Bristol-Myers Squibb to Present New Data on 20 Types of Cancer from Across its Oncology Portfolio at ASCO and EHA 2019

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Terms: Corporate/Financial News #ASCO19 #BMS #cancer #CheckMate #EHA24 #oncology #Opdivo #Yervoy $BMY ASCO19 BMS BMY Bristol-Myers Cancer caregiver CheckMate cHL CML colorectal doctor EHA24 ELOQUENT genitourinary HCC I-O Immuno-Oncology Immunotherapy ipilimumab kidney melanoma myeloma nivolumab nurse Oncology Opdivo patients PD-1 RCC Research Squibb treatment tumor Yervoy

Dateline City: PRINCETON, N.J.

New data on Opdivo (nivolumab) plus Yervoy (ipilimumab) in patients with advanced hepatocellular carcinoma and in melanoma patients with symptomatic brain metastases

New long-term survival data and health outcomes research on Opdivo in combination with Yervoy in advanced melanoma

Eighteen-month efficacy results for Empliciti (elotuzumab) plus pomalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma

Translational research exploring the use of novel technologies and artificial intelligence to understand the association of inflammation gene signatures with tumor immune cells

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced the presentation of data from across the company's oncology portfolio at the American Society of Clinical Oncology (ASCO) Annual Meeting 2019 in Chicago, May 31-June 4, and the 24th Annual Congress of the European Hematology Association (EHA) in Amsterdam, June 13-16. Data from over 90 Company-sponsored studies, investigator-sponsored studies and collaborations evaluating oncology compounds and early translational medicine across 20 types of cancer will be featured at the two meetings. Presentations will highlight the role of Immuno-Oncology (I-O) monotherapy and combination approaches in improving survival and quality of life outcomes, as well as translational research investigating novel biomarkers and diagnostics to aid in the selection of tailored treatments for each patient based on their unique disease biology.

2019 ASCO Annual Meeting - Highlights of Bristol-Myers Squibb data include:

*All times noted are Central Daylight Time

**Hepatocellular Carcinoma**

- Primary efficacy and safety results from the Phase 1/2 CheckMate -040 study evaluating the combination of Opdivo (nivolumab) plus Yervoy (ipilimumab) in patients with advanced hepatocellular carcinoma, the most common type of liver cancer, will be presented. These data (Abstract #4012), including objective response rate and overall survival, will be featured in a poster display on Monday, June 3 from 8-11 AM CDT, and in a poster discussion from 3-4:30 PM CDT.

**Melanoma**

- Safety and efficacy of Opdivo in combination with Yervoy in patients with symptomatic melanoma brain metastases (Abstract #9501) will be featured in an oral session on Tuesday, June 4, from 9:45 AM-12:45 PM CDT.

- New long-term survival data and health outcomes research evaluating Opdivo in combination with Yervoy in advanced melanoma—in terms of survival outcomes (CA209-004, Abstract #9533), quality of life after four years and during the
Renal Cell Carcinoma

- Safety and efficacy of Opdivo in combination with Yervoy in patients with asymptomatic advanced renal cell carcinoma brain metastases (Abstract #4517) will be featured in a poster display on Monday, June 3 from 1:15-4:15 PM CDT, and in a poster discussion from 4:30-6 PM CDT.

Translational Medicine and Tumor Biology

- Translational data to identify potentially predictive biomarkers and expand translational research capabilities will be presented. Through the use of gene expression profiling (GEP) and machine-learning modeling, a novel, tumor-associated inflammation gene signature was identified through correlative, immunohistochemistry assessment of CD8 expression on T cells. This CD8-derived signature was then used to assess inflammation of the tumor microenvironment across 12 tumor types (Abstract #2593). Additionally, using an innovative artificial intelligence-based approach, combined with T-cell localization gene signatures by GEP, researchers quantified the abundance of immune cells and their spatial location within the tumor microenvironment (Abstract #2594). Both abstracts will be featured in a poster session on Saturday, June 1 from 8-11 AM CDT.

24th Annual Congress of the EHA - Highlights of Bristol-Myers Squibb data include:

*All times noted are Central European Standard Time

Multiple Myeloma

- Extended 18-month follow-up data from the Phase 2 ELOQUENT-3 trial (Abstract #PS1370) evaluating the addition of Empliciti (elotuzumab) to pomalidomide and low-dose dexamethasone in relapsed/refractory (R/R) multiple myeloma, including a descriptive overall survival analysis for the combination, will be featured in a poster session on Saturday, June 15 from 5:30-7 PM CEST.

Classical Hodgkin and Non-Hodgkin Lymphoma

- Updated safety and efficacy results in two patient subgroups from the Phase 2 CheckMate -744 study, the first risk-stratified, response-adapted study of Opdivo and ADCETRIS (brentuximab vedotin), followed by ADCETRIS and bendamustine for suboptimal response, in children, adolescents and young adults with R/R classical Hodgkin lymphoma (cHL), prior to autologous stem cell transplantation (Abstract #S822) will be presented in an oral presentation on Saturday, June 15 from 12:30-12:45 PM CEST.

- Two-year results from cohort D of the Phase 2 CheckMate -205 study, evaluating Opdivo plus doxorubicin, vinblastine and dacarbazine in patients with newly diagnosed advanced-stage cHL (Abstract #S821), will be presented in an oral presentation on Saturday, June 15 from 12:15-12:30 PM CEST.

- A full analysis of the Phase 1/2 CheckMate -436 study, evaluating Opdivo and ADCETRIS in patients with R/R primary mediastinal large B-cell lymphoma (Abstract #S1601), will be presented in an oral presentation on Sunday, June 16 from 9-9:15 AM CEST.

2019 ASCO Annual Meeting - Company-sponsored and collaborative data include:

*All times noted are Central Daylight Time

Gastrointestinal Malignancies

- Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040
  Author: Yau
  Abstract: #4012
  Poster Discussion Session: Gastrointestinal (Noncolorectal) Cancer
  Monday, June 3, Poster Display: 8-11 AM, Hall A
  Discussion: 3-4:30 PM, Arie Crown Theater

- Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/DNA mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Clinical update
  Author: Lenz
  Abstract: #3521
  Poster Session: Gastrointestinal (Colorectal) Cancer
  Monday, June 3, Poster Display: 8-11 AM, Hall A

Melanoma

- Long-term follow-up of CA209-004: A phase I dose-escalation study of combined nivolumab (NIVO) and ipilimumab (IPI) in patients with advanced melanoma
  Author: Atkins
  Abstract: #9533
  Poster Session: Melanoma/Skin Cancers
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- Sensitivity of treatment-free survival (TFS), a novel outcome, to subgroup analyses of patients (pts) with advanced melanoma (MEL) treated with immune checkpoint inhibitors (ICI)
  Author: Mantia
Abstract: #9550
Poster Session: Melanoma/Skin Cancers
Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **Patient-reported quality of life (QoL) of advanced melanoma patients in a Phase 3 study of nivolumab (NIVO) with or without ipilimumab (IPI) versus IPI: CheckMate 067 4-year data**
  Author: Schadendorf
  Abstract: #9551
  Poster Session: Melanoma/Skin Cancers
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **Quality of life (QoL) and symptom burden in patients (pts) with advanced melanoma during the treatment-free interval (TFI) after discontinuation of nivolumab (NIVO) or NIVO plus ipilimumab (IPI)**
  Author: Taylor
  Abstract: #9568
  Poster Session: Melanoma/Skin Cancers
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **An analysis of nivolumab-mediated adverse events and association with clinical efficacy in resected stage III or IV melanoma (CheckMate 238)**
  Author: Mandala
  Abstract: #9584
  Poster Session: Melanoma/Skin Cancers
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204)**
  Author: Tawbi
  Abstract: #9501
  Oral Session: Melanoma/Skin Cancers
  Tuesday, June 4, 9:45 AM-12:45 PM, S406
  Presentation: 9:57-10:09 AM, S406

Genitourinary Malignancies

- **CheckMate 214 post-hoc analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features**
  Author: McDermott
  Abstract: #4513
  Poster Discussion Session: Genitourinary (Nonprostate) Cancer
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A
  Discussion: 4:30-6 PM, Hall D2

- **Safety and efficacy of nivolumab plus ipilimumab (NIVO+IPI) in patients with advanced renal cell carcinoma (aRCC) with brain metastases: Interim analysis of CheckMate 920**
  Author: Emamekhoo
  Abstract: #4517
  Poster Discussion Session: Genitourinary (Nonprostate) Cancer
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A
  Discussion: 4:30-6 PM, Hall D2

- **Consistent efficacy of nivolumab plus ipilimumab across number of International Metastatic Database Consortium (IMDC) risk factors in CheckMate 214**
  Author: Escudier
  Abstract: #4575
  Poster Session: Genitourinary (Nonprostate) Cancer
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **Clinical and economic outcomes associated with sequential treatment in patients with advanced renal cell carcinoma (aRCC)**
  Author: Regan
  Abstract: #4566
  Poster Session: Genitourinary (Nonprostate) Cancer
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **Nivolumab monotherapy in patients with advanced platinum-resistant urothelial carcinoma: Efficacy and safety update from CheckMate 275**
  Author: Siefker-Radtke
  Abstract: #4524
  Poster Session: Genitourinary (Nonprostate) Cancer
  Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

- **Real-world outcomes with IO therapies: A prospective observational cohort study in patients (pts) with advanced melanoma (OPTIMizE)**
  Author: Kirkwood
  Abstract: #e14144
Serum IL-6 and CRP as prognostic factors in melanoma patients receiving single agent and combination checkpoint inhibition
Author: Weber
Abstract: #100
Clinical Science Symposium: Fine-Tuning Checkpoint Inhibition: Biomarkers of Response and Resistance
Saturday, June 1, Clinical Science Symposium: 8-9:30 AM, Hall D1
Presentation: 8-8:12 AM, Hall D1

Development of a baseline prognostic cytokine signature that correlates with nivolumab (NIVO) clearance (CL): Translational pharmacokinetic/pharmacodynamic (PK/PD) analysis in patients with renal cell carcinoma (RCC)
Author: Wang
Abstract: #2544
Poster Session: Developmental Immunotherapy and Tumor Immunobiology
Saturday, June 1, Poster Display: 8-11 AM, Hall A

Association of an inflammatory gene signature with CD8 expression by immunohistochemistry (IHC) in multiple tumor types
Author: Szabo
Abstract: #2593
Poster Session: Developmental Immunotherapy and Tumor Immunobiology
Saturday, June 1, Poster Display: 8-11 AM, Hall A

CD8+ T cells in tumor parenchyma and stroma by image analysis (IA) and gene expression profiling (GEP): Potential biomarkers for immuno-oncology (I-O) therapy
Author: Szabo
Abstract: #2594
Poster Session: Developmental Immunotherapy and Tumor Immunobiology
Saturday, June 1, Poster Display: 8-11 AM, Hall A

Association of human endogenous retrovirus (hERV) expression with clinical efficacy of PD-1 blockade in metastatic clear cell renal cell carcinoma (mccRCC)
Author: Pignon
Abstract: #4568
Poster Session: Genitourinary (Nonprostate) Cancer
Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

Baseline tumor-immune signatures associated with response to bempegaldesleukin (NKTR-214) and nivolumab
Author: Hurwitz
Abstract: #2623
Poster Session: Developmental Immunotherapy and Tumor Immunobiology
Saturday, June 1, Poster Display: 8-11 AM, Hall A

CA224-060: A randomized, open label, phase II trial of relatlimab (anti-LAG-3) and nivolumab with chemotherapy versus nivolumab with chemotherapy as first-line treatment in patients with gastric or gastroesophageal junction adenocarcinoma
Author: Feeney
Abstract: #TPS4143
Poster Session: Gastrointestinal (Noncolorectal) Cancer
Monday, June 3, Poster Display: 8-11 AM, Hall A

CA045-001: A phase III, randomized, open label study of bempegaldesleukin (NKTR-214) plus nivolumab (NIVO) versus NIVO monotherapy in patients (pts) with previously untreated, unresectable or metastatic melanoma (MEL)
Author: Khushalani
Abstract: #TPS9601
Poster Session: Melanoma/Skin Cancers
Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

A phase III randomized open label study comparing bempegaldesleukin (NKTR-214) plus nivolumab to sunitinib or cabozantinib (investigator’s choice) in patients with previously untreated advanced renal cell carcinoma
Author: Tannir
Abstract: #TPS4595
Poster Session: Genitourinary (Nonprostate) Cancer
Monday, June 3, Poster Display: 1:15-4:15 PM, Hall A

A phase 3 randomized study of neoadjuvant chemotherapy (NAC) alone or in combination with nivolumab (NIVO) ± BMS-986205 in cisplatin-eligible muscle invasive bladder cancer (MIBC)
Author: Sonpavde
Abstract: #TPS4587
Poster Session: Genitourinary (Nonprostate) Cancer
Clinical Collaborations

- Preliminary immunogenicity, safety, and efficacy of JNJ-64041757 (JNJ-757) in non-small cell lung cancer (NSCLC): Results from two phase 1 studies
  Author: Brahmer
  Poster Session: Lung Cancer-Non-Small Cell Metastatic
  Sunday, June 2, Poster Display: 8-11 AM, Hall A

- An open label, multicenter, phase I/II study of RP1 as a single agent and in combination with PD1 blockade in patients with solid tumors
  Author: Middleton
  Poster Session: Developmental Immunotherapy and Tumor Immunobiology
  Saturday, June 1, Poster Display: 8-11 AM, Hall A

- Ph1/2 study of Rova-T in combination with nivolumab (Nivo) ± ipilimumab (Ipi) for patients (pts) with 2L+ extensive-stage (ED) SCLC
  Author: Malhotra
  Poster Session: Lung Cancer-Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
  Sunday, June 2, Poster Display: 8-11 AM; Hall A

24th Congress of the EHA - Company-sponsored and collaborative data include:
*All times noted are Central European Summer Time

Lymphoma

- Nivolumab Plus Doxorubicin, Vinblastine and Dacarbazine for Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma: 2-Year Extended Follow-Up From Cohort D of the Phase 2 CheckMate 205 Study
  Author: Domingo-Domènech
  Abstract: #S821
  Oral Session: Hodgkin lymphoma – Clinical
  Saturday, June 15, 11:30 AM-12:45 PM, Hall 5
  Presentation: 12:15-12:30 PM, Hall 5

- Nivolumab and Brentuximab Vedotin-Based, Response-Adapted Treatment in Primary Refractory and in Pediatric Patients with Relapsed/Refractory Classical Hodgkin Lymphoma in CheckMate 744
  Author: LeBlanc
  Abstract: #S822
  Oral Session: Hodgkin lymphoma – Clinical
  Saturday, June 15, 11:30 AM-12:45 PM, Hall 5
  Presentation: 12:30-12:45 PM, Hall 5

- Nivolumab Combined with Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-cell Lymphoma: Efficacy and Safety Results from the Phase 2 CheckMate 436 Study
  Author: Zinzani
  Abstract: #S1601
  Oral Session: Aggressive lymphomas – First line, combination therapy and real-life data
  Sunday, June 16, 8-9:15 AM, Hall 5
  Presentation: 9-9:15 AM, Hall 5

Multiple Myeloma

- Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Efficacy Results After Additional Follow-Up of the Phase 2, Randomized ELOQUENT-3 Study
  Author: Dimopoulos
  Abstract: #PS1370
  Poster Session: Myeloma and other monoclonal gammopathies – Clinical
  Saturday, June 15, 5:30-7 PM, Poster Area

- Investigating Mechanisms of Elotuzumab and Lenalidomide in Multiple Myeloma
  Author: Richardson
  Abstract: #PF568
  Poster Session: Myeloma and other monoclonal gammopathies – Biology & Translational Research
  Friday, June 14, 5:30-7 PM, Poster Area

- Use of Pomalidomide-Based Regimens in Relapsed/Refractory Multiple Myeloma in Four European Countries - Findings From PREAMBLE
  Author: Moreau
  Abstract: #PS1405
  Poster Session: Myeloma and other monoclonal gammopathies – Clinical
  Saturday, June 15, 5:30-7 PM, Poster Area

Leukemia
• **DASCERN 2-Year Extended Follow-Up of Dasatinib Efficacy and Safety in Patients (Pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Who Have Suboptimal Responses to 3 Months of Imatinib**
  Author: Saglio
  Abstract: #PF405
  Poster Session: Chronic myeloid leukemia - Clinical
  Friday, June 14, 5:30-7 PM, Poster Area

• **DASFREE: 2-Year Update: Dasatinib Discontinuation in Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) and Deep Molecular Response (DMR)**
  Author: Shah
  Abstract: #PF408
  Poster Session: Chronic myeloid leukemia - Clinical
  Friday, June 14, 5:30-7 PM, Poster Area

• **Growth Rate and Endocrine Effects of Dasatinib Therapy Observed in Retrospective Analysis of a Phase II Clinical Trial for Pediatric Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP)**
  Author: Patterson
  Abstract: #PF416
  Poster Session: Chronic myeloid leukemia - Clinical
  Friday, June 14, 5:30-7 PM, Poster Area

• **Dosing Patterns of Dasatinib and Nilotinib Use in SIMPLICITY, an Observational Study in Chronic-Phase Chronic Myeloid Leukemia (CP-CML) Patients (pts) in Routine Clinical Practice**
  Author: Cortes
  Abstract: #PS1181
  Poster Session: Chronic myeloid leukemia - Clinical
  Saturday, June 15, 5:30-7 PM, Poster Area

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

At Bristol-Myers Squibb, patients are at the center of everything we do. The focus of our research is to increase quality, long-term survival for patients and make cure a possibility. Through a unique multidisciplinary approach powered by translational science, we harness our deep scientific experience in oncology and Immuno-Oncology (I-O) research to identify novel treatments tailored to individual patient needs. Our researchers are developing a diverse, purposefully built pipeline designed to target different immune system pathways and address the complex and specific interactions between the tumor, its microenvironment and the immune system. We source innovation internally, and in collaboration with academia, government, advocacy groups and biotechnology companies, to help make the promise of transformational medicines, like I-O, a reality for patients.

**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 treated more than 35,000 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 65 countries, including the United States, the European Union, Japan and China. 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®**

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

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma.

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 metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

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

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

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

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated pneumonitis occurred in 6% (25/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 4.4% (24/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) of patients.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. In RCC patients...
receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 10% (52/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated colitis occurred in 7% (8/119) 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

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. For patients without HCC, withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3 and up to 5 times the upper limit of normal (ULN), if AST/ALT is >1 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 13% (51/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 7% (38/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 8% (10/119) of patients.

In Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.

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

### Immune-Mediated Neuropathies

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

### Immune-Mediated Endocrinopathies

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 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 hypothyroidism. 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 1 mg/kg with YERVOY 3 mg/kg, hypophysitis occurred in 9% (36/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis occurred in 4.6% (25/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hypophysitis occurred in 3.4% (4/119) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, adrenal insufficiency occurred in 5% (21/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 7% (41/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 5.9% (7/119) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hypothyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, hypothyroidism or thyroiditis occurring in hypothyroidism occurred in 22% (89/407) of patients. Hypothyroidism occurred in 8% (34/407) of patients receiving this dose of OPDIVO with YERVOY. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypothyroidism or thyroiditis occurring in hypothyroidism occurred in 15% (18/119) of patients. Hypothyroidism occurred in 12% (14/119) of patients. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, diabetes occurred in 1.5% (6/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, diabetes occurred in 2.7% (15/547) 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. Six 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 1 mg/kg with YERVOY 3 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients. In RCC patients...
Increased Mortality in Patients with Multiple Myeloma when OPDIVO is added to a Thalidomide-containing regimen and for at least 5 months after the last dose of OPDIVO.

Immune-Mediated Skin Adverse Reactions and Dermatitis

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated rash occurred in 22.6% (92/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 16.6% (91/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 14% (17/1219) 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 1 mg/kg with YERVOY 3 mg/kg (0.2%) after 1.7 months of exposure. Encephalitis occurred in one RCC patient receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg (0.2%) after approximately 4 months of exposure. Encephalitis occurred in one MSI-H/dMMR mCRC patient (0.8%) receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg after 15 days of exposure.

Other Immune-Mediated Adverse Reactions

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

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

Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate study in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/369) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, infusion-related reactions occurred in 4.2% (5/119) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

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.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide
Analogue and Dexamethasone

In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

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 breastfeeding during treatment with YERVOY and for 3 months following the final dose.

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in ≥2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diaphragn (3.4%). In Checkmate 205, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dose reductions (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). 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 ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 032, serious adverse reactions occurred in 45% of patients receiving OPDIVO (n=245). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, pneumonitis, pleural effusions, and dehydration. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406) were most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diaphragn, and hypercalcemia. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY and in 43% of patients receiving sunitinib. The most frequent serious adverse reactions reported in ≥2% of patients were diabetes, pyrexia, pneumonia, pneumonitis, hypophysisit, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infuson-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were urinary tract infection, sepsis, diabetes, small intestinre obstruction, and general physical health deterioration. In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diaphragn, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in ≥2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia. In Checkmate 231, serious adverse reactions reported in ≥2% of patients treated with OPDIVO (n=452). The most frequent (≥10%) serious adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diaphragn (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common adverse reactions (≥20%) in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diaphragn (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=406) were most frequent musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 032, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diaphragn (21%), constipation (20%), and cough (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diaphragn (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) vs sunitinib (n=535) were fatigue (58% vs 69%), rash (39% vs 25%), diaphragn (38% vs 58%), musculoskeletal pain (37% vs 40%), pruritus (33% vs 11%), nausea (30% vs 43%), cough (28% vs 25%), pyrexia (25% vs 17%), arthralgia (23% vs 16%), decreased appetite (21% vs 29%), dyspnea (20% vs 21%), and vomiting (20% vs 28%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were
upper respiratory tract infection (4%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough and dyspnea at a higher incidence than investigator’s choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent, the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), cough (26%), pyrexia (24%), rash (23%), constipation (20%), and upper respiratory tract infection (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colicits (6%), and hepatitis (3%).

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

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

Checkmate Trials and Patient Populations
Checkmate 037—previously treated metastatic melanoma; Checkmate 066—previously untreated metastatic melanoma; Checkmate 067—previously untreated metastatic melanoma, as a single agent or in combination with YERVOY; Checkmate 017—second-line treatment of metastatic squamous non-small cell lung cancer; Checkmate 057—second-line treatment of metastatic non-squamous non-small cell lung cancer; Checkmate 032—small cell lung cancer; Checkmate 025—previously treated renal cell carcinoma; Checkmate 214—previously untreated renal cell carcinoma, in combination with YERVOY; Checkmate 205/039—classical Hodgkin lymphoma; Checkmate 141—recurrent or metastatic squamous cell carcinoma of the head and neck; Checkmate 275—urothelial carcinoma; Checkmate 142—MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY; Checkmate 040—hepatocellular carcinoma; Checkmate 238—adjunct treatment of melanoma.

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.

Empliciti was initially approved by the FDA in 2015 in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

U.S. FDA-APPROVED INDICATIONS FOR EMPLICITI®

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

EMPLICITI® (elotuzumab) is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

IMPORTANT SAFETY INFORMATION

Infusion Reactions
Infusion reactions were reported in 10% of patients treated with EMPLICITI in the ELOQUENT-2 trial [EMPLICITI + lenalidomide + dexamethasone (ERd) vs lenalidomide + dexamethasone (Rd)] and 3.3% in the ELOQUENT-3 trial [EMPLICITI + pomalidomide + dexamethasone (EPd) vs pomalidomide + dexamethasone (Pd)].

In the ELOQUENT-2 trial, all infusion reactions were Grade 3 or lower, with Grade 3 infusion reactions occurring in 1% of patients. The most common symptoms included fever, chills, and hypotension. Bradycardia and hypertension 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.

In the ELOQUENT-3 trial, the only infusion reaction symptom was chest discomfort (2%), which was Grade 1. All the patients who experienced an infusion reaction had them during the first treatment cycle.

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 EMPLICITI infusion.

Infections

In the ELOQUENT-2 trial (N=635), infections were reported in 81% of patients in the ERd arm and 74% in the Rd arm. Grade 3-4 infections were 28% (ERd) and 24% (Rd). Discontinuations due to infections were 3.5% (ERd) and 4.1% (Rd). Fungal infections were 2.5% (ERd) and 2.2% (Rd). Opportunistic infections were reported in 22% (ERd) and 13% (Rd). Fungal infections were 10% (ERd) and 5% (Rd). Herpes zoster was 14% (ERd) and 7% (Rd).

In the ELOQUENT-3 trial (N=115), infections were reported in 65% of patients in both the EPd arm and the Pd arm. Grade 3-4 infections were reported in 13% (EPd) and 22% (Pd). Discontinuations due to infections were 7% (EPd) and 5% (Pd). Fungal infections were 5% (EPd) and 3.6% (Pd). Opportunistic infections were reported in 10% (EPd) and 9% (Pd). Herpes zoster was reported in 5% (EPd) and 1.8% (Pd).

Monitor patients for development of infections and treat promptly.

Second Primary Malignancies

In the ELOQUENT-2 trial (N=635), invasive second primary malignancies (SPM) were 9% (ERd) and 6% (Rd). The rate of hematologic malignancies was 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).

In the ELOQUENT-3 trial (N=115), invasive SPMs were 0% (EPd) and 1.8% (Pd).

Monitor patients for the development of SPMs.

Hepatotoxicity

In the ELOQUENT-2 trial (N=635), AST/ALT >3X the upper limit, total bilirubin >2X the upper limit, and alkaline phosphatase <2X the upper limit were 2.5% (ERd) vs 0.6% (Rd). Of 8 patients experiencing hepatotoxicity, 2 patients discontinued treatment while 6 patients had resolution and continued. Monitor liver enzymes periodically. Stop EMPLICITI upon ≥Grade 3 elevation of liver enzymes. Continuation of treatment may be considered after return to baseline values.

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 available data on EMPLICITI use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage.

There is a risk of fetal harm, including severe life-threatening human birth defects, associated with lenalidomide and pomalidomide, and they are contraindicated for use in pregnancy. Refer to the respective product 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

ELOQUENT-2 trial:

- Serious adverse reactions were 65% (ERd) and 57% (Rd). The most frequent serious adverse reactions in the ERd arm compared to the Rd arm were: pneumonia (15%, 11%), pyrexia (7%, 5%), 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 (62%, 52%), diarrhea (47%, 36%), pyrexia (37%, 25%), constipation (36%, 27%), cough (34%, 19%), peripheral neuropathy (27%, 21%), nasopharyngitis (25%, 19%), upper respiratory tract infection (23%, 17%), decreased appetite (21%, 13%), and pneumonia (20%, 14%).

ELOQUENT-3 trial:

- Serious adverse reactions were 22% (EPd) and 15% (Pd). The most frequent serious adverse reactions in the EPd arm compared to the Pd arm were: pneumonia (13%, 11%) and respiratory tract infection (7%, 3.6%).
- The most common adverse reactions in EPd arm (≥20% EPd) and Pd, respectively, were constipation (22%, 11%) and hyperglycemia (20%, 15%).

Please see the full Prescribing Information.

About Sprycel

Sprycel is a second-generation tyrosine kinase inhibitor (TKI) designed to help inhibit BCR-ABL, an abnormal protein found on the mutated Philadelphia chromosome in most patients with chronic myeloid leukemia (CML) and some patients with ALL, which can trigger the overproduction of damaged or immature white blood cells. By targeting the BCR-ABL protein, Sprycel can reduce the number of damaged white blood cells in the body, allowing for the production of more normal cells.

Sprycel is currently approved in more than 60 countries for the treatment of adults with Ph+ ALL or Ph+ CML in chronic phase (CP-CML) who are resistant or intolerant to prior therapy, and in more than 50 countries for the treatment of adults with...
newly diagnosed Ph+ CP-CML. In 2017, Sprycel received its first pediatric indication when it became the first second-generation TKI approved for the treatment of patients one year of age and older with Ph+ CP-CML. Sprycel is also approved in combination with chemotherapy for the treatment of pediatric patients with newly diagnosed Ph+ ALL.

In Europe, both pediatric indications for Sprycel include the PFOS formulation, the approvals of which made Sprycel the first TKI with an approved powder formulation for administration in pediatric patients with Ph+ CP-CML and Ph+ ALL. The PFOS formulation is also approved for adult patients with Ph+ CP-CML who cannot swallow tablets.

U.S. FDA-APPROVED INDICATIONS FOR SPRYCEL®

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

- Newly diagnosed 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

SPRYCEL® is indicated for the treatment of pediatric patients 1 year of age and older with:

- Ph+ CML in chronic phase
- Newly diagnosed Ph+ ALL in combination with chemotherapy

IMPORTANT SAFETY INFORMATION

Myelosuppression:

Treatment with SPRYCEL is associated with severe (NCI CTCAE 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
- In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery
- 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 can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. The incidence of Grade 3/4 hemorrhage occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients. The most frequent site of hemorrhage was gastrointestinal.

- Most bleeding events in clinical studies were associated with severe thrombocytopenia
- In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction in vitro
- 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 adult 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 adult 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 adult 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. In pediatric patients with chronic phase CML, cases of Grade 1 or 2 fluid retention were reported in 10.3% 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:
SPRYCEL can cause cardiac dysfunction. After 5 years of follow-up in the randomized, newly diagnosed chronic phase CML trial in adults (n=258), the following cardiac adverse reactions 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 in adult and pediatric patients, 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:
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

Effects on Growth and Development in Pediatric Patients:
In pediatric trials of SPRYCEL in chronic phase CML after at least 2 years of treatment, adverse reactions associated with bone growth and development were reported in 5 (5.2%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 5 cases included cases of epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia. Of these 5 cases, 1 case of osteopenia and 1 case of gynecomastia resolved during treatment.

Monitor bone growth and development in pediatric patients.

Lactation:
No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed child, 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 children from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose

Drug Interactions:
Effect of Other Drugs on Dasatinib
- Strong CYP3A4 inhibitors: The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL
hypertension, pulmonary edema and weight decrease, and diarrhea, dyspnea, cough, lower gastrointestinal hemorrhage, and appetite disturbance, and patients ≥65 years are more likely to experience the commonly reported (1%).

Among the 97 CML pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

In two non-randomized trials in 97 pediatric patients with chronic phase CML (51 patients newly diagnosed and 46 patients resistant or intolerant to previous treatment with imatinib), the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).

In a multicohort study of SPRYCEL administered continuously in combination with multiagent chemotherapy in 81 pediatric patients with newly diagnosed Ph+ ALL, the median duration of therapy was 24 months (range 2 to 27 months).

In the newly diagnosed adult 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 adult patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation.

Among the 1618 adult patients with chronic phase CML, drug-related adverse reactions leading to discontinuation were reported in 329 (20.3%) patients.

- In the adult 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 adult patients with advanced phase CML or Ph+ ALL, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

Among the 97 CML pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 1 patient (1%).

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 adult newly diagnosed chronic phase CML patients:
  - Drug-related serious adverse reactions (SARs) were reported for 16.7% of patients. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%)
  - Grade 3/4 laboratory abnormalities included neutropenia (29%), thrombocytopenia (22%), anemia (13%), hypophosphatemia (7%), hypocalcemia (4%), elevated bilirubin (1%), and elevated creatinine (1%)

- In adult patients resistant or intolerant to prior imatinib therapy:
  - Drug-related SARs 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%)
  - 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%)

Do not administer H2 antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H2 antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

Adverse Reactions:

The safety data reflects exposure to SPRYCEL administered as single-agent therapy at all doses tested in clinical studies (n=2809) including 324 adult patients with newly diagnosed chronic phase CML, 2388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 97 pediatric patients with chronic phase CML.

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

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

In two non-randomized trials in 97 pediatric patients with chronic phase CML (51 patients newly diagnosed and 46 patients resistant or intolerant to previous treatment with imatinib), the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).

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Among the 97 CML pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 1 patient (1%).

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.

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- In adult patients resistant or intolerant to prior imatinib therapy:
  - Drug-related SARs 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%)
  - 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%)

Avoid simultaneous administration of SPRYCEL with antacids. Consider the use of antacids in place of H2 antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Do not administer H2 antagonists or proton pump inhibitors with SPRYCEL.

Gastric Acid Reducing Agents:
The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

- **Strong CYP3A4 inducers:** The coadministration of SPRYCEL with strong CYP3A4 inducers may decrease dasatinib concentrations. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase.
- **St. John’s wort** may decrease plasma concentrations of SPRYCEL and should be avoided.

- **Gastric Acid Reducing Agents:** The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

Avoid simultaneous administration of SPRYCEL with antacids.
- 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.
- In pediatric subjects with Ph+ CML in chronic phase:
  - Drug-related SARs were reported for 14.4% of pediatric patients.
  - Adverse reactions associated with bone growth and development were reported in 5 (5.2%) pediatric patients with chronic phase CML.
  - In the pediatric studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.
- In pediatric subjects with Ph+ ALL who were administered SPRYCEL in combination with multiagent chemotherapy:
  - Fatal adverse reactions occurred in 3 patients (4%), all of which were due to infections.
  - Eight patients (10%) experienced adverse reactions leading to treatment discontinuation.
  - The most common serious adverse reactions (incidence ≥10%) were pyrexia, febrile neutropenia, mucositis, diarrhea, sepsis, hypotension, infections (bacterial, viral, and fungal), hypersensitivity, vomiting, renal insufficiency, abdominal pain, and musculoskeletal pain.
  - Grade 3/4 laboratory abnormalities (≥10%) included neutropenia (96%), thrombocytopenia (88%), anemia (82%), elevated SGPT (ALT) (47%), hypokalemia (40%), elevated SGOT (AST) (26%), hypocalcemia (19%), hyponatremia (19%), elevated bilirubin (11%), and hypophosphatemia (11%).

Most common adverse reactions (≥15%) in patients receiving SPRYCEL as single-agent therapy included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain.

Most common adverse reactions (≥30%) in pediatric patients receiving SPRYCEL in combination with chemotherapy included mucositis, febrile neutropenia, pyrexia, diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, constipation, arrhythmia, hypertension, edema, infections (bacterial, viral, and fungal), hypotension, decreased appetite, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, and altered state of consciousness.

Please see full Prescribing Information.

About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., 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, Ono and Bristol-Myers Squibb further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. No forward-looking statement can be guaranteed. 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, 2018, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by federal securities law, Bristol-Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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$BMY highlights research across solid tumors and hematologic malignancies at #ASCO19 and #EHA24: