Clinical Oncology Care Pathways Supporting the Use of High-value Treatments for NSCLC

In 2022, an estimated 235,000 new diagnoses of lung cancer will be made in the United States, accounting for 12.3% of all new cancer cases.1 Approximately 82% of all lung cancers are non–small cell lung cancer (NSCLC), and of those, nearly 70% are diagnosed at an advanced stage.1,2 Immunotherapy has greatly changed the therapeutic landscape for advanced NSCLC. PD-L1 expression is used to identify populations of patients with NSCLC who may respond well to immunotherapy.3,4 As single agents, immune checkpoint inhibitors (ICIs) have shown activity in NSCLC, benefiting mostly populations with a tumor proportion score (TPS) of 50% or more. PD-L1 expression levels vary in advanced NSCLC, and PD-L1 expression of less than 50% is common.3,4 Patients with advanced NSCLC with tumor expression of PD-L1 that is less than 50% benefit from a combination therapy approach. Combining approved PD-1/PD-L1 inhibitors with other approved treatments may facilitate rapid FDA approval of an effective combination.

ADVANCEMENTS IN THE NSCLC TREATMENT LANDSCAPE

The FDA has approved immunotherapies for many different indications in advanced NSCLC, including single-agent immunotherapy for some and combination regimens for others. In recent years, clinical trial evidence has shown the benefits of platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors (ie, pembrolizumab, atezolizumab, nivolumab and ipilimumab, cemiplimab) in first-line treatment for adult patients with advanced NSCLC, so additional FDA approvals are anticipated for expanded indications of immunotherapy.5-9 Combination therapy—immune checkpoint blockade plus platinum-based chemotherapy—has shown promising efficacy in NSCLC in numerous trials, including KEYNOTE-189 (NCT0257868), IMPower150 (NCT02366143), CheckMate 9LA (NCT03157060), and EMPOWER-Lung 3 (NCT03409614).10-15 Notably, the FDA will review the supplemental Biologics License Application (BLA) for cemiplimab-rwlc, a PD-1 inhibitor, in combination with chemotherapy as first-line treatment in advanced NSCLC. The target action date for the FDA decision is September 19, 2022. This BLA was based on the results from the phase 3 EMPOWER-Lung 3 trial, which demonstrated the efficacy and safety of cemiplimab-rwlc in combination with platinum-doublet chemotherapy in patients with advanced or metastatic NSCLC with no ALK, EGFR, or ROS1 aberrations regardless of whether tumors were marked by low or high PD-L1 expression.12,16,17

As drug developments continue to expand the treatment landscape of metastatic NSCLC, there may be challenges due to the complexity of evidence-based decision-making when multiple therapeutic regimens are available. In an interview with AJMC®, Edward Arrowsmith, MD, MPH, the medical director for pathways at OneOncology, which includes 13 leading community oncology practices across the United States said, “The checkpoint inhibitors really are agents that have revolutionized treatment. For those of us who have been treating NSCLC for years or decades, we’re clearly seeing responses and durable responses that are unbelievable compared with what we saw 10 or 15 years ago. These are agents that we integrated very quickly into the therapy of NSCLC and into our pathways program.” Oncology care pathways (OCPs) are an important resource that establish standards of patient care and guide decision-making in the treatment of advanced NSCLC based on a review of the available evidence, including data from clinical trials and FDA indications.

OCPs for Quality and Value of NSCLC Care

OCPs are intended to improve the quality of treatment and to promote consistent, evidence-based care in a changing NSCLC treatment landscape. Health care systems, academic institutions, oncology care practices, and payers are increasingly adopting the use of OCPs as...
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 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

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

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

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

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

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

• Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff. Please see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

Immune-mediated endocrinopathies: (cont’d)

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

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

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

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

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

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

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

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 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–Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

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

- Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

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

- Musculoskeletal and connective tissue: Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

- Endocrine: Hyoparathyroidism

- 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.
LIBTAYO® (cemiplimab-rwlc) 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 (mCSCC) or locally advanced CSCC (lCSCC) 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.

1.3 Non-Small Cell Lung Cancer

LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) > 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1) in the full prescribing information], with no EGFR, ALK or ROS1 aberrations, and is:

- locally advanced where patients are not candidates for surgical resection
- definitive chemoradiation or definitive chemoradiation and systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent)

In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

2 WARNINGS AND PRECAUTIONS

2.1 Non-Small Cell Lung Cancer

Emergency identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor closely for symptoms and signs that may be clear 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.

2.2 Basal Cell Carcinoma

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 PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Write to close to for symptoms and signs that may be clear 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.

2.3 Cutaneous Squamous Cell Carcinoma

Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

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. If 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.

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

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

Immune-Mediated Pneumonitis

LIBTAYO can cause immune-mediated pneumonitis. The definition of immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of 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%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.4% of patients and withholding of LIBTAYO in 2.1% of the 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 for pneumonitis, 9 reinstituted LIBTAYO after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis.

Immune-Mediated Colitis

LIBTAYO can cause immune-mediated colitis. The definition of immune-mediated colitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. The primary component of the immune-mediated colitis was diarrhea. Immune-mediated colitis occurred in 15.5% (18/115) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%) adverse reactions. Colitis led to permanent discontinuation of LIBTAYO 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 for colitis, 4 reinstituted LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence of colitis.

Immune-Mediated Hepatitis

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

Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in all patients with hepatitis. Nineteen percent (19%) of these patients (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 59% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients reinstituted LIBTAYO after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 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.

Hypophysitis

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypothalamic-pituitary dysfunction. 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].
Hyphophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hyphophysitis 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) patients with hyphophysitis. Hyphophysitis 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 [see Dosage and Administration (2.3) in the full prescribing information].

**Thyroïditis:** Thyroïditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroïditis. Thyroïditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroïditis. Thyroïditis 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%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 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%) adverse reactions. 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. The majority of 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 patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%) adverse reactions. 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. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% 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 for nephritis, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

**Immune-Mediated Dermatologic Adverse Reactions**

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), 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 LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

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

**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.

**Cardiovascular:** Myocarditis, pericarditis, vasculitis

**Nervous System:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

**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, duodenal/Jejunum

**Musculoskeletal and Connective Tissue:** Myositis/polyarthropathy, rhabdomyolysis and associated sequelae including renal failure, arthritis, polyalgia rheumatica

**Endocrine:** Hyperparathyroidism

**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 or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.3) in the full prescribing information].

**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**

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-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)].

**ADVERSE REACTIONS**

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

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

6.1 Clinical Trials Experience

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 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, 57% were exposed for ≥ 6 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, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Cutaneous Squamous Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 [see Clinical Studies (14.1) in the full prescribing information]. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% White, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%). Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonia, cellulitis, sepsis, and pneumonia.

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

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin and Subcutaneous Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
</tr>
</tbody>
</table>

(continued)
The most common adverse reactions reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection.

The most common Grade 3 or 4 adverse reactions (> 2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hypokalemia and visual impairment. The most common (> 3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hypotension.

Table 4 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 5 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

### Table 4: Adverse Reactions in ≥ 10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO N=132</th>
<th>All Grades %</th>
<th>Grades 3-4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>33</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>22</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

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

- a. Composite term includes fatigue, asthenia, and malaise
- b. Composite term includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain
- c. Composite term includes rash maculo-papular, rash, dermatitis, dermatitis acneiform, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, rash erythematosus, and urticaria
- d. Composite term includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection
- e. Composite term includes dyspnea and dyspnea exertional
- f. Composite term includes hypertension and hypertensive crisis

Table 5: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrolytes</strong></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time prolonged</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte 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
As with all therapeutic proteins, there is a potential for immunogenicity.

6.2 Immunogenicity

Toxicity graded per NCI CTCAE v. 4.03

1% of Patients with Locally Advanced or Baseline in ≥

Table 7: Laboratory Abnormalities Worsening from Baseline in ≤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>Grades 3-4*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></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>Hypoalbuminemia</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Hematology</strong></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><strong>Electrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>4.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypercalcemia</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 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

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Appropriate Treatment Selection

OCPs are detailed, evidence-based treatment protocols that delineate optimal treatment options for patients with NSCLC; they may include recommended dosing, time frames, and sequencing of therapies. Selection from a shorter list of treatment choices can support the delivery of high-quality, cost-effective patient care. Arrowsmith shared that when it comes to quality, pathways support selection of the best drug for a particular patient. “A clinician can follow pathways, particularly in the increasingly complex landscape of a disease like NSCLC, and choose the optimal therapy for the patient,” he said. When provided with guidance for selecting treatment from a list of treatment choices, oncologists and care teams can make an appropriate choice for an individual patient based on an expert evaluation of available evidence.

Standardization

Clinical practice guidelines for the treatment of NSCLC provide all of the possible treatment options available, which can lead to variability in clinical practice and patient care; oncologists may select different agents. Pathways, described Arrowsmith, reinforce standardization of care: “In our pathways—and a lot of pathways—sometimes several therapies appear clinically equivalent based on either head-to-head comparisons or the [results of] trials that look pretty similar. Standardizing one of those regimens, particularly for intravenous therapy, can lead to improvement in quality, because the whole treatment team [gains] experience with 1 particular way of treating a patient. Everyone is on board with the logistics, with [monitoring for] the [adverse] effects [AEs], and [with ensuring that] patients [receive proper education and care].”

Although standardization is a goal for quality of care, OCPs should also allow for flexibility in decision-making, as physicians have to account for individual patient needs and preferences (eg, oral vs intravenous drugs) and considerations of precision medicine. Per ASCO guidance on OCP development, 100% conformity with OCPs should not be a goal because of the frequently legitimate reasons for variance.

Physician adherence rates may differ among the major cancers, including NSCLC; it is more difficult to achieve conformity in treatments of some cancers than others. Investigators from Roswell Park Comprehensive Cancer Center in Buffalo, New York, conducted an analysis of 2997 treatment decisions made between October 2018 and September 2019.
(in a population of 2389 patients) that were entered in the electronic medical record (EMR) with ClinicalPath, a point-of-care oncology decision support tool that delivers defined OCPs for individual patient scenarios; the goal was to evaluate the appropriateness of off-pathway cancer care. In the 485 patients with metastatic NSCLC, 85% of treatment decisions were aligned with the clinical OCPs for this disease (“on pathway”). Of the NSCLC cases handled off pathway, the driver for off-pathway decision-making in almost half (47%) was documented drug toxicity or treatment-limiting comorbidity. Other leading reasons for treatment decision-making not on pathway were rationales that were clearly documented and reviewed by the provider or multidisciplinary team (19%), patient preference (14%), prior treatment that precluded pathway treatment (10%), new drug indication or molecular targeted therapy not in clinical oncology pathway (8%), or continuation of treatment started prior to referral (1%). The results of this analysis showed that flexibility is needed for quality, personalized care delivery.

Some organizations provide financial incentives that focus on the percentage of care that is on pathway. However, off-pathway treatment decisions may be appropriate for many patients, especially those with advanced NSCLC. OCPs can ensure that patients, each with a unique diagnosis, receive tailored treatments while other individualized needs, goals, and preferences are considered.

Value

OCPs can support the use of high-value treatments for NSCLC, because the development of an OCP is based on a review of the latest evidence and information available. Embodying standards of care, OCPs can streamline patient care by using established guidance to drive treatment decisions and make treatment more cost-effective. Evidence-based treatment options are based on efficacy, toxicity, and an evaluation of financial impact to the patient and payer. “If [2 or more] treatments appear to have the same efficacy and AE profile, sometimes one of those will create more value for the patient or the health care system,” said Arrowsmith. “Often, it is the treatment that has a lower cost of care or lower out-of-pocket expense for patients. By having pathways, the OneOncology system or other systems can look into value.” By providing integrated financial information at the point of care, OCPs support the use of high-value treatments. Payers increasingly recognize the savings that can accrue when institutions implement OCPs.

For example, the Dana-Farber Cancer Institute implemented their OCP in 2014 and showed implementation reduced spending for stage IV NSCLC by approximately $15,000 per patient in the year following their diagnosis, compared with the 12-month costs of care before OCP implementation (in 2012). As pathways are not static documents, OCP programs should support regular reviews and revisions. Stakeholders who participate in the development of institutional NSCLC OCPs should also participate in the ongoing, timely evaluation of the OCPs, taking into account emerging evidence from FDA approvals, updates to leading clinical practice guidelines, and any clinical trial data that might support revisions.

Stakeholders Involved

OCPs are an important resource with which to share key learnings, advancements, and treatment updates. They can be used to inform oncology care teams about how such advancements fit into an overall treatment strategy. Arrowsmith shared that at OneOncology, the key stakeholders involved in reviewing and updating OCPs are physician representatives from all 13 practices. Pharmacists, he added, actively bring the decision makers together to discuss emerging and existing data and to make decisions about OCPs. Further, new information is disseminated to OncOncology clinicians, both at the point of care and through educational programs narrowed by disease-related groups.

Experts in their disciplines in NSCLC have a role in developing integrated, multidisciplinary OCPs: This is the future of oncology care. Both payers and the multidisciplinary care teams who are involved in treating patients with NSCLC are stakeholders in the development of OCPs, and all stakeholders should contribute to their development and implementation. During the OCP design process, developers must ensure that the OCP is evidence based and leads to better outcomes.

Evidence Reviewed

If a new drug, or a drug with a new indication, is going to be used in treating NSCLC, OCP updates should be considered. Stakeholders have to determine—using the data available and discussion of the evidence—if and where in the pathway this option will be incorporated. OCP decision makers meet to discuss the body of evidence and level of evidence (eg, from randomized clinical studies and support from clinical practice guidelines). If appropriate, sources of real-world evidence (RWE; eg, claims data, EMR data, prospective cohort studies) may be reviewed and integrated. The option’s efficacy, safety (toxicity), and value (in relation to costs of care and drug costs) have to be considered in supporting or rejecting its addition to a clinical pathway. That order of assessment is also used when...
reviewing the evidence and weighing one treatment option against another, per Arrowsmith. A stepwise approach is best when factoring an agent’s AE profile, cost, and high-quality overall survival outcomes data into the OCP decision-making process. According to Arrowsmith, “The most effective treatment [is the] one that helps patients live longer and live better and [efficacy] will be the key driving metric in pathway formation.” If 2 treatments are available, head-to-head clinical trials provide the best evidence of comparative efficacy. Without head-to-head studies, safety profiles are evaluated. “Obviously, [we will] go with a treatment that we feel is likely to be easier on patients from an [AE] perspective,” Arrowsmith noted.

When 2 agents’ efficacy and safety are approximately equal, value is the determining factor. Arrowsmith asks, “Is one of them a lower-cost agent? Or, possibly, is it an agent [for which] there is a much better patient assistance program for patients who are uninsured or underinsured, such that there is particular value for those patients?”

Many of the ICIs have similarly high quality of evidence, and differentiating them from one another may be challenging. An OCP may include different treatment choices based on drug-specific efficacy, toxicity profiles, and costs of these high-value treatment options. From a payer perspective, drugs that are FDA approved and provide relatively small improvements in survival advantage and the same safety profile are assessed by value. Arrowsmith said, “The [combination] chemotherapy-with-[ICI] landscape is complicated. In some situations, there might be a clinical reason to use a certain [ICI] rather than another. In other circumstances, the trials appear to be very similar. Some of the [results from ICI] studies look similar enough to me and to other experts that choosing one [ICI over another] in order to maximize value maybe does make sense. Some of the economic considerations of cost for the patient and the health care system maybe are going to come back into play. We’re actively [examining that] at OneOncology.”

**Evaluating Emerging Clinical Data**

A large body of evidence exists regarding emerging therapies and expanded indications in niche patient populations with NSCLC. The number of FDA approvals, accelerated approvals, expanded indications, and novel treatments on the horizon create a need to put a framework in place for pathway evaluation, development, and maintenance process. Pathway developers (eg, individual practices, payers, and pathways vendors) are learning how to operate in an ever-changing treatment landscape where the body of evidence is being generated rapidly. At OneOncology, Arrowsmith noted, “We try to make decisions [that are] very close to real time as new data come out or as new molecular compounds receive FDA approval and are available for use.” He provided a few ways that OneOncology updates their OCPs as quickly as they can to account for the large amount of research in the NSCLC treatment pipeline, ensuring that the OCPs remain current and that physicians have access to therapies.

Organizations with pathway programs for NSCLC may benefit from a dedicated team that monitors new data and FDA approvals, and that alerts stakeholders when an update or evidence review is necessary. As such, pathways can be revised and disseminated as early as possible. Arrowsmith shared that OneOncology has a dedicated clinical team looking for upcoming new therapies, “We have a robust clinical team at OneOncology that is tracking both new approvals of drugs for NSCLC and clinical trials for NSCLC. Months or years in advance, we are following compounds, studies, and data presented at [major] conferences or published in peer-reviewed journals, and anticipating those results.”

Pathway developers and users can also learn from each other. Arrowsmith noted, “We pool the clinical wisdom of the physicians across our practices. If a physician, or a handful of physicians, are at a conference, the learnings [from that meeting] are passed down to all the physicians across OneOncology.”

**Leveraging EMR Data**

OCP programs have become easier to access from within EMRs. At the point of care, clinicians have the OCPs interface with EMR decision support available in their workflow, providing physicians with a data analysis and treatment selection process. Arrowsmith shared, “We’re really excited about a tool called Flatiron Assist. Flatiron Health is the maker of OncoEMR, which is our EMR vendor across OneOncology. This point-of-care tool guides clinicians as they’re ordering treatment for NSCLC and other cancers. It uses clinical inputs to suggest the kind of optimal or pathway-based treatment to prescribe right at the point of care.”

All stakeholders—patients, providers, employers, and payers—can benefit from OCPs that are integrated into the EMR. With new FDA approvals, access to EMR data allows providers to review previous genomic sequencing data and identify patients who may be good candidates for a new specific therapy. Arrowsmith said, “Another thing we try to do is to harvest analyses from all types of different sources to identify patients who may be best for specific therapies. We have active partnerships to have next-generation sequencing (NGS) data available to us as raw computer data. We can then find all patients with specific molecular abnormalities if new treatments become available for those patients.”

If [2 or more] treatments appear to have the same efficacy and AE profile, sometimes one of those will create more value for the patient or the health care system. Often, it is the treatment that has a lower cost of care or lower out-of-pocket expense for patients. By having pathways, the OneOncology system or other systems can look into value. -Edward Arrowsmith, MD, MPH
Real-World Evidence
Integration of OCPs in the EMR can allow the collection of longitudinal RWE and its analysis. This form of OCP utilization empowers value-based care and encompasses both quality and financial metrics.

Arrowsmith expressed that tracking the use of pathways is critical at OneOncology, and they strive to use real-time data to follow pathway adherence as a unique feature of their pathways program. He explained, “At OneOncology, we have a robust program that we call OneAnalytics that pulls information from a variety of sources and allows clinicians and other practice leaders to better manage the patient care experience. We’re able to follow how patients are doing, how providers are doing, and [whether providers are] adherent to the pathways.”

The complexity of the NSCLC landscape creates challenges of incomplete evidence regarding efficacy and toxicity that may not be representative of RWE, resulting in difficulty in analyzing the overall costs. Clinical oncology pathway development may have the addition of RWE to support decisions based on experience rather than trials.

In February 2020, the perceptions of 106 US payers regarding the use and relevance of RWE in informing oncology formulary decision-making were assessed in a national survey. Participants were from managed care organizations or pharmacy benefit managers, employed by both large (>1 million lives) and small (<1 million lives) plans. The majority (85%) used RWE to inform formulary decisions in oncology to support comparative effectiveness in the absence of head-to-head clinical trials. Payers valued RWE prior to launch to inform formulary and contracting decisions, and they desired real-world comparative effectiveness data post launch to validate coverage decisions.

Having OCPs integrated in the EMR can support RWE collection on treatment patterns in NSCLC. Given that RWE reflects the patient population in clinical practice vs clinical trials, it can be used to help understand long-term toxicities associated with treatment options and inform decision makers if adjustments are needed to the OCPs to improve care.

Participation in Clinical Trials
Pathway programs can be built to accommodate enrollment in clinical trials in emerging areas of therapeutic advancements. Across the United States, 71 National Cancer Institute–designated Cancer Centers, along with other research sites, provide access to clinical trials and research that advances cancer treatment. Detailed OCPs can be developed to embed information about clinical trials; if a patient presents who might be a candidate for such a trial, the provider would be alerted through the EMR. At OneOncology, Arrowsmith shared, “[They are] actively trying to improve therapy both through promoting participation in clinical trials and updating our pathways as quickly as we can.”

By leveraging the EMR at the point of care, clinicians can access key information about open clinical trials; they can use the integrated OCPs to measure quality, cost, and efficiencies, open clinical trials and identify patients eligible for trials. Clinicians can use the integrated trials that require regular maintenance of the pathway. However, savings accrue when patients are enrolled in clinical trials, because the drugs are supplied by pharmaceutical companies, allowing clinical trial study sites to achieve success with value-based payment models. Clinical trials also provide valuable data to support clinical research services.

OCP data can be used to assess the feasibility of prospective trials and to assess performance of individual trials in practice. Research programs at institutions that sponsor trials can be integrated within OCPs, providing clinicians with information about available trials and providing patients with written documentation and individualized information about their cancer type and treatment plan. Instructional data, such as how many patients have been treated with specific disease presentation and eligibility information for patient participation for a trial, can be provided.

PATIENT DIAGNOSIS INFORMATION AND BIOMARKER TESTING
OCPs in NSCLC take into account patient clinical presentation and disease type. These clinical factors—including staging with the tumor, nodes, metastases protocol; histology (squamous or nonsquamous); and ECOG performance status—are needed to guide the decision-making process for distinct patient populations who have been diagnosed with NSCLC. Clinical pathways can also account for other factors to consider when selecting treatments, including patient-level decisions, extent of disease, symptom burden, and tumor mutation burden.

Molecular testing is necessary to determine the optimal treatment of patients, both those newly diagnosed with NSCLC and those whose tumor has progressed after targeted therapy. The recognition of targetable gene alterations and immune responses identified in a patient’s molecular testing profile has resulted in rapid changes to the NSCLC therapeutic spectrum in recent years. There are several genomic alterations that can be targeted with FDA-approved therapies or for which treatments are under development (eg, EGFR, ALK, ROS1, RET, MET, KRAS, HER2, NTRK1, NTRK2, and NTRK3). Guidelines support that all patients with advanced nonsquamous NSCLC have PD-L1 and genomic alteration tests at the time of diagnosis.

A patient’s PD-L1 expression status is an important component of OCPs for advanced NSCLC. TPS is a scoring method that is determined using FDA-approved diagnostic PD-L1 IHC 22C3 pharmDx; it evaluates the percentage (0%-100%) of viable tumor cells showing partial or complete membrane staining at any intensity. Emerging biomarkers that are predictive for greater response to immune checkpoint blockades, such as tumor mutational burden (TMB), are also being investigated as patients with high TMB may be more likely to derive clinical benefit from ICIs.

NGS Comprehensive molecular profiling with the use of NGS is an important inclusion in OCPs to detect genomic alterations and biomarkers, and, with several FDA-approved NGS-based platforms, it is commonly used in advanced NSCLC. In 2018, CMS approved a national coverage
decision for NGS testing in patients with advanced NSCLC to include US FDA-approved NGS tests for recurrent, metastatic, relapsed, refractory, or stage III or IV cancer with a companion diagnostic claim. CMS proposed insurance coverage of NGS in vitro diagnostics for Medicare beneficiaries under the Parallel Review Program, designed to reduce the time of FDA approval of an in vitro diagnostic and its coverage determination by the CMS.45,46

As targetable biomarkers continue to be identified, potentially leading to therapeutic advances, switching from a single-gene testing strategy to broad molecular panels with NGS will be necessary to accommodate the evolving NSCLC landscape. While NGS coverage through private payers may still be variable,46 it is important for payers to support the expansion of comprehensive genomic profiling.

According to Arrowsmith, OneOncology leverages its active partnerships with institutions that provide NGS data in order to identify patients who may be best for specific therapies. OneOncology updates pathways as quickly as possible and make decisions that are very close to real-time as new data come out or as new molecular compounds receive FDA approval and are available for use. He explained that by using available NGS data, “We can find all patients with specific molecular abnormalities if new treatments become available for those patients[...],and identify all those patients who maybe had genomic sequencing done a year or 2 ago to make sure we don’t overlook any patients who may be good candidates for a specific therapy.”

Results from 2 RWE analyses were presented at the 2021 ASCO Quality Care Symposium; they evaluated genomic profiling, biomarker testing, and patterns of treatment decisions with pathways implemented across 4 OneOncology community oncology centers that use Flatiron Health’s OncoEMR EMR.47 A larger percentage of patients with advanced NSCLC received NGS with or without other genetic profile testing within OneOncology practices compared with patients within the broader nationwide Flatiron EMR–derived unidentified NSCLC database (63% vs 46%). There was an increase over time in biomarker testing for 6 selected biomarkers (ALK, EGER, BRAF, KRAS, ROS-1, PD-L1) among patients with advanced NSCLC, rising from 13% in 2015 to 57% in 2020 at OneOncology sites. In this study, the median time from advanced diagnosis to the first test result was 20 days. Reducing the turnaround time of NGS tests can allow more patients who have actionable mutations to receive appropriate treatment.47

Some institutions have not implemented NGS panel testing. Instead, they use biomarker testing strategies that are performed as a series of single-gene tests. Because NGS-based assays can evaluate all established and emerging biomarkers in a single test, their advantages include lower overall total testing costs, an increased number of patients who can have complete testing done, and reduced needs for rebiopsy compared with single-gene tests.48-50 A budget impact analysis conducted from the US payer perspective assessing the economic effects of increasing the proportion of patients with metastatic NSCLC who use NGS assays showed that this change would be associated with cost savings and shorter time to test results vs other testing modalities (NGS results, 2 weeks, vs single-gene panel results, 5 weeks). The results assumed a hypothetical plan of 1 million members (75% commercial, 25% Medicare) and 1119 patients with metastatic NSCLC eligible for NGS testing at the time of diagnosis.50 With NGS, patients initiated appropriate therapy 2.8 and 2.7 weeks faster than with sequential or exclusionary testing, respectively. For both CMS and commercial payers, NGS was also associated with substantial cost savings.49 From a commercial payer perspective, costs per patient with NGS were lower compared with a sequence of individual single-gene tests ($6225 vs $8430) with total estimated savings of $127,402 annually for commercial health plans.50

OCPs provide support to make decisions among the evidence-based treatment options and to provide benchmarks against national standards. Including NGS within the OCPs can ensure that molecular testing is not only conducted, but it is completed early enough in the diagnostic journey for the most appropriate decision-making available. Delayed or inappropriate treatment adversely affects clinical and economic outcomes, and overall, the appropriate use of NGS reduces the time to optimal treatment. Moreover, access to NGS data can help identify patients who are eligible for new FDA-approved therapies as they become available for use.

CONCLUSIONS

Oncology practices that develop and implement specific OCP programs can help provide high-quality cancer care for their patients by standardizing and streamlining their treatment decisions. Immunotherapy has greatly changed the therapeutic landscape for advanced NSCLC. Combination therapy, utilizing ICIs, and chemotherapy has been extensively evaluated in clinical trials leading to recent and anticipated FDA approvals. In the absence of specific tumor mutations, first-line treatment with a combination of platinum-based chemotherapy and immunotherapy with an ICI, such as a PD-1 or PD-L1 inhibitor, is an option that is important to add to OCPs. Many clinical trials are in development to further support expanded indications for combination chemotherapy/immunotherapy regimens, and FDA approvals of these regimens are anticipated; these will be changing the landscape of NSCLC treatment. Stakeholders who review and make updates to OCPs for NSCLC must take into account many considerations to create the best possible base for evidence-based oncology decision-making.

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Q&A With Edward Arrowsmith, MD, on the Value of Clinical Pathways for NSCLC Treatment Decisions

Edward Arrowsmith, MD: We really think of 2 areas [in which] pathways can improve the overall patient experience. One is quality, and the other is the creation of value.

When it comes to quality, there are 2 related things. One is selecting the best drug for a particular patient. A clinician can follow pathways, particularly in the increasingly complex landscape of a disease like NSCLC, and choose the optimal therapy for the patient. The other consideration is standardization. In our pathways—and a lot of pathways—there are sometimes several therapies that appear clinically equivalent based on either head-to-head comparisons or the [results of] trials that look pretty similar. Standardizing on 1 of those regimens, particularly for intravenous therapy, can lead to improvement in quality as the whole treatment team has experience with 1 particular way of treating a patient. Everyone is on board with the logistics, with the side effects, and [with ensuring that] patients receive proper education and care.

[Another area in which pathways can improve the overall patient experience] is value. If there are treatments that appear to have the same efficacy and side effect profile, sometimes 1 of those will create more value for the patient or the health care system. Often, it is the treatment that has a lower cost of care or lower out-of-pocket expense for patients. By having pathways, the OneOncology system or other systems can look into [that kind of thing]—value. It’s unlikely that an individual clinician with a busy schedule seeing patients is going to have [information regarding value] at top of mind. Really, [for those of us with pathways for NSCLC], those are the 2 key things: improving quality and increasing value.

Arrowsmith: [The] pathways program at OneOncology is relatively new. It is something that we’re trying to improve all the time. Our basic idea—what we come back to again and again—is that we’re trying to pool the clinical wisdom of the physicians across our practices. We come together, make decisions, and then try to push that knowledge back out to our physicians across the country.

Pharmacists really lead our pathways [as part] of our clinical teams. They help [in gathering] our key physicians from across the practices. We’re broken down into disease-related groups. We have a lung cancer program that has representatives from all 13 practices of OneOncology. We discuss new data and existing data, make decisions about pathways, and then try to get that information out to clinicians, both at the point of care and through educational programs.

Arrowsmith: The key stakeholders in OneOncology are the physicians in our practices. They are the main drivers of our pathway program. We are fortunate that we have a robust clinical team at OneOncology that is tracking both new approvals of drugs for NSCLC and clinical trials for NSCLC. [Tracking this evidence means] that, months or years in advance, we are following compounds or studies and anticipating those results as well as data presented at [major] conferences or published in peer-reviewed journals.

Arrowsmith: I believe that you mentioned that you had 13 practices using these clinical pathways with OneOncology. How are you handling the unique [patient] populations of those practices?

Arrowsmith: We have sites of care in really diverse locations across the nation: urban, suburban, and rural. [We see] all types of patients and have all types of providers. Some [providers see] patients with lung cancer almost exclusively, and other providers see all types of hematologic and oncology [cases], for instance, in a rural [setting] where they may be the only oncologist for many miles. We really want to focus on providing resources for all of those physicians and all of those patients. The scientific background is really the same for [all providers], but there are tweaks in how we want to present data [to specific providers], depending on the practice. It’s different for someone who sees all lung cancer [versus] someone who is seeing
everything that comes in through the door. [The ways that] we try to educate and assist those [providers] are a little different.

[Our] goal with the pathways program is not to have 100% of the patients following a pathway. We know that some patients, particularly those with a lot of comorbidities, may need customization of their care.

**AJMC®:** Are you monitoring adherence for individual physicians—how well they are following these clinical pathways? Are you providing incentives or disincentives to keep them close to that pathway when it makes sense for patient care?

**Arrowsmith:** We have a couple of ways that we’re tracking use of the pathways, and that’s something that we [believe] is really critical. We’re really striving to use real-time data to follow pathway adherence, and we hope that this will differentiate our pathways program [from others] both now and over time. At OneOncology, we have a robust program that we call OneAnalytics that pulls information from a variety of sources and allows clinicians and other practice leaders to better manage the patient care experience. We’re able to follow how patients are doing, how providers are doing, and [whether providers are] adherent to the pathways. Something we’re really excited about is a tool called Flatiron Assist. Flatiron Health is the maker of OncoEMR, which is our electronic medical record vendor across OneOncology. This point of care tool guides clinicians as they’re ordering treatment for NSCLC and other cancers. It uses clinical inputs to suggest the kind of optimal or pathway-based treatment to prescribe right at the point of care.

**AJMC®:** What sort of clinical or nonclinical outcomes do you find to be of high value in NSCLC?

**Arrowsmith:** In some ways, [NSCLC] has almost bifurcated a little bit how we analyze data. There’s an increasing [number] of patients with stage 4 or advanced disease [who] have a specific target with EGFR-mutant or ALK-rearranged lung cancer as being the kind of first examples of this. Increasingly, [there are] other targets, such as the KRAS G12C mutation [that became targetable] a little less than a year ago. Sometimes, we see really dramatic results of phase 2 trials in highly targeted patient populations. Sometimes, based on phase 2 data in those groups, we [at OneOncology], and really sort of the lung cancer community as a whole, are integrating those treatments [into pathways]. Those generally are the new compounds getting FDA approvals for [a] specific indication. Sotorasib for second-line therapy of KRAS G12C–mutated NSCLC would be a good example of that.

The other is the more common group of patients who we are treating with a combination of chemotherapy with immunotherapy or chemotherapy and radiation followed by immunotherapy. There we’re really looking at overall survival as the primary end point that [we evaluate when we] update our pathways and change our treatment algorithms.

**AJMC®:** When developing a clinical pathway, what data do you consider? How do you factor an agent’s adverse event profile, cost, and high-quality overall survival outcomes data into the clinical pathway decision-making process?

**Arrowsmith:** There’s a sort of a stepwise approach to development of a pathway. The first [consideration] is efficacy. The most effective treatment that helps patients live longer and live better is going to be the key driving metric in pathway formation. The next step is to determine whether there are 2 treatments of equal efficacy or that we think are likely to have equal efficacy. If they have not been compared in a head-to-head trial, we look at the side effect profiles. Obviously, [we will] go with a treatment that we feel is likely to be easier on patients from a side effect perspective. If efficacy and side effects appear to be roughly equivalent, then [we proceed with the] third criteria, [which is to] look at value. Is it a lower cost agent? Or, possibly, is it an agent [for which] there is a much better patient assistance program for patients who are uninsured or underinsured such that there is particular value for those patients? It’s roughly evaluated in that order of efficacy, safety, and, then, value when we think about agents [comparatively]. Obviously, with biosimilars or generics, there is a clear example of when value becomes paramount.

**AJMC®:** The immune checkpoint inhibitors like atezolizumab, cemiplimab, and pembrolizumab have taken NSCLC treatment to the next level in a lot of ways, and they are recommended by leading guidelines for use as monotherapy. What has been OneOncology’s approach to integrating these therapies into your clinical pathways program?

**Arrowsmith:** The checkpoint inhibitors really are agents that have revolutionized treatment. For those of us who have been treating NSCLC for years or decades, we’re clearly seeing responses and durable responses that are unbelievable compared with what we saw 10 or 15 years ago. [We now have] patients who are free of symptoms of disease for 3, 4, 5, or more years down the road. These are agents that we integrated very quickly into the therapy of NSCLC and into our pathways program. We utilize them both as single agents or combined with chemotherapy and following chemoradiation or adjuvant therapy. They’re really spreading across the landscape in lung cancer therapy.

**AJMC®:** Some of these immune checkpoint inhibitors are FDA-approved for use in combination with chemotherapy for NSCLC and have a similar recommendation from the leading guidelines. Whether for these [FDA-approved or guideline-recommended] combination regimens or others that may be in the process of being evaluated [by the FDA], how are you looking at a combination regimen and deciding where this falls in your clinical pathways program?

**Arrowsmith:** As the checkpoint inhibitors have been combined with chemotherapy, we’ve been fortunate that we’ve seen very high-quality data with really large differences in outcomes between the chemotherapy-alone arms and the chemotherapy-plus-checkpoint inhibitor arms. However, what we have seen more recently is really a proliferation of different strategies—whether it’s limited cycles of chemotherapy followed by checkpoint inhibitors or combinations of PD-1 and CTLA-4 targeted drugs—the landscape has [become] more
The chemotherapy-with-checkpoint inhibitor landscape is complicated. There are some situations where there might be a clinical reason to use a certain checkpoint inhibitor rather than another. There are other circumstances where the trials appear to be very similar. Some of the results from checkpoint inhibitor studies look similar enough to me and to other experts that choosing 1 checkpoint inhibitor over another in order to maximize value maybe does make sense. Some of the economic considerations of cost for the patient and the health care system maybe are going to come back into play. That's something that we're actively examining at OneOncology.

AJMC®: How do you [and other pathways decision makers] stay on top of the large body of evidence regarding emerging therapies? How do you keep track of updates to the treatment pipeline and the immense amount of research that is being conducted in NSCLC? How do you ensure that your clinical pathways remain up to date and that physicians have access to all the tools that they would like in their armamentarium to treat this disease?

Arrowsmith: Something that we at OneOncology consider—really the core of our mission—is being dynamic and improving our therapies. All of us who treat patients with cancer—or really anyone who has had cancer or a loved one with cancer—know that our therapies are not what they need to be. They're not what we want them to be. We're actively trying to improve therapy, of course, both through [promoting] participation in clinical trials [and] updating our pathways as quickly as we can.

There are several ways that we do that. One is that we really don't have a cadence for decision-making. We try to make decisions [that are] very close to real-time as new data come out or as new molecular compounds receive FDA approval and are available for use. Another thing we try to do is to harvest analyses from all types of different sources to identify patients who may be best for specific therapies. We have active partnerships to have next-generation sequencing data available to us as raw computer data. We can then find all patients with specific molecular abnormalities if new treatments become available for those patients. [The] KRAS-G12C [mutation] is a good example of an abnormality for which a treatment became available [last summer. By analyzing the data,] on day 1 [after FDA approval], we can identify all those patients who maybe had genomic sequencing done a year or 2 ago to make sure we don't overlook any patients who may be good candidates for a specific therapy.

The other thing that we do is to have the dedicated clinical team looking for upcoming new therapies, and [we also] pool wisdom [from] across our practices. If 1 physician or a handful of physicians are at a conference in Europe, the learnings [from that meeting] are passed down to all the physicians across OneOncology.

AJMC®: This has been a very insightful interview. Do you have any closing thoughts that you'd like to share with your colleagues and the readership of AJMC® on the areas we have touched on regarding clinical pathways and the treatment of NSCLC?

Arrowsmith: It has been an incredible last 5 to 10 years [in terms of] improving the outlook for patients with NSCLC, with targeted therapies and immunotherapies becoming available for our patients. Based on some of the exciting compounds in development, there will be continued improvements in outcomes over the next 5 to 10 years. That's why we at OneOncology are really committed to a dynamic process of continuously updating our pathways and using data to identify the best patients for the best treatments at the best times. It's an exciting time in the care of patients with NSCLC, and we are really looking forward to the future. •

*This interview has been edited for clarity.
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