believe that those patients didn’t do well.”

He said the benefits of zanubrutinib occurred “across every important prognostic subgroup,” except for a small group of patients with mutated IGHV (HR, 0.67; 1-sided P = .0929).

Adverse Events
When looking at a table of common AEs such as rash, nausea, constipation, anemia, pyrexia, and thrombocytopenias, Tam noted that all were seen far less in the zanubrutinib arm.

“Looking at the more common AEs, including nausea, as well as an increased risk of cytopenias, even looking at the adverse events of special interest—one once again, no surprises here,” Tam said.

More patients in the BR group stopped treatment due to AEs (31 patients; 15.7%) than in the zanubrutinib group (20 patients; 8.3%). AEs leading to death occurred in 11 patients in the zanubrutinib group (4.6%) vs 12 patients in the BR group (5.3%). No sudden deaths were reported.

In response to a question about infections, Tam revealed a remarkable point about the difference between the 2 arms: The most common infection was grade 2 upper respiratory tract infections. “We know the clinical significance of COVID is very important,” he said. As it turns out, the patients in the BR arm had completed treatment when the pandemic hit, but not so for the zanubrutinib arm. Five patients [in the zanubrutinib arm] had severe infections due to COVID-19, and 4 died. “So, there was actually a major difference in the severe infection[s],” Tam said.

**REFERENCE**
CLINICAL SPOTLIGHT

Constantine S. Tam, MBBS, MD, Touts Outcomes of Zanubrutinib vs Bendamustine/ Rituiximab Therapy in CLL/SLL

Produced by Matthew Gavidia

CONSTANTINE TAM, MBBS, MD, Peter MacCallum Cancer Centre, Melbourne, Australia; hematologist and disease group lead, low-grade lymphoma and chronic lymphocytic leukemia.

TREATMENT-NAIVE PATIENTS with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) exhibited significantly superior progression-free survival (PFS) and a favorable safety profile when given the Bruton tyrosine kinase (BTK) inhibitor zanubrutinib vs bendamustine/rituximab (Rituxan), according to Constantine S. Tam, MD, MBBS, consulting hematologist and associate professor at Peter MacCallum Cancer Centre in Melbourne, Australia. Tam is lead author of the abstract “SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib Versus Bendamustine + Rituximab in Patients With Treatment-Naïve Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma,” which was presented the 2021 American Society of Hematology (ASH) Meeting & Exposition.

“What’s really noteworthy in terms of the toxicity comparison was that there is a reduced risk of neutropenia, febrile neutropenia, or cytopenia in favor of zanubrutinib. And in fact, the other notable finding of the toxicity comparison was that the atrial fibrillation rate for zanubrutinib was identical to the bendamustine/rituximab arm.”

—Constantine Tam, MBBS, MD, Peter MacCallum Cancer Centre

EVIDENCE-BASED ONCOLOGY™ (EBO): Can you discuss the final efficacy and safety outcomes of zanubrutinib vs bendamustine and rituximab in treatment-naïve patients with CLL/SLL?

TAM: SEQUOIA is a study that compared frontline patients with CLL, who are unfit for intensive chemotherapy, directly head-to-head with zanubrutinib vs bendamustine/rituximab treatment. In all, we randomized 479 patients. These are older patients with a median age of 70. The headline result is a superior PFS in favor of the zanubrutinib arm, where the PFS at 2 years is 85.5% vs 69.5% for bendamustine/rituximab—for a hazard ratio of 0.422, meaning a 58% reduction in the risk of progression, and a highly significant P value of .0001. Every subgroup that we examined showed a benefit to zanubrutinib over bendamustine/rituximab. The only possible subgroup where we haven’t seen a statistically significant difference includes those patients with IGVH-mutated CLL—who we know do benefit [more] with bendamustine/rituximab anyway—where there is still a difference in the PFS curve, but at this short follow-up, the PFS curve has not yet translated into a positive P value.

EBO: How do these phase 3 results align with early findings reported for the use of BTK inhibitors in this population?

TAM: We’ve previously reported that zanubrutinib is effective in earlier phase 1 and 2 studies in patients with CLL, both in the frontline and the relapsed/refractory settings. And at EHA [European Hematology Association 2021 Virtual Congress], only 6 months ago, we reported a direct head-to-head study comparing zanubrutinib vs ibrutinib [Imbruvica] in relapsed CLL, showing a superior PFS and better adverse event [AE] profile in favor of zanubrutinib. Now, what this current study does is extend the experience to the front line, where zanubrutinib is directly compared against a standard of bendamustine/rituximab for frontline CLL—one once again, confirming good tolerance and confirming a superior PFS against an established standard of care. So really, what this does is extend the data of zanubrutinib from the phase 1/2 experience into the phase 3 confirmation experience.

EBO: What has SEQUOIA demonstrated about the importance of a patient’s ability to stay on a drug for a longer period?

TAM: When you compare the AEs between zanubrutinib and bendamustine/rituximab in SEQUOIA, the zanubrutinib arm was associated with much better tolerance, with reduced AEs leading to dose reduction, dose interruption, or discontinuation compared with the bendamustine/rituximab arm. I think this really confirms the highly tolerable nature of BTK inhibitors in general. And it shows that for elderly patients with CLL, one has to choose a regimen that can be taken by the patient and completed by the patients, because if you don’t finish your regimen, you’re not going to get the efficacy outcome. Having said that, bendamustine/rituximab was still well tolerated, and most patients still complete the assigned chemotherapy.

What’s really noteworthy in terms of the toxicity comparison was that there is a reduced risk of neutropenia, febrile neutropenia, or cytopenia in favor of zanubrutinib. And in fact, the other notable finding of the toxicity comparison was that the atrial fibrillation rate for zanubrutinib was identical to that of the bendamustine/rituximab arm.

As the audience would know, BTK inhibitors are associated with atrial fibrillation, and it is very reassuring to see a phase 3 study where the atrial fibrillation rate in the BTK arm is the same as a comparator arm. I think this confirms earlier data that zanubrutinib is less cardiotoxic than other BTK inhibitors and, in particular, less cardiotoxic than ibrutinib.

REFERENCE

PROPHYLAXIS FOR HERPES SIMPLEX VIRUS, INFECTIONS DUE TO HEPATITIS B VIRUS (HBV) REACTIVATION HAVE OCCURRED.

INFECTIONS
FATAL AND SERIOUS INFECTION EVENTS HAVE OCCURRED IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES TREATED WITH BRUKINSA MONOTHERAPY. GRANULOCYTIC NEUTROPENIA OCCURRED IN 11% OF PATIENTS, GRANULOCYTIC NEUTROPENIA AND THROMBOCYTOPENIA OCCURRED IN 5% OF PATIENTS, AND GRADE 4 NEUTROPENIA OCCURRED IN 3% OF PATIENTS.

SECOND PRIMARY MALIGNANCIES
SECOND PRIMARY MALIGNANCIES, INCLUDING NON-SKIN CARCINOMA, HAVE OCCURRED IN 14% OF PATIENTS TREATED WITH BRUKINSA MONOTHERAPY. THE MOST FREQUENT SECOND PRIMARY MALIGNANCY WAS NON-MELANOMA SKIN CANCER REPORTED IN 8% OF PATIENTS. OTHER SECOND PRIMARY MALIGNANCIES INCLUDED MALIGNANT SOLID TUMORS (4.0%), MELANOMA (1.7%) AND HEMATOLOGIC MALIGNANCIES (1.2%). ADVISE PATIENTS TO USE SUN PROTECTION, AND MONITOR PATIENTS FOR THE DEVELOPMENT OF SECOND PRIMARY MALIGNANCIES.

CARDIAC ARRHYTHMIAS
ATRIAL FIBRILLATION AND ATRIAL FLUTTER WERE REPORTED IN 3.2% OF PATIENTS TREATED WITH BRUKINSA MONOTHERAPY. PATIENTS WITH CARDIAC RISK FACTORS, HYPERTENSION AND ACUTE INFECTIONS MAY BE AT INCREASED RISK. GRADE 3 OR HIGHER EVENTS WERE REPORTED IN 1.1% OF PATIENTS TREATED WITH BRUKINSA MONOTHERAPY. MONITOR SIGNS AND SYMPTOMS FOR ATRIAL FIBRILLATION AND ATRIAL FLUTTER AND MANAGE AS APPROPRIATE.

EMBRYO-FETAL TOXICITY
BASED ON FINDINGS IN ANIMALS, BRUKINSA CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. ADMINISTRATION OF ZANUBRUTINIB TO PREGNANT RATS DURING THE PERIOD OF ORGANOGENESIS CAUSED EMBRYO-FETAL TOXICITY INCLUDING MALFORMATIONS AT EXPOSURES THAT WERE 5 TIMES HIGHER THAN THOSE REPORTED IN PATIENTS AT THE RECOMMENDED DOSE OF 100 MG TWICE DAILY. ADVISE WOMEN TO AVOID BEING PREGNANT WHILE TAKING BRUKINSA AND FOR 1 WEEK AFTER THE LAST DOSE. ADVISE MEN TO AVOID FATHERING A CHILD DURING TREATMENT AND FOR 1 WEEK AFTER THE LAST DOSE.

IF THIS DRUG IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO A Fetus.

ADVERSE REACTIONS
THE MOST COMMON ADVERSE REACTIONS, INCLUDING LABORATORY ABNORMALITIES, IN 30% OF PATIENTS WHO RECEIVED BRUKINSA (N=847) INCLUDED DECREASED NEUTROPHIL COUNT (54%), UPPER RESPIRATORY TRACT INFECTION (47%), DECREASED PLATELET COUNT (41%), HEMORRHAGE (35%), DECREASED LYMPHOCYTE COUNT (31%), RASH (31%) AND MUSCULOSKELETAL PAIN (30%).

DRUG INTERACTIONS
CYP3A INHIBITORS: WHEN BRUKINSA IS CO-ADMINISTERED WITH A STRONG CYP3A INHIBITOR, REDUCE BRUKINSA DOSE TO 80 MG ONCE DAILY. FOR CO-ADMINISTRATION WITH A MODERATE CYP3A INHIBITOR, REDUCE BRUKINSA DOSE TO 80 MG TWICE DAILY.
CYP3A INDUCERS: AVOID CO-ADMINISTRATION WITH MODERATE OR STRONG CYP3A INDUCERS.

SPECIFIC POPULATIONS
HEPATIC IMPAIRMENT: THE RECOMMENDED DOSE OF BRUKINSA FOR PATIENTS WITH SEVERE HEPATIC IMPAIRMENT IS 80 MG ORALY TWICE DAILY.

Please see Brief Summary of full Prescribing Information on following pages.
THE BTK INHIBITOR THAT DELIVERS POWERFUL AND CONSISTENT RESPONSES

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with Waldenström’s macroglobulinemia.

Powerful Responses Across WM Patients

While the primary endpoint of superiority did not reach statistical significance, numerically higher VGPR/CR rates were achieved in the BRUKINSA treatment arm.¹

<table>
<thead>
<tr>
<th>All patients¹</th>
<th>All patients¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IWWM-6 criteria¹</strong></td>
<td><strong>Modified IWWM-6 criteria¹</strong></td>
</tr>
<tr>
<td><strong>BRUKINSA (n=102)</strong></td>
<td><strong>BRUKINSA (n=102)</strong></td>
</tr>
<tr>
<td>CR+VGPR+PR¹ (95% CI: 68, 85)</td>
<td>CR+VGPR+PR¹ (95% CI: 68, 86)</td>
</tr>
<tr>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td><strong>Ibrutinib (n=99)</strong></td>
<td><strong>Ibrutinib (n=99)</strong></td>
</tr>
<tr>
<td>CR+VGPR+PR¹ (95% CI: 68, 86)</td>
<td>CR+VGPR+PR¹ (95% CI: 68, 86)</td>
</tr>
<tr>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>VGPR/CR²</td>
<td>VGPR/CR³</td>
</tr>
<tr>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>62%</td>
<td>71%</td>
</tr>
<tr>
<td>49%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Median follow-up time was 19.4 months.²
The prespecified efficacy outcome measure of VGPR/CR was assessed by IRC.¹

Safety in WM is consistent with the established BRUKINSA profile¹

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias. The most common adverse reactions (≥30%) include neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, lymphocyte count decreased, rash, and musculoskeletal pain.

¹Patients were enrolled from the United States, Europe, and Australia/New Zealand.
²Modified IWMM-6 criteria (Owen et al, 2015) requires complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed.
³There were no DIs in either treatment arm.

1 INDICATIONS AND USAGE

1.1 Margette Lymphoma
BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate (see Clinical Studies [14.1]). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.2 Waldenström’s Macroglobulinemia
BRUKINSA is indicated for the treatment of adult patients with Waldenström’s macroglobulinemia (WM).

1.3 Marginal Zone Lymphoma
BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen. This indication is approved under accelerated approval based on overall response rate (see Clinical Studies [14.1]). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4.2 Adverse Reactions

5.1 Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematoma, and hematomas have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade, excluding purpura and petechiae, occurred in 35% of patients. Bleeding events have occurred in patients with and without concomitant antithrombotic or anticoagulation therapy.

5.2 Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections in 27% of patients. Most common opportunistic infections due to hepatitis B virus (19%) and Varicella-zoster virus have occurred.

5.7 Pyrexia
Pyrexia was reported in 39% of patients treated with BRUKINSA monotherapy. Two patients (1.2%) developed pyrexia >38° C during treatment. In one patient, the pyrexia was associated with worsening of the patient’s underlying baseline infection.

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.

7.4 CYP3A Interactions
Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

8.1 Pregnancy
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily.

8.3 Lactation
There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or adverse reactions in patients with hepatic impairment

9.3 Postmarketing Experience
Other serious clinical adverse reactions that occurred in <10% of patients with mantle cell lymphoma include major hemorrhage (defined as ≥ Grade 3 hemorrhage or CNS hemorrhage of any grade), hypertension (6%), and headache (4%).
Infections and infestations
Upper respiratory tract infection\(a\)
44 0 40 2
Pneumonia
12 4 26 10
Urinary tract infection
11 0 13 2
Gastrointestinal disorders
Diarrhea
22 3 34 2
Nausea
18 0 13 1
Constipation
16 0 7 0
Vomiting
12 0 14 1
General disorders and administration site conditions
Fatigue\(a\)
31 1 25 1
Paresthesia
16 4 13 2
Edema peripheral
12 0 20 2
Skin and subcutaneous tissue disorders
Brutus\(a\)
20 0 34 0
Rash\(a\)
9 29 0 32 0
Pruritus
11 0 6 0
Musculoskeletal and connective tissue disorders
Musculoskeletal pain\(a\)
45 8 39 2
Muscle spasms
10 0 28 1
Nervous system disorders
Dizziness
13 1 12 0
Respiratory, thoracic and mediastinal disorders
Cough
16 0 18 0
Gynecomastia
14 0 7 0
Vascular disorders
Hypertension\(a\)
42 4 43 3
Hemorrhage\(a\)
14 9 19 14

\(a\)Brutus includes all related terms containing ‘bruise’, ‘contusion’, or ‘ecchymosis’.

Hematologic abnormalities
Neutrophils decreased
50 24 34 9
Platelets decreased
35 8 39 5
Hemoglobin decreased
20 7 20 7
Chemistry abnormalities
Mineral decreased
12 1.0 33 1.0
Calcium decreased
27 2.0 26 0
Creatinine increased
31 1.0 21 0
Glucose increased
45 2.3 33 2.3
Potassium increased
24 2.0 12 0
Urate increased
16 3.2 34 6
Phosphate decreased
20 3.1 18 0

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BRUKINSA(a)</th>
<th>Brutus(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic abnormalities</td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>50 24</td>
<td>34 9</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>35 8</td>
<td>39 5</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>20 7</td>
<td>20 7</td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Mineral decreased</td>
<td>12 1.0</td>
<td>33 1.0</td>
</tr>
<tr>
<td>Calcium decreased</td>
<td>27 2.0</td>
<td>26 0</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>31 1.0</td>
<td>21 0</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>45 2.3</td>
<td>33 2.3</td>
</tr>
<tr>
<td>Potassium increased</td>
<td>24 2.0</td>
<td>12 0</td>
</tr>
<tr>
<td>Urate increased</td>
<td>16 3.2</td>
<td>34 6</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>20 3.1</td>
<td>18 0</td>
</tr>
</tbody>
</table>

\(a\)Based on laboratory measurements.

The abnormality listed was calculated to be the rate (value) from 89 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

**Table 6: Laboratory Abnormalities (\(a\)%) That Were Observed in Patients with MZL Who Received BRUKINSA in Cohort 1**

Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count in practice.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice.

Rash includes all related terms containing rash.

Table 7: Adverse Reactions Occurring in ≥ 10% Patients with MZL Who Received BRUKINSA

**Table 8: List of Laboratory Abnormalities (\(a\)%) That Were Observed in Patients With MZL Who Received BRUKINSA in Cohort 1**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>BRUKINSA (N=101)</th>
<th>Brutus (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>26</td>
<td>3.4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea(a)</td>
<td>25</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising(a)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasm(a)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>Hemorrhage</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>General disorders</td>
<td>Fatigue</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>10</td>
</tr>
</tbody>
</table>

BRUKINSA is indicated for the treatment of adult patients with Waldenström’s macroglobulinemia (WM). 1.2 Waldenström’s Macroglobulinemia

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a

This indication is approved under accelerated approval based on overall response rate

fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included myocardial infarction, myocarditis, and a Covid-19 related death.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19 related death.

Serious adverse reactions occurred in 40% of the patients. The most frequent serious adverse reactions were pneumonia (5%) and pneumonitis (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%

For the BGB-3111-AU-003 trial, the median age was 62 years (range: 27 to 95). 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 or 1. 89% of patients were treated for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19 related death.

Serious adverse reactions occurred in 40% of the patients. The most frequent serious adverse reactions were pneumonia (5%) and pneumonitis (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%.
Booster mRNA COVID-19 Vaccine Helps Some Patients With Blood Cancer Produce Antibodies for First Time

MARY CAFFREY

A YEAR AFTER THE FDA allowed distribution of the first COVID-19 vaccines and a month after booster shots were authorized for Americans over age 18, a registry study has found that a third shot of mRNA vaccine could be crucial for some patients with blood cancers.1

Data presented by the Leukemia & Lymphoma Society (LLS) at the 2021 American Society of Hematology Meeting & Exposition show that 43% of patients with blood cancers will produce antibodies after receiving a third dose of mRNA vaccine. For most patients, this booster shot comes 6 months after the initial 2 doses, which are given either 3 or 4 weeks apart, depending on the vaccine.

Some patients who received their third dose reached antibody levels on par with healthy adults, confirmed by measuring levels of detectable antibodies to the spike protein in SARS-CoV-2 before and after the third dose of the mRNA COVID-19 vaccines. As of December 13, 2021, two such vaccines were in use in the United States: The Pfizer-BioNTech vaccine was fully approved for adults for the first 2 doses for those 16 years and older and authorized for those aged 5 to 15, and the Moderna vaccine had an emergency use authorization for those 18 years and older.

Results from a study based on the LLS registry demonstrated that patients with blood cancers who had at least some antibodies after the first 2 doses are likely to produce large amounts after they receive their boosters.

“Our data [show] a clear benefit of giving blood cancer patients 3 primary vaccine doses, but there is still a large portion of patients who will remain at risk even with the additional dose,” Lee Greenberger, PhD, LLS chief scientific officer, said in a statement.2

In this study, about 20% (139 of 699) of patients with blood cancer still had no measurable COVID-19 antibodies after the third dose. The results, reported December 11, 2021, come from the largest pool of patients with blood cancer reported thus far.

As of July 2021, the LLS registry includes 24 patients who received a third dose of an mRNA vaccine. Twenty of these patients were seronegative more than 14 days after their second shot, as measured by the Roche Elecsys assay; 4 patients had low positive serology results. All patients were nucleocapsid antibody negative.

These patients ranged in age from 51 to 79 years; 11 had chronic lymphocytic leukemia; 7, non-Hodgkin lymphoma; 5, Waldenström macroglobulinemia; and 1, multiple myeloma. As for therapy, 6 patients were not currently receiving anti–B-cell therapy; 11 had received anti-CD20 therapy, including 8 within the prior 6 months; 6 had received Bruton tyrosine kinase inhibitors within the past 6 months; and 1 had received recent chemotherapy.

Third shots were received between April and June 2021, 21 to 114 days after patients their second shot; clinical guidelines called for patients with cancer to get boosters first and have shifted to give the third shot earlier to some patients, with a fourth added later.

The abstract offered details of each patient’s type of therapy and response to the vaccine. “In this limited set of patients, there was no evident pattern of antibody response amongst patients who received homologous versus heterologous vaccine nor between disease types,” the authors wrote. “While anti-CD20 therapy appeared to reduce antibody response to booster vaccination, there was substantial heterogeneity.” In the authors noted that although patients with B-cell malignancies did not mount a robust response to the first 2 mRNA vaccines, several patients demonstrated an antibody response to the booster. The authors called for clinical trials to understand which patients may benefit from a booster strategy, whether prior therapy affects response to vaccines, and how to offer these shots safely.

REFERENCES

Findings Show Need for Earlier Conversations About End-of-Life Care With Patients Who Have High-Risk AML

MARY CAFFREY

RESULTS OF A STUDY of older adults with high-risk acute myeloid leukemia (AML) reveals missed opportunities for doctors to discuss end-of-life decisions when patients can still understand their options and express their wishes.3

The findings, presented during the 2021 American Society of Hematology Meeting & Exposition, come 6 years after the Institute of Medicine report Dying in America found that most clinicians fail to initiate conversations with patients about end-of-life preferences, especially if patients are poor or young or have less education.4 The need for better medical education in this area has received more attention over the past decade, but gaps remain.2
In the new study, investigators from Massachusetts General Hospital in Boston found that 60.5% of patients with AML took part in their final change of code status, the term used in hospitals and other health care settings to show whether lifesaving interventions will be given. The results suggest that 39.5% of the patients were too ill to take part in discussions about their own end-of-life care. This leaves families and clinicians to make choices about resuscitation or other measures without the patient’s participation, study author Hannah R. Abrams, MD, clinical fellow in medicine at Massachusetts General Hospital, said during a press briefing held during the meeting.

“The code status often reflects a deeper conversation happening between patients and clinicians about what the patient’s goals are. We found that patients and physicians are having these conversations very late in the course of disease...It’s not built into our clinic visits to talk about this earlier in a patient’s course with [acute myeloid leukemia].”

―Hannah R. Abrams, MD, clinical fellow in medicine, Massachusetts General Hospital

Among the patients, 86.0% were “full code,” and 8.5% had restrictions on life-sustaining therapies. Overall, 57% experienced a code status transition, with a total of 206 transitions across the group. The median time from diagnosis to the first code status transition was 212 days; most code changes took place in the final weeks of life, with a median of 2 days between the last code change and a patient’s death. More than half of the conversations leading to code status changes occurred when intensive life-sustaining measures were deemed futile and were transitions to comfort measures, whereas just 1 in 6 involved preemptive conversations held before a major health transition (15.6%). Two other processes that led to conversations were anticipatory conversations at the time of acute clinical deterioration (32.2%) and futility conversations after acute clinical conversations, focused on withdrawing life-sustaining therapies (51.0%).

Both older age and receipt of non-intensive chemotherapy were associated with a shorter period from the last code status transition to death compared with preemptive or anticipatory conversations. Investigators found that “a substantial minority” of the final code status transitions took place in the intensive care unit or emergency department (26.3%).

“It’s not built into our clinic visits to talk about this earlier in a patient’s course with AML,” Abrams said. Having these conversations preemptively during routine outpatient visits could help ensure that patients have an accurate understanding of their prognosis and help clinicians align treatment strategies with patients’ goals and preferences, she said. It is also important to have these discussions with patients more than once, because patients’ attitudes can shift as their disease progresses. Investigators found that palliative care specialists were involved in just 42% of final code transitions, pointing to an area of need for people with high-risk AML.

Sharing these data could lead to both clinicians and patients starting these conversations much earlier, allowing patients to be more involved in their own end-of-life care, she said.●

REFERENCES

CALL FOR PAPERS
We accept original research/informed commentary that can help translate clinical discoveries into better health outcomes and examine the impact of medical interventions on clinicians’ practice or health plans’ policies.

Benefits of publication with AJMC®:
• Indexing in many of the top scientific databases, including MEDLINE/PUBMED, Current Contents/Clinical Medicine, EMBASE, and Science Citation Index Expanded.
• Considerable exposure through multi-platform opportunities.
• Circulation to more than 48,000 readers across HMO/PPO/HMOs, hospitals, long-term care, PBMs, VA/gov, and employers.

Please submit all manuscripts for consideration: http://mc.manuscriptcentral.com/ajmc
Also, view our calls for papers at: AJMC.com/link/cfp
Elizabeth L. Budde, MD, PhD: Mosunetuzumab Shows Promise in R/R Follicular Lymphoma

Produced by Matthew Gavidia

ELIZABETH L. BUDDE, MD, PhD, oncologist and associate professor, City of Hope, Duarte, California.

USING MOSUNETUZUMAB proved effective, with a manageable safety profile, in study participants with relapsed/refractory (R/R) follicular lymphoma (FL) who had received at least 2 prior lines of therapy, according to Elizabeth L. Budde, MD, PhD, an oncologist and associate professor at City of Hope in Duarte, California.

Budde is lead author of the abstract “Mosunetuzumab Monotherapy Is an Effective and Well-Tolerated Treatment Option for Patients With Relapsed/Refractory (R/R) Follicular Lymphoma (FL) Who Have Received ≥2 Prior Lines of Therapy: Pivotal Results From a Phase 1/2 Study.”

Results were presented at the 2021 American Society of Hematology (ASH) Meeting & Exposition.

EVIDENCE-BASED ONCOLOGY™ (EBO): Can you describe the expanded phase 1/2 results presented at ASH 2021 on mosunetuzumab for patients with relapsed/refractory follicular lymphoma?

BUDDE: In our study, the pivotal phase 2 trial, using mosunetuzumab as a monotherapy for patients with follicular lymphoma who had at least 2 prior lines of therapy, we actually restricted these patients to needing at least 1 anti-CD20 therapy and an alkylating agent.

The majority of patients—a total of 90—were double refractory; also, most of them were refractory to prior lines of anti-CD20 therapy. More importantly, more than half of the patients had POD24 [progression of disease within 2 years]. POD24 is what we call a subset of patients with follicular lymphoma who had initial treatment but subsequently relapsed or [became] refractory within 24 months of initial treatment. These patients are historically known to be very difficult to manage, and they have follicular lymphoma with very aggressive and poor prognosis.

In our study, the 90 patients are treated regardless of if they have POD24—regardless of any of those historical poor factors. They all responded the same. The overall response rate is 80%, and the CR [complete response] rate is 60%, and it does not matter what kind of risk factors they have. So this is quite convincing, and I think it’s a good statement to support the different mechanisms of action and the power of immunotherapy to overcome the resistance of the follicular lymphoma cells to otherwise conventional treatment.

EBO: Would you discuss the potential of mosunetuzumab as a cost-effective option for patients with relapsed/refractory FL prior to consideration for chimeric antigen receptor (CAR) T-cell therapy?

BUDDE: It’s not clear with mosunetuzumab—once it’s approved, which I hope will be early [in 2022]—what the price tag will be. But given the different delivery route—meaning that mosunetuzumab is off the shelf—it would be available immediately, and there’s no involvement of ex vivo manufacturing [and] no cell expansion, as well as no requirement of lymphodepletion, which is part of the CAR T-cell therapy.

In addition to this, note, with its manageable safety profile, I suspect the cost of mosunetuzumab will be lower than that of CAR T-cell therapies. But it’s given in multiple cycles—so, 8 cycles for patients who achieve complete remission, and it can be given up to 17 cycles for patients who are not in remission; for example, a patient with stable disease or with a partial response.

It’s difficult for me as a researcher and clinician to really map out the exact comparison between these 2, but I think there’s definitely an advantage to giving mosunetuzumab in the community setting. I hope the associated cost will be very reasonable.

“We’re testing giving mosunetuzumab subcutaneously instead of intravenously to see if we can further reduce the incidence of cytokine release syndrome and make it even safer.”

—Elizabeth L. Budde, MD, PhD, associate professor, City of Hope

EBO: What are some next steps following the findings presented at ASH?

BUDDE: The focus is to optimize the way we give mosunetuzumab. We’re testing mosunetuzumab given subcutaneously instead of intravenously to see if we can further reduce the incidence of cytokine release syndrome and make it even safer.

Of course, we’re also testing mosunetuzumab in combination with lenalidomide [Revlimid]. This is also in patients with relapsed/refractory follicular lymphoma. And we know [the] rituximab [Rituxan] and lenalidomide combination is a good regimen that can also benefit multiple patients. Therefore, a phase 3 study is now comparing mosunetuzumab in combination with lenalidomide vs rituximab in combination with lenalidomide. It’s being conducted in patients with relapsed/refractory follicular lymphoma.

The goal is to try to further improve the overall response rate and complete response rate, as well as the original response, and maintain the safety profile. In addition, ongoing studies are investigating mosunetuzumab in follicular lymphoma, as well as the use of mosunetuzumab either alone or combined with other drugs—for example, polatuzumab [Polivy]—in patients with aggressive B-cell lymphoma or mantle cell lymphoma with various stages of disease in an up-front or a relapsed/refractory setting.

REFERENCE

Sub-Q Isatuximab Combo Offers Safety, Efficacy Profile Comparable With Phase 3 Results in IV Formulation

MARY CAFFREY

RESULTS FROM A PHASE 1B STUDY of subcutaneous (sub-Q) isatuximab, used along with pomalidomide and dexamethasone, produced safety and efficacy results consistent with those seen in the phase 3 study that led to FDA approval of intravenous (IV) isatuximab with this combination to treat relapsed and refractory multiple myeloma (RRMM) in patients who have received at least 2 prior therapies.1,2

The findings were presented during the 2021 American Society of Hematology Meeting & Exposition, held in Atlanta, Georgia, and online.1 Isatuximab, sold as Sarclisa, was approved in March 2020 to treat certain patients with RRMM based on results of the ICARIA-MM study (NCT02990338), which found that isatuximab added to pomalidomide (Pomalyst) and dexamethasone demonstrated significant progression-free survival (PFS) of 11.53 months compared with 6.47 months with pomalidomide and dexamethasone alone (HR, 0.596; 95% CI, 0.44-0.81; P = .001).2

This triplet combination also demonstrated an improved overall response rate (ORR) compared with pomalidomide and dexamethasone: 60.4% vs 35.3% (P < .0001).

Pharmacists have heralded sub-Q drug delivery in multiple myeloma as more convenient for patients and more efficient for hospital administrators; the arrival of sub-Q delivery for isatuximab gives this anti-CD38 therapy a feature achieved by a competitor, daratumumab (Darzalex).

The multicenter, open-label study presented at ASH 2021 evaluated the safety, pharmacokinetics (PKs), and efficacy of sub-Q vs IV isatuximab and pomalidomide in patients with RRMM who had received at least 2 prior treatments, including lenalidomide and a protease inhibitor.

Patients were randomized 2:1 to receive sub-Q 1000-mg isatuximab or IV 10-mg/kg isatuximab. Following evaluation of the safety, PKs, and CD38-receptor occupancy of isatuximab in the sub-Q formulation, new patients were randomized in 2 new cohorts to receive sub-Q 1400 mg or IV 10 mg/kg. Both formulations were administered once weekly for 4 weeks (cycle 1) and then every 2 weeks in combination with pomalidomide.

Primary end points assessed safety, including dose-limiting toxicity, injection-site reactions, and PK parameters. Secondary end points included ORR, PFS, CD38 receptor occupancy, and patient-reported outcomes.

Of the 34 patients randomized and treated, 12 received IV isatuximab 10 mg/kg with pomalidomide; 12, isatuximab sub-Q 1000 mg with pomalidomide; and 10, isatuximab sub-Q 1400 mg with pomalidomide. As of March 31, 2021, 7 patients (58%) from the IV group, 14 (33%) from the sub-Q 1000-mg group, and 7 from the sub-Q 1400-mg group remained on treatment.

The median time from the initial multiple myeloma diagnosis to the first study treatment was approximately 5 years; average number of prior lines of therapy was 3.5, with a range of 2 to 7 in the IV cohort, 2 to 6 in the sub-Q 1000-mg cohort, and 1 to 4 in the sub-Q 1400-mg group. When patients entered this study, the International Staging System classified them 58.4%, 33.3%, and 60.0%, respectively. Due to time of accrual, follow-up was longer with the IV patients.

SAFETY. Infusion reactions were infrequent, with less than 10% across all groups, and all grade 2 and at the first infusion. Local tolerability of the sub-Q infusion was very good, with a single instance of grade 2 site reaction of erythema and pain. There were similar instances of grade 3 or higher treatment-emergent adverse events and neutropenia across all groups and no treatment-related events that led to death or premature discontinuation.

There was 1 case of neutropenia in the sub-Q 1000-mg group and 1 case of pulmonary infection in the sub-Q 1400-mg group. No maximum tolerated dose was identified.

OUTCOMES. At 8 months, PFS was 73% in the IV and sub-Q 1000-mg groups and 89% in the sub-Q 1400-mg group. ORR, very good partial, and complete response rates were 66.7%, 33%, and 16.7%, respectively, in the IV group; 66.7%, 41.7%, and 25% in the sub-Q 1000-mg group; and 80%, 49%, and 20% in the sub-Q 1400-mg groups.

The authors concluded that sub-Q isatuximab and pomalidomide administration “appears to be a promising and convenient option for patients with RRMM.”

REFERENCES


JANUARY 2022 | AJMC.COM

Phase 1/2 Trial Results Underscore Teclistamab’s Efficacy in RRMM

GIANNA MELILLO

UPDATED RESULTS of the MajesTEC-1 phase 1/2 study on teclistamab show that the treatment resulted in an overall response rate (ORR) of 62% (95% CI, 53.7%-69.8%) among patients with relapsed/refractory multiple myeloma (RRMM), suggesting that treatment responses were durable and deepened over time. These additional findings were presented at the 2021 American Society of Hematology Annual Meeting & Exposition.

Teclistamab is a T-cell–redirecting, bispecific immunoglobulin G4 antibody that targets the B-cell maturation antigen (BCMA) and CD3 receptors to induce T-cell-mediated cytolysis of BCMA-expressing myeloma cells, researchers explained.

The off-the-shelf therapy is manufactured by Janssen and received a Breakthrough Therapy Designation from the FDA in June 2021. Results of prior preclinical studies revealed that teclistamab »
killed myeloma cell lines and bone-marrow-derived myeloma cells. The ORR was reported after a median follow-up of nearly 8 months in 150 patients who received the recommended subcutaneous (SC) phase 2 dose (RP2D) of 1.5 mg/kg across the phase 1 and 2 studies. All participants had received at least 3 prior lines of therapy and were triple-class exposed. In the phase 1 study, the researchers sought to identify the SC RP2D and to characterize the treatment’s safety and tolerability; phase 2 was carried out to determine efficacy at RP2D. Among responders, the median time to first confirmed response was 1.2 months (range, 0.2-5.5), while the ORR was consistent independent of cytogenetic risk or extent of prior therapy refractoriness. However, median duration of response was not reached at the clinical cutoff; at this time, 92 of 93 confirmed response was 1.2 months/uni\(^{50}\) (range, 0.2-5.5), and 91 of 92 patients were alive and continuing treatment. Median overall survival was also not reached. Additional findings include:

- 56% of patients receiving teclistamab achieved a very good partial response or better
- 29% achieved a complete response (CR) or better
- 21% achieved a stringent CR
- By intent to treat, 25% of patients achieved minimal residual disease (MRD) negativity at a threshold of 10\(^{-5}\) (95% CI, 18.0%-32.4%)
- In patients who achieved a CR or better, the MRD negativity rate was 42%
- Progression-free survival rate at 9 months was 59% (95% CI, 48.8%-67.0%)

Throughout the course of the trial, no patients required a dose reduction and the most commonly reported adverse events (AEs) were cytokine release syndrome (CRS; 72%), injection-site erythema (26%), and fatigue (25%). One patient discontinued use due to adenoviral pneumonia. All CRS events were low grade, with the exception of one grade 3 event, and all resolved without treatment discontinuation.

Neutropenia, anemia, and thrombocytopenia were the most common hematologic AEs reported, while 5 patients developed immune effector cell-associated neurotoxicity syndrome.

A phase 3 study is currently underway, in part to evaluate the treatment in earlier-line settings and in combination with other agents. Additional data regarding patients with prior BCMA will also be reported.

**REFERENCE**


**NEW**

“iStopMM: Investigators From Iceland Report First Results of Population-Based Screening for Multiple Myeloma

**MARY CAFFREY**

**BEFORE THE BLOOD CANCER**

multiple myeloma (MM) develops, clinicians can detect precursor conditions, including monoclonal gammopathy of undetermined significance (MGUS), or related lymphoproliferative disorders (LPs). If patients receive a diagnosis at this stage, the chances of survival are greatly improved, but less than 5% of cases are caught at this point.

Five years ago, investigators in Iceland led by Sigurdur Kristinsson, MD, PhD, professor of hematology at the University of Iceland in Reykjavik, sought to evaluate what would happen if screening for MGUS were widely available: Would it lead to an improvement in overall survival?

They launched the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study (NCT03327597), described as “the first population-based screening study for MGUS that includes a randomized clinical trial of follow-up and treatment strategies.”

Early results from iStopMM were presented in 4 abstracts during the 2021 American Society of Hematology Meeting & Exposition, held in Atlanta, Georgia, and online.

In a video prepared for the International Myeloma Foundation, Kristinsson outlined the scope and mission of the project. “No one has ever done anything like this before—ever....The president of Iceland was the first to give informed consent.”

—Sigurdur Kristinsson, MD, PhD, professor of hematology, University of Iceland, Reykjavik, Iceland

Although early results are “encouraging” and show that following patients with detected MGUS closely does yield more positive diagnoses, investigators are cautious. “Until final results of the iStopMM study become available, including data on survival and quality of life, we advise against systematic MGUS screening in healthy individuals,” they wrote.

According to the study authors, iStopMM was open to all Iceland residents born before 1976. Of the 148,708 eligible residents, just over half (54.3%; 80,759) provided consent for screening, and serum samples were collected over a 4-year period through the end of 2020. Investigators collected samples from 75,422 people (93.4%) who provided their initial consent. Investigators collected samples from 75,422 people (93.4%) who provided their initial consent.

Samples were tested for M proteins and free light chains; those with a prior diagnosis of MGUS were excluded. Per protocol and informed consent, those found to have MGUS were randomized to 3 study arms. Arm 1’s 1164 participants...
were not contacted, arm 2’s 1159 participants were followed based on current guidelines, and arm 3’s 1164 participants will be given intensive diagnostic and monitoring. Those who progress will receive early treatment.

Of the participants screened, 3725 (4.9%) were found to have MGUS over the course of the study. The condition was more likely to be seen as participants grew older: 2.3% among those aged 40 to 59 years; 6.2%; 60 to 79 years; 12.9%; 80 to 103 years. MGUS prevalence was higher in men than women (5.9% vs 4.1%). Most participants were low risk (38%) or low to intermediate risk (36%); 26% had high-intermediate risk, and high-risk MGUS was seen in just 0.2% of cases (9 participants).

After a median follow-up of 3 years, 194 patients were identified with MGUS. Of these, 1164 participants will be given intensive diagnostic and treatment. Most participants were low risk (1124) with a complete response rate of 83% now at 2 years’ worth of follow-up. You don’t even see that type of response rate or stringent CR rate even with quad therapy, followed by transplant, followed by consolidation.

WILDGUST: [During ASH,] we presented the updated data from the cilta-cel phase 1b/2 study, where we now have up to 2 years’ worth of follow-up for the patients. But what we really see is that with longer follow-up, we still haven’t reached the median progression-free survival (PFS) at 2 years. Actually at 2 years, the PFS is around 60%.

[You’re really asking], what do the data look like in terms of these meta-analyses that we have done and we presented, as well as the comparison vs the LocoMMotion study? From a clinical perspective, for myself, it’s somewhat clear that the data that we’re seeing from cilta-cel are transformational.

In a separate abstract, the investigators found that they “did not find MGUS to be associated with SARS-CoV-2 susceptibility or COVID-19 severity. This is contrary to MM, which is preceded by MGUS.” The findings, they wrote, suggest that the immunosuppression in MGUS is different from that in MM, which has important implications for management and treatment.

REFERENCES

CHALLENGES
1. The use of CAR-TITUDE-1 data in comparison with LocoMMotion data represented a creative way to evaluate therapies that could offer guidance on the ability of cilta-cel to meet unmet needs in multiple myeloma. Can you speak on this abstract?

WILDGUST: We looked at [the data for] cilta-cel vs the LocoMMotion study, and I think that [compares] another piece of really trying to understand how the cilta-cel data and the phase 1b/2 study look vs standard of care—[along with, as] I talked about just a few moments ago, the meta-analysis that we did.

Probably one of the most robust ways of looking at that is to observe a prospective observational cohort, where you collect in real time •

CLINICAL SPOTLIGHT
Mark Wildgust, PhD, Reviews Key Cilta-Cel Research Presented at ASH 2021
Produced by Matthew Gavidia

MARK WILDGUST, PHD, vice president, Global Medical Affairs, Oncology, Janssen

FINDINGS PRESENTED AT the 2021 American Society of Hematology (ASH) Meeting & Exposition on cilta-cel, showed potential as a transformational therapeutic option in multiple myeloma, with patient outcomes significantly improved vs standard-of-care or physician’s choice of therapy, said Mark Wildgust, PhD, vice president, Global Medical Affairs, Oncology, Janssen.

This interview is slightly edited for clarity.

EVIDENCE-BASED ONCOLOGY (EBO): Several studies were presented at ASH 2021 involving cilta-cel, including a meta-analysis of cilta-cel vs physician’s choice of therapy. What are the most significant findings on cilta-cel for relapsed/refractory patients with triple-class exposed multiple myeloma?

WILDGUST: [During ASH,] we presented the updated data from the cilta-cel phase 1b/2 study, where we now have up to 2 years’ worth of follow-up for the patients. But what we really see is that with longer follow-up, we still haven’t reached the median progression-free survival (PFS) at 2 years. Actually at 2 years, the PFS is around 60%.

[You’re really asking], what do the data look like in terms of these meta-analyses that we have done and we presented, as well as the comparison vs the LocoMMotion study? From a clinical perspective, for myself, it’s somewhat clear that the data that we’re seeing from cilta-cel are transformational.

We’re seeing a response rate of 98%; we’re seeing a stringent CR [complete response] rate of 83% now at 2 years’ worth of follow-up. You don’t even see that type of response rate or stringent CR rate even with quad therapy, followed by transplant, followed by consolidation.

But I think that it’s a reasonable question: What does this look like vs standard of care?

When you think about standard of care for somebody who is refractory to their last line of therapy—is triple refractory—the outcomes for those patients are poor. So, from an equipoise perspective, you can’t really do a randomized study of cilta-cel vs standard of care. One way we can address that is to take a look at real-world data sets, and that’s exactly what we did.

We looked at data from Flatiron Health, from MAMMOTH. We looked at data from a number of other sources, even including our own data from daratumumab studies in terms of what they got later. What we see is a consistent benefit in terms of using cilta-cel instead of that kind of physician’s choice in those late lines of therapy.

I think that gives us more confidence and confirmation that what we’re seeing in the cilta-cel study, for the clinicians and scientists out there, is transformational. I think that comparative data vs real-world data really just confirm that in many ways—[these data] cross any T’s and dot any I’s [that remain].

EBO: The use of CAR-TITUDE-1 data in comparison with LocoMMotion data represented a creative way to evaluate therapies that could offer guidance on the ability of cilta-cel to meet unmet needs in multiple myeloma. Can you speak on this abstract?

WILDGUST: We looked at [the data for] cilta-cel vs the LocoMMotion study, and I think that [compares] another piece of really trying to understand how the cilta-cel data and the phase 1b/2 study look vs standard of care—[along with, as] I talked about just a few moments ago, the meta-analysis that we did.

Probably one of the most robust ways of looking at that is to observe a prospective observational cohort, where you collect in real time •

We looked at the comparison vs the LocoMMotion study. One way we can address that is to take a look at real-world data sets, and that’s exactly what we did.

We looked at data from Flatiron Health, from MAMMOTH. We looked at data from a number of other sources, even including our own data from daratumumab studies in terms of what they got later. What we see is a consistent benefit in terms of using cilta-cel instead of that kind of physician’s choice in those late lines of therapy.

I think that gives us more confidence and confirmation that what we’re seeing in the cilta-cel study, for the clinicians and scientists out there, is transformational. I think that comparative data vs real-world data really just confirm that in many ways—[these data] cross any T’s and dot any I’s [that remain].

EBO: The use of CAR-TITUDE-1 data in comparison with LocoMMotion data represented a creative way to evaluate therapies that could offer guidance on the ability of cilta-cel to meet unmet needs in multiple myeloma. Can you speak on this abstract?
the data for what patients are getting. That LocoMMotion study was enrolled in 9 countries in Europe and in the United States as well. The first thing that you see, looking at the standards of care in those late lines of therapy, is that there were 91 different regimens used, which really shows you that there is no standard of care and that there’s a real lack of treatment options, Really, physicians are trying anything they can [at that point], because [they] have run out of treatment.

When we looked at those LocoMMotion data, we saw between a 30% and 40% response rate, a PFS of about 3 months, and an overall survival [OS] of between 9 and 12 months. So, the outcomes for that prospective observational cohort were poor.

“One aspect of cilt-a-cel that we’re really starting to see now is that in those patients who are achieving a sustained minimal residual disease negativity, or sustained kind of remission...that the data on MRD [negativity] for 6 or 12 months suggest that those patients have really transformational outcomes in terms of [progression-free survival].”

—Mark Wildgust, PhD, vice president, Global Medical Affairs, Oncology, Janssen

In the presentation at ASH, we actually compared, in a propensity-matched way, really comparing side by side, the cilt-a-cel data vs those LocoMMotion data. You can kind of almost step up the quality of that type of work by looking at that prospective observational cohort. It was designed in a way where we could actually match the parameters and match the patients from LocoMMotion to the phase 1b/2 study, so we can really take patients who are like for like and make that type of comparison—again, without randomizing patients, [because] I think there would be concern from an equipoise perspective. What we see is a hazard ratio of about 0.15 for PFS and a hazard ratio of 0.2 for OS, [both] in favor of cilt-a-cel. You’re seeing an 80% reduction in the risk of death with cilt-a-cel. This is another data set that really confirms what I think a lot of clinicians feel: that cilt-a-cel is really providing a transformational kind of step forward in terms of outcomes for patients.

EBO: What are some future considerations regarding cilt-a-cel?

WILDGUST: One aspect of cilt-a-cel that we’re really starting to see now is that in those patients who are achieving a sustained minimal residual disease [MRD] [negativity], or sustained kind of remission— as you saw when Tom Martin, MD, presented those data—that the data on sustained MRD [negativity] for 6 or 12 months suggest that those patients have really transformational outcomes in terms of PFS.

Median PFS of more than 2 years in this patient population is remarkable. Bear in mind, in LocoMMotion, it was 3 months, and OS was 9 months. Here, you’ve got 60% of patients still progression free—60% of them—at 2 years. And then you start to look at those individuals who had sustained MRD negativity. At 2 years, for those patients who had sustained MRD negativity for 6 months, you have a PFS of 92%, and those who had sustained MRD negativity for 12 months had 100% PFS.

So, I think the data are really starting to suggest that in those patients taking cilt-a-cel—those patients getting to that deep response, which we see are more than 80% getting stringent CRs—that the durability of response is really something that we perhaps have not seen before. While the data look fantastic in the relapse setting, I think the most exciting piece now is when we go into earlier lines of therapy. We’re excited [about] opening up the CARTITUDE-5 study, which is our first study in the treatment-naïve setting.

REFERENCES
Racial Disparities Are Seen in Survival Among Pediatric Patients With Acute Lymphoblastic Leukemia

MARY CAFFREY

WHITE PATIENTS WITH acute lymphoblastic leukemia (ALL) had 5-year event-free survival (EFS) rates that were significantly higher than those seen among Hispanic and Black patients in a study of nearly 25,000 young people by the Children’s Oncology Group (COG). The findings were presented during 2021 American Society of Hematology Meeting & Exposition, held in Atlanta, Georgia, and online.

Of note for policy makers, US children with Medicaid coverage have lower survival rates than those not in Medicaid. But more surprising was the fact that children in the study living outside the United States—in countries such as Canada, Australia, or New Zealand—had event-free survival 29% higher than that of White children in the United States.

Sumit Gupta, MD, PhD, associate professor, Department of Pediatrics, The Hospital for Sick Children in Toronto, Canada, said that biological or genetic factors accounted for some of the gap in survival rates, but not all. “Our study shows that race- and ethnicity-based disparities continue to exist and are substantial,” Gupta said. “All groups do well overall, but some do substantially better than others.”

For the study, investigators examined a cohort of 24,979 children, adolescents, and young adults with ALL; about 92% were US residents. Patients who were non-Hispanic White accounted for 13,872 (65.6%) of the group, followed by 4354 (20.6%) who were Hispanic and 1517 who were non-Hispanic Black.

A little more than a quarter (27.8%; 6944 patients) were covered by US Medicaid. The 5-year EFS was 87.4% (±0.3%) among non-Hispanic White patients vs 82.8% (±0.6%) for Hispanic patients (HR, 1.37; 95% CI, 1.25–1.49; P < .0001) and 81.9% (±1.2%) for non-Hispanic Black patients (HR, 1.45; 95% CI, 1.28–1.56; P < .0001). Investigators reported that outcomes for non-Hispanic Asian patients were similar to those of White patients.

INSURANCE STATUS. US patients on Medicaid had worse outcomes compared with other US patients. Medicaid was associated with a 5-year EFS of 83.2% vs 86.3% for US patients not on Medicaid, (HR, 1.21; 95% CI, 1.12–1.30; P < .0001). Patients outside the US who were in this cohort had even better outcomes in 5-year EFS (89.0%; HR, 0.78; 95% CI, 0.71–0.88; P < .0001). However, this group was small relative to the overall group at 3151 patients.

EXPLANATIONS FOR THE FINDINGS. Gupta said the investigators sought to identify how these disparities could be explained by imbalances in other prognosticators. “For example, socioeconomic status did, unsurprisingly, vary by race ethnicity—50% of Hispanic patients were on Medicaid vs less than 20% of non-Hispanic White patients,” he said. “Similarly, disease prognosticators also vary by race and ethnicity.”

Investigators found that the worse outcome in EFS among Hispanic patients was substantially attenuated by the addition of disease prognosticators, with HR reduced from 1.37 to 1.17; this was further attenuated by including socioeconomic status (SES; HR, 1.11).

By contrast, investigators wrote, “the increased risk among non-Hispanic Black children (initially HR 1.45) was minimally attenuated by both the addition of disease prognosticators (to HR 1.38) and subsequent addition of SES (to HR 1.32).”

Notably, this process produced patterns in which “disparities in overall survival were wider than those seen in event-free survival,” Gupta said.

During the session, participants brought up possible confounders such as increased obesity rates or pulmonary arterial hypertension rates among Hispanic patients. Each of these may tell part of the story, and all are worth exploring.

“It is possible that there is residual confounding by disease prognosticators here that we did not fully account for,” Gupta said. “However, that seems unlikely to explain the full medical experience we’re seeing, so that we are then left with somewhat uncomfortable mechanisms to talk about such as differential access to care, differential quality of care.

“And when we use the unfortunately politically charged ‘systemic racism’ or another term, the possibility that even pediatric oncology health care systems are systematically delivering disparate care to patients across racial groups.”

B-ALL VS T-ALL. A key difference uncovered by this process is fact that disparities “restricted to children with B-ALL,” and not those whose leukemia is of T-cell lineage, Gupta noted, as he presented a slide showing the differences in the data.

During the press briefing, Gupta also stated, “The treatment [for both types of ALL] is pretty similar and delivered by the same centers.” Typically, a patient receives 8 to 10 months of intensive therapy followed by 18 to 24 months of lower-intensity or maintenance treatment. This second phase is where investigators may need to look for explanations for survival gaps, he said.

“There isn’t quite as much control and not quite as much monitoring that oncologists will do,” he said. “Maybe if, across these ethnic and racial groups, we’re delivering different care and maintenance, that might explain some of those findings.”

REFERENCE
Lori Muffly, MD, MS, Spotlights Disparities in Clinical Trial Enrollment, Patient Outcomes in Pediatric ALL

Produced by Matthew Gavidia

LORI MUFFLY, MD, MS associate professor of medicine (blood and marrow transplantation and cellular therapy), Stanford University.

We came to the conclusion that likely thinking about a priori when a trial is designed—thinking about how site location may affect the distribution of different subgroups within the trial—is, I think, really important.

EBO: What notable differences by race/ethnicity were observed in clinical trial participation and patient outcomes for AYAs given the study's pediatric-inspired ALL regimen? How may findings influence future clinical trial enrollment criteria for these patient populations?

MUFFLY: We then looked at outcomes on study based on background. So, we looked at the Hispanic AYAs enrolled on study relative to the non-Hispanic White population, which was a much larger population relative to the non-Hispanic Black AYAs who enrolled on trial. In population data in the United States—and this has been shown in a multitude of ways—in AYA ALL, Hispanic and Black populations tend to do significantly worse than non-Hispanic White populations.

There have been a lot of reasons, including ALL biology that had been posited to explain this difference. In our study, we actually found that the Hispanic patients on trial did as well as the non-Hispanic White patients. It’s difficult to compare trial data with population-based data, but the trial outcomes for the Hispanic population were better than what would be expected based on the population estimate.

So, we made somewhat of a leap to say it’s possible that if these patients can get onto clinical trials—and this was a big clinical trial and led to, really, a treatment change in this country for young adults—then the potential to do better is possibly there.

EBO: What efforts should be considered to improve access and uptake to cancer clinical trials in underserved communities, and what further research is warranted specific to ALL and other cancers known to have great impact on minority populations?

MUFFLY: This is an area of great interest to me. I have been studying patterns of care and access to care in ALL for a while. In one of our studies from a couple of years ago, we noted that there is great dispersion of care for this potentially curable leukemia in this country.
So, with patients under the age of 18, about 90% of that population is treated at centers that have access to clinical trials that have designation from the Children’s Oncology Group or the NCI (National Cancer Institute) as being a specialty cancer center. However, once you get over the age of 18 in the state I live in, California, that flips dramatically, and over half of the patients are treated at centers that don’t have ALL-specific clinical trials or readily accessible studies.

I think it speaks to the patterns of treatment in this country, and I think that we need to start looking more at how outcomes differ based on where patients are treated for curable diseases in young people, because our studies in the past have shown that there is a difference in outcome. I also think that for investigators and companies planning clinical trials, the only way to make this geographic alignment better is to think about it in the beginning—to make it a priority. So, if you’re running an ALL trial, have some idea of what the cancer incidence is in the areas in which you’re planning to open the trial, because it’s no surprise that if you go to places that have very low rates of Hispanic people, your trial is not going to look like the true ALL population in this country.

I think this is a very important topic right now. I’ve been sitting at ASH and hearing all these abstracts on similar topics, and I think the time is now. We need to invest in ways, research, and interventions to really change this, because there are things we can do that are not so hard, and I think it’s just time that we really [need to] invest in to make it a priority.

**REFERENCE**


---

**Most Medicare Beneficiaries With CLL Diagnosis Don’t Get Therapy, Claims Analysis Finds**

**MARY CAFFREY**

**AN ANALYSIS OF MEDICARE CLAIMS** by University of Maryland investigators found that just 16% of beneficiaries who have a diagnosis of chronic lymphocytic leukemia (CLL) ever receive treatment, and the likelihood of receiving therapy declines as patients reach advanced age or if they are female.

Investigators from the Department of Pharmaceutical Health Services Research and the Department of Medicine at the University of Maryland in College Park, along with investigators from BeiGene, examined these patterns through a claims study, which involved Medicare beneficiaries who received a diagnosis of CLL from 2017 to 2019. The results were presented in a poster during a session on health outcomes research at the 2021 American Society of Hematology Meeting & Exposition in Atlanta, Georgia.

According to the authors, 67% of patients with a new diagnosis of CLL are at least 65 years old. Thus, Medicare reimbursement policy has an outsize effect on access to care for the majority of the CLL patient population in the United States.

“While new agents and treatment combinations have been approved for CLL and treatment guidelines take into consideration age, frailty, and comorbidity status, limited information exists on current prescribing patterns or the demographic and clinical characteristics of individuals receiving them,” the study authors wrote.

Investigators used the Chronic Conditions Data Warehouse and identified Medicare beneficiaries with billing codes. Patients were included in the study if they (1) were 65 years or older and (2) were not treated for CLL during a continuous 6-month period when they were also enrolled in Medicare parts A, B, and D at baseline, with no evidence of enrollment in Medicare Advantage.

An index date was triggered by the date of first claim with a CLL diagnosis code during the cohort identification period, which ran from July 1, 2017, to June 30, 2019. Individuals were followed from the index date until they lost Medicare eligibility; until death, or until the end of the study, whichever came first. CLL treatments were evaluated based on whether they were included in the National Comprehensive Cancer Network guidelines; individuals were grouped by which treatment they received first.

CLL treatments included rituximab (Rituxan) monotherapy, ibrutinib (Imbruvica) monotherapy, bendamustine/rituximab (BR), obinutuzumab, and other treatment. Data points included share of patients who received first course of treatment, top-ranked regimens in the first course, median time to starting first course, and time in days from index date to initiation. The team created a visual representation of individual data points, adding demographic data, preventive health scores, and Charlson Comorbidity Index scores to see which factors made treatment more or less likely.

**RESULTS.** The investigators reported a covariate-adjusted odds ratio (AOR), and an AOR less than 1 shows that “the comparison was negatively associated with the receipt of CLL treatment,” they said.

Investigators identified 3440 patients with CLL for evaluation; of these, just 16% (550) received CLL treatment, and the mean follow-up time was 540 days. Of the overall group, the mean age was 77 years; 49% were male.

Of the 556 treated patients, the first course of treatment was rituximab in 34%, BR in 12%, obinutuzumab in 4%, and other treatment in 14%. The mean (interquartile range) time to receipt of CLL treatment was 61 days; the median time to receipt of different therapies was as follows: ibrutinib, 109 days; rituximab, 49 days; BR, 53 days; and obinutuzumab, 140 days.

Less than half the patients in the BR group completed the recommended 6 doses. Compared with those in the rituximab group, a larger share of the ibrutinib and BR groups remained on their first treatment course.

Among Medicare beneficiaries diagnosed with CLL, less than 2 out of 10 patients received CLL treatment,” they concluded. “The most common treatments administered during this time period were ibrutinib or rituximab. Younger age and male gender were factors associated with increased receipt of treatment.”

**REFERENCE**

TeCENTRIQ®
atezolizumab

NOW APPROVED IN PD-L1+ STAGE II-IIIA NSCLC

ADVANCING THE STANDARD OF ADJUVANT TREATMENT

TeCENTRIQ: The first and only FDA-approved adjuvant immunotherapy in PD-L1+ (TC ≥1%) NSCLC, offering new hope in the fight against stage II-IIIA* disease.

*Per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition.

Indication
TeCENTRIQ, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II-IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥1% of tumor cells, as determined by an FDA-approved test.

Important Safety Information

Severe and Fatal Immune-Mediated Adverse Reactions
TeCENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions can occur in any organ system or tissue and at any time after starting TeCENTRIQ. While immune-mediated adverse reactions usually manifest during treatment with TeCENTRIQ, they can also manifest after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of TeCENTRIQ. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions.

In general, if TeCENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less, then initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other PD-1/PD-L1 blocking antibodies (including exacerbation), Guillain-Barré syndrome, nerve damage, osteoporosis, pancreatitis.

Other Immune-Mediated Adverse Reactions

Immune-mediated pneumonitis occurred in 3.8% (91/495) of patients receiving TeCENTRIQ alone as adjuvant treatment, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (0.6%) adverse reactions.

Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TeCENTRIQ alone, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions.

Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TeCENTRIQ alone, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions.

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

Genentech
A Member of the Roche Group

© 2021 Genentech USA, Inc. All rights reserved. M-US-00011907(v1.0)
Important Safety Information (cont’d)

**Immune-Mediated Endocrinopathies**

- **Adrenal Insufficiency**
  - TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated.
  - Adrenal insufficiency occurred in 12% (64/595) of patients with NSCLC receiving TECENTRIQ alone as adjuvant treatment, including Grade 3 (0.4%) adverse reactions.

- **Hypophysitis**
  - TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated.
  - Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ alone, including Grade 2 (1 patient, <0.1%) adverse reactions.

- **Thyroid Disorders**
  - TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hyperthyroidism or medical management for hypothyroidism as clinically indicated.
  - Thyroiditis occurred in 12% (64/595) of patients with NSCLC receiving TECENTRIQ alone as adjuvant treatment, including Grade 2 (0.4%) adverse reactions. Thyroiditis led to withholding of TECENTRIQ in 1 patient.
  - Hyperthyroidism occurred in 6% (32/595) of patients with NSCLC receiving TECENTRIQ alone as adjuvant treatment, including Grade 3 (0.4%) adverse reactions.
  - Hypothyroidism occurred in 17% (86/495) of patients with NSCLC receiving TECENTRIQ alone as adjuvant treatment.

- **Immune-Mediated Nephritis With Renal Dysfunction**
  - TECENTRIQ can cause immune-mediated nephritis.
  - Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ alone, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction.

- **Immune-Mediated Dermatologic Adverse Reactions**
  - TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.
  - Immune-mediated dermatologic adverse reactions occurred in 0.1% (5/2616) of patients receiving TECENTRIQ alone, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions.

- **Other Immune-Mediated Adverse Reactions**
  - The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received TECENTRIQ or were reported with the use of other PD-1/PD-L1 blocking antibodies.
    - **Cardiac/Vascular:** Myocarditis, pericarditis, vasculitis.
    - **Nervous System:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis.
    - **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in conjunction 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.
    - **Musculoskeletal and Connective Tissue:** Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.
    - **Endocrine:** Hypoparathyroidism.
    - **Other (Hematologic/Immunologic):** 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

- TECENTRIQ can cause severe or life-threatening infusion-related reactions. Interrupt, slow the rate of infusion, or permanently discontinue based on severity.

Complications of Allogeneic HSCT After PD-1/PD-L1 Inhibitors

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

Embryo-Fetal Toxicity

- TECENTRIQ can cause fetal harm when administered to a pregnant woman.

Use in Specific Populations

- Advise female patients not to breastfeed during treatment and for at least 5 months after the last dose.
- You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

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

References:


Learn more at TECENTRIQ-HCP.com/adjNSCLC
TECENTRIQ® (atezolizumab)

Initial U.S. Approval: 2016

This is a brief summary of information about TECENTRIQ. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

1.1 Indicated Cancer

TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

• are not eligible for platinum-containing chemotherapy and whose tumors express PD-L1 \( \geq 50\% \) of tumor cells (TC) or PD-L1 stained tumor-infiltrating immune cells (IC) \( \geq 10\% \) of tumor cells, as determined by an FDA-approved test (see Dosage and Administration (2.1)), or

• are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

This indication is approved under accelerated approval based on tumor response rate and durability of response (see Clinical Studies (14.2)). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Non-Small Cell Lung Cancer

• TECENTRIQ, in combination with pembrolizumab, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer whose tumors have PD-L1 expression \( > \) 1\% of tumor cells, as determined by an FDA-approved test (see Dosage and Administration (2.1)).

• TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (see Dosage and Administration (2.1)).

1.3 Non-Small Cell Lung Cancer in Combination with Cobimetinib and Vemurafenib

TECENTRIQ, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600-mutated metastatic or unresectable malignant melanoma (MCM) who have not received prior systemic therapy.

1.4 Melanoma

TECENTRIQ, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600-mutated metastatic or unresectable malignant melanoma (MCM) who have not received prior systemic therapy.

2 CONTRAINDICATIONS

None.

3 WARNINGS AND PRECAUTIONS

3.1 Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions include severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1 blocking therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement, repeat infectious workup to exclude alternative etiologies.

3.2 Metastatic Non-Small-Cell Lung Cancer

Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1 blocking therapy. Immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions can also manifest after discontinuation of PD-1/ PD-L1 blocking antibodies. Early identification and management of immune-mediated adverse reactions is essential to ensure safe use of TECENTRIQ. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during therapy. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold TECENTRIQ depending on severity (see Dosage and Administration (2.3)). In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroids to treat the underlying immune-mediated reaction. Reduce the dose of corticosteroids or discontinue corticosteroids as clinically indicated.

3.3 Endocrinopathies

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

### Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

**TECENTRIQ as a Single Agent**

• TECENTRIQ Broadcom occurred in 5.0% (13/262) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.5%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients. Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis.

**Immun-Mediated Hepatitis**

TECENTRIQ can cause immune-mediated hepatitis.

• Immune-mediated hepatitis occurred in 1.8% (4/216) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%), Grade 2 (0.5%), and Grade 1 (0.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 50% (2/4) of patients with colitis. Colitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated treatment with TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis.

**Immune-Mediated Endocrinopathies**

Adrenal Insufficiency

TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity (see Dosage and Administration (2.3)).

• Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.1%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 1.0% and withholding of TECENTRIQ in 1.0% of patients.

**Immune-Mediated Hypothyroidism**

• Immune-mediated hypothyroidism occurred in 1.8% (4/216) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 1.7% of patients.

**Hypophysitis**

• Immune-mediated hypophysitis can occur in 0.2% (4/216) of patients receiving TECENTRIQ as a single agent, including Grade 2 (<0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of TECENTRIQ in 0.6% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 50% (2/4) of patients with colitis. Colitis resolved in 73% of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of hepatitis.

**Immune-Mediated Colitis**

• Immune-mediated colitis occurred in 0.9% (20/216) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% of patients with colitis. Systemic corticosteroids were required in 50% (10/20) of patients with colitis. Colitis resolved in 73% of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis.
Grade 2 (5.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 0.1% and severe and fatal immune-mediated adverse reactions occurred in 1.6% of patients.

Hypothyroidism therapy was required in 71% (198/277) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 39 patients in whom TECENTRIQ was withheld for hypothyroidism, 9 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Cabozantinib and Vemurafenib
Hypothyroidism occurred in 26% (60/230) of patients receiving TECENTRIQ in combination with cabozantinib and vemurafenib. Of these, 20% (48/230) of patients received TECENTRIQ in a single-agent setting. In this setting, grade 2 (1.7%) adverse reactions occurred in 20% (48/230) of patients. Hypothyroidism was the most common adverse reaction leading to discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in two patients.

Vertigo was the only adverse reaction required for all Type 1 diabetes mellitus insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

Immune-Mediated Nephritis with Renal Dysfunction
TECENTRIQ can cause immune-mediated nephritis.

TECENTRIQ as a Single-Agent
Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/230) of patients receiving TECENTRIQ as a single-agent, and this adverse reaction was a Grade 3 (>10%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient. This patient required systemic corticosteroids. In this patient, nephritis did not resolve.

TECENTRIQ in Combination with Cabozantinib and Vemurafenib
Immune-mediated nephritis with renal dysfunction occurred in 1.3% (3/230) of patients receiving TECENTRIQ in combination with cabozantinib and vemurafenib, including Grade 2 (1.3%) adverse reactions.

Dermatologic Adverse Reactions
TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with 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 TECENTRIQ depending on severity (see Adverse Reactions [6.1], Table 3).

Type 1 diabetes mellitus occurred in 0.3% (7/2306) of patients receiving TECENTRIQ, including Grade 2 (0.9%) adverse reactions. Five (3.8%) of these patients had Type 1 diabetes mellitus that led to permanent discontinuation of TECENTRIQ and withholding of TECENTRIQ in one patient and two patients, respectively.

Treatment with TECENTRIQ was required for all Type 1 diabetes mellitus insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

Immune-Mediated Nephritis with Renal Dysfunction
TECENTRIQ can cause immune-mediated nephritis.

TECENTRIQ as a Single-Agent
Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/230) of patients receiving TECENTRIQ as a single-agent, and this adverse reaction was a Grade 3 (>10%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient. This patient required systemic corticosteroids. In this patient, nephritis did not resolve.

TECENTRIQ in Combination with Cabozantinib and Vemurafenib
Immune-mediated nephritis with renal dysfunction occurred in 1.3% (3/230) of patients receiving TECENTRIQ in combination with cabozantinib and vemurafenib, including Grade 2 (1.3%) adverse reactions.

Dermatologic Adverse Reactions
TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with 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 TECENTRIQ depending on severity (see Adverse Reactions [6.1], Table 3).

Type 1 diabetes mellitus occurred in 0.3% (7/2306) of patients receiving TECENTRIQ, including Grade 2 (0.9%) adverse reactions. Five (3.8%) of these patients had Type 1 diabetes mellitus that led to permanent discontinuation of TECENTRIQ and withholding of TECENTRIQ in one patient and two patients, respectively.

Treatment with TECENTRIQ was required for all Type 1 diabetes mellitus insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors

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 complications including hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile complications.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There is no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that TECENTRIQ administered to pregnant rats can lead to increased risk of maternal toxicity and rejection of the developing fetus resulting in fetal death. Verifying pregnancy at the time of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose in Women of Reproductive Potential (2.5).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another 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 TECENTRIQ as a single-agent in 2816 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single-arm studies (PDC04395V, IMwigh210, IMwigh212, JAVELIN Pancreatic ADC) which enrolled 324 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PDC04395V, where a dose of 1200 mg every 2 weeks was used.

Among the 2016 patients who received a single-agent TECENTRIQ, 38% were exposed for more than 6 months and 23% were exposed for longer than 12 months. Using the dataset described in WARNINGS AND PRECAUTIONS, patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and diarrhea (22%). In addition, the data reflect exposure to TECENTRIQ as a single-agent as adjunct therapy in 495 patients with early stage NSCLC enrolled in a randomized study (IMPower101).

In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in a cohort of patients with NSCLC (N = 2223) enrolled in five randomized, active-controlled trials, including IMwigh105, IMwigh130 and IMwigh133. Among the 2421 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 23% were exposed to TECENTRIQ for longer than 12 months. Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with another antineoplastic drug, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (49%), nausea (38%), anemia (35%), constipation (29%), diarrhea (28%) and decreased appetite (27%).

The data also reflect exposure to TECENTRIQ administered in combination with cobimetinib and vemurafenib in 230 patients enrolled in IMwigh150. Among the 230 patients, 62% were exposed to TECENTRIQ for longer than 6 months and 44% were exposed to TECENTRIQ for longer than 12 months. Urothelial Carcinoma

5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors

Fetal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile complications.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that TECENTRIQ administered to pregnant rats can lead to increased risk of maternal toxicity and rejection of the developing fetus resulting in fetal death. Verifying pregnancy at the time of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose in Women of Reproductive Potential (2.5).

6 ADVERSE REACTIONS

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

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

Infusion-Related Adverse Reactions [see Warnings and Precautions (5.2)]

Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors [see Warnings and Precautions (6.3)]

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMwigh210 (Cohort 1)
The safety of TECENTRIQ was evaluated in IMpower010, a multicenter, open-label, randomized trial for the first-line treatment of patients with stage IIIB or IV NSCLC who had completed tumor resection and received at least 4 weeks of platinum-based adjuvant chemotherapy. Patients received TECENTRIQ 1200 mg every 3 weeks (n=495) for 1 year (16 cycles), unless disease progression or unacceptable toxicity occurred, or best supportive care [see Clinical Studies (14.2)]. The median number of cycles received was 16 range: 1-16 cycles).

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) reactions leading to discontinuation were pneumonitis (1.8%), febrile neutropenia, pneumonia, diarrhea, and hemoptysis. Serious adverse reactions occurred in 18% of patients receiving TECENTRIQ; these included hemoptysis, aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical failure, sepsis, cerebral infarction, and device occlusion (1 patient each).

Serious adverse reactions occurred in 29% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were pneumonia (2.8%), chronic obstructive pulmonary disease (2.1%) and hypothyroidism (2.1%).

TECENTRIQ was discontinued due to adverse reactions in 6% of patients; the most common adverse reactions (>2%) leading to discontinuation were peripheral neuropathy and pneumonitis.

Adverse reactions leading to interruption of TECENTRIQ occurred in 26% of patients: the most common (>1%) reactions were rash (3.0%), hyperthyroidism (2.8%), hypothyroidism (1.6%), increased AST (1.6%), pyrexia (1.0%) and upper respiratory tract infection (1.4%).

Tables 8 and 9 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower010.

### Table 8: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Early Stage NSCLC Receiving TECENTRIQ in IMpower010

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Best Supportive Care Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Note: Adverse reaction events were graded based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

### Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower110

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Best Supportive Care Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Note: Adverse reaction events were graded based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

### Table 10: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in IMpower110

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3–4 (%)</th>
<th>Best Supportive Care Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>0.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Note: Adverse reaction events were graded based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

### Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower110

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Best Supportive Care Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Note: Adverse reaction events were graded based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

### Table 12: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Stage IV NSCLC Receiving TECENTRIQ in IMpower110

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Best Supportive Care Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Note: Adverse reaction events were graded based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

### Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Stage IV NSCLC Receiving TECENTRIQ in IMpower110

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grades 3–4 (%)</th>
<th>Best Supportive Care Grades 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17</td>
<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Among patients receiving TECENTRIQ, 55% were exposed for 6 months or longer and 3.5% were exposed for greater than one year. Fatal adverse reactions occurred in 5.3% of patients receiving TECENTRIQ; these included pneumonia (1.1%), pulmonary embolism (0.6%), myocardial infarction (0.6%), cardiac arrest (0.4%), pneumonitis (0.4%) and sepsis, septic shock, diphtheria, sepsis, aspergillosis, respiratory distress, cardiopulmonary arrest, ventricular tachycardia, death (not otherwise specified), and hepatic cirrhosis (0.3%). Serious adverse reactions occurred in 51% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were pneumonitis (6%), diabetes (4%), pneumonitis (4%), pneumonitis (2%), pneumonia (2%), neutropenia (2%), pneumonia (2%), nausea, acute kidney injury, vomiting, pulmonary embolism, arrhythmia, infusion-related reaction, abdominal pain, chronic obstructive pulmonary disease exacerbation, dehydration, and hypokalemia. Tables 12 and 13 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with paclitaxel protein-bound and carboplatin in IMpower130.

Table 10: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin</th>
<th>Bevacizumab, Paclitaxel and Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neupathy1</td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
<td>0.8</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthema</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>0.3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Rash2</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/Pain2</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhe3</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>28</td>
<td>0.8</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>16</td>
<td>3</td>
</tr>
</tbody>
</table>

Graded per NCI CTCAE v4.0
1 Includes neuropathy peripheral, peripheral sensory neuropathy, hypothyreosis, parasthesia, dysarthria, paresthesia, paresthesia.
2 Includes rash, rash maculo-papular, drug eruption, eczema, eczema atopic, dermatitis, contact dermatitis, rash erythematous, rash maculo-papular, rash pruritic, rash papulosquamous, papulosquamous.
3 Includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, back pain, myalgia, and bone pain.
4 Includes diarreha, gastroenteritis, colitis, enterocolitis.
5 Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected.

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin</th>
<th>Bevacizumab, Paclitaxel and Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>83</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>Increased BUN</td>
<td>52</td>
<td>NA</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Hypouabuminemaa</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Hypotaenemia</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Increased Alkaline Phosphate</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>39</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Hypercalciemia</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>25</td>
<td>NA</td>
</tr>
</tbody>
</table>

Graded per NCI CTCAE v4.0
1 Includes diarreha, gastroenteritis, colitis, enterocolitis.
2 Includes back pain, pain in extremity, myalgia, musculoskeletal chest pain, bone pain, neck pain and musculoskeletal discomfort.
3 Includes neuropathy peripheral, peripheral sensory neuropathy, hypothyreosis, parasthesia, dysarthria, paresthesia, paresthesia.
4 Includes diarreha, gastroenteritis, colitis, enterocolitis.
5 Includes rash, rash maculo-papular, eczema, rash pruritic, rash erythematous, dermatitis, contact dermatitis, drug eruption, seborrhoeic dermatitis and rash macular.

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower130

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin</th>
<th>Paclitaxel Protein-Bound and Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>92</td>
<td>33</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>73</td>
<td>19</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Hypothyreosis</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>35</td>
<td>1.3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>31</td>
<td>2.8</td>
</tr>
<tr>
<td>Hypopotassium</td>
<td>29</td>
<td>2.6</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Increased AST</td>
<td>28</td>
<td>2.2</td>
</tr>
<tr>
<td>Increased TSH</td>
<td>26</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Increased Alkaline Phosphate</td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>Increased Blood Creatinine</td>
<td>23</td>
<td>2.8</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>21</td>
<td>NA</td>
</tr>
</tbody>
</table>

Graded per NCI CTCAE v4.0
1 Includes diarreha, gastroenteritis, colitis, enterocolitis.
2 Not applicable. NCI CTCAE does not provide a Grades 3–4 definition for these laboratory abnormalities.
The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who had failed at least one prior systemic therapy and who were considered chemotherapy eligible. In this study, 553 patients with locally advanced or metastatic NSCLC were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.4)]. The median duration of exposure to TECENTRIQ was 7.4 months (range: 0–21 months). The most frequent serious adverse reactions leading to death were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2%). Serious adverse reactions leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to death were gastrointestinal hemorrhage and esophageal varices hemorrhage (1.2%) and infections (1.2%). Serious adverse reactions occurred in 36% of patients in the TECENTRIQ and bevacizumab arm. The most frequent serious adverse reactions (≥2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to discontinuation of TECENTRIQ were gastrointestinal hemorrhage (1.2%), infections (1.2%), and deaths (1%). Serious adverse reactions occurred in 36% of patients in the TECENTRIQ and bevacizumab arm. The most frequent serious adverse reactions (≥2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ and bevacizumab arm.
Table 18: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving TECENTRIQ in IMbrave150

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ in combination with Bevacizumab (n = 329)</th>
<th>Sorafenib (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>1.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>18</td>
<td>1.2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related Reaction</td>
<td>11</td>
<td>2.4</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Graded per NCI CTCAE v4.0

Table 19: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving TECENTRIQ in IMbrave150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ in combination with Bevacizumab (n=329)</th>
<th>Sorafenib (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>86</td>
<td>16</td>
</tr>
<tr>
<td>Increased Alkaline Phosphatase</td>
<td>70</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>Decreased Creatinine</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Decreased Sodium</td>
<td>54</td>
<td>13</td>
</tr>
<tr>
<td>Increased Glucose</td>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td>Decreased Calcium</td>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>Decreased Phosphorus</td>
<td>24</td>
<td>4.7</td>
</tr>
<tr>
<td>Increased Potassium</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Platelet</td>
<td>68</td>
<td>7</td>
</tr>
<tr>
<td>Decreased Lymphocytes</td>
<td>62</td>
<td>13</td>
</tr>
<tr>
<td>Decreased Hemoglobin</td>
<td>58</td>
<td>3.1</td>
</tr>
<tr>
<td>Increased Bilirubin</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td>Decreased Leucocyte</td>
<td>32</td>
<td>4.3</td>
</tr>
<tr>
<td>Decreased Neutrophils</td>
<td>23</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Asthma (10%), increased lipase (9%), increased amylase (7%), pneumonitis (5%), increased CPK (4.3%), diabetes (2.5%), pneumonia (3.5%), asthma (3%), rash (3%), influenza (3%), arthralgia (2.5%), fatigue (2.5%), pyrexia (2.2%), cough (2.2%), peripheral edema (2.2%), uveitis (2.2%), bronchitis (2.2%), hyperthyroidism (2.2%), and respiratory tract infection (2.2%).

Table 20: Adverse Reactions Occurring in ≥10% of Patients on the TECENTRIQ plus Cobimetinib and Vemurafenib Arm or the Placebo plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3–4) in IMspire150

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)</th>
<th>Placebo with Cobimetinib and Vemurafenib (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>75</td>
<td>27</td>
</tr>
<tr>
<td>Pruritus</td>
<td>26</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Photosensitivity reaction</td>
<td>21</td>
<td>&lt;1</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>49</td>
<td>1.7</td>
</tr>
<tr>
<td>Edema</td>
<td>26</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>23</td>
<td>1.3</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>62</td>
<td>4.3</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>10</td>
<td>2.6</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders: Hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders: Dizziness, dysgeusia, syncope Respiratory, thoracic and mediastinal disorders: Dyspnea, ophthalmic pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders: Vitiligo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 21: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ Plus Cobimetinib and Vemurafenib Arm or the Placebo Plus Cobimetinib and Vemurafenib Arm at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3–4) in IMspire150

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)</th>
<th>Placebo with Cobimetinib and Vemurafenib (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Lymphocytes</td>
<td>80</td>
<td>24</td>
</tr>
<tr>
<td>Decreased Hemoglobin</td>
<td>77</td>
<td>2.6</td>
</tr>
<tr>
<td>Decreased Platelet</td>
<td>34</td>
<td>1.3</td>
</tr>
<tr>
<td>Decreased Neutrophils</td>
<td>26</td>
<td>2.2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Creatine Kinase</td>
<td>88</td>
<td>22</td>
</tr>
<tr>
<td>Increased AST</td>
<td>80</td>
<td>33</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>79</td>
<td>18</td>
</tr>
<tr>
<td>Increased Triacylglyceride Lipase</td>
<td>75</td>
<td>46</td>
</tr>
</tbody>
</table>
Risk Summary

Animals have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death (see Data). Advise females of reproductive potential of the potential risk to a fetus.

8.1 Pregnancy

Animal Data

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

8.2 Lactation

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ (see Use in Specific Populations [8.5]).

Contraception

Females

Based on mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations [8.3]). Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment (see Nonclinical Toxicology [13.2]).

8.4 Pediatric Use

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

The safety and antitumor activity of TECENTRIQ were assessed but not established in a single-arm, multicenter, multi-cohort trial (NCT01649019) in 63 patients 12 years of age or younger. Treatment-related adverse reactions occurred in 25% of all patients and was comparable to that in adult patients who received TECENTRIQ 1200 mg every 3 weeks, while the exposure found lower in pediatric patients less than 12 years old.

8.5 Geriatric Use

The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative [see Clinical Pharmacology (12.3)]. The plasma levels of ADA-positive patients were comparable to that in adult patients who received TECENTRIQ 1200 mg every 3 weeks, while the exposure found lower in pediatric patients less than 12 years old.

9. Lactation

Advisers of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider immediately for signs or symptoms of infection related to treatment (see Warnings and Precautions [8.5]).

Complications of Allogeneic HSCT after PD-L1/PD-1 inhibitors

Follow patients closely for evidence of transplant-related complications and intervene promptly, consider the benefits versus risks of treatment with a PD-L1/PD-1 blocking antibody prior to or after an allogeneic HSCT (see Warnings and Precautions [5.8]).

Endometrial Toxicity

Advisers of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider immediately for signs or symptoms of infection related to treatment (see Warnings and Precautions [8.5]).

Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose (see Use in Specific Populations [8.3]).

Table 21: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TECENTRIQ in combination with Cabozantinib and Vemurafenib (n=230)</th>
<th>Placebo with Cabozantinib and Vemurafenib (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Increased Alkaline Phosphate</td>
<td>63 ± 6</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>Decreased Phosphorus</td>
<td>14 ± 6</td>
<td>2.9 ± 6</td>
</tr>
<tr>
<td>Increased Aspartate Aminotransferase</td>
<td>13.5 ± 14</td>
<td>1.4 ± 1</td>
</tr>
<tr>
<td>Increased Blood Urea Nitrogen</td>
<td>27 ± 6</td>
<td>24 ± 6</td>
</tr>
<tr>
<td>Decreased Albumin</td>
<td>34 ± 6</td>
<td>1.5 ± 6</td>
</tr>
<tr>
<td>Increased Bilirubin</td>
<td>33 ± 6</td>
<td>3.0 ± 6</td>
</tr>
<tr>
<td>Decreased Calcium</td>
<td>23 ± 6</td>
<td>2.8 ± 6</td>
</tr>
<tr>
<td>Decreased Sodium</td>
<td>7 ± 6</td>
<td>4 ± 6</td>
</tr>
<tr>
<td>Decreased Thyroid-Stimulating Hormone</td>
<td>23 ± 6</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>Increased Thyroid-Stimulating Hormone</td>
<td>33 ± 6</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Decreased Potassium</td>
<td>22 ± 6</td>
<td>4 ± 6</td>
</tr>
<tr>
<td>Increased Triiodothyronine</td>
<td>18 ± 6</td>
<td>3 ± 6</td>
</tr>
<tr>
<td>Increased Free Thyroxine</td>
<td>21 ± 6</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>Decreased Total Thyroid Hormone</td>
<td>8 ± 6</td>
<td>8 ± 6</td>
</tr>
<tr>
<td>Decreased Potassium</td>
<td>19 ± 6</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>Increased Triiodothyronine</td>
<td>21 ± 6</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>Decreased Sodium</td>
<td>13 ± 6</td>
<td>6 ± 6</td>
</tr>
</tbody>
</table>

Graded by NCI CTCAE v4.0.

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. TECENTRIQ plus cabozantinib and vemurafenib (28-277), placebo plus cabozantinib and vemurafenib (23-230).

NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.

Increased Thyroid Stimulating Hormone has a difference <5% (All Grades) between arms and is included for clinical completeness.

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 sample handling, timing of collection, concurrent medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to antibodies described above with the incidence of antibodies in other studies or to other products may be misleading.

Among 111 patients in IMvigor210 (Cohort 1), 48% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposures. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 364 ADA-evaluable patients with NSCLC who received TECENTRIQ with bevacizumab, paclitaxel and carboplatin in IMpower161, 30% tested positive for treatment-emergent anti-drug antibodies (ADA) at one or more post-dose time points. The median onset time to ADA formation was 3 weeks. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposure (see Clinical Pharmacology [12.3]). Exploratory analyses showed that the subset of patients who were ADA-positive by week 4 (21%; 118/568) appeared to have less efficacy (effect on overall survival) as compared to patients who tested positive for treatment-emergent ADA by week 4 (see Clinical Studies [14.2]). The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 427 ADA-evaluable patients with NSCLC who received atezolizumab in IMpower010 (31%; n=125) tested positive for treatment-emergent ADA at one or more post-dose time points. Among patients in the PD-L1 SP263 ≥1% TC Stage II-IIIA population, 28% (n=67) tested positive for treatment-emergent ADA. Of the 132 patients who were ADA-positive by week 4 (21%; 118/568), 83% of these 132 patients tested ADA positive prior to receiving the second dose of atezolizumab. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative [see Clinical Pharmacology (12.3)]. The presence of ADA did not increase the incidence or severity of adverse reactions [see Clinical Studies (14.2)].

Among 312 ADA-evaluable patients with HCC who received TECENTRIQ and bevacizumab in MIRad0510, 28% (n=88) tested positive for treatment-emergent ADA at one or more post-dose time points and 66% of these 88 patients tested ADA-positive prior to receiving the second dose of atezolizumab. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative [see Clinical Pharmacology (12.3)]. Exploratory analyses showed that the subset of patients who were ADA-positive by week 6 (20%; 58/285) appeared to have less efficacy (effect on overall survival) as compared to patients who tested positive for treatment-emergent ADA by week 6 [see Clinical Studies (14.6)]. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 218 ADA-evaluable patients with melanoma who received TECENTRIQ in combination with cobimetinib and vemurafenib in Miprep150, 13% (n=29) tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure (see Clinical Pharmacology [12.3]). There are insufficient numbers of ADA-positive patients with positive ADA to determine whether ADA alters the efficacy or incidence of severe adverse reactions.
Collecting Real-World Data in Hematologic Malignancies, at Home and Abroad

MARY CAFFREY

GREATER USE OF REAL-WORLD DATA (RWD) in studying and treating hematologic malignancies promises to speed up the delivery of new therapies and create more tailored regimens for groups who have not been well represented in clinical trials, including Black patients who have multiple myeloma.

That’s the mission of 2 research initiatives that seek to collect and curate data in blood cancers and disorders, according to a group of experts who gathered for a symposium, “The Role of Real-World Data Collection in Hematologic Malignancies,” during the 2021 American Society of Hematology (ASH) Meeting & Exposition, held in Atlanta, Georgia, and online.1

ASH president Martin S. Tallman, MD, of Memorial Sloan-Kettering Cancer Center in New York, convened the wide-ranging panel of both US and European speakers, who discussed efforts by the ASH Research Collaborative and its counterpart in Europe, the HARMONY Alliance.

Tallman opened with an overview of where RWD comes from and who collects them. “RWD sources in the United States typically include electronic health records, insurance claims, patient registries, and digital health solutions such as mobile applications and devices,” he said.

The ASH collaborative and HARMONY Alliance, said Tallman, “are positioned to make major impact” in using these data sources in both research and regulated settings. He then introduced John Gribben, MD, DSc, of Barts Cancer Institute and the London School of Medicine, a past president of the European Hematology Association, who began his talk by explaining HARMONY’s structure and funding. HARMONY now has more than 97,000 patient records, including those in acute myeloid leukemia (AML), chronic lymphocytic leukemia (CML), multiple myeloma, and myelodysplastic syndromes. An additional program, HARMONY Plus, covers data from chronic myeloid leukemia and Hodgkin lymphoma. Gribben made clear that data for some diseases are more complete than for others, but collecting more and better data is part of the work that’s ahead.

“Clearly, the aim of the project is to speed up the development of more effective treatment, predictions of blood cancers, and the use of big data to develop more personalized treatment for blood cancer patients,” Gribben said. “So, building the big data platform has allowed for a better understanding of these diseases. Obviously, everyone in this room understands the need for and importance of looking at RWD sets in terms of being more representative of our patients.”

William A. Wood, MD, MPH, a bone marrow transplant specialist at the University of North Carolina at Chapel Hill, who serves as chair of the ASH Research Collaborative data hub oversight group, discussed expectations, challenges, and solutions to accelerate research. For starters, he said, “The goal of aggregating completed RCT [randomized clinical trial] data is different than the goal of aggregating consensus RWD.”

Unlike traditional RCT data, RWD are likely being collected for some other use. “Some concepts overlap, yet some are different,” Wood said. “We can use RWD, for example, in a continuous fashion to facilitate ongoing clinical practice improvement and indeed, our dual goals.”

Wood explained the challenges of bringing together disparate data sources and using natural language processing to make the different data sets work together. It takes working with many stakeholders to achieve both the stakeholders’ goals along with 2 primary research purposes, which are: (1) to accelerate research with different methods and analytical approaches, and (2) to “improve clinical practice done locally at the site level, and also across sites in a collaborative way, something that is unprecedented at this scale in hematology,” said Wood.

Wood was the lead author of a paper by the ASH Research Collaborative that was published during the meeting; it discusses the start of a dedicated website on multiple myeloma.2 Said Wood, “It is launching, and it is here.”

Guillermo Sanz, MD, PhD, of Valencia, Spain, the HARMONY Alliance cochair, sought to explain where HARMONY ranks in terms of key research items in the European agenda. “It would be considered the start project of the Big Data for Better Outcomes program of the Innovative Medicines Initiative,” he said, referring to the effort to link major databases across the continent to find cures and treatments for Alzheimer disease, other cancers, and cardiovascular disease.3 Public and private entities have equal voices in HARMONY’s governance, he said.

In the United States, the FDA has advanced the cause of real-world evidence in several ways, notably through a 2018 guidance directed by the 21st Century Cures Act, said hematologist Nicole J. Gormley, MD, who is the FDA’s division director for histological indices.

Gormley outlined some concepts to be weighed when using RWD:

- Do the data represent what they are intended to represent?
- Do the data contain relevant information on exposure covariates and outcomes of interest for the study hypothesis?

She noted that while the FDA “does not endorse one data source over another,” some may have limits, depending on the study question. An electronic health record (EHR), for example, was created to assist with clinical care. “The data are limited to information captured in the EHR within a particular system and may not represent the entire clinical picture,” Gormley said. Other confounders may need to be considered.

Factors such as trial design and population selection matter—but nothing matters more than drug sponsors engaging with the FDA upfront before they make plans to use RWD in a submission.

Jan Geissler, chair of LeukaNET and cofounder of CML Advocates, in Riemerling, Germany, spoke from the perspective of what patients can gain from the use of RWD. To begin, Geissler said, this shift could better capture who actually lives with certain blood cancers. “If you look at CML data, the patients in most of the studies have an average age of 46 [or] 47 years, but the average [age of] incidence of CML is 65 years. So, limited external validity of that exists in a real-world patient population.”

But Geissler sees real potential in the use of RWD in understanding patient preferences, in explaining “the difficult tradeoffs that patients have, the actual patient experiences on therapies with all the symptoms, and what having these diseases means in real life.” Data captured remotely with mobile devices would offer a rich resource for researchers and drug developers, he said.

“We want to capture patient reality—what it means to get these therapies and diagnostics, and, [also], all the new innovations out there in the real world with a variety of populations: the elderly, »
migrant communities, and [other] people who we actually don’t have on the studies,” Geissler said. “I think we all agree that clinical and regulatory decisions need to be based on the data.”

Patients and the public do have concerns about how data are used, Geissler said. While patients have a personal stake in participating in trials and sharing data, the general public doesn’t. In the overall population, only about one-third of people support sharing medical data. “They’re concerned about data being shared with third parties,” he said. Tallman then shifted the discussion to the clinical angle, starting with Kenneth C. Anderson, MD, of the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute. Anderson addressed clinical applications of the ASH Research Collaborative and discussed its priorities:

1. Aggregating data on minimal residual disease (MRD) in multiple myeloma to optimize patient care.
2. Collecting data from Black patients, to improve their access to novel agents in multiple myeloma.
3. Understanding the relationship between COVID-19 and multiple myeloma, so that the infection can be better managed in patients who have this blood cancer.

Anderson said that the great strides that have been made recently in multiple myeloma—more than a dozen new therapies, increased progression-free and overall survival—all are associated with MRD negativity. Now, he said, priority tasks are to inventory medical centers to know how often MRD is being used in clinical decision making, and to collect longitudinal MRD tests to develop meaningful long-term data. “We want to analyze the relationship of real-world MRD negativity with clinical outcomes, so that we can ultimately make informed use of MRD in multiple myeloma care,” he said.

Despite the advances in multiple myeloma, Black patients, compared with White patients, have not shared equally in the benefits. And it is known that monoclonal gammapathy of unknown significance—a precursor to myeloma—is more common in the Black population. RWD can help overcome current barriers to drug access and allow more Black patients to benefit, Anderson said. Finally, he pointed to results showing that myeloma patients don’t respond as well as others to COVID-19 vaccination, especially if they are receiving CD38- or BCMA-targeted treatments. Starting at 5 sites, “We will capture longitudinal myeloma data to create a new COVID module for diagnosis, treatment, vaccination, and outcome of COVID-19 infection. [Then we] will expand our effort to 10 to 15 sites. And we will, in fact, identify and address disparities that are present in this context as well.”

Mario Boccadoro, MD, of the hematology division at Cattedra Ematologia, Torino, Italy, discussed efforts to create a registry of RWD from medical centers across Italy. The aims, he said, are to describe: (1) the disease in clinical practices; (2) subgroups; (3) different sequences and time to events; and (4) “last, but not the least important, the patient-reported outcome.”

Early plans call for including 30 medical centers (beyond major academic centers) and 1900 patients. So far, 210 patients are enrolled. The case for RWD collection in AML came from Laura C. Michaelis, MD, of the Medical College of Wisconsin in Milwaukee. Using RWD, she emphasized, will benefit patients and community providers by:

1. “helping us accelerate trials for rare variants of an already rare disease”;
2. “illuminating valid contemporary outcomes” and possibly answer questions “that may not be appropriate for RCTs”;
3. “showing us where bias exists in the clinical trials that we already have out there and help us develop a more equitable system of delivering care.”

The challenge of rare variants is especially problematic in AML. This disease, Michaelis said, has only 14,000 US diagnoses a year, with both prognosis and outcome dependent on molecular mutations. One study that needed 700 patients for a rare variant took 4 years to complete enrollment, for example—and patients may balk if they know they could be in a control arm.

“These rare variants require lots of patients, and it increases the amount of time that we need to get an answer,” Michaelis said. “This also not only increases the time for patients, but it also puts a number of subjects on therapies in which the outcomes are already largely known. And it decreases the likelihood of patient participation in clinical trials when you put patients on control arms. And that’s sort of been published before. So how can we bypass that? Well, RWD can help us understand what would be happening on the control arm.”

Using RWD to study questions that would be inappropriate for a RCT is very useful, Michaelis said. These include “operational questions,” such as “Should we perform a 14-day bone marrow?”; pharmacological questions, such as “Does everybody need 28 days of BCL2 inhibitor?”; and laboratory questions in MRD, such as whether the quality of tests in local laboratories is the same as that of specialized laboratories.

Additionally, unraveling bias is overdue and necessary, especially when it’s known that many patients from minority groups cannot get into trials because of comorbidities. Michaelis pointed to a Cleveland Clinic analysis that used 100,082 patients from its own database who were not in clinical trials; 88% had a comorbidity. Notably, when their data were swapped into a trial protocol, the results were nearly the same.

“A database of RWD can increase efficiency in clinical trials, especially for some of the rare variants of AML. It can provide useful answers to questions that we won’t or aren’t likely to test in a randomized fashion,” Michaelis said.

Lars Bullinger, MD, of the University of Berlin, then presented some of the first results with AML from the HARMONY consortium: 20,289 cases from 14 groups have been collected, and more are in the process of being transferred into the database. He highlighted an abstract that was being presented the next day at ASH that showed how gender affected molecular AML subclasses. “Models are being developed that can guide treatment decisions down to the patient level,” he explained, and that’s just the beginning.

“We continue to collect RWD at unprecedented speed,” Bullinger said. “While I have shown you that we have a lot of transfer data sets... many more have been identified and people are willing to contribute to HARMONY. So, I’m looking forward to the next year. We will definitely create more reliable data and do many more meaningful analyses.”

Jesus Maria Hernández-Rivas, MD, PhD, the chair of HARMONY and HARMONY Plus, then offered closing remarks. “In recent years, we have seen, incredibly, almost unpredictable developments in the field of hematology. We’re getting to know our genome increasingly better every day, and how that has an impact in the development of hematological diseases. At hospitals, we produce a huge amount of data that must be used in the benefit of patients.”

Patients, Hernández-Rivas said, are demanding that their data be used to speed the development of new treatments, and new protocols and systems must be created to make this happen. “We need to open our minds to reach cooperation agreements that facilitate data sharing,” he exhorted. “Moreover, all these data must be harmonized... to facilitate the data analytics.”

Hernández-Rivas expressed optimism that the ASH Research Collaborative and the HARMONY Alliance could work through these issues. However, he noted, “the only way to produce results combining all these databases is having the data with the same structure.”

**REFERENCES**


More From ASH: Novel Agents Help Bridge Gaps in Multiple Myeloma

ACCC Presents Survey Responses on Adoption of Bispecific Antibodies

MARY CAFFREY

BISPECIFIC ANTIBODIES HAVE BEEN big news in the world of hematology for some time, ever since the 2014 approval of the first such therapy, blinatumomab, which targets both CD19 on the surface of B-cell lymphoblasts and CD3 on the surface of T cells. The 2-for-1 punch of these novel immunotherapies can overcome limitations of conventional monoclonal antibodies.

In 2020, the Association of Community Cancer Centers (ACCC) created an ongoing education program to identify and address barriers to adoption of bispecific antibodies for the treatment of hematological malignancies. For this program, ACCC created a survey to better understand multidisciplinary cancer providers’ experiences with these therapies, with a focus on experiences with blinatumomab. Results of the survey were presented in an abstract during the 2021 American Society of Hematology Meeting & Exposition.

According to the abstract, the survey received 129 individual responses, with 66% of those reporting that they prescribed, dispensed, and administered blinatumomab and/or cared for patients being treated with it. Of these, 44% were medical oncologists/hematologists, 8% were advanced practice providers (APPs), 17% were nurses, 23% were pharmacists, and 9% fell into an “other” category of various other disciplines.

Provider experiences with blinatumomab varied; 92% of oncologists had experience with blinatumomab while only 35% of nurses reported this. Regarding community use, respondents said 59% of their institutions use it to treat relapsed or refractory acute lymphoblastic leukemia (ALL) and 41% use it to treat ALL with minimal residual disease positivity. Of note, 74% of oncologists said they use blinatumomab before chimeric antigen receptor T-cell therapy when deciding between the 2 options for patients with ALL.

The survey also found:

- 79% of providers are comfortable caring for patients treated with blinatumomab, but 59% identified barriers when caring for these patients.
- Challenges include transitioning patients from the inpatient to outpatient setting (41%), managing patients who live in remote areas (33%), securing insurance coverage (28%), managing adverse events (27%), helping patients address financial costs, (24%), and lacking in-house expertise with the drug (22%).
- Managing neurotoxicity and cytokine release syndrome was also reported as a challenge. Fewer than half of oncologists reported experience in this area, and only 6% to 9% of APPs reported having experience. Of note, 23% of nurses did not feel they had all the information needed to safely administer blinatumomab.
- 86% of respondents said written guidelines, best practices, and care recommendations would help. Requested resources included a list of home health pharmacies and agencies familiar with blinatumomab, care coordinators or navigators, best practices on care transitions, and information on outpatient administration.
- Expertise from the drug manufacturer and direct patient education were seen as beneficial, and 70% thought that peer support services for patients would also be helpful.

REFERENCES

Phase 1 Study in R/R Hodgkin Lymphoma Shows Significant Responses to Pembrolizumab Plus Oral Vorinostat

AJMC STAFF

PHASE 1 RESULTS PRESENTED at the 2021 American Society of Hematology Meeting & Exposition show that adult patients with relapsed or refractory (R/R) Hodgkin lymphoma (HL) who were transplant ineligible had significant responses to intravenous pembrolizumab taken with oral vorinostat, a histone deacetylase (HDAC) inhibitor.

In preclinical studies, HDAC inhibitors have been shown to have immunomodulatory effects—including enhancing antigen presentation, recruiting T cells into tumors, and promoting T-cell function—when combined with PD-1 inhibitors, according to investigators from City of Hope, led by Alex F. Herrera, MD.

Oral vorinostat (Zolinza; Merck) is being studied with pembrolizumab in R/R HL as well as in diffuse large B-cell lymphoma and follicular lymphoma. Herrera reported on the phase 1 results involving 32 patients with R/R HL. "
According to the abstract, these patients were heavily pretreated. The median number of prior therapies was 4 (range, 2-12), with 94% having had prior brentuximab vedotin, with 66% refractory; 78% had prior PD-1 blockade, with 56% refractory to PD-1 inhibition. At baseline, 75% had stage III-IV disease; 69% were male and 72% were White, with a median age of 35 years (range, 18-79).

**STUDY DESIGN.** Patients were treated in a dose-escalation cohort with 2 dose levels (DLs) using a Rolling 6 design, followed by an expansion cohort with treatment at the recommended phase 2 dose. At the first DL, vorinostat was given orally at 100 mg a day for days 1 to 5 and 8 to 12; at the phase 2 DL, patients received 200 mg a day of vorinostat on days 1 to 5 and 8 to 12. The pembrolizumab doses were 200 mg intravenously every 3 weeks on both days 1 to 5 and 8 to 12; at the phase 2 DL, patients received 200 mg a day of vorinostat on days 1 to 5 and 8 to 12. The pembrolizumab doses could be evaluated, investigators reported the following results:

- Ten evaluable patients were anti-PD1 refractory patients with PD1 blockade as their most recent therapy prior to the study, and all had partial responses.
- Median follow-up time in 28 surviving patients was 28 months (range, 1-41).
- Patients had 1-year progression-free survival (PFS) of 52% and an overall survival (OS) of 93%.
- Median duration of response, PFS, and OS in all R/R HL patients were 14 months, 14.9 months, and not reached, respectively.

The investigators concluded, “Pembrolizumab and vorinostat was tolerable and produced a high ORR and CR rate in patients with anti–PD-1 naive/sensitive R/R HL. A majority of patients with anti–PD-1 refractory R/R HL had objective responses, including patients who had progressed while receiving PD-1 blockade as their most recent therapy.”

**REFERENCE**


---

**RESEARCH FROM OUR PARTNERS**

Blue Ridge Cancer Care’s Goldschmidt Presents Data on Managing Hematological Events

MARY CAFFREY

**WHAT IS AN ABSTRACT?** involving patients with small cell lung cancer (SCLC) doing at a meeting on hematology? As Jerome Goldschmidt, MD, an oncologist at Blue Ridge Cancer Care, in Blacksburg, Virginia, explained, the findings aren’t about SCLC per se, but about managing common hematological adverse events (HAEs) that can occur when patients are treated with chemotherapy. Many patients experience anemia, neutropenia, and thrombocytopenia, and managing these events—or better yet, preventing them—is key to patients staying on the recommended dose of therapy and avoiding AEs that lead to costly hospital stays.

Goldschmidt served as principal investigator for a retrospective, observational study conducted with Ontada, the oncology real-world data and evidence, clinical education, and technology business of The US Oncology Network, which includes Blue Ridge Cancer Care. Their findings were presented during the 2021 American Society of Hematology Meeting & Exposition.

Investigators used KnovMed electronic health record data from January 1, 2015, through January 31, 2020, to identify patients for the study. Goldschmidt said that about 1400 patients fit the overall inclusion criteria, and patients were then divided into 2 groups: those who had experienced a grade ≥3 HAE and those who had not. Investigators found that 778 patients experienced a grade ≥3 HAE during that period. “That’s a majority of the patients,” Goldschmidt said in an interview with Evidence-Based Oncology” during the meeting in Atlanta.

“Future studies will address the benefits of trilaciclib from the standpoint of health economics, as well as relieving suffering from the patient’s end while on chemotherapy.”

—Jerome Goldschmidt, MD, oncologist, Blue Ridge Cancer Care, Blacksburg, Virginia

Digging deeper, the analysis showed that myelosuppression HAEs in extensive-stage SCLC bring a heavy burden in the community oncology setting. “We looked at the burden on patients, which translated into transfusions, missed doses, dose reductions, and lower dose intensity.”
Goldschmidt said. All of these were higher in patients with grade ≥ 3 AEs. Health care costs were higher, too. Goldschmidt noted that the study calculated the differences in outpatient costs only, and they were still substantial. “Our hypothesis was that there would be more health care utilization if you had these adverse events. And indeed, that’s what we showed,” he said.

Health outcomes data from the Ontada analysis showed the following:

- Of those patients with at least one grade ≥ 3 HAE after starting chemotherapy, 50.3% had grade 3 anemia, 46.0% had grade 3 neutropenia, 28.0% had grade 4 neutropenia, 33.8% had grade 3 thrombocytopenia, and 18.1% had grade 4 thrombocytopenia.
- Of the 778 patients with grade ≥ 3 HAEs, 454 (58.4%) had 2 or more types, and 12.2% had anemia, neutropenia, and thrombocytopenia.
- 43.1% of the patients were eligible for red-blood-cell infusion, and 3.9% for platelet infusion; 12.2% of patients had major bleeding events.
- Compared with patients who did not have grade 3 HAEs, those with grade ≥ 3 HAEs were more likely to have dose reductions (46.7% vs 32.2%, respectively); treatment holds (12.7% vs 5.0%); and treatment delays (92.3% vs 84.3%; all P < .001).

Cost of care data underscore the burden of grade ≥ 3 HAEs:
- Total outpatient costs within 12 months after the start of chemotherapy were higher for patients with vs without grade ≥ 3 HAEs ($37,613 vs $31,176; P = .004).
- Patients with grade ≥ 3 HAEs had an mean of 10.7 outpatient visits within 12 months of starting chemotherapy vs 7.7 outpatient visits for those without grade ≥ 3 HAEs (P < .0001).
- Patients with grade ≥ 3 HAEs had greater use of granulocyte colony-stimulating factor, more intravenous hydration, and greater use of erythropoiesis-stimulating agents, at higher costs.

Goldschmidt has studied the use of trilaciclib in this SCLC population. He coauthored an analysis of 3 related studies, which found that administering trilaciclib prior to chemotherapy reduces myelosuppression and improves health-related quality of life for these patients.

"Pegfilgrastim and filgrastim are phenomenal drugs," Goldschmidt elaborated, “but they do have their costs, their side effects, and their difficulties in delivery. Plus, they really only treat 1 cell line.” Newer therapies can prevent more hematological events in more cancers and are worth studying, he said.

“Future studies will address the benefits of trilaciclib from the standpoint of health economics, as well as relieving suffering from the patient’s end while on chemotherapy,” said Goldschmidt. “We’ll also look at how it interacts with immunotherapy,” as well as its potential benefits in other types of cancers, such as breast and colon cancer.

REFERENCES
ONE PROVEN PORTFOLIO. TWO FDA-APPROVED OPTIONS.
THAT’S OUR FOUNDATION.

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

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

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

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

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

© 2021 Foundation Medicine, Inc.
US-PF-200071