Research from Bristol-Myers Squibb’s Innovative Oncology Development Program to Be Presented at AACR 2018 Demonstrates Commitment to Advancing Precision Medicine Research for Patients with Cancer

Release Date:
Wednesday, March 14, 2018 5:49 pm EDT

Terms:
Corporate/Financial News #AACR18 #BMS #cancer #CheckMate #oncology #Opdivo $BMY AACR BMS BMY Bristol-Myers Cancer carcinoma caregiver CheckMate doctor Immuno-Oncology Immunotherapy ipilimumab LAG-3 lung MSI-H/dMMR nivolumab NSCLC nurse Oncology Opdivo patients PD-L1 Research SCLC TMB treatment tumor Yervoy

Dateline City:
PRINCETON, N.J.

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced the presentation of new data showcasing advances in the science of Immuno-Oncology at the American Association for Cancer Research (AACR) Annual Meeting in Chicago from April 14-18. Investigations of novel agents and Opdivo (nivolumab)-based combinations will be featured in 24 abstracts, including six late-breaking or oral presentations, across seven therapeutic areas. Abstracts to be presented include the first disclosure of data from the Phase 3 CheckMate -227 trial evaluating the combination of Opdivo plus Yervoy (ipilimumab) in first-line non-small cell lung cancer patients with high tumor mutational burden (≥10 mutations/megabase), as well as two-year overall survival data from pivotal studies of Opdivo in bladder and head and neck cancers. The Company will also present the first clinical data on its investigational anti-CD73 antibody in combination with Opdivo.

Key late-breaking and oral presentations representing the breadth of the Company's leading translational and basic research include:

- **Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: initial results from CheckMate -227**
  Author: M. Hellmann
  Abstract #CT077
  Session: CTPL03 - Immunotherapy Combinations: The New Frontier in Lung Cancer
  Monday, April 16, 10:30 AM-12:30 PM CDT, N Hall B (Plenary Hall, Level 3)

- **Tumor mutation burden (TMB) as a biomarker for clinical benefit from dual immune checkpoint blockade with nivolumab + ipilimumab in first-line non-small cell lung cancer: identification of TMB cutoff from CheckMate -568**
  Author: S. Ramalingam
  Abstract #CT078
  Session: CTPL03 - Immunotherapy Combinations: The New Frontier in Lung Cancer
  Monday, April 16, 10:30 AM-12:30 PM CDT, N Hall B (Plenary Hall, Level 3)

- **Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced non-small cell lung cancer: results of the Phase 3 CheckMate -078 study**
  Author: Y-L. Wu
  Abstract #CT114
  Session: CTMS02 - Updates in Immuno-Oncology Trials
  Monday, April 16, 3-5 PM CDT, N Hall C (Level 1)

- **Nivolumab versus investigator’s choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-yr outcomes in the overall population and PD-L1 subgroups of CheckMate -141**
  Author: R. Ferris
  Abstract #CT116
  Session: CTMS02 - Updates in Immuno-Oncology Trials
  Monday, April 16, 3-5 PM CDT, N Hall C (Level 1)

- **Nivolumab monotherapy in patients with advanced platinum-resistant urothelial carcinoma: Efficacy and safety update and association between biomarkers and overall survival in CheckMate -275**
  Author: P. Sharma
  Abstract #CT178
  Session: CTMS03 - Biomarkers in Immuno-Oncology
  Tuesday, April 17 2:45-5 PM CDT, N Hall C (Level 1)

- **Preliminary Phase 1 profile of BMS-986179, an anti-CD73 antibody, in combination with nivolumab in patients with advanced solid tumors**
Additional data to be presented include:

**Gastrointestinal Malignancies**

- **Exploratory analysis of Janus kinase 1 loss-of-function mutations in patients with DNA mismatch repair-deficient/microsatellite instability-high metastatic (dMMR/MSI-H) colorectal cancer treated with nivolumab + ipilimumab in CheckMate -142**
  Author: S. Kopetz
  Abstract #2603
  Session: PO.CC10.04 - Biomarkers of Therapeutic Response in Clinical Trials
  Monday, April 16, 1-5 PM CDT, Exhibit Hall A, Poster Section 26, Board #4

- **Integrated analysis of colorectal carcinoma by co-extraction of RNA, DNA and protein from FFPE tumor samples**
  Author: V. Patel
  Abstract #2707
  Session: PO.CH03.01 - Cancer Biology Insights Emerging from Proteomic Investigations
  Monday, April 16, 1-5 PM CDT, Exhibit Hall A, Poster Section 31, Board #17

**Genitourinary Cancers**

- **Double positive CD4+CD8+ T cells with an exhausted phenotype in renal cell carcinoma patients**
  Author: L. Menard
  Abstract #4687
  Session: PO.IM01.01 - Adaptive Immunity in Tumors
  Tuesday, April 17, 1-5 PM CDT, Exhibit Hall A, Poster Section 32, Board #20

**Melanoma**

- **Use of adjuvant interferon alfa-2b or ipilimumab 10mg/kg for high-risk patients with melanoma, and associated adverse events and duration of therapy**
  Author: A. Tarhini
  Abstract #3641
  Session: PO.CL06.04 - Immune Checkpoints 3
  Tuesday, April 17, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 26, Board #19

- **Matching-adjusted indirect comparison of nivolumab + ipilimumab and BRAF+MEK inhibitors for the treatment of BRAF-mutant treatment-naïve advanced melanoma**
  Author: M. Atkins
  Abstract #3639
  Session: PO.CL06.04 - Immune Checkpoints 3
  Tuesday, April 17, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 26, Board #17

**Non-Small Cell Lung Cancer**

- **Tumor intrinsic properties associate with differential effects on CD8+ tumor-infiltrating lymphocyte density and immune gene expression in non-small cell lung cancer samples**
  Author: C. Hedvat
  Abstract #1024
  Session: PO.TB06.04 - Adaptation and Checkpoints in Tumorigenesis
  Monday, April 16, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 1, Board #26

- **Evaluation of tumor mutation burden as a biomarker for immune checkpoint inhibitor efficacy: A calibration study of whole exome sequencing with FoundationOne®**
  Author: J. Szustakowski
  Abstract #5528
  Session: PO.CL10.05 - Diagnostic and Prognostic Biomarkers in Clinical Trials
  Wednesday, April 18, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 24, Board #1

**Early Assets**

- **From bench to bedside: Exploring OX40 receptor modulation in a Phase 1/2a study of the OX40 agonist BMS-986178 ± nivolumab or ipilimumab in patients with advanced solid tumors**
  Author: R. Wang
  Abstract #LB-127
  Session: LBPO.IM01 - Late-Breaking Research: Immunology 1
  Monday, April 16, 8 AM-12 PM CDT, Poster Section 45, Board #24

- **Examining the dynamic regulation of OX40 following receptor agonism and T cell activation: Implications for antibody-mediated enhancement of T cell function**
  Author: M-C. Gaudreau
  Abstract #2782
  Session: PO.IM02.11 - Therapeutic Antibodies, Including Engineered Antibodies 2
  Monday, April 16, 1-5 PM CDT, Exhibit Hall A, Poster Section 34, Board #15
- A Phase 1b/2 study of BMS-813160, a CC chemokine receptor 2/5 dual antagonist, in combination with chemotherapy or nivolumab in patients with advanced pancreatic or colorectal cancer
  Author: D. Le
  Abstract #CT124
  Session: Phase I Trials in Progress
  Tuesday, April 17, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 42, Board #7

- Preclinical antitumor activity of a CC chemokine receptor 2/5 dual antagonist as monotherapy and in combination with immune checkpoint blockade
  Author: Q. Zhao
  Abstract #3760
  Session: PO.IM02.07 - Immunomodulatory Agents and Interventions 1
  Tuesday, April 17, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 32, Board #10

- Preclinical antitumor activity of BMS-986158, an oral BET inhibitor, for the treatment of cancer
  Author: S. Wee
  Abstract #5792
  Session: PO.ET06.10 - Canonical Targets 2
  Wednesday, April 18, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 36, Board #18

- Discovery of clinical candidate BMS-986158, an oral BET inhibitor, for the treatment of cancer
  Author: A. Gavai
  Abstract #5789
  Session: PO.ET06.10 - Canonical Targets 2
  Wednesday, April 18, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 36, Board #15

Clinical Collaborations

- A novel heterologous prime boost vaccine system drives tumor specific and potent CD8 T cell responses for cancer immunotherapy
  Author: W. Blair
  Abstract #724
  Session: PO.IM02.13 - Vaccines 1
  Sunday, April 15, 1-5 PM CDT, Exhibit Hall A, Poster Section 34, Board #9

- Antitumor activity associated with dual targeting of CD38 and PD-1 pathways in preclinical models
  Author: N. Bezman
  Abstract #1727
  Session: PO.IM02.05 - Immune Response to Therapies 2
  Monday, April 16, 8 AM-12 PM CDT, Exhibit Hall A, Poster Section 32, Board #22

- Prophylactic TNFα blockade unplugs toxicity and efficacy in immunotherapy anti-PD-1 + anti-CTLA-4 combination
  Author: E. Perez-Ruiz
  Abstract #LB-151
  Session: LBPO.CL01 - Late-Breaking Research: Clinical Research 1
  Monday, April 16, 1-5 PM CDT, Exhibit Hall A, Poster Section 43, Board #18

- The immunosuppressive tumor microenvironment in nasopharyngeal carcinoma: implications for immunotherapy
  Author: A. Duffield
  Abstract #4750
  Session: PO.IM01.02 - New Immunosuppressive Mechanisms in Cancer
  Tuesday, April 17, 1-5 PM CDT, Exhibit Hall A, Poster Section 34, Board #24

- Characterization of the tumor immune microenvironment in head and neck squamous cell carcinoma
  Author: F. Succaria
  Abstract #4693
  Session: PO.IM01.01 - Adaptive Immunity in Tumors
  Tuesday, April 17, 1-5 PM CDT, Exhibit Hall A, Poster Section 32, Board #26

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 advancing 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. Through our leading translational capabilities, we are pioneering immune biology research and identifying a number of potentially predictive biomarkers, including PD-L1, TMB, MSI-H/dMMR and LAG-3, advancing the possibility of precision medicine for more patients with cancer.

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.

**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* 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.

**INDICATIONS**

**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 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.

**OPDIVO®** (nivolumab) is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

**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 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, 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 Adverse Reactions and Dermatitis

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in 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.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

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 as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate study in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In patients receiving OPDIVO as a 60-minute infusion prior to the infusion of 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 (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 (n=236). 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. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

**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) 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 frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 205 and 039, 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 (n=236) 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 40, 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%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper
respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). 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, decreasde appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain.

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® (ipilimumab); 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, Checkmate 238 – adjuvant treatment of melanoma.

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.

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 Opdivo as a monotherapy or in combination with any of the oncology compounds mentioned in this release will receive regulatory approval for an additional indication. 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, 2017 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, 919-605-4521
audrey.abernathy@bms.com
or
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com

Ticker Slug:

Ticker: BMY
Exchange: NYSE

#MEDIA: $BMY announces innovative oncology research to be presented at #AACR18: