Seattle Genetics and Bristol-Myers Squibb Highlight Interim Phase 1/2 Data Evaluating Combination of ADCETRIS® (Brentuximab Vedotin) and Opdivo® (Nivolumab) in Relapsed Hodgkin Lymphoma at the International Conference on Malignant Lymphoma

Release Date:
Thursday, June 15, 2017 6:58 am EDT

Terms:
Corporate/Financial News #ADCETRIS #BMS #cancer #oncology #Opdivo #patients #BMY ASCO BMS Oncology Opdivo patients Research Squibb treatment

Dateline City:
BOTHELL, Wash. & PRINCETON, N.J.

Combination Data Show 85 Percent Objective Response Rate and 63 Percent Complete Response Rate with an Acceptable Safety Profile in these Pre-Transplant Relapsed or Refractory Classical Hodgkin Lymphoma Patients

Data Support Recently Initiated Pivotal Phase 3 Clinical Trial Evaluating ADCETRIS and Opdivo Combination in Relapsed Hodgkin Lymphoma

BOTHELL, Wash. & PRINCETON, N.J.--(BUSINESS WIRE)--Seattle Genetics, Inc. (Nasdaq: SGEN) and Bristol-Myers Squibb Company (NYSE: BMY) today highlighted an updated interim analysis from the ongoing phase 1/2 clinical trial evaluating ADCETRIS (brentuximab vedotin) and Opdivo (nivolumab) in relapsed or refractory (RR) classical Hodgkin lymphoma (HL) at the International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland. The data reported from 62 patients, including 59 evaluable for response, will be featured in an oral presentation on June 15, 2017. ADCETRIS is an antibody-drug conjugate (ADC) directed to CD30, a defining marker of classical HL. Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to help restore anti-tumor immune response. ADCETRIS and Opdivo are not approved in combination for the treatment of RR classical HL or for other indications.

“The phase 1/2 study combining the antibody-drug conjugate brentuximab vedotin with the PD-1 immune checkpoint inhibitor nivolumab is a promising investigational approach as it combines a targeted therapy with a therapy designed to activate the immune system and the combination may have additive activity,” said Alex Herrera, M.D., lead trial investigator and assistant professor at the City of Hope, Duarte, California. “The interim results support further exploration of this novel regimen, free of traditional chemotherapy.”

“We are evaluating ADCETRIS in novel combinations in order to identify potential treatment regimens for patients with CD30-expressing lymphomas,” said Jonathan Drachman, M.D., Chief Medical Officer and Executive Vice President, Research and Development of Seattle Genetics. “We are pleased to share updated interim results from this ongoing phase 1/2 clinical trial evaluating ADCETRIS in combination with Opdivo in relapsed or refractory HL patients. Since our first patient treated with the combination regimen, the data continue to demonstrate encouraging activity with an acceptable safety profile. These updated data support findings first presented at ASH 2016. We have nearly doubled the number of patients in our trial evaluating the ADCETRIS/Opdivo combination strategy and recently announced a collaboration with BMS to initiate a pivotal phase 3 clinical trial in relapsed HL patients in mid-2017.”

“Bristol-Myers Squibb continues to strengthen our broad Immuno-Oncology and hematology development programs for Opdivo,” said Fouad Namouni, M.D., head of Oncology Development, Bristol-Myers Squibb. “Our continued partnership with Seattle Genetics, combines our deep I-O experience and shared commitment to innovative combination treatment options that have the potential to improve the lives of patients impacted by blood cancers. We look forward to further evaluation of ADCETRIS in combination with Opdivo for the treatment of relapsed Hodgkin lymphoma.”

Interim Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma (Abstract #074, oral presentation at 6:05 p.m. CEST)

Data were reported from 62 patients with RR classical HL after failure of frontline therapy who received the combination regimen of ADCETRIS plus Opdivo. Patients were treated once every three weeks with up to four cycles of combination
therapy. After completion of the fourth cycle of treatment, patients were eligible to undergo an autologous stem cell transplant (ASCT). The median age of patients was 36 years. Forty-five percent of patients had primary refractory disease and 55 percent progressed after responding to frontline therapy, among whom 90 percent received standard of care frontline treatment ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine).

Key findings presented include:

- Of 59 response-evaluable patients, 50 patients (85 percent) had an objective response, including 37 patients (63 percent) with a complete response and 13 patients (22 percent) with a partial response. Five patients (eight percent) had stable disease and four patients (seven percent) had progressive disease.

- Of the 62 patients enrolled, 61 patients (98 percent) received one or more dose of the study therapies. No patients remain on treatment, 59 patients (94 percent) have completed treatment and four patients (six percent) discontinued prior to the end of treatment. At the time of data analysis in the ongoing trial, 37 patients (60 percent) initiated an ASCT and 12 patients (19 percent) received an alternative salvage therapy subsequent to combination therapy. No unusual post-ASCT adverse events were reported. Preliminary analysis shows no impact of ADCETRIS and Opdivo combination on stem cell mobilization or engraftment.

- Prior to ASCT, the most common adverse events of any grade occurring in more than 25 percent of patients were nausea (56 percent); fatigue (43 percent); infusion-related reactions (IRRs, 36 percent); pruritus (31 percent); headache (28 percent); and diarrhea, rash and vomiting (all at 26 percent). Treatment-related serious adverse events occurred in five patients (eight percent), including pneumonitis and pyrexia (two patients each) and colitis, malaise, nausea, pneumonia, respiratory failure and sepsis (one patient each).

- Infusion related reactions (IRRs) were observed in 41 percent of patients. All IRRs were Grade 3 or less, with the rate of Grade 3 IRRs less than five percent.

ADCETRIS and Opdivo are being evaluated as combination therapy in multiple ongoing clinical trials. In addition to the study presented at ICML, a pivotal phase 3 clinical trial evaluating ADCETRIS in combination with Opdivo compared to ADCETRIS alone in relapsed/refractory HL patients is planned to begin enrollment in mid-2017. In addition, a trial titled “A Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas” is ongoing and focuses on patients with relapsed or refractory disease, including diffuse large B-cell lymphoma (DLBCL), and other rare subtypes of B-cell, including mediastinal B-cell lymphoma and mediastinal gray zone lymphoma. The companies recently extended the clinical evaluation of ADCETRIS and Opdivo into a clinical trial evaluating the combination as frontline treatment for older HL patients.

About Classical Hodgkin Lymphoma

Lymphoma is a general term for a group of cancers that originate in the lymphatic system and is the most common type of blood cancer. There are two major categories of lymphoma: HL, also known as Hodgkin disease, and non-Hodgkin lymphoma. HL is a cancer that starts in white blood cells called lymphocytes, which are part of the body’s immune system. The disease is most often diagnosed in early adulthood (ages 20-40) and late adulthood (older than 55 years of age). Classical Hodgkin lymphoma is the most common type of HL, accounting for 95 percent of cases. Classical HL is distinguished from other lymphomas by the characteristic presence of CD30-positive Reed-Sternberg cells.

According to the American Cancer Society, more than 8,000 cases of HL will be diagnosed in the United States during 2017 and approximately 1,000 will die from the disease. According to the Lymphoma Coalition, over 62,000 people worldwide are diagnosed with HL each year and approximately 25,000 people die each year from this cancer. In the European Union, about 12,200 new cases and 2,600 deaths occurred in 2012 as a result of HL.

About ADCETRIS

ADCETRIS is an ADC comprising an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E (MMAE), utilizing Seattle Genetics’ proprietary technology. The ADC employs a linker system that is designed to be stable in the bloodstream but to release MMAE upon internalization into CD30-expressing tumor cells.

Seattle Genetics and Takeda are jointly developing ADCETRIS. Under the terms of the collaboration agreement, Seattle Genetics has U.S. and Canadian commercialization rights and Takeda has rights to commercialize ADCETRIS in the rest of the world. ADCETRIS has received marketing authorization by regulatory authorities in 67 countries for relapsed or refractory HL and systemic anaplastic large cell lymphoma (sALCL). In addition, ADCETRIS is being evaluated broadly in more than 70 ongoing clinical trials, including three phase 3 studies, the ongoing ECHELON-1 trial in frontline classical Hodgkin lymphoma and the ongoing ECHELON-2 trial in frontline mature T-cell lymphomas, as well as the completed ALCANZA trial in cutaneous T-cell lymphoma for which a supplemental Biologics License Application is planned in mid-2017. See important safety information below.

About Opdivo

Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body’s own immune system to help restore anti-tumor immune response. By harnessing the body’s own immune system to fight cancer, Opdivo has become an important treatment option across multiple cancers.

Opdivo’s leading global development program is based on Bristol-Myers Squibb’s scientific expertise in the field of Immuno-Oncology and includes a broad range of clinical trials across all phases, including Phase 3, in a variety of tumor types. To date, the Opdivo clinical development program has enrolled more than 25,000 patients. The Opdivo trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from Opdivo across the continuum of PD-1/L1 expression.

In July 2014, Opdivo was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. Opdivo is currently approved in more than 60 countries, including the United States, the European Union and Japan. In
October 2015, the company's Opdivo and Yervoy combination regimen was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 50 countries, including the United States and the European Union.

About Seattle Genetics

Seattle Genetics is an innovative biotechnology company that develops and commercializes novel antibody-based therapies for the treatment of cancer. The company’s industry-leading antibody-drug conjugate (ADC) technology harnesses the targeting ability of antibodies to deliver cell-killing agents directly to cancer cells. ADCETRIS® (brentuximab vedotin), the company’s lead product, in collaboration with Takeda Pharmaceutical Company Limited, is the first in a new class of ADCs and is commercially available globally in 67 countries for relapsed classical Hodgkin lymphoma and relapsed systemic anaplastic large cell lymphoma (sALCL). Seattle Genetics is also advancing vadastuximab talirine (SGN-CD33A; 33A), an ADC in a phase 3 trial for acute myeloid leukemia and in collaboration with Astellas, enfortumab vedotin, an ADC in a planned pivotal phase 2 trial for metastatic urothelial cancer. Headquartered in Bothell, Washington, Seattle Genetics has a robust pipeline of innovative therapies for blood-related cancers and solid tumors designed to address significant unmet medical needs and improve treatment outcomes for patients. The company has collaborations for its proprietary ADC technology with a number of companies including AbbVie, Astellas, Bayer, Celldex, Genentech, GlaxoSmithKline and Pfizer. More information can be found at www.seattlegenetics.com

Bristol-Myers Squibb & Immuno-Oncology: Advancing Oncology Research

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational Immuno-Oncology (I-O) medicines for hard-to-treat cancers that could potentially improve outcomes for these patients.

We are leading the scientific understanding of I-O through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 50 types of cancers with 14 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance I-O/chemotherapy, I-O/targeted therapies and I-O/radiation therapies across multiple tumors and potentially deliver the next wave of therapies with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and how patients’ individual tumor biology can be used as a guide for treatment decisions throughout their journey.

We understand making the promise of I-O a reality for the many patients who may benefit from these therapies requires not only innovation on our part but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

ADCETRIS (brentuximab vedotin) U.S. Important Safety Information

BOXED WARNING

Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.

Contraindication

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

Warnings and Precautions

- Peripheral neuropathy (PN): ADCETRIS treatment causes a PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.

- Anaphylaxis and infusion reactions: Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Patients who experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

- Hematologic toxicities: Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with ADCETRIS. Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

- Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Closely monitor patients during treatment for the emergence of possible bacterial, fungal or viral infections.

- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor and high tumor burden.

- Increased toxicity in the presence of severe renal impairment: The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment.

- Increased toxicity in the presence of moderate or severe hepatic impairment: The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with
normal hepatic function. Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment.

- Hepatotoxicity: Serious cases of hepatotoxicity, including fatal outcomes, have occurred with ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first dose of ADCETRIS or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk.

- Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

- Pulmonary toxicity
  Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

- Serious dermatologic reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- Gastrointestinal (GI) complications: Fatal and serious GI complications, including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus have been reported in ADCETRIS-treated patients. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

- Embryo-fetal toxicity: Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Adverse Reactions

In two uncontrolled single-arm trials of ADCETRIS as monotherapy in 160 patients with relapsed classical HL and sALCL, the most common adverse reactions (≥20%), regardless of causality, were: neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting.

In a placebo-controlled trial of ADCETRIS in 329 patients with classical HL at high risk of relapse or progression post-auto-HSCT, the most common adverse reactions (≥20%) in the ADCETRIS-treatment arm (167 patients), regardless of causality, were: neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea.

Drug Interactions

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE).

Use in Specific Populations

MMAE exposure and adverse reactions are increased in patients with moderate or severe hepatic impairment or severe renal impairment. Avoid use.

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

For additional Important Safety Information, including Boxed WARNING, please see the full Prescribing Information for ADCETRIS at www.seattlegenetics.com or www.ADCETRIS.com.

U.S. FDA-APPROVED INDICATIONS FOR OPDIVO ®

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the
OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progressive disease on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

OPDIVO® (nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

OPDIVO® (nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated pneumonitis occurred in 6% (25/407) of patients.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that study (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated hepatitis occurred in 13% (51/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%.
Immune-Mediated Neuropathies

In a separate Phase 3 study of YERVOY 3 mg/kg, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.

Immune-Mediated Endocrinopathies

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO with YERVOY, hypophysitis occurred in 9% (36/407) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO with YERVOY, adrenal insufficiency occurred in 5% (21/407) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO with YERVOY, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with YERVOY. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO with YERVOY, diabetes occurred in 1.5% (6/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. 6 of the 9 patients were hospitalized for severe endocrinopathies.

Immune-Mediated Nephritis and Renal Dysfunction

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients.

Immune-Mediated Skin Adverse Reactions and Dermatitis

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated rash occurred in 22.6% (92/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 (2.5%) patients. 1 (0.2%) patient died as a result of toxic epidermal necrolysis. 1 additional patient required hospitalization for severe dermatitis.

Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. In patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one patient receiving OPDIVO with YERVOY (0.2%) after 1.7 months of exposure.

Other Immune-Mediated Adverse Reactions

Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO the following clinically significant immune-mediated adverse reactions occurred in <1.0% of patients receiving OPDIVO: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy, infusion-related reactions occurred in 6.4% (127/1994) of patients. In patients receiving OPDIVO with YERVOY, infusion-related reactions occurred in 2.5% (10/407) of patients.
Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Embryo-Fetal Toxicity

Based on their mechanisms of action, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with an OPDIVO- or YERVOY- containing regimen and for at least 5 months after the last dose of OPDIVO.

Lactation

It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from an OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions occurred in 73% (3.7%) of patients receiving OPDIVO. In checkmate 025, serious adverse reactions in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). In Checkmate 017 and 057, serious adverse reactions occurred in 40% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) were dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (59%), rash (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common (≥20%) adverse reactions in the OPDIVO (n=313) arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were asthenic conditions (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO were cough and dyspnea at a
higher incidence than investigator’s choice. In Checkmate 275, the most common adverse reactions (≥ 20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%).

In a separate Phase 3 study of YERVOY 3 mg/kg, the most common adverse reactions (≥5%) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

Checkmate Trials and Patient Populations

Checkmate 067 - advanced melanoma alone or in combination with YERVOY; Checkmate 037 and 066 - advanced melanoma; Checkmate 017 - squamous non-small cell lung cancer (NSCLC); Checkmate 057 - non-squamous NSCLC; Checkmate 025 - renal cell carcinoma; Checkmate 205/039 - classical Hodgkin lymphoma; Checkmate 141 - squamous cell carcinoma of the head and neck; Checkmate 275 - urothelial carcinoma.

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY.

About the Bristol-Myers Squibb and Ono Pharmaceutical Co., Ltd. Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Ltd (Ono), Bristol-Myers Squibb expanded its territorial rights to develop and commercialize Opdivo globally except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Bristol-Myers Squibb and Ono further expanded the companies’ strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

Seattle Genetics Forward-Looking Statement

Certain of the statements made in this press release are forward looking, such as those, among others, relating to the future potential therapeutic uses of ADCETRIS (including in combination with Opdivo) and future clinical and regulatory progress. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. Factors that may cause such a difference include risks related to adverse clinical results associated with the use of ADCETRIS or Opdivo (or the combination), the failure of the companies to continue their collaboration or execute on the planned clinical trials or adverse regulatory action. More information about the risks and uncertainties faced by Seattle Genetics is contained in the Company’s Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 filed with the Securities and Exchange Commission. Seattle Genetics disclaims any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that ADCETRIS in combination with Opdivo will be successfully developed or approved for any of the indications described in this release. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2016, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Language: English

Contact:

Bristol-Myers Squibb
Media:
Audrey Abernathy, 609-419-5375
audrey.abernathy@bms.com
or
Investors:
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com
or
Seattle Genetics
Investors:
Peggy Pinkston, 425-527-4160
ppinkston@seagen.com
or
Media:
Tricia Larson, 425-527-4180
tlarson@seagen.com

Ticker Slug:
Ticker: BMY
Exchange: NYSE
Ticker: SGEN
Exchange: NASDAQ