Breadth and Depth of Bristol-Myers Squibb’s Immuno-Oncology Clinical Development Program to be Showcased at 2016 American Society of Clinical Oncology (ASCO) Annual Meeting

Release Date:
Wednesday, May 18, 2016 6:59 am EDT

Terms:
$BMY ASCO bladder bristol-myer Cancer carcinoma caregiver CheckMate Chronic Myeloid Leukemia CML colorectal Combination Therapy dasatinib doctor elotuzumab Empliciti Esophageal gastric Glioblastoma head and neck Hepatocellular Hodgkin Lymphoma Immuno-Oncology ipilimumab Leukemia lung melanoma metastatic Monotherapy Multiple Myeloma nivolumab non-Hodgkin nurse nursing Oncology Opdivo patients R&D RCC renal cell carcinoma Research sprycel Squibb survival treatment tumor urothelial Yervoy

Dateline City:
PRINCETON, N.J.

Long-term survival data for a broad set of tumor types including advanced non-small and small cell lung cancer, advanced melanoma, and up to 5-year follow up in renal cell carcinoma, to be presented

Broad data set for the Opdivo and Yervoy combination in several tumors, including first-line non-small cell lung cancer, recurrent glioblastoma multiforme, and MSI-high metastatic colorectal cancer, to be presented

Data across 13 types of cancers, including first time presentations in advanced bladder and MSI-high metastatic colorectal cancers, and new research in classical Hodgkin lymphoma, for which Opdivo was recently approved in the U.S.

PRINCETON, N.J.---(BUSINESS WIRE)---Bristol-Myers Squibb Company (NYSE:BMY) announced today 36 presentations, including seven oral presentations and eight poster discussions, highlighting data from studies evaluating **Opdivo** (nivolumab), **Yervoy** (ipilimumab), *Empliciti*™ (elotuzumab) and **Sprycel**® (dasatinib), across 13 types of cancers, will be featured at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL from June 3-7. The data presented at this meeting builds on the Company’s understanding of the clinical profile of these agents – as monotherapy or in combination – and reinforce its commitment to addressing significant unmet patient needs in a wide range of solid tumors and blood cancers.

Jean Viallet, M.D., Global Clinical Research Lead, Oncology, Bristol-Myers Squibb, commented, “Our Immuno-Oncology research goal is centered around increasing quality long-term survival – and doing so through the use of Immuno-Oncology combination regimens. Our development program has led to the introduction of several treatment options for cancers such as metastatic melanoma, previously treated advanced lung, renal cell carcinoma, multiple myeloma, and classical Hodgkin lymphoma, and through our robust research pipeline we continue to evaluate the potential of Immuno-Oncology in additional tumor types. At this year’s ASCO, we look forward to sharing research from our ongoing clinical trials evaluating our medicines - as monotherapy or in combination - in several types of difficult-to-treat cancers.”

The key data presentations, including clinical science symposia and oral presentations, are:

- **CheckMate -012**: New overall survival data evaluating the **Opdivo** and **Yervoy** combination in first-line advanced non-small cell lung cancer (Abstract #3001). Data will be presented during an oral abstract session on Saturday, June 4, 1:27 PM – 1:39 PM CDT.

- **CheckMate -032**: New overall survival data from a phase 1/2 trial evaluating **Opdivo** as monotherapy and in combination with **Yervoy** in patients with advanced small cell lung cancer (Abstract #100). Data from CheckMate -032 will be presented
CheckMate -067: Updated results from pivotal, phase 3 trial of Opdivo in combination with Yervoy in treatment-naive patients with advanced melanoma (Abstract #9505). Data will be presented during an oral abstract session on Monday, June 6, 2:39 PM – 2:51 PM CDT.

Study -010/-003: Long-term overall survival with Opdivo in previously treated patients with advanced renal cell carcinoma from phase 1 and 2 studies (Abstract #4507). Data will be presented during an oral abstract session on Sunday, June 5, 10:24 AM – 10:36 AM CDT.

CheckMate -141: Updated phase 3 data evaluating Opdivo versus investigator's choice for recurrent or metastatic head and neck squamous cell carcinoma, including quality of life assessments (Abstract #6009). Data will be presented during a Clinical Science Symposium on Monday, June 6, 11:30 AM – 11:42 AM CDT.

CheckMate -032: First presentation of clinical results from phase 1/2 trial evaluating Opdivo in metastatic urothelial cancer in previously treated patients (Abstract #4501). Data will be presented during an oral abstract session on Sunday, June 5, 8:12 AM – 8:24 AM CDT.

CheckMate -142: First disclosure of clinical results of the Opdivo and Yervoy combination regimen in patients with metastatic colorectal cancer with and without high microsatellite instability (Abstract #3501). Data will be presented during an oral abstract session on Sunday, June 5, 8:12 AM – 8:24 AM CDT.

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

Bladder

- Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer: Results from the phase 1/2 CheckMate -032 study
  Author: P. Sharma
  Abstract #4501
  Oral Abstract Session, Genitourinary (Nonprostate) Cancer
  Sunday, June 5, 2016, 8:12 AM – 8:24 AM CDT, Hall D2

Chronic Myeloid Leukemia

- Achievement of early molecular response in patients with chronic myeloid leukemia in chronic phase treated with dasatinib or imatinib from DASISION
  Author: N. Shah
  Abstract #7055, Poster Board #47
  Poster Session, Hematologic Malignancies – Leukemia, Myelodysplastic Syndromes, and Allotransplant
  Monday, June 6, 2016, 8:00 AM – 11:30 AM CDT, Hall A

Colorectal

- Nivolumab ± ipilimumab in treatment of patients with metastatic colorectal cancer with and without high microsatellite instability: CheckMate -142 interim results
  Author: M. Overman
  Abstract #3501
  Oral Abstract Session, Gastrointestinal (Colorectal) Cancer
  Sunday, June 5, 2016, 8:12 AM – 8:24 AM CDT, Hall B1

Esophageal / Gastric

- A randomized, open-label, two-arm phase 2 trial comparing the efficacy of sequential ipilimumab versus best supportive care following first-line chemotherapy in patients with unresectable, locally advanced/metastatic gastric or gastro-esophageal junction cancer
  Author: M. Moehler
  Abstract #4011, Poster Board #3
  Poster Discussion Session, Gastrointestinal (Noncolorectal) Cancer
  Saturday, June 4, 2016, 3:00 PM – 4:15 PM CDT, Hall D1

- CheckMate -032: Phase 1/2, open-label study of safety and activity of nivolumab alone or with ipilimumab in advanced and metastatic gastric cancer
  Author: Y. Yanjigian
  Abstract #4010, Poster Board #2
  Poster Discussion Session, Gastrointestinal (Noncolorectal) Cancer
  Saturday, June 4, 2016, 3:00 PM – 4:15 PM CDT, Hall D1

Glioblastoma

- A randomized, phase 3, open-label study of nivolumab versus temozolomide in combination with radiotherapy in adult patients with newly diagnosed, O-6-methylguanine DNA methyltransferase (MGMT)-unmethylated glioblastoma [CheckMate -498]
  Author: J. Sampson
  Abstract #TPS2079, Poster Board #265b
  Poster Session, Central Nervous System Tumors
  Saturday, June 4, 2016, 1:00 PM – 4:30 PM CDT, Hall A

- Safety and activity of nivolumab monotherapy and nivolumab in combination with ipilimumab in recurrent glioblastoma: Updated results from CheckMate -143
  Author: D. A. Reardon
Head and Neck

- **Further evaluations of nivolumab versus investigator’s choice chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck: CheckMate -141**
  
  **Author:** R. Ferris  
  **Abstract #6009**  
  Clinical Science Symposium, Harnessing the Immune System in Head and Neck Cancer: Evolving Standards in Metastatic Disease  
  **Monday, June 6, 2016, 11:30 AM – 11:42 AM CDT, S100bc**

Hepatocellular Carcinoma

- **Safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma: Interim analysis of dose-expansion cohorts from the phase 1/2 CheckMate -040 study**
  
  **Author:** B. Sangro  
  **Abstract #4078, Poster Board #70**  
  Poster Session, Gastrointestinal (Noncolorectal) Cancer  
  **Saturday, June 4, 2016, 8:00 AM – 11:30 AM CDT, Hall A**

- **A randomized, multicenter, phase 3 study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma: CheckMate -459**
  
  **Author:** B. Sangro  
  **Abstract #TPS4147, Poster Board #131a**  
  **Poster Session, Gastrointestinal (Noncolorectal) Cancer**  
  **Saturday, June 4, 2016, 8:00 AM – 11:30 AM CDT, Hall A**

- **Phase 1/2 safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma: Interim analysis of the CheckMate -040 dose escalation study**
  
  **Author:** A. B. El-Khoueiry  
  **Abstract #4012, Poster Board #4**  
  **Poster Discussion Session, Gastrointestinal (Noncolorectal) Cancer**  
  **Saturday, June 4, 2016, 3:00 PM – 4:15 PM CDT, Hall D1**

Lung

- **CheckMate -032: Nivolumab alone or in combination with ipilimumab for the treatment of recurrent small cell lung cancer**
  
  **Author:** S. Antonia  
  **Abstract #100**  
  Clinical Science Symposium, The View Beyond Single-Agent Checkpoint Blockade  
  **Saturday, June 4, 2016, 8:12 AM – 8:24 AM CDT, Hall D1**

- **Nivolumab versus docetaxel in patients with advanced NSCLC: CheckMate -017/-057 2-year update and exploratory cytokine profile analyses**
  
  **Author:** H. Borghaei  
  **Abstract #9025, Poster Board #348**  
  **Poster Session, Lung Cancer—Non-Small Cell Metastatic**  
  **Saturday, June 4, 2016, 8:00 AM – 11:30 AM CDT, Hall A**

- **Nivolumab in patients with advanced non-small cell lung cancer and central nervous system metastases**
  
  **Author:** J. Goldman  
  **Abstract #9038, Poster Board #361**  
  **Poster Session, Lung Cancer—Non-Small Cell Metastatic**  
  **Saturday, June 4, 2016, 8:00 AM – 11:30 AM CDT, Hall A**

- **Lung Cancer Symptom Scale as a marker of treatment benefit with nivolumab versus docetaxel in patients with advanced non-squamous non-small cell lung cancer from CheckMate -057**
  
  **Author:** R. Gralla  
  **Abstract #9031, Poster Board #354**  
  **Poster Session, Lung Cancer—Non-Small Cell Metastatic**  
  **Saturday, June 4, 2016, 8:00 AM – 11:30 AM CDT, Hall A**

- **Estimated costs of managing treatment-related adverse events of nivolumab and docetaxel in the CheckMate -017 and CheckMate -057 phase 3 non-small cell lung cancer trials**
  
  **Author:** M. Venkatachalam  
  **Abstract #6617, Poster Board #100**  
  **Poster Session, Health Services Research and Quality of Care**  
  **Saturday, June 4, 2016, 1:00 PM – 4:30 PM CDT, Hall A**

- **CheckMate -331: An open-label, randomized phase 3 trial of nivolumab versus chemotherapy in patients with relapsed small cell lung cancer after first-line platinum-based chemotherapy**
  
  **Author:** L. Horn  
  **Abstract #TPS8578, Poster Board #202a**  
  **Poster Session, Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers**
CheckMate -451: A randomized, double-blind, phase 3 trial of nivolumab, nivolumab plus ipilimumab, or placebo as maintenance therapy in patients with extensive-stage disease small cell lung cancer after first-line platinum-based doublet chemotherapy
Author: N. Ready
Abstract #TPS8579, Poster Board #202b
Poster Session, Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
Saturday, June 4, 2016, 8:00 AM – 11:30 AM CDT, Hall A

Safety profile of nivolumab administered as 30-minute infusion: Analysis of data from CheckMate -153
Author: D. Waterhouse
Abstract #3059, Poster Board #381
Poster Session, Developmental Therapeutics—Immunotherapy
Sunday, June 5, 2016, 8:00 AM – 11:30 AM CDT, Hall A

CheckMate -012: Safety and efficacy of first-line nivolumab and ipilimumab in advanced non-small cell lung cancer
Author: M. Hellmann
Abstract #3001
Oral Abstract Session, Developmental Therapeutics—Immunotherapy
Saturday, June 4, 2016, 1:27 PM – 1:39 PM CDT, Hall B1

Lymphoma (Hodgkin and non-Hodgkin)

Checkmate -205: Nivolumab in classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin—A phase 2 study
Author: A. Younes
Abstract #7535, Poster Board #91
Poster Discussion Session, Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
Monday, June 6, 2016, 1:15 PM – 2:45 PM CDT, E354b

A phase 2 study of a nivolumab-containing regimen in patients with newly diagnosed classical Hodgkin lymphoma (Study 205 Cohort D)
Author: P. Armand
Abstract #TPS7573, Poster Board #128b
Poster Session, Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
Monday, June 6, 2016, 8:00 AM – 11:30 AM CDT, Hall A

A phase 1/2 study to evaluate safety and efficacy of nivolumab plus brentuximab vedotin in patients with CD30-expressing relapsed/refractory non-Hodgkin lymphomas
Author: P. Armand
Abstract #TPS7576, Poster Board #130a
Poster Session, Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
Monday, June 6, 2016, 8:00 AM – 11:30 AM CDT, Hall A

Melanoma

Safety data from an expanded access program of nivolumab in combination with ipilimumab in patients with advanced melanoma
Author: P. Chapman
Abstract #9525, Poster Board #130
Poster Session, Melanoma/Skin Cancers
Saturday, June 4, 2016, 1:00 PM – 4:30 PM CDT, Hall A

Real-world overall survival in advanced melanoma from the IMAGE study
Author: M. Middleton
Abstract #9531, Poster Board #136
Poster Session, Melanoma/Skin Cancers
Saturday, June 4, 2016, 1:00 PM – 4:30 PM CDT, Hall A

Overall survival in patients with advanced melanoma who discontinued treatment with nivolumab plus ipilimumab due to toxicity in a phase 2 trial (CheckMate -069)
Author: F. S. Hodi
Abstract #9518, Poster Board #123
Poster Discussion Session, Melanoma/Skin Cancers
Saturday, June 4, 2016, 4:45 PM – 6:00 PM CDT, E354b

Survival outcomes of nivolumab given sequentially with ipilimumab in patients with advanced melanoma (CheckMate -064)
Author: J. Weber
Abstract #9517, Poster Board #122
Poster Discussion Session, Melanoma/Skin Cancers
Saturday, June 4, 2016, 4:45 PM – 6:00 PM CDT, E354b

Nivolumab safety in patients with advanced melanoma who have progressed on or after ipilimumab: a single-arm, open-label, multicenter, phase 2 study (CheckMate -172)
Author: P. Ascierto
**Abstract #9526, Poster Board #131**
Poster Session, Melanoma/Skin Cancers  
Saturday, June 4, 2016, 1:00 PM – 4:30 PM CDT, Hall A

- **Updated results from a phase 3 trial of nivolumab combined with ipilimumab in treatment-naive patients with advanced melanoma (CheckMate -067)**  
  Author: J. Wolchok  
  Abstract #9505  
  Oral Abstract Session, Melanoma/Skin Cancers  
  Monday, June 6, 2016, 2:39 PM - 2:51 PM CDT, Arie Crown Theater

**Multiple Myeloma**

- **Health care resource utilization in relapsed/refractory multiple myeloma: Results from PREAMBLE**  
  Author: H. Goldschmidt  
  Abstract #6621, Poster Board #104  
  Poster Session, Health Services Research and Quality of Care  
  Saturday, June 4, 2016, 1:00 PM – 4:30 PM CDT, Hall A

- **ELOQUENT-2 update: Phase 3 study of elotuzumab plus lenalidomide/dexamethasone versus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma - Identifying responders by subset analysis**  
  Author: S. Lonial  
  Abstract #8037, Poster Board #302  
  Poster Session, Hematologic Malignancies—Plasma Cell Dyscrasias  
  Monday, June 6, 2016, 8:00 AM - 11:30 AM CDT, Hall A

- **A randomized phase 2 study of pomalidomide/dexamethasone with or without elotuzumab in patients with relapsed/refractory multiple myeloma**  
  Author: J. San Miguel  
  Abstract #TPS8066, Poster Board #331a  
  Poster Session, Hematologic Malignancies—Plasma Cell Dyscrasias  
  Monday, June 6, 2016, 8:00 AM - 11:30 AM CDT, Hall A

**Renal Cell Carcinoma**

- **Long-term overall survival with nivolumab in previously treated patients with advanced renal cell carcinoma from phase 1 and 2 studies**  
  Author: D. McDermott  
  Abstract #4507  
  Oral Abstract Session, Genitourinary (Nonprostate) Cancer  
  Sunday, June 5, 2016, 10:24 AM – 10:36 AM CDT, Hall D2

- **Correlation of response with overall survival for nivolumab versus everolimus in advanced renal cell carcinoma: Results from the phase 3 CheckMate -025 study**  
  Author: R. Motzer  
  Abstract #4552, Poster Board #174  
  Poster Session, Genitourinary (Nonprostate) Cancer  
  Monday, June 6, 2016, 1:00 PM – 4:30 PM CDT, Hall A

- **Quality of life and overall survival in patients with advanced clear-cell renal cell carcinoma treated with nivolumab versus everolimus in the phase 3 CheckMate -025 study**  
  Author: D. Cella  
  Abstract #4549, Poster Board #171  
  Poster Session, Genitourinary (Nonprostate) Cancer  
  Monday, June 6, 2016, 1:00 PM – 4:30 PM CDT, Hall A

- **Treatment beyond progression with nivolumab in patients with advanced renal cell carcinoma in the phase 3 CheckMate -025 study**  
  Author: B. Escudier  
  Abstract #4509, Poster Board #132  
  Poster Discussion Session, Genitourinary (Nonprostate) Cancer  
  Monday, June 6, 2016, 4:45 PM – 6:00 PM CDT, Arie Crown Theater

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

At Bristol-Myers Squibb, we have a vision for the future of cancer care that is focused on Immuno-Oncology, now considered a major treatment choice alongside surgery, radiation, chemotherapy and targeted therapies for certain types of cancer.

We have a comprehensive clinical portfolio of investigational and approved Immuno-Oncology agents, many of which were discovered and developed by our scientists. Our ongoing Immuno-Oncology clinical program is looking at broad patient populations, across multiple solid tumors and hematologic malignancies, and lines of therapy and histologies, with the intent of powering our trials for overall survival and other important measures like durability of response. We pioneered the research leading to the first regulatory approval for the combination of two Immuno-Oncology agents, and continue to study the role of combinations in cancer.

We are also investigating other immune system pathways in the treatment of cancer including CTLA-4, CD-137, KIR, SLAMF7, PD-1, GITR, CSF1R, IDO, and LAG-3. These pathways may lead to potential new treatment options – in combination or monotherapy – to help patients fight different types of cancers.
Our collaboration with academia, as well as small and large biotech companies, to research the potential of Immuno-Oncology and non-Immuno-Oncology combinations, helps achieve our goal of providing new treatment options in clinical practice.

At Bristol-Myers Squibb, we are committed to changing survival expectations in hard-to-treat cancers and the way patients live with cancer.

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

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

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

OPDIVO® (nivolumab), 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 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.

Permanently discontinue *YERVOY* and initiate 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 with radiographic imaging 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 3.4% (10/287) of patients: Grade 3 (n=5), Grade 2 (n=2), and Grade 1 (n=3). 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 permanently discontinue for Grade 3 or 4 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=2), 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 (Grade 3) 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 (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

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 (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 1 (n=1). In Checkmate 069 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. Hypothyroidism/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=3), Grade 3 (n=1), Grade 2 (n=1), and Grade 1 (n=1).
Complications of allogeneic HSCT after OPDIVO. Five deaths occurred in 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 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**

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 9.8% (6/62) of patients: Grade 4 (n=4) and Grade 2 (n=2). In Checkmate 057, Grade 2 immune-mediated renal dysfunction occurred in 0.8% (1/128) of patients receiving OPDIVO. In Checkmate 025, renal injury occurred in 7% (27/406) 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% (72/807) 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 5% (17/287) of patients 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% (50/263) 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**

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 rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastri, 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 069 and 067, 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 205 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 (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO vs dacarbazine were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 057, the most common adverse reactions (≥20%) reported with OPDIVO were fatigue (49%), musculoskeletal pain (36%), cough (30%), decreased appetite (29%), and constipation (23%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO vs everolimus 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, among all patients (safety population [n=263]) and the subset of patients in the efficacy population (n=95), respectively, the most common adverse reactions (reported in at least 20%) were fatigue (32% and 43%), upper respiratory tract infection (28% and 48%), pyrexia (24% and 35%), diarrhea (23% and 30%), and cough (22% and 35%). In the subset of patients in the efficacy population (n=95), the most common adverse reactions also included rash (31%), musculoskeletal pain (27%), pruritus (25%), nausea (23%), arthralgia (21%), and peripheral neuropathy (21%).

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 069 and 067 - advanced melanoma alone or in combination with YERVOY; Checkmate 037 and 066 - advanced melanoma; Checkmate 057 - non-squamous non-small cell lung cancer (NSCLC); Checkmate 025 - renal cell carcinoma; Checkmate 205/039 - classical Hodgkin lymphoma

U.S. FDA APPROVED INDICATIONS FOR YERVOY®
YERVOY® (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma.

YERVOY® (ipilimumab) is indicated for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

**IMPORTANT SAFETY INFORMATION**

**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). Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids (1-2 mg/kg/day of 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 enterocolitis 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 or severe hepatitis despite high-dose corticosteroids. In patients receiving YERVOY 3 mg/kg in Trial 1, severe, life-threatening, or fatal hepatitis (AST or ALT elevations >5x the ULN or total bilirubin elevations >3x 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 >2.5x but ≤5x the ULN or total bilirubin elevation >1.5x but ≤3x 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 QD 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. Initiate medical intervention as appropriate for management of 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-Barré 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-Barré 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 or clinical chemistry, 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 endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY. In patients receiving YERVOY 10 mg/kg in Trial 2, Grade 3-4 immune-mediated endocrinopathies occurred in 39 patients (8%) and Grade 2 immune-mediated endocrinopathies occurred in 93 patients (20%). Of the 39 patients with Grade 3-4 immune-mediated endocrinopathies, 35 patients had hypopituitarism (associated with 1 or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 3 patients had hyperthyroidism, and 1 had primary hypothyroidism. The median time to onset of Grade 3-4 immune-mediated endocrinopathy was 2.2 months (range: 2 days-8 months). Twenty-seven (69.2%) of the 39 patients were hospitalized for immune-mediated endocrinopathies. Of the 93 patients with Grade 2 immune-mediated endocrinopathy, 74 had primary hypopituitarism (associated with 1 or more secondary endocrinopathy, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 9 had primary hyperthyroidism, 3 had hyperthyroidism, 3 had thyroiditis with hypo- or hyperthyroidism, 2 had hypogonadism, 1 had both hypothyroidism and hypopituitarism, and 1 subject developed Graves’ ophthalmopathy. The median time to onset of Grade 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days-19.3 months).

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent) for severe immune-mediated adverse reactions. Administer corticosteroid eye drops for uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease unresponsive to local immunosuppressive therapy. In Trial 1, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients: nephritis, pneumonitis, menigitis, pericarditis, uveitis, iritis, and hemolytic anemia. In Trial 2, the following clinically significant immune-mediated adverse reactions were seen in <1% of YERVOY-treated patients unless specified: eosinophilia (2.1%), pancreatitis (1.3%), menigitis, pneumonitis, sarcoidosis, pericarditis, uveitis and fatal myocarditis. Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with <1% incidence: angiohypophyseal, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, rheumatoid arthritis, autoimmune central nervous system (encephalitis), myositis, polymyositis, ocular myositis, hemolytic anemia, and nephritis.
Embryo-fetal Toxicity

Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a YERVOY-containing regimen and for 3 months after the last dose of YERVOY.

Lactation

It is not known whether YERVOY is secreted in human milk. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

Common Adverse Reactions

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%). The most common adverse reactions (≥5%) in patients who received YERVOY at 10 mg/kg were rash (50%), diarrhea (49%), fatigue (46%), pruritus (45%), headache (33%), weight loss (32%), nausea (25%), pyrexia (18%), colitis (16%), decreased appetite (14%), vomiting (13%), and insomnia (10%).

U.S. FDA APPROVED INDICATION FOR EMPLICITI™

EMPLICITI™ (elotuzumab) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

IMPORTANT SAFETY INFORMATION

Infusion Reactions

- EMPLICITI can cause infusion reactions. Common symptoms include fever, chills, and hypertension. Bradycardia and hypotension also developed during infusions. In the trial, 5% of patients required interruption of the administration of EMPLICITI for a median of 25 minutes due to infusion reactions, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had them during the first dose. If a Grade 2 or higher infusion reaction occurs, interrupt the EMPLICITI infusion and institute appropriate medical and supportive measures. If the infusion reaction recurs, stop the EMPLICITI infusion and do not restart it on that day. Severe infusion reactions may require permanent discontinuation of EMPLICITI therapy and emergency treatment.
- Premedicate with dexamethasone, H1 Blocker, H2 Blocker, and acetaminophen prior to infusing with EMPLICITI.

Infections

- In a clinical trial of patients with multiple myeloma (N=635), infections were reported in 81.4% of patients in the EMPLICITI with lenalidomide/dexamethasone arm (ERd) and 74.4% in the lenalidomide/dexamethasone arm (Rd). Grade 3-4 infections were 28% (ERd) and 24.3% (Rd). Opportunistic infections were reported in 22% (ERd) and 12.9% (Rd). Fungal infections were 9.7% (ERd) and 5.4% (Rd). Herpes zoster was 13.5% (ERd) and 6.9% (Rd). Discontinuations due to infections were 3.5% (ERd) and 4.1% (Rd). Fatal infections were 2.5% (ERd) and 2.2% (Rd). Monitor patients for development of infections and treat promptly.

Second Primary Malignancies

- In a clinical trial of patients with multiple myeloma (N=635), invasive second primary malignancies (SPM) were 9.1% (ERd) and 5.7% (Rd). The rate of hematologic malignancies were the same between ERd and Rd treatment arms (1.6%). Solid tumors were reported in 3.5% (ERd) and 2.2% (Rd). Skin cancer was reported in 4.4% (ERd) and 2.8% (Rd). Monitor patients for the development of SPMs.

Hepatotoxicity

- Elevations in liver enzymes (AST/ALT greater than 3 times the upper limit, total bilirubin greater than 2 times the upper limit, and alkaline phosphatase less than 2 times the upper limit) consistent with hepatotoxicity were 2.5% (ERd) and 0.6% (Rd). Two patients experiencing hepatotoxicity discontinued treatment; however, 6 out of 8 patients had resolution and continued treatment. Monitor liver enzymes periodically. Stop EMPLICITI upon Grade 3 or higher elevation of liver enzymes. After return to baseline values, continuation of treatment may be considered.

Interference with Determination of Complete Response

- EMPLICITI is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

Pregnancy/Females and Males of Reproductive Potential

- There are no studies with EMPLICITI with pregnant women to inform any drug associated risks.
- There is a risk of fetal harm, including severe life-threatening human birth defects associated with lenalidomide and it is contraindicated for use in pregnancy. Refer to the lenalidomide full prescribing information for requirements regarding contraception and the prohibitions against blood and/or sperm donation due to presence and transmission in blood and/or semen and for additional information.

Adverse Reactions

- Infusion reactions were reported in approximately 10% of patients treated with EMPLICITI with lenalidomide and
dexamethasone. All reports of infusion reaction were Grade 3 or lower. Grade 3 infusion reactions occurred in 1% of patients.

- Serious adverse reactions were 65.4% (ERd) and 56.5% (Rd). The most frequent serious adverse reactions in the ERd arm compared to the Rd arm were: pneumonia (15.4%, 11%), pyrexia (6.9%, 4.7%), respiratory tract infection (3.1%, 1.3%), anemia (2.8%, 1.9%), pulmonary embolism (3.1%, 2.5%), and acute renal failure (2.5%, 1.9%).

- The most common adverse reactions in ERd and Rd, respectively (>20%) were: fatigue (61.6%, 51.7%), diarrhea (46.9%, 36.0%), pyrexia (37.4%, 24.6%), constipation (35.5%, 27.1%), cough (34.3%, 18.9%), peripheral neuropathy (26.7%, 20.8%), nasopharyngitis (24.5%, 19.2%), upper respiratory tract infection (22.6%, 17.4%), decreased appetite (20.8%, 12.6%), and pneumonia (20.1%, 14.2%).

**SPRYCEL® (dasatinib) U.S. INDICATIONS & IMPORTANT SAFETY INFORMATION**

**INDICATIONS**

SPRYCEL® (dasatinib) is indicated for the treatment of adults with:

- Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

**IMPORTANT SAFETY INFORMATION**

**Myelosuppression:**

Treatment with SPRYCEL is associated with severe (NCI CTC Grade 3/4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML.

- In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated.
- In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated.

- Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose reduction.
  - In clinical studies, myelosuppression may have also been managed by discontinuation of study therapy.
  - Hematopoietic growth factor has been used in patients with resistant myelosuppression.

**Bleeding Related Events:**

SPRYCEL caused thrombocytopenia in human subjects. In addition, dasatinib caused platelet dysfunction in vitro. In all CML or Ph+ ALL clinical studies, ≥grade 3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. Grade 3 or greater gastrointestinal hemorrhage, including fatalities, occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of ≥grade 3 hemorrhage occurred in 2% of patients.

- Most bleeding events in clinical studies were associated with severe thrombocytopenia.
- Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

**Fluid Retention:**

SPRYCEL may cause fluid retention. After 5 years of follow-up in the randomized newly diagnosed chronic phase CML study (n=258), grade 3/4 fluid retention was reported in 5% of patients, including 3% of patients with grade 3/4 pleural effusion. In patients with newly diagnosed or imatinib resistant or intolerant chronic phase CML, grade 3/4 fluid retention occurred in 6% of patients treated with SPRYCEL at the recommended dose (n=548). In patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), grade 3/4 fluid retention was reported in 8% of patients, including grade 3/4 pleural effusion reported in 7% of patients.

- Patients who develop symptoms of pleural effusion or other fluid retention, such as new or worsened dyspnea on exertion or at rest, pleuritic chest pain, or dry cough should be evaluated promptly with a chest x-ray or additional diagnostic imaging as appropriate.
- Fluid retention events were typically managed by supportive care measures that may include diuretics or short courses of steroids.
- Severe pleural effusion may require thoracentesis and oxygen therapy.
- Consider dose reduction or treatment interruption.

**Cardiovascular Events:**

After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial (n=258), the following cardiac adverse events occurred:

- Cardiac ischemic events (3.9% dasatinib vs 1.6% imatinib), cardiac related fluid retention (8.5% dasatinib vs 3.9%
imatinib), and conduction system abnormalities, most commonly arrhythmia and palpitations (7.0% dasatinib vs 5.0% imatinib). Two cases (0.8%) of peripheral arterial occlusive disease occurred with imatinib and 2 (0.8%) transient ischemic attacks occurred with dasatinib.

Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

**Pulmonary Arterial Hypertension (PAH):**
SPRYCEL may increase the risk of developing PAH, which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of SPRYCEL.

- Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL and during treatment. If PAH is confirmed, SPRYCEL should be permanently discontinued.

**QT Prolongation:**
In vitro data suggest that SPRYCEL has the potential to prolong cardiac ventricular repolarization (QT interval).

- Most bleeding events in clinical studies were associated with severe thrombocytopenia.
- Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

**Severe Dermatologic Reactions:**
Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported in patients treated with SPRYCEL.

- Discontinue permanently in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

**Tumor Lysis Syndrome (TLS):**
TLS has been reported in patients with resistance to prior imatinib therapy, primarily in advanced phase disease.

- Due to potential for TLS, maintain adequate hydration, correct uric acid levels prior to initiating therapy with SPRYCEL, and monitor electrolyte levels.
- Patients with advanced stage disease and/or high tumor burden may be at increased risk and should be monitored more frequently.

**Embryo-Fetal Toxicity:**
Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Hydrops fetalis, fetal leukopenia and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Transplacental transfer of dasatinib has been measured in fetal plasma and amniotic fluid at concentrations comparable to those in maternal plasma.

- Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with SPRYCEL and for 30 days after the final dose.

**Lactation:**
No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, dasatinib is present in the milk of lactating rats.

- Because of the potential for serious adverse reactions in nursing infants from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose.

**Drug Interactions:**
SPRYCEL is a CYP3A4 substrate and a weak time-dependent inhibitor of CYP3A4.

- Drugs that may increase SPRYCEL plasma concentrations are:
  - **CYP3A4 inhibitors:** Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 should be avoided. If administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and a SPRYCEL dose reduction should be considered
  - **Strong CYP3A4 inhibitors** (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease or temporary discontinuation should be considered
    - **Grapefruit juice** may also increase plasma concentrations of SPRYCEL and should be avoided

- Drugs that may decrease SPRYCEL plasma concentrations are:
  - **CYP3A4 inducers:** If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered
  - **Strong CYP3A4 inducers** (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) should be avoided. Alternative agents with less enzyme induction potential should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity
    - **St John’s Wort** may decrease SPRYCEL plasma concentrations unpredictably and should be avoided
  - **Antacids** may decrease SPRYCEL drug levels. Simultaneous administration of SPRYCEL and antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours
after the dose of SPRYCEL

- **H₂ antagonists/proton pump inhibitors** (eg, famotidine and omeprazole): Long-term suppression of gastric acid secretion by use of H₂ antagonists or proton pump inhibitors is likely to reduce SPRYCEL exposure. Therefore, concomitant use of H₂ antagonists or proton pump inhibitors with SPRYCEL is not recommended.
- Drugs that may have their plasma concentration altered by SPRYCEL are:
  - **CYP3A4 substrates** (eg, simvastatin) with a narrow therapeutic index should be administered with caution in patients receiving SPRYCEL.

**Adverse Reactions:**

- In newly diagnosed chronic phase CML patients:
  - Drug-related serious adverse events (SAEs) were reported for 16.7% of SPRYCEL-treated patients. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%).
  - Most common adverse reactions (≥15%) included myelosuppression, fluid retention, and diarrhea.
- In patients resistant or intolerant to prior imatinib therapy:
  - Drug-related SAEs were reported for 26.1% of Sprycel-treated patients treated at the recommended dose of 100 mg once daily in the randomized dose-optimization trial of patients with chronic phase CML resistant or intolerant to prior imatinib therapy. Serious adverse reactions reported in ≥5% of patients included pleural effusion (10%).
  - Most common adverse reactions (≥15%) included myelosuppression, fluid retention events, diarrhea, headache, fatigue, dyspnea, skin rash, nausea, hemorrhage and musculoskeletal pain.

Please see the full Prescribing Information here.

**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 the Bristol-Myers Squibb and AbbVie Collaboration**

Bristol-Myers Squibb and AbbVie are co-developing Empliciti, with Bristol-Myers Squibb solely responsible for commercial activities.

**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 single agent or in combination with Yervoy, or Empliciti will receive regulatory approval for the additional indications described herein. 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 discussed 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.

**Language:**

English

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