New Research From Bristol-Myers Squibb at ESMO 2016 Congress Reinforces Leadership in Immuno-Oncology and Differentiated Research Approach

Release Date:
Monday, October 3, 2016 5:13 pm EDT

Terms:
#BristolMyers #cancer #carcinoma #CheckMate #doctor #ESMO2016 #FDA #HeadandNeck
#ImmunoOncology #nivolumab #nurse #oncology #Opdivo #recurrent #Regulatory #SCCHN #squamous
#Squibb $BMY Bristol-Myers Cancer carcinoma CheckMate doctor ESMO2016 FDA HeadandNeck
ImmunoOncology nivolumab nurse Oncology Opdivo recurrent Regulatory SCCHN squamous Squibb

Dateline City:
PRINCETON, N.J.

Broad set of data across eight tumor types evaluating Opdivo and Yervoy, as monotherapy or in combination, to be presented

First disclosure of novel assets, including lirilumab in combination with Opdivo or Yervoy in squamous cell carcinoma of the head and neck, and fucosyl GM1 in small cell lung cancer

New Opdivo data in advanced bladder cancer to be highlighted, and first presentation of overall survival with Yervoy in adjuvant melanoma

Immuno-Oncology strategy update to be provided at Investor Teleconference

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol-Myers Squibb Company (NYSE:BMY) today announced new data across eight tumor types evaluating Opdivo (nivolumab) and Yervoy (ipilimumab), as monotherapy or in combination, as well as new assets, to be presented at the 2016 European Society for Medical Oncology (ESMO) Congress in Copenhagen, Denmark from October 7–11. Data presented at this congress underscore the Company’s commitment to its portfolio and to discover the next wave of transformational Immuno-Oncology medicines, including combination therapies, for difficult-to-treat cancers.

“Bristol-Myers Squibb continues to lead the scientific understanding of Immuno-Oncology with an extensive portfolio and a differentiated clinical development program where we have set a high bar of success to look for clear and differentiated improvements over currently available therapies,” said Fouad Namouni, M.D., head of development, Oncology, Bristol-Myers Squibb. “We remain focused on expanding the use of the Opdivo and Yervoy combination to more tumors, and bringing forward novel agents and combination regimens in earlier lines of therapy, to help even more patients with cancer.”

Bristol-Myers Squibb assets featured in a total of 26 data presentations. A select listing of Presidential Symposia and oral abstract sessions is included below:

- **CheckMate -064**: Baseline tumor T cell receptor sequencing analysis and neo-antigen load is associated with response and survival in melanoma patients receiving sequential Opdivo and Yervoy (Abstract #1047O). Data will be presented during an oral proffered paper session on Friday, October 7 at 4:45 – 5:00 p.m. CEST.

- **CheckMate -275**: First disclosure of efficacy and safety of Opdivo monotherapy in patients with metastatic urothelial cancer who have received prior treatment (Abstract #LBA31_PR). Data will be presented during an oral proffered paper session on Saturday, October 8 at 9:15 – 9:30 a.m. CEST.

- **CA184-169**: Initial report of survival data from a Phase 3 trial evaluating Yervoy at 3 mg/kg vs. 10 mg/kg in patients with metastatic melanoma (Abstract #1106O). Data will be presented during an oral proffered paper session on Saturday, October 8 at 3:37 – 3:50 p.m. CEST.

- **CA184-029 (EORTC 18071)**: Initial report of survival data from a Phase 3 trial evaluating Yervoy versus placebo after complete resection of stage III melanoma (Abstract #LBA2 PR). Data will be featured during the ESMO Press Program on Saturday, October 8 at 8:15 a.m. CEST and presented during a Presidential Symposium at 5:00 – 5:15 p.m. CEST.
CheckMate -040: Interim analysis of a Phase 1/2 study evaluating the safety and preliminary efficacy of Opdivo in patients with advanced hepatocellular carcinoma (Abstract #6150). Data will be presented during an oral proffered paper session on Sunday, October 9 at 12:00 – 12:15 p.m. CEST.

CheckMate -141: Evaluation of patient-reported outcomes data in recurrent or metastatic squamous cell carcinoma of the head and neck treated with Opdivo or investigator's choice (Abstract #LBA4_PR). Data will be presented during a Presidential Symposium on Sunday, October 9 at 4:25 – 4:40 p.m. CEST.

CheckMate -026: Phase 3 trial of Opdivo versus investigator's choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent PD-L1 positive non-small cell lung cancer (Abstract #LBA7_PR). Data will be presented during a Presidential Symposium on Sunday, October 9 at 5:35 – 5:50 p.m. CEST.

The full set of data to be presented by Bristol-Myers Squibb include:

**Bladder**

CheckMate -275: Efficacy and safety of nivolumab monotherapy in patients with metastatic urothelial cancer who have received prior treatment; results from the phase 2 study

- Author: Galsky
- Abstract # LBA31_PR
- Proffered Paper Session, Genitourinary Tumors, Non-Prostate
- Saturday, October 8, 2016, 9:15 – 9:30 a.m. CEST, Madrid

CheckMate -032: Nivolumab monotherapy in metastatic urothelial cancer: Updated efficacy by subgroups and safety results

- Author: J. Rosenberg
- Abstract #784P
- Poster Session, Genitourinary Tumours, Non-Prostate
- Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

**Colorectal**

CheckMate -142: Nivolumab ± ipilimumab treatment efficacy, safety, and biomarkers in patients with metastatic colorectal cancer with and without high microsatellite instability

- Author: M. Overman
- Abstract #479P
- Poster Session, Gastrointestinal Tumours, Colorectal
- Saturday, October 8, 2016, 1:00 – 2:00 p.m. CEST, Hall E

**Glioblastoma**

CheckMate -548: A randomized phase 2, single-blind study of temozolomide and radiotherapy combined with nivolumab or placebo in newly diagnosed adult patients with tumor O6-methylguanine DNA methyltransferase-methylated glioblastoma

- Author: M. Weller
- Abstract # 356TiP
- Poster Session, CNS Tumors
- Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

**Head and Neck**

Safety of the natural killer cell-targeted anti-KIR antibody, lirilumab, in combination with nivolumab or ipilimumab in two phase 1 studies in advanced refractory solid tumors

- Author: N. Segal
- Abstract #1086P
- Poster Session, Immunotherapy of Cancer
- Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

CheckMate -651: A randomized, open-label, phase 3 study of nivolumab in combination with ipilimumab vs extreme regimen (cetuximab + cisplatin/carboplatin + fluorouracil) as first-line therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck

- Author: A. Argiris
- Abstract #1016TiP
- Poster Session, Head and Neck Cancer
- Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

CheckMate -714: Double-blind, two-arm, phase 2 study of nivolumab in combination with ipilimumab versus nivo and ipi-placebo as first-line therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck

- Author: R. Haddad
- Abstract #1017TiP
- Poster Session, Head and Neck Cancer
- Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E
CheckMate -141: Evaluation of patient-reported outcomes data in recurrent or metastatic squamous cell carcinoma of the head and neck treated with nivolumab or investigator’s choice

Author: K. Harrington
Abstract # LBA4_PR
Presidential Symposium 2
Sunday, October 9, 2016, 4:25 – 4:40 p.m. CEST, Copenhagen

Hepatocellular Carcinoma
CheckMate -040: Safety and preliminary efficacy of nivolumab in patients with advanced hepatocellular carcinoma: Phase 1/2 interim analysis

Author: I. Melero
Abstract # 6150
P roffered Paper, Gastrointestinal Tumors, Non-Colorectal 2
Sunday, October 9, 2016, 12:00 – 12:15 p.m. CEST, Vienna

Lung
CheckMate -017 and -057: Healthcare resource utilization in patients with advanced non-small cell lung cancer based on treatment-related adverse events

Author: M. Venkatachalam
Abstract #1220P
Poster Session, NSCLC, Metastatic
Saturday, October 8, 2016, 1:00 – 2:00 p.m. CEST, Hall E

Cost of care in first line advanced non-small cell lung cancer patients: Chemotherapy vs. targeted therapy

Author: J. Radtchenko
Abstract #1273P
Poster Session, NSCLC, Metastatic
Saturday, October 8, 2016, 1:00 – 2:00 p.m. CEST, Hall E


Author: P. Fracasso
Abstract #1295TiP
Poster Session, NSCLC, Metastatic
Saturday, October 8, 2016, 1:00 – 2:00 p.m. CEST, Hall E

The humanistic burden of small cell lung cancer: A systematic review of health-related quality of life literature

Author: C. Panter
Abstract: #1429P
Poster Session, SCLC
Saturday, October 8, 2016, 1:00 – 2:00 p.m. CEST, Hall E

CheckMate -017 and CheckMate -057: Long-term outcomes with nivolumab versus docetaxel in patients with advanced non-small cell lung cancer: two-year update

Author: F. Barlesi
Abstract #1215PD
Poster Discussion, NSCLC, Metastatic
Sunday, October 9, 2016, 2:45 – 4:15 p.m. CEST (3:46 – 4:06 p.m. CEST), Oslo

CheckMate -057: Overall health status in patients with advanced non-squamous non-small cell lung cancer treated with nivolumab or docetaxel

Author: M. Reck
Abstract #1217PD
Poster Discussion, NSCLC, Metastatic
Sunday, October 9, 2016, 2:45 – 4:15 p.m. CEST (3:46 – 4:06 p.m. CEST), Oslo

A phase 1/2 trial of a monoclonal antibody targeting fucosyl GM1 in relapsed/refractory small cell lung cancer: Safety and preliminary efficacy

Author: Q. Chu
Abstract #1427PD
Poster Discussion, Non-Metastatic NSCLC and Other Thoracic Malignancies
Monday, October 10, 2016, 3:00 – 4:00 p.m. CEST (3:20 – 3:30 p.m. CEST), Berlin

CheckMate -026: A phase 3 trial of nivolumab vs investigator’s Choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent programmed death ligand 1–positive non-small cell lung cancer
Melanoma

Baseline tumor T cell receptor sequencing analysis and neo antigen load is associated with benefit in melanoma patients receiving sequential nivolumab and ipilimumab

Author: J. Weber
Abstract #1047O
Proffered Paper, Immunotherapy of Cancer
Friday, October 07, 2016, 4:45 – 5:00 p.m. CEST, Copenhagen

Overall survival and safety results from a phase 3 trial of ipilimumab at 3 mg/kg vs. 10 mg/kg in patients with metastatic melanoma

Author: P. Ascierto
Abstract #1106O
Proffered Paper, Melanoma and Other Skin Tumors
Saturday, October 8, 2016, 3:37 – 3:50 p.m. CEST, Copenhagen

Ipilimumab vs. placebo after complete resection of stage III melanoma: final overall survival results from the EORTC 18071 randomized, double-blind, phase 3 trial

Author: L. Eggemont
Abstract #LBA2_PR
Presidential Symposium 1
Saturday, October 8, 2016, 5:00 – 5:15 p.m. CEST, Copenhagen

Safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma

Author: M. Sznol
Abstract #1123P
Poster Session, Melanoma And Other Skin Tumors
Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

Safety of reduced infusion times for nivolumab plus ipilimumab and nivolumab alone in advanced melanoma

Author: S. Martin-Algarra
Abstract #1125P
Poster Session, Melanoma And Other Skin Tumors
Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

PD-L1 expression as a biomarker for nivolumab plus ipilimumab and nivolumab alone in advanced melanoma: A pooled analysis

Author: G. Long
Abstract #1112PD
Poster Discussion, Melanoma and Other Skin Tumors
Monday, October 10, 2016, 11:00 a.m. – 12:00 p.m. CEST (11:30 – 11:50 a.m. CEST), Rome

Renal Cell Carcinoma

Cost-effectiveness of nivolumab in patients with advanced renal cell carcinoma in Sweden

Author: S. Johal
Abstract #1032P
Poster Session, Health Economics
Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

CheckMate -016: Updated results from a phase 1 study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma

Author: H. Hammers
Abstract #1062P
Poster Session, Immunotherapy of Cancer
Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E

Pan-Tumor

Assessment of nivolumab benefit-risk profile from a 240-mg flat dose versus a 3-mg/kg dosing regimen in patients with solid tumors

Author: X. Zhao
Abstract #1098P
Poster Session, Immunotherapy of Cancer
Sunday, October 9, 2016, 1:00 – 2:00 p.m. CEST, Hall E
The company will host an investor teleconference on Sunday, October 9, 2016, at 7:30 p.m. CEST (1:30 p.m. EDT) to review new data presented during the ESMO 2016 Congress, including results from CheckMate -026, a Phase 3 study of Opdivo as a first-line therapy in a broad PDL-1 positive population with advanced non-small cell lung cancer (NSCLC). Company executives will also discuss more mature follow-up data not presented at ESMO from CheckMate -012, a multi-arm Phase 1b trial evaluating the safety and tolerability of Opdivo in patients with chemotherapy-naive advanced NSCLC, as either a monotherapy or in combination with other agents including Yervoy, at different doses and schedules.

Investors and the general public are invited to listen to a live webcast of the call at: investor.bms.com, by dialing toll free (877) 258-2708 or international (647) 252-4456, confirmation code: 74677318. Materials related to the call will be available at the same website prior to the call. A replay of the call will be available beginning at 4:30 p.m. EDT on October 9, 2016 through 11:59 p.m. EDT on October 16. The replay can be accessed at investor.bms.com or by dialing (855) 859-2056 or (404) 537-3406, confirmation code: 74677318.

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 that will raise survival expectations in hard-to-treat cancers and will change the way patients live with cancer.

We are leading the scientific understanding of I-O through our extensive portfolio of investigational and approved agents - including the first combination of two I-O agents in metastatic melanoma - and our differentiated clinical development program, which is studying broad patient populations across more than 20 types of cancers with 11 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs uniquely position us to advance the science of combinations across multiple tumors and potentially deliver the next wave of I-O combination regimens 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 inform which patients will benefit most from I-O therapies.

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.

**U.S. FDA APPROVED INDICATIONS FOR OPDIVO®**

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

OPDVO® (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.

OPDVO® (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.

OPDVO® (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.

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

OPDVO® (nivolumab) is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. 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.

Please refer to the end of the Important Safety Information for a brief description of the patient populations studied in the CheckMate trials.

**IMPORTANT SAFETY INFORMATION**

**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

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

Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.
Permanent discontinuation of YERVOY and initiation of systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

**Immune-Mediated Pneumonitis**

Immune-mediated pneumonitis, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience with solid tumors, fatal immune-mediated pneumonitis occurred with OPDIVO. In addition, in CheckMate 069, there were six patients who died without resolution of abnormal respiratory findings. Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In CheckMate 069 and 067, immune-mediated pneumonitis occurred in 6% (25/407) of patients receiving OPDIVO with YERVOY: Fatal (n=1), Grade 3 (n=6), Grade 2 (n=17), and Grade 1 (n=1). In CheckMate 037, 066, and 067, immune-mediated pneumonitis occurred in 1.8% (14/787) of patients receiving OPDIVO: Grade 3 (n=2) and Grade 2 (n=12). In CheckMate 057, immune-mediated pneumonitis, including interstitial lung disease, occurred in 25% (101/410) of patients receiving OPDIVO: Grade 3 (n=5), Grade 2 (n=13), and Grade 1 (n=1). In CheckMate 025, pneumonitis, including interstitial lung disease, occurred in 5% (21/406) of patients receiving OPDIVO and 18% (73/397) of patients receiving everolimus. Immune-mediated pneumonitis occurred in 4.4% (18/406) of patients receiving OPDIVO: Grade 4 (n=1), Grade 3 (n=4), Grade 2 (n=12), and Grade 1 (n=1). In CheckMate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 4.9% (13/263) of patients receiving OPDIVO: Immune-mediated pneumonitis occurred in 3.4% (9/263) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=8).

**Immune-Mediated Colitis**

Immune-mediated colitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. As a single agent, withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon restarting OPDIVO. When administered with YERVOY, withhold OPDIVO for Grade 2 and Grade 3 or 4 and permanently discontinue for Grade 4 or recurrent colitis upon restarting OPDIVO. In CheckMate 069 and 067, diarrhea or colitis occurred in 56% (228/407) of patients receiving OPDIVO with YERVOY. Immune-mediated colitis occurred in 25% (107/407) of patients, Grade 4 (n=2), Grade 3 (n=60), Grade 2 (n=32), and Grade 1 (n=13). In CheckMate 037, 066, and 067, diarrhea or colitis occurred in 31% (242/787) of patients receiving OPDIVO. Immune-mediated colitis occurred in 4.1% (32/787) of patients: Grade 3 (n=20), Grade 2 (n=10), and Grade 1 (n=2). In CheckMate 057, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: Grade 3 (n=3), Grade 2 (n=2), and Grade 1 (n=2). In CheckMate 025, diarrhea or colitis occurred in 25% (100/406) of patients receiving OPDIVO and 32% (126/397) of patients receiving everolimus. Immune-mediated diarrhea or colitis occurred in 3.2% (13/406) of patients receiving OPDIVO: Grade 3 (n=5), Grade 2 (n=7), and Grade 1 (n=1). In CheckMate 205 and 039, diarrhea or colitis occurred in 30% (80/263) of patients receiving OPDIVO. Immune-mediated diarrhea occurred in 1.1% (3/263) of patients.

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% (71/211) of patients receiving OPDIVO with YERVOY: Grade 4 (n=12), Grade 3 (n=22), Grade 2 (n=15), and Grade 1 (n=6). In CheckMate 025, one patient (0.3%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

**Immune-Mediated Hepatitis**

Immune-mediated hepatitis can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In CheckMate 069 and 067, immune-mediated hepatitis occurred in 13% (51/407) of patients receiving OPDIVO with YERVOY: Grade 4 (n=8), Grade 3 (n=37), Grade 2 (n=5), and Grade 1 (n=1). In CheckMate 037, 066, and 067, immune-mediated hepatitis occurred in 2.3% (18/787) of patients receiving OPDIVO: Grade 4 (n=3), Grade 3 (n=11), and Grade 2 (n=4). In CheckMate 057, one patient (0.3%) developed immune-mediated hepatitis. In CheckMate 025, there was an increased incidence of liver test abnormalities compared to baseline in AST (33 vs 39%), alkaline phosphatase (32% vs 32%), ALT (22% vs 31%), and total bilirubin (9% vs 3.5%) in the OPDIVO and everolimus arms, respectively. Immune-mediated hepatitis requiring systemic immunosuppression occurred in 1.5% (6/406) of patients receiving OPDIVO: Grade 3 (n=5) and Grade 2 (n=1). In CheckMate 205 and 039, hepatitis occurred in 11% (30/263) of patients receiving OPDIVO. Immune-mediated hepatitis occurred in 3.4% (9/263): Grade 3 (n=7) and Grade 2 (n=2).

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 Dermatitis**

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 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**

Hypophysitis, adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency during and after treatment, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer 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. Administer insulin for type 1 diabetes. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In CheckMate 069 and 067, hypophysitis occurred in 9% (36/407) of patients receiving OPDIVO with YERVOY: Grade 3 (n=8), Grade 2 (n=25), and Grade 1 (n=3). In CheckMate 037, 066, and 067, hypophysitis occurred in 0.9% (7/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=3), and Grade 1 (n=2). In CheckMate 025, hypophysitis occurred in 0.5% (2/406) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=1). In CheckMate 037, 066, and 067, adrenal insufficiency occurred in 5% (21/407) of patients receiving OPDIVO with YERVOY: Grade 4 (n=1), Grade 3 (n=7), Grade 2 (n=11), and Grade 1 (n=2). In CheckMate 037, 066, and 067, adrenal insufficiency occurred in 1% (8/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=5), and Grade 1 (n=1). In CheckMate 057, 0.3% (1/287) of OPDIVO-treated patients developed adrenal insufficiency. In CheckMate 025, adrenal insufficiency occurred in 2.0% (8/406) of patients receiving OPDIVO: Grade 3 (n=3), Grade 2 (n=4), and Grade 1 (n=1). In CheckMate 205 and 039, adrenal insufficiency (Grade 2) occurred in 0.4% (1/263) of patients receiving OPDIVO. In CheckMate 069 and 067, hypothyroidism or thyroiditis occurred in 22% (89/407) of patients receiving OPDIVO with YERVOY: Grade 3 (n=6), Grade 2 (n=47), and Grade 1 (n=36). Hyperthyroidism occurred in 8% (34/407) of patients: Grade 3 (n=4), Grade 2 (n=17), and Grade 1 (n=13). In CheckMate 037, 066, and 067, hypothyroidism or thyroiditis occurred in 9% (73/787) of patients receiving OPDIVO: Grade 3 (n=1), Grade 2 (n=37), Grade 1 (n=35). Hyperthyroidism occurred in 4.4% (35/787) of patients receiving OPDIVO: Grade 3 (n=1), Grade 2 (n=12), and Grade 1 (n=22).

In CheckMate 057, Grade 1 or 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) and elevated thyroid stimulating hormone occurred in 17% of patients receiving OPDIVO. Grade 1 or 2 hyperthyroidism occurred in 1.4% (4/287) of patients. In CheckMate 025, thyroid disease occurred in 11% (43/406) of patients receiving OPDIVO, including one Grade 3 event, and in 3.0% (12/397) of patients receiving everolimus. Hyperthyroidism/thyroiditis occurred in 8% (33/406) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=17), and Grade 1 (n=14). Hyperthyroidism occurred in 2.5% (10/406) of patients receiving OPDIVO: Grade 2 (n=5) and Grade 1 (n=5). In CheckMate 205 and 039, hypothyroidism/thyroiditis occurred in 12% (32/263) of patients receiving OPDIVO: Grade 2 (n=18) and Grade 1 (n=14). Hyperthyroidism occurred in 1.5% (4/263) of patients receiving OPDIVO: Grade 2 (n=3) and Grade 1 (n=1). In CheckMate 069 and 067, diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/407) of patients: Grade 4 (n=1), Grade 2 (n=1), and Grade 1 (n=1). In CheckMate 037, 066, and 067, diabetes mellitus or diabetic ketoacidosis occurred in 0.8% (6/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=3), and Grade 1 (n=1). In CheckMate 025, hyperglycemic adverse events occurred in 9% (37/406) patients. Diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/406) of patients receiving OPDIVO: Grade 3 (n=3), Grade 2 (n=2), and Grade 1 (n=1). In CheckMate 205 and 039, diabetes mellitus occurred in 0.8% (2/263) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 1 (n=1).

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 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.**

Immune-mediated nephritis can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 increased serum creatinine, withhold and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue. In CheckMate 069 and 067, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients: Grade 4 (n=4), Grade 3 (n=3), and Grade 2 (n=2). In CheckMate 037, 066, and 067, nephritis and renal dysfunction of any grade occurred in 5% (40/787) of patients receiving OPDIVO. Immune-mediated nephritis and renal dysfunction occurred in 0.8% (6/787) of patients: Grade 3 (n=4) and Grade 2 (n=2). In CheckMate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.3% (1/287) of patients receiving OPDIVO. In CheckMate 025, renal injury occurred in 7% (27/397) of patients receiving OPDIVO and 3.0% (12/397) of patients receiving everolimus. Immune-mediated nephritis and renal dysfunction occurred in 3.2% (13/406) of patients receiving OPDIVO: Grade 5 (n=1), Grade 4 (n=1), Grade 3 (n=5), and Grade 2 (n=6). In CheckMate 205 and 039, nephritis and renal dysfunction occurred in 4.9% (13/263) of patients treated with OPDIVO. This included one reported case (0.3%) of Grade 3 autoimmune nephritis.

**Immune-Mediated Rash.**

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4. In CheckMate 069 and 067, immune-mediated rash occurred in 22.6% (92/407) of patients receiving OPDIVO with YERVOY: Grade 3 (n=15), Grade 2 (n=31), and Grade 1 (n=46). In CheckMate 037, 066, and 067, immune-mediated rash occurred in 9% (72/787) of patients receiving OPDIVO: Grade 3 (n=7), Grade 2 (n=15), and Grade 1 (n=50). In CheckMate 057, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO including four Grade 3 cases. In CheckMate 025, rash occurred in 28% (112/406) of patients receiving OPDIVO and 36% (143/397) of patients receiving everolimus. Immune-mediated rash, defined as a rash treated with systemic or topical corticosteroids, occurred in 7% (30/406) of patients receiving OPDIVO: Grade 3 (n=4), Grade 2 (n=7), and Grade 1 (n=19). In CheckMate 205 and 039, rash occurred in 22% (58/263) of patients receiving OPDIVO. Immune-mediated rash occurred in 7% (18/263) of patients on OPDIVO: Grade 3 (n=4), Grade 2 (n=3), and Grade 1 (n=11).

**Immune-Mediated Encephalitis.**

Immune-mediated encephalitis can occur with OPDIVO treatment. 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 CheckMate 067, encephalitis was identified in one patient (0.2%) receiving OPDIVO with YERVOY. In CheckMate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO. In CheckMate 205 and 039, encephalitis occurred in 0.8% (2/263) of patients after allogeneic HSCT after OPDIVO.

**Other Immune-Mediated Adverse Reactions.**

Immune-mediated adverse effects can occur with OPDIVO treatment. 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 adverse effects. In CheckMate 067, encephalitis was identified in one patient (0.2%) receiving OPDIVO with YERVOY. In CheckMate 057, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO. In CheckMate 205 and 039, encephalitis occurred in 0.8% (2/263) of patients after allogeneic HSCT after OPDIVO.
Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. In < 1.0% of patients receiving OPDIVO, the following clinically significant, immune-mediated adverse reactions occurred: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatic, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, and sarcoidosis. Across clinical trials of OPDIVO as a single agent administered at doses of 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, and myasthenic syndrome.

Infusion Reactions
Severe infusion reactions have been reported in <1.0% of patients in clinical trials of OPDIVO. 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 CheckMate 067 and 069, infusion-related reactions occurred in 2.5% (10/407) of patients receiving OPDIVO with YERVOY: Grade 2 (n=6) and Grade 1 (n=4). In CheckMate 037, 066, and 067, Grade 2 infusion related reactions occurred in 2.7% (21/787) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=8), and Grade 1 (n=11). In CheckMate 057, Grade 2 infusion reactions requiring corticosteroids occurred in 1.0% (3/287) of patients receiving OPDIVO. In CheckMate 025, hypersensitivity/infusion-related reactions occurred in 6% (25/406) of patients receiving OPDIVO and 1.0% (4/397) of patients receiving everolimus. In CheckMate 205 and 039, hypersensitivity/infusion-related reactions occurred in 16% (42/263) of patients receiving OPDIVO: Grade 3 (n=2), Grade 2 (n=24), and Grade 1 (n=16).

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 SCT 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 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 relative to the OPDIVO arm. 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 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO. 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. 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 057, serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In CheckMate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In CheckMate 025 and 039, among all patients (safety population n=263), adverse reactions leading to discontinuation (4.2%) or to dosing delays (23%) occurred. The most frequent serious adverse reactions reported in ≥1% of patients were infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash, and pneumonitis. Ten patients died from causes other than disease progression, including 6 who died from complications of allogeneic HSCT. Serious adverse reactions occurred in 21% of patients in the safety population (n=263) and 27% of patients in the subset of patients evaluated for efficacy (efficacy population n=95).

Common Adverse Reactions
In CheckMate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm were fatigue (59%), rash
adding rapid corticosteroid tapering resulted in recurrence or YERVOY in patients persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day persistent or severe symptoms. Withhold YERVOY as peritoneal signs and ileus). In
enterocolitis (such Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of enterocolitis, dermatitis, 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.

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

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.

Recommended Dose Modifications

Endocrine: Withhold YERVOY for systemic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

Immune-mediated Enterocolitis:

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms. Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY (ipilimumab) 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.

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

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.

Recommended Dose Modifications

Endocrine: Withhold YERVOY for systemic endocrinopathy. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for symptomatic reactions lasting 6 weeks or longer or an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

Ophthalmologic: Permanently discontinue YERVOY for Grade 2-4 reactions not improving to Grade 1 within 2 weeks while receiving topical therapy or requiring systemic treatment.

All Other Organ Systems: Withhold YERVOY for Grade 2 adverse reactions. Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0-1) and who are receiving <7.5 mg prednisone or equivalent per day. Permanently discontinue YERVOY for Grade 2 reactions lasting 6 weeks or longer, an inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day, and Grade 3 or 4 adverse reactions.

Immune-mediated Enterocolitis:

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms. Withhold YERVOY for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for >1 week, initiate systemic corticosteroids (0.5 mg/kg/day prednisone or equivalent). Upon improvement to ≤Grade 1, initiate corticosteroid taper and continue over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to
systemic corticosteroids within 3-5 days or recurring after symptom improvement. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal (diarrhea of ≥7 stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%) and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis. Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 entero colitis occurred in 68 patients (14%). Seven (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications.

Immune-mediated Hepatitis:

Immune-mediated hepatitis, including fatal cases, can occur with YERVOY. Monitor LFTs (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of LFT monitoring until resolution. Withhold YERVOY in patients with Grade 2 hepatotoxicity. Permanently discontinue YERVOY in patients with Grade 3-4 hepatotoxicity and administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When LFTs show sustained improvement or return to baseline, initiate corticosteroid tapering and continue over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients with persistent severe hepatitis despite high-dose corticosteroids. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations ≥5× the ULN or total bilirubin elevations ≥3× the ULN; Grade 3-5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4%. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by LFT abnormalities (AST or ALT elevations ≥2.5× but ≤5× the ULN or total bilirubin elevation ≥1.5× but ≤3× the ULN; Grade 2). In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-4 immune-mediated hepatitis occurred in 51 patients (11%) and moderate Grade 2 immune-mediated hepatitis occurred in 22 patients (5%). Liver biopsy performed in 6 patients with Grade 3-4 hepatitis showed evidence of toxic or autoimmune hepatitis.

Immune-mediated Dermatitis:

Immune-mediated dermatitis, including fatal cases, can occur with YERVOY. Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Treat mild to moderate dermatitis (e.g., localized rash and pruritus) symptomatically; administer topical or systemic corticosteroids if there is no improvement within 1 week. Withhold YERVOY in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY in patients with severe, life-threatening, or fatal immune-mediated dermatitis (Grade 3-5). Administer systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., 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 YERVOY-treated patients (2.5%); 1 patient (0.2%) died as a result of toxic epidermal necrolysis and 1 additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-4 immune-mediated dermatitis occurred in 19 patients (4%). There were 99 patients (21%) with moderate Grade 2 dermatitis.

Immune-mediated Neuropathies:

Immune-mediated neuropathies, including fatal cases, can occur with YERVOY. Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Withhold YERVOY in patients with moderate neuropathy (not interfering with daily activities). Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities), such as Guillain-Barre-like syndromes. Institute medical intervention as appropriate for management for severe neuropathy. Consider initiation of systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe neuropathies. In patients receiving YERVOY 3 mg/kg in Trial 1, 1 case of fatal Guillain-Barre syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barre syndrome have been reported. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-5 immune-mediated neuropathy occurred in 8 patients (2%); the sole fatality was due to complications of Guillain-Barre syndrome. Moderate Grade 2 immune-mediated neuropathy occurred in 1 patient (0.2%).

Immune-mediated Endocrinopathies:

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY. Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms should be considered immune-mediated. Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Withhold YERVOY in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) and initiate appropriate hormone replacement therapy. In patients receiving YERVOY 3 mg/kg in Trial 1, 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 YERVOY-treated patients (1.8%). All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated
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® or Yervoy® 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, 2015 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.
Bristol-Myers Squibb Company
Media:
Audrey Abernathy, 609-419-5375
Cell: 919-605-4521
audrey.abernathy@bms.com
or
Investors:
Tim Power, 609-252-7509
timothy.power@bms.com
or
Bill Szablewski, 609-252-5894
william.szablewski@bms.com

Ticker Slug:
Ticker: BMY
Exchange: NYSE