Seattle Genetics and Bristol-Myers Squibb Highlight Interim Results from Phase 1/2 Study Evaluating the Combination of ADCETRIS® (Brentuximab Vedotin) and Opdivo® (Nivolumab) in Relapsed or Refractory Hodgkin Lymphoma

Release Date:
Monday, December 11, 2017 10:30 am EST

Terms:
Corporate/Financial News #ASH17 #BMS #cancer #CheckMate #Lymphoma #oecology #Opdivo SBMY SGEN Adcetris BMS BMY Bristol-Myers Cancer caregiver CheckMate Immuno-Oncology Immunotherapy nivolumab nurse Oncology Opdivo patients Research Squibb treatment

Dateline City:
ATLANTA

-Data Presented in Oral Session at the American Society of Hematology (ASH) Annual Meeting with Simultaneous Publication in Blood-

-Combination Data Showed 83 Percent Objective Response Rate and 62 Percent Complete Response Rate with an Acceptable Safety Profile in Pre-Transplant Relapsed or Refractory Classical Hodgkin Lymphoma Patients-

-Data Support the Ongoing Pivotal Phase 3 CHECKMATE 812 Clinical Trial Evaluating Combination of ADCETRIS and Opdivo in Relapsed Hodgkin Lymphoma-

ATLANTA--(BUSINESS WIRE)--Seattle Genetics, Inc. (NASDAQ:SGEN) and Bristol-Myers Squibb Company (NYSE:BMY) today highlighted updated interim results from an ongoing phase 1/2 clinical trial evaluating the combination of ADCETRIS (brentuximab vedotin) and Opdivo (nivolumab) in relapsed or refractory classical Hodgkin lymphoma (HL) at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition taking place in Atlanta, Georgia, December 9-12, 2017. The data were also simultaneously published online in the journal Blood. The data reported from 62 patients, including 60 evaluable for response, were featured in an oral presentation and selected to be included in the 2018 Highlights of ASH post-meeting program. ADCETRIS is an antibody-drug conjugate (ADC) directed to CD30, a defining marker of classical HL that plays a role in tumor growth and survival. Opdivo is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to harness the body's own immune system to help restore anti-tumor immune response. ADCETRIS and Opdivo are not approved in combination for the treatment of relapsed or refractory HL or for other indications.

"The phase 1/2 study combining the antibody-drug conjugate ADCETRIS with the PD-1 immune checkpoint inhibitor Opdivo is a promising investigational approach as it combines a CD30-targeted therapy with a therapy designed to activate the immune system. The antitumor activity of the drugs may be enhanced when administered in combination," said Alex Herrera, M.D., lead trial investigator and assistant professor at the City of Hope Medical Center, Duarte, California. "The interim results evaluating the combination regimen in relapsed or refractory HL patients continue to look compelling, demonstrating both promising activity in addition to a manageable overall safety profile. These data support further exploration of this novel, chemotherapy-free investigational regimen in HL patients."

"We are evaluating ADCETRIS broadly as the foundation of care for CD30-expressing lymphomas, including combination strategies that have the potential to improve efficacy. At this year's ASH Annual Meeting, we are presenting significant clinical updates that support this goal, including results from the phase 3 ECHELON-1 clinical trial evaluating ADCETRIS in combination with chemotherapy in frontline HL as well as interim results from this phase 1/2 study evaluating ADCETRIS in combination with Opdivo in relapsed HL," said Jonathan Drachman, M.D., Chief Medical Officer and Executive Vice President, Research and Development at Seattle Genetics. "Interim results from the trial evaluating ADCETRIS in combination with Opdivo as pre-transplant salvage therapy for classical HL patients continue to look promising, demonstrating an 83 percent objective response rate, with a 62 percent complete response rate and an acceptable safety profile. We look forward to
further evaluation of this innovative combination regimen in other disease settings, including the ongoing pivotal phase 3 CHECKMATE 812 study in patients with relapsed HL, in partnership with Bristol-Myers Squibb.”

“Our ongoing collaboration to evaluate Opdivo in combination with Seattle Genetics’ ADCETRIS reinforces Bristol-Myers Squibb’s commitment to addressing cancer from all angles for patients with high unmet needs,” said Fouad Namouni, M.D., head of Oncology Development, Bristol-Myers Squibb. “We look forward to further evaluation of the ADCETRIS and Opdivo combination in Hodgkin lymphoma and other hematologic malignancies in several ongoing trials.”

**Interim Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma (Abstract #649, oral presentation at 10:30 a.m. ET)**

Data were reported from 62 patients with relapsed or refractory HL who received the combination regimen of ADCETRIS plus Opdivo after failure of frontline therapy. Patients were treated once every three weeks, with up to four cycles of combination therapy in the outpatient setting. 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. The majority of patients (95 percent) were refractory or had relapsed after receiving the standard of care frontline treatment ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine) or some variation of the standard of care (ABVE-PC, R-ABVD).

Key findings presented include:

- Of 60 response-evaluable patients, 50 patients (83 percent) had an objective response, including 37 patients (62 percent) with a complete response and 13 patients (22 percent) with a partial response. Five patients (eight percent) had stable disease and five patients (eight percent) had progressive disease. Median follow-up time was eight months and median duration of response was not yet reached. The estimated six-month progression-free survival rate was 89 percent.
- Of the 62 patients enrolled, 58 patients completed all four cycles of study treatment and four patients discontinued prior to the end of treatment. At the time of data analysis, 54 patients received an ASCT. Preliminary analysis shows no impact of combination treatment with ADCETRIS and Opdivo on stem cell mobilization or engraftment.
- The most common adverse events (AEs) of any grade occurring prior to ASCT or subsequent salvage therapy in at least 20 percent of patients were nausea, fatigue, infusion-related reaction (IRR), pruritus, diarrhea, headache, cough, vomiting, dyspnea, nasal congestion, pyrexia and rash. Grade 3 or 4 adverse events occurred in 19 patients (31 percent), with 17 patients (28 percent) having Grade 3 AEs (fatigue, IRR, pruritus and diarrhea) and two patients (three percent) having Grade 4 AEs (thrombocytopenia and increased lipase).

- Infusion-related reactions (IRRs) were observed in 44 percent of patients, of which the majority (41 percent) were Grade 1 or 2. No patients discontinued treatment due to an IRR.
- Potential immune-related adverse events, excluding IRRs, occurred in 50 patients (82 percent), and five patients required treatment with systemic steroids, including patients with Grade 3 diarrhea and Grade 2 colitis, Grade 3 aspartate aminotransferase elevation, Grade 4 colitis and pneumonitis (after receiving additional salvage therapy), Grade 2 pneumonitis, and Grade 4 pneumonitis (after BEAM, as part of the conditioning regimen). No patients discontinued treatment due to an immune-related adverse event.

ADCETRIS and Opdivo are being evaluated as combination therapy in multiple ongoing clinical trials. In addition to the study presented at ASH, a trial titled “A Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas” is ongoing and enrolling patients with relapsed or refractory disease, including diffuse large B-cell lymphoma (DLBCL), and other rare subtypes of B-cell lymphoma, including mediastinal B-cell lymphoma and mediastinal gray zone lymphoma. The companies have also extended the clinical evaluation of ADCETRIS and Opdivo into a clinical trial evaluating the combination as frontline treatment for older HL patients. Lastly, the companies initiated a pivotal phase 3 clinical trial called CHECKMATE 812 trial evaluating ADCETRIS alone versus ADCETRIS in combination with Opdivo in relapsed/refractory 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% 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, approximately 8,260 cases of Hodgkin lymphoma will be diagnosed in the United States during 2017 and more than 1,000 will die from the disease. According to the Lymphoma Coalition, over 62,000 people worldwide are diagnosed with Hodgkin lymphoma each year and approximately 25,000 people die each year from this cancer.

**About ADCETRIS**

ADCETRIS is an antibody-drug conjugate (ADC) directed to CD30 and is being evaluated broadly in more than 70 clinical trials, including three phase 3 studies: the completed ECHELON-1 trial in frontline classical Hodgkin lymphoma that supported the recent FDA Breakthrough Therapy Designation and submission of the supplemental Biologics License Application (BLA) for use in this setting, the ongoing ECHELON-2 trial in frontline mature T-cell lymphomas, and the ongoing CHECKMATE 812 trial of ADCETRIS in combination with Opdivo (nivolumab) for relapsed/refractory Hodgkin lymphoma.

ADCETRIS is an ADC comprising an anti-CD30 monoclonal antibody attached to 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.
ADCETRIS injection for intravenous infusion has received FDA approval for four indications: (1) regular approval for adult patients with primary cutaneous anaplastic large cell lymphoma (PCALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy, (2) regular approval for the treatment of patients with classical Hodgkin lymphoma after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, (3) regular approval for the treatment of classical Hodgkin lymphoma patients at high risk of relapse or progression as post-auto-HSCT consolidation, and (4) accelerated approval for the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen. The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for the sALCL indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Health Canada granted ADCETRIS approval with conditions for relapsed or refractory Hodgkin lymphoma and sALCL in 2013, and non-conditional approval for post-ASCT consolidation treatment of Hodgkin lymphoma patients at increased risk of relapse or progression.

ADCETRIS was granted conditional marketing authorization by the European Commission in October 2012 for two indications: (1) for the treatment of adult patients with relapsed or refractory CD30-positive Hodgkin lymphoma following autologous stem cell transplant (ASCT), or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and (2) the treatment of adult patients with relapsed or refractory sALCL. The European Commission extended the current conditional marketing authorization of ADCETRIS and approved ADCETRIS for the treatment of adult patients with CD30-positive Hodgkin lymphoma at increased risk of relapse or progression following ASCT.

ADCETRIS has received marketing authorization by regulatory authorities in 69 countries for relapsed or refractory Hodgkin lymphoma and sALCL. See important safety information below.

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. Seattle Genetics and Takeda are funding joint development costs for ADCETRIS on a 50:50 basis, except in Japan where Takeda is solely responsible for development costs.

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-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 + Yervoy combination 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 dedicated to improving the lives of people with cancer through novel antibody-based therapies. 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. Seattle Genetics commercializes ADCETRIS® (brentuximab vedotin) for the treatment of several types of CD30-expressing lymphomas. The company is also advancing a robust pipeline of novel therapies for solid tumors and blood-related cancers designed to address significant unmet medical needs and improve treatment outcomes for patients. More information can be found at www.seattlegenetics.com and follow @SeattleGenetics on Twitter.

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/I-O, 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’ 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 ADCETRIS-treated patients.

Contraindication

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

Warnings and Precautions

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

- **Anaphylaxis and infusion reactions:** Infusion-related reactions (IRR), including anaphylaxis have occurred with ADCETRIS. Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before 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 ADCETRIS dose. 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 ADCETRIS-treated patients. Closely monitor patients during treatment for 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 use 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 use in patients with moderate or severe hepatic impairment.

- **Hepatotoxicity:** Serious cases, including fatal outcomes, have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- **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. Other possible contributory factors other than ADCETRIS include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients 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:** Noninfectious pulmonary toxicity events including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported. Monitor patients for signs and symptoms, 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:** Acute pancreatitis, including fatal outcomes, has been reported in ADCETRIS-treated patients. Other 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 animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

**Most Common (≥20%) Adverse Reactions:** peripheral sensory neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, and pyrexia.

**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**

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.
medication pneumonitis have occurred. Patients should be monitored for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more. In patients receiving OPDIVO with YERVOY, 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.

**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 OPDIVO 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.

**IMPORTANT SAFETY INFORMATION**

**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 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 confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression 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.

OPDIVO® (nivolumab) is indicated for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

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

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.
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. For patients without HCC, withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3 and up to 5 times the upper limit of normal (ULN), if AST/ALT is >1 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. 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 Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.

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, hyperthyroidism or thyroiditis resulting in hypothyroidism 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 the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, 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), 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%).
Checkmate 067, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) all occurred more frequently 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 46% 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. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia.

Common Adverse Reactions

In Checkmate 037, the most common adverse reactions (≥20%) reported with OPDIVO (n=268) were rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs 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 arm (n=313) 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 Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). The most common adverse reactions (≥20%) in patients who received OPDIVO as a single agent were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia.

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%).

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

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; Checkmate 040 – hepatocellular carcinoma.

About the Bristol-Myers Squibb and Ono Pharmaceutical 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 collaborations to develop and commercialize multiple immuno-therapeutics – 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 therapeutic and commercial potential of ADCETRIS including in combination with Opdivo, and as the foundation of care for
CD30-expressing lymphomas, and its safety and efficacy for these uses, as well as other statements that are not historical facts. 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 the difficulty and uncertainty of pharmaceutical product development, unexpected efficacy or safety events or profiles associated with the use of each or drug or in combination, or adverse regulatory action. More information about the risks and uncertainties faced by Seattle Genetics is contained under the caption “Risk Factors” included in the company’s Quarterly Report on Form 10-Q for the quarter ended September 30, 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 the Opdivo plus ADCETRIS combination will receive regulatory approval 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 Abemathy, 609-419-5375
audrey.abemathy@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

#MEDIA: $BMY and $SGEN to announce new data in classical Hodgkin lymphoma at #ASH17