Bristol-Myers Squibb Research Showcases Expansive Oncology Clinical Development Program and Commitment to Exploring Novel Combinations at ASCO 2017

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Terms:
#ASCO17  #BMS  #cancer  $BMY  BMS  BMY  Bristol-Myers  Cancer  caregiver  CheckMate  dasatinib  doctor  elotuzumab  Empliciti  ipilimumab  nivolumab  nurse  Oncology  Opdivo  patients  sprycel  Squibb  treatment  Yervoy

Dateline City:
PRINCETON, N.J.

BMS compounds to be featured in more than 80 presentations spanning 20 types of cancer, with focus on research of precision therapies aimed at improving standards of care

First efficacy data for investigational anti-LAG-3 in combination with Opdivo in anti-PD-1/PD-L1 relapsed or refractory patients and for Opdivo in combination with epacadostat showcases next wave of cancer research approaches

Opdivo plus Yervoy data to be featured in 18 presentations across multiple tumor types, including advanced small cell lung cancer, melanoma and colorectal cancer

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that more than 80 presentations, including 16 oral presentations and seven poster discussions, highlighting data from Company-sponsored studies, collaborations and investigator-sponsored research evaluating its oncology compounds across 20 types of cancer, will be featured at the American Society of Clinical Oncology (ASCO) Annual Meeting 2017 in Chicago from June 2-6. Results to be presented represent the breadth of the Company’s Oncology research portfolio, including monotherapy and combination studies of Opdivo (nivolumab) and Yervoy (ipilimumab), as well as studies of Empliciti (elotuzumab) and Sprycel (dasatinib). The Company will also present updates from its robust investigational pipeline, including proof-of-concept efficacy data for its anti-lymphocyte activation gene-3 (LAG-3) monoclonal antibody in combination with Opdivo and pharmacokinetic, pharmacodynamic and safety data on its investigational glucocorticoid-induced tumor necrosis factor receptor-related gene (GITR) agonist alone and for the first time, in combination with Opdivo in advanced solid tumors.

Several presentations will report data from clinical collaborations supportive of the Company’s efforts to advance understanding of the potential role for Opdivo in combination with novel mechanisms of action for several tumor types, including the first presentation of data evaluating the safety and efficacy of Opdivo in combination with epacadostat, Incyte’s selective IDO1 enzyme inhibitor. Presentations featuring translational medicine research underscore Bristol-Myers Squibb’s scientific leadership in driving understanding of how a patient’s tumor biology can potentially guide treatment decisions.

Data from research on the Company’s medicines to be presented during the meeting include:

Gastrointestinal Malignancies

- Combination of nivolumab + ipilimumab in the treatment of patients with deficient DNA mismatch repair/high microsatellite instability metastatic colorectal cancer: CheckMate 142 study
  
  Author: Thierry Andre
  
  Abstract #3531
  
  Poster Session: Gastrointestinal (Colorectal) Cancer
  
  Saturday, June 3, 8:00–11:30 AM, Hall A

- Concordance of DNA mismatch repair deficient/microsatellite instability assessment by local and
central testing in patients with metastatic CRC receiving nivolumab in CheckMate 142
Author: Scott Kopetz
Abstract #3548
Poster Session: Gastrointestinal (Colorectal) Cancer
Saturday, June 3, 8:00–11:30 AM, Hall A

- **Nivolumab in sorafenib-naive and -experienced patients with advanced hepatocellular carcinoma: The CheckMate 040 study**
  Author: Todd S. Crocenzi
  Abstract #4013
  Poster Discussion Session: Gastrointestinal (Noncolorectal) Cancer
  Saturday, June 3, 8:00–11:30 AM, Hall A
  Discussed at the Poster Discussion Session on Saturday, June 3, 2017, 4:45–6:00 PM, Hall D2

- **CheckMate 577: A randomized, double-blind, phase 3 study of adjuvant nivolumab or placebo in patients with resected esophageal or gastroesophageal junction cancer**
  Author: Ronan Joseph Kelly
  Abstract #TPS4131
  Poster Session: Gastrointestinal (Noncolorectal) Cancer
  Saturday, June 3, 8:00–11:30 AM, Hall A

- **CheckMate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab + ipilimumab or nivo + chemotherapy vs CTX alone in patients with previously untreated advanced gastric or gastroesophageal junction cancer**
  Author: Markus H. Moehler
  Abstract #TPS4132
  Poster Session: Gastrointestinal (Noncolorectal) Cancer
  Saturday, June 3, 8:00–11:30 AM, Hall A

Genitourinary Cancer

- **Health-related quality of life as a marker of treatment benefit with nivolumab in platinum-refractory patients with metastatic or unresectable urothelial carcinoma from CheckMate 275**
  Author: Andrea Necchi
  Abstract #4526
  Poster Session: Genitourinary (Nonprostate) Cancer
  Sunday, June 4, 8:00–11:30 AM, Hall A

Glioblastoma

- **Histopathologic review of suspected disease progression in patients with recurrent glioblastoma receiving nivolumab ± ipilimumab: CheckMate 143**
  Author: Solmaz Sahebjam
  Abstract #2001
  Oral Abstract Session: Central Nervous System Tumors
  Sunday, June 4, 8:12–8:24 AM, S100a

- **Overall survival by line of therapy in Medicare-enrolled glioblastoma multiforme patients**
  Author: Abdalla Aly
  Abstract #2039
  Poster Session: Central Nervous System Tumors
  Monday, June 5, 1:15–4:45 PM, Hall A

Gynecologic Cancers

- **An open-label, multicohort, phase 1/2 study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic cervical, vaginal and vulvar cancers**
  Author: Antoine Hollebecque
  Abstract #5504
  Oral Abstract Session: Gynecologic Cancer
  Friday, June 2, 4:12–4:24 PM, S406

Head and Neck Cancer

- **Nivolumab vs investigator’s choice for platinum-refractory recurrent or metastatic squamous cell carcinoma of the head and neck (Checkmate 141): Outcomes in first-line R/M patients and updated safety and efficacy**
  Author: Maura L. Gillison
  Abstract #6019
  Poster Discussion Session: Head and Neck Cancer
  Monday, June 5, 1:15–4:45 PM, Hall A
• Nivolumab vs investigator’s choice in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: Efficacy and safety in CheckMate 141 by prior cetuximab use
  Author: Robert L. Ferris
  Abstract #6020
  Poster Discussion Session: Head and Neck Cancer
  Monday, June 5, 1:15–4:45 PM, Hall A
  Discussed at the Poster Discussion Session on Monday, June 5, 2017, 4:45–6:00 PM, S406

• An open-label, multicohort, phase 1/2 study to evaluate nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic nasopharyngeal carcinoma
  Author: Jean-Pierre Delord
  Abstract #6025
  Poster Session: Head and Neck Cancer
  Monday, June 5, 1:15–4:45 PM, Hall A

• Characterization of potential predictive biomarkers of response to nivolumab in CheckMate 141 in patients with squamous cell carcinoma of the head and neck
  Author: Fernando Concha-Benavente
  Abstract #6050
  Poster Session: Head and Neck Cancer
  Monday, June 5, 1:15–4:45 PM, Hall A

Hematologic Malignancies

• Phase 2 trial of dasatinib in pediatric patients with chronic myeloid leukemia in chronic phase
  Author: Lia Gore
  Abstract #10511
  Oral Abstract Session: Pediatric Oncology II
  Monday, June 5, 8:24–8:36 AM, S504

• Impact of dose reductions on 5-year efficacy in newly diagnosed patients with chronic myeloid leukemia in chronic phase from DASISION
  Author: Jorge E. Cortes
  Abstract #7051
  Poster Session: Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant
  Monday, June 5, 8:00–11:30 AM, Hall A

• Phase 3 ELOQUENT-2 study: Extended four-year follow-up of elotuzumab plus lenalidomide/dexamethasone vs Ld in relapsed/refractory multiple myeloma
  Author: Sagar Lonial
  Abstract #8028
  Poster Session: Hematologic Malignancies—Plasma Cell Dyscrasia
  Monday, June 5, 8:00–11:30 AM, Hall A

• Nivolumab in combination with daratumumab, with or without pomalidomide and dexamethasone, for relapsed/refractory multiple myeloma: 2 cohorts of the phase 1 CheckMate 039 safety study
  Author: Alexander M. Lesokhin
  Abstract #TPS3102
  Poster Session: Developmental Therapeutics—Immunotherapy
  Monday, June 5, 8:00–11:30 AM, Hall A

• CheckMate 436: 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: Paul M. Barr
  Abstract #TPS7577
  Poster Session: Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
  Monday, June 5, 8:00–11:30 AM, Hall A

• CheckMate 602: An open-label, randomized, phase 3 trial of combinations of nivolumab, elotuzumab, pomalidomide and dexamethasone in relapsed/refractory multiple myeloma
  Author: Sagar Lonial
  Abstract #TPS8052
  Poster Session: Hematologic Malignancies—Plasma Cell Dyscrasia
  Monday, June 5, 8:00–11:30 AM, Hall A

Melanoma

• Overall survival analysis from an expanded access program of nivolumab in combination with ipilimumab in patients with advanced melanoma (CheckMate 218)
  Author: David Hogg
  Abstract #9522
  Poster Session: Melanoma/Skin Cancers
  Saturday, June 3, 1:15–4:45 PM, Hall A

• Association of distinct baseline tissue biomarkers with response to nivolumab and ipilimumab in melanoma: CheckMate 064
• Management of gastrointestinal toxicity associated with nivolumab plus ipilimumab (IPI) or IPI alone in phase 2 and 3 trials in advanced melanoma
  Author: Jeffrey S. Weber
  Abstract #9523
  Poster Session: Melanoma/Skin Cancers
  Saturday, June 3, 1:15–4:45 PM, Hall A

• Efficacy and safety of nivolumab in patients with advanced melanoma and poor prognostic factors who progressed on or after ipilimumab: Results from a phase 2 study (CheckMate 172)
  Author: Dirk Schadendorf
  Abstract #9524
  Poster Session: Melanoma/Skin Cancers
  Saturday, June 3, 1:15–4:45 PM, Hall A

• Efficacy and safety of nivolumab plus ipilimumab in patients with melanoma metastatic to the brain: Results of the phase 2 study CheckMate 204
  Author: Hussein Abdul-Hassan Tawbi
  Abstract #9507
  Oral Abstract Session: Melanoma/Skin Cancers
  Sunday, June 4, 10:12–10:24 AM, Arie Crown Theater

**Thoracic Malignancies**

• Nivolumab plus ipilimumab as first-line treatment for advanced NSCLC: 2-year OS and long-term outcomes from CheckMate 012
  Author: Jonathan Wade Goldman
  Abstract #9093
  Poster Session: Lung Cancer—Non-Small Cell Metastatic
  Saturday, June 3, 8:00–11:30 AM, Hall A

• Checkmate 816: A phase 3, randomized, open-label trial of nivolumab plus ipilimumab vs platinum-doublet chemotherapy as neoadjuvant treatment for early-stage NSCLC
  Author: Patrick M. Forde
  Abstract #TPS8577
  Poster Session: Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
  Saturday, June 3, 8:00–11:30 AM, Hall A

• Checkmate 743: A phase 3, randomized, open-label trial of nivolumab plus ipilimumab vs pemetrexed plus cisplatin or carboplatin as first-line therapy in unresectable pleural mesothelioma
  Author: Gerard Zalcman
  Abstract #TPS8581
  Poster Session: Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
  Saturday, June 3, 8:00–11:30 AM, Hall A

• Nivolumab ± ipilimumab in advanced small cell lung cancer: first report of a randomized expansion cohort from CheckMate 032
  Author: Matthew David Hellmann
  Abstract #8503
  Oral Abstract Session: Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
  Monday, June 5, 9:00–9:12 AM, Hall B1

**Pipeline**

• FRACTION (Fast Real-time Assessment of Combination Therapies in Immuno-ONcology)-gastric cancer (GC): A randomized, open-label, adaptive phase 2 study of nivolumab in combination with other immuno-oncology agents in patients with advanced GC
  Author: Praveen Aanur
  Abstract #TPS4137
  Poster Session: Gastrointestinal (Noncolorectal) Cancer
  Saturday, June 3, 8:00–11:30 AM, Hall A

• Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab in patients with melanoma previously treated with anti–PD-1/PD-L1 therapy
  Author: Paolo Antonio Ascierto
  Abstract #9520
  Poster Discussion Session: Melanoma/Skin Cancers
  Saturday, June 3, 1:15–4:45 PM, Hall A
  Discussed at the Poster Discussion Session on Saturday, June 3, 2017, 4:45–6:00 PM, E354b

• Preliminary results of a phase 1/2a study of BMS-986156 (glucocorticoid-induced tumor necrosis factor receptor-related gene [GITR] agonist), alone and in combination with nivolumab in patients with advanced solid tumors
  Author: Lillian L. Siu
Clinical Collaborations

- **Nivolumab + nab-paclitaxel + carboplatin in patients with non-small cell lung cancer: Interim results from a multicenter phase 1 study**
  Author: David Michael Waterhouse
  Abstract #9095
  Poster Session: Lung Cancer—Non-Small Cell Metastatic
  Saturday, June 3, 8:00–11:30 AM, Hall A

- **Ceritinib plus nivolumab in patients with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer**
  Author: Enriqueta Felip
  Abstract #2502
  Oral Abstract Session: Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics
  Saturday, June 3, 1:39–1:51 PM, E450ab

- **Effect of a novel IL-2 cytokine immune agonist (NKTR-214) on proliferating CD8+T cells and PD-1 expression on immune cells in the tumor microenvironment in patients with prior checkpoint therapy**
  Author: Chantale Bernatchez
  Abstract #2545
  Poster Session: Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics
  Monday, June 5, 8:00–11:30 AM, Hall A

- **A phase I study of enadenotucirev (EnAd), an oncolytic Ad11/Ad3 chimeric group B adenovirus, in combination with nivolumab in tumors of epithelial origin**
  Author: Wael A. Harb
  Abstract #TPS3115
  Poster Session: Developmental Therapeutics—Immunotherapy
  Monday, June 5, 8:00–11:30 AM, Hall A

- **Epacadostat plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of ECHO-204**
  Author: Raymond P. Perez
  Abstract #3003
  Oral Abstract Session: Developmental Therapeutics—Immunotherapy
  Monday, June 5, 2:15–2:27 PM, Hall D1

- **Clinical results with combination of anti-CD27 agonist antibody, varililumab, with anti-PD1 antibody nivolumab in advanced cancer patients**
  Author: Rachel E. Sanborn
  Abstract #3007
  Oral Abstract Session: Developmental Therapeutics—Immunotherapy
  Monday, June 5, 3:27–3:39 PM, Hall D1

International Immuno-Oncology Network (II-ON)

- **Function and expression of checkpoint inhibitors and immune agonists on immune cells in monoclonal gammopathy of undetermined significance, smoldering multiple myeloma and MM and tumor-specific T lymphocytes**
  Author: Jooeun Bae
  Abstract #11577
  Poster Session: Tumor Biology
  Saturday, June 3, 1:15–4:45 PM, Hall A

- **Loss-of-function of PBRM1 to predict response to anti-PD-1/PD-L1 therapy in metastatic renal cell carcinoma**
  Author: Diana Miao
  Abstract #3016
  Poster Session: Developmental Therapeutics—Immunotherapy
  Monday, June 5, 8:00–11:30 AM, Hall A
  Discussed at the Poster Discussion Session on Monday, June 5, 2017, 4:45–6:00 PM, Hall D1

- **Metabolomic correlates of response in nivolumab-treated renal cell carcinoma and melanoma patients**
  Author: Marios Giannakis
  Abstract #3036
  Poster Session: Developmental Therapeutics—Immunotherapy
  Monday, June 5, 8:00–11:30 AM, Hall A

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

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational Immuno-Oncology (I-O) medicines for hard-to-treat cancers that could potentially improve outcomes for these patients.
We are leading the scientific understanding of I-O through our extensive portfolio of investigational compounds and approved agents. Our differentiated clinical development program is studying broad patient populations across more than 35 types of cancers with 14 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs position us to advance I-O/I-O, I-O/chemotherapy, I-O/targeted therapies and I-O/radiation therapies across multiple tumors and potentially deliver the next wave of therapies with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and how patients’ individual tumor biology can be used as a guide for treatment decisions throughout their journey.

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

About the International Immuno-Oncology Network (II-ON)

The II-ON, formed in 2012, is a global peer-to-peer collaboration between Bristol-Myers Squibb and academia advancing the science of Immuno-Oncology (I-O) through a series of preclinical, translational and biology-focused research objectives. The research in the collaboration is focused on three fundamental scientific pillars: understanding the mechanisms of resistance to immunotherapy; identifying patient populations likely to benefit from immunotherapy; and exploring novel combination therapies that may enhance anti-tumor response through complementary mechanisms of action. The II-ON facilitates the translation of scientific research findings into drug discovery and development, with the goal of introducing new treatment options into clinical practice.

In addition to Bristol-Myers Squibb, the II-ON currently comprises 15 leading cancer research institutions, including: Clinica Universidad Navarra, Columbia University Medical Center, Dana-Farber Cancer Institute, The Earle A. Chiles Research Institute (Providence Health & Services), Institut Gustave Roussey, Istituto Nazionale per lo Studio e la Cura dei Tumori “Fondazione G. Pascale”, Bloomberg-Kimmel Institute for Cancer Immunotherapy at the Johns Hopkins Kimmel Cancer Center, Memorial Sloan Kettering Cancer Center, National Cancer Center Japan, The Netherlands Cancer Institute, Peter MacCallum Cancer Centre, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, University College London, The University of Chicago and West German Cancer Center/University Hospital Essen.

About Opdivo

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

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

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

U.S. FDA-APPROVED INDICATIONS FOR OPDIVO®

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 the confirmatory trials.

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

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 OPDVO.

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.

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

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

IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

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

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

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

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 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

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

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

Immune-Mediated Hepatitis

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

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

Immune-Mediated Neuropathies

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

Immune-Mediated Endocrinopathies

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

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

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

**Immune-Mediated Nephritis and Renal Dysfunction**

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

**Immune-Mediated Skin Adverse Reactions and Dermatitis**

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

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

**Immune-Mediated Encephalitis**

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. In patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one patient receiving OPDIVO with YERVOY (0.2%) after 1.7 months of exposure. For Grade 3 or 4 rash complicated by fatal immune-mediated rash, such as 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.

**Other Immune-Mediated Adverse Reactions**

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

**Infusion Reactions**

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

**Complications of Allogeneic HSCT after OPDIVO**

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 171 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

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

**Embryo-Fetal Toxicity**

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

**Lactation**

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

**Serious Adverse Reactions**

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were fatigue (21%), cough and dyspnea at a higher incidence than OPDIVO (n=406) vs everolimus (n=397) were fatigue, musculoskeletal pain, cough, diarrhea (23% and 30%), and cough (22% and 35%). In the subset of patients in the safety population (n=263) and 27% of patients in the subset of patients (≥10%) in Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were urinary tract infection, sepsis, 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]). In Checkmate 067, serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infections, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.

**Common Adverse Reactions**

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

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

**Checkmate Trials and Patient Populations**

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

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

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

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

About Empliciti

Empliciti is an immunostimulatory antibody that specifically targets Signaling Lymphocyte Activation Molecule Family member 7 (SLAMF7), a cell-surface glycoprotein. SLAMF7 is expressed on myeloma cells independent of cytogenetic abnormalities. SLAMF7 also is expressed on Natural Killer cells, plasma cells and at lower levels on specific immune cell subsets of differentiated cells within the hematopoietic lineage.

Empliciti has a dual mechanism-of-action. It directly activates the immune system through Natural Killer cells via the SLAMF7 pathway. Empliciti also targets SLAMF7 on myeloma cells, tagging these malignant cells for Natural Killer cell-mediated destruction via antibody-dependent cellular toxicity.

On November 30, 2015, the U.S. Food and Drug Administration (FDA) approved Empliciti in combination with lenalidomide and dexamethasone in patients with multiple myeloma who have received one to three prior therapies. On May 11, 2016, the European Commission approved Empliciti in combination with lenalidomide and dexamethasone in patients with multiple myeloma who have received at least one prior therapy. The safety and efficacy of Empliciti is being evaluated by other health authorities.

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

U.S. FDA-APPROVED INDICATION FOR EMPLICITI™

EMPLICTI™ (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%).

Please see the full Prescribing Information for EMPLICITI.

About Sprycel

Sprycel was first approved by the FDA in 2006 for the treatment of adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) who are resistant or intolerant to prior therapy including imatinib. At that time, Sprycel was also approved for adults with Ph+ acute lymphoblastic leukemia (ALL) who are resistant or intolerant to prior therapy. Sprycel is approved and marketed worldwide for these indications in more than 60 countries.

Sprycel is also an FDA-approved treatment for adults with newly diagnosed CP Ph+ CML (since October 2010). Sprycel received accelerated FDA approval for this indication. Additional country approvals for this indication total more than 50.

U.S. FDA-APPROVED INDICATIONS FOR SPRYCEL®

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.
- Chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- 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. Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

- 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 dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval).

- In clinical trials of patients treated with SPRYCEL at all doses (n=2440), 16 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF >500 ms.
- In 865 patients with leukemia treated with SPRYCEL in five Phase 2 single-arm studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7.0 to 13.4 ms.
- SPRYCEL may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.
  - Correct hypokalemia or hypomagnesemia prior to and during SPRYCEL administration.

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,teitllormycin,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

The safety data reflects exposure to SPRYCEL at all doses tested in clinical studies including 324 patients with newly diagnosed chronic phase CML and 2388 patients with imatinib resistant or intolerant chronic or advanced phase CML or Ph+ ALL.

The median duration of therapy in all 2712 SPRYCEL-treated patients was 19.2 months (range 0–93.2 months). Median duration of therapy in:

- 1618 patients with chronic phase CML was 29 months (range 0–92.9 months)
  - Median duration for 324 patients in the newly diagnosed chronic phase CML trial was approximately 60 months
- 1094 patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0–93.2 months)

In the newly diagnosed chronic phase CML trial, after a minimum of 60 months of follow-up, the cumulative discontinuation rate for 258 patients was 39%.

In the overall population of 2712 SPRYCEL-treated patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation. Among the 1618 SPRYCEL-treated patients with chronic phase CML, drug-related adverse events leading to discontinuation were reported in 329 (20.3%) patients.

- In the newly diagnosed chronic phase CML trial, drug was discontinued for adverse reactions in 16% of SPRYCEL-treated patients with a minimum of 60 months of follow-up.

Among the 1094 SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, drug-related adverse events leading to discontinuation were reported in 191 (17.5%) patients.

Patients ≥65 years are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, diarrhea, dyspea, cough, lower gastrointestinal hemorrhage, and appetite disturbance, and more likely to experience the less frequently reported adverse reactions of abdominal distention, dizziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema and weight decrease, and should be monitored closely.

- 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%) and dyspea (3%).
  - The most common adverse reactions (≥15%) included myelosuppression, fluid retention, and diarrhea.
  - Grade 3/4 laboratory abnormalities included neutropenia (29%), thrombocytopenia (22%), anemia (13%), hypophosphatemia (7%), hypocalcemia (4%), elevated bilirubin (1%), and elevated creatinine (1%).
  - 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%).

The most common adverse reactions (≥15%) included myelosuppression, fluid retention events, diarrhea, headache, fatigue, dyspnea, skin rash, nausea, hemorrhage and musculoskeletal pain.

Grade 3/4 hematologic laboratory abnormalities in chronic phase CML patients resistant or intolerant to prior imatinib therapy who received SPRYCEL 100 mg once daily with a minimum follow up of 60 months included neutropenia (36%), thrombocytopenia (24%), and anemia (13%). Other grade 3/4 laboratory abnormalities included: hypophosphatemia (10%), and hypokalemia (2%).

Among chronic phase CML patients with resistance or intolerance to prior imatinib therapy, cumulative grade 3/4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

- Grade 3/4 elevations of transaminases or bilirubin and Grade 3/4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML.
- Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption.
- Patients developing Grade 3/4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation.

Please see the full Prescribing Information for SPRYCEL.

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 any of the oncology compounds mentioned in this release will receive regulatory approval for an additional indication. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb’s business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2016, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Language:
English

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#MEDIA: BMY announces data to be presented at #ASCO17