Bristol-Myers Squibb to Highlight New Data from Broad Oncology Portfolio at the 60th American Society of Hematology Annual Meeting

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Terms:
- Corporate/Financial News
- #BMS
- #cancer
- #CheckMate
- #Empliciti
- #oncology
- #Opdivo
- #Sprycel
- #Yervoy
- Immunotherapy
- #iplimumab
- Multiple Myeloma
- nivolumab
- nurse
- Oncology
- Opdivo
- patients
- PD-1
- Research
- Squibb
- treatment
- Tumor
- Yervoy

Dateline City:
PRINCETON, N.J.

Nineteen presentations and publications featuring data from three Bristol-Myers Squibb medicines, alone and in combination, across four hematologic malignancies

First disclosure of results from a Phase 2 trial supports safety and efficacy of Empliciti (elotuzumab) plus pomalidomide and low-dose dexamethasone in relapsed/refractory (R/R) multiple myeloma

Updates from Opdivo (nivolumab) plus ADCETRIS® (brentuximab vedotin) combination include first disclosure of data in R/R primary mediastinal large B-cell lymphoma, and an oral presentation in children, adolescents and young adults with standard-risk R/R classical Hodgkin lymphoma

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that 19 data presentations and publications, including two oral presentations, from Company-sponsored studies and collaborations evaluating Opdivo (nivolumab), Sprycel (dasatinib) and Empliciti (elotuzumab) will be featured at the 60th American Society of Hematology (ASH) Annual Meeting in San Diego, Calif., from December 1-4.

“Our presence at ASH, in Immuno-Oncology and beyond, underscores the breadth of our oncology portfolio, which is designed to deliver a wide range of possible treatment options to patients,” said Joseph E. Eid, M.D., senior vice president and head, Medical, Bristol-Myers Squibb. “These data reiterate the potential of our medicines for patients with blood cancers, from patients with rare malignancies, like primary mediastinal large B-cell lymphoma, to those with unique and oftentimes unmet needs, like children and young adults with relapsed/refractory classical Hodgkin lymphoma.”

Featured data include:

Multiple Myeloma

- New Phase 2 data from CA204-142, a single-arm study conducted in the United States, evaluating Empliciti plus pomalidomide and low-dose dexamethasone (EPd) in patients with multiple myeloma who were relapsed, refractory or intolerant to lenalidomide, who received one to two prior therapies and whose disease progressed during or after their last therapy. Safety and efficacy data from CA204-142 (Abstract #1991) will be featured on Saturday, December 1, from 6:15-8:15 PM PST.

Classical Hodgkin and Non-Hodgkin Lymphoma

- Primary safety and efficacy results from the Phase 1/2 CheckMate -436 study, evaluating Opdivo and ADCETRIS (brentuximab vedotin) in patients with relapsed/refractory (R/R) primary mediastinal large B-cell lymphoma. The results, including objective and complete response (CR) rates, from CheckMate -436 (Abstract #1691) will be featured in the presentation on Saturday, December 1, from 6:15-8:15 PM PST.

- Updated data from the Phase 1/2 trial evaluating Opdivo and ADCETRIS in adult patients with R/R classical Hodgkin
lymphoma (cHL), including results from the RNA sequencing analyses of tumor biopsies from study participants prior to the start of treatment. These analyses were designed to determine whether tumor characteristics are associated with response to treatment. These data (Abstract #2837) will be featured on Sunday, December 2, from 6-8 PM PST.

- First results from the Phase 2 CheckMate -744 study, the first risk-stratified, response-adapted study of Opdivo and ADCETRIS, followed by ADCETRIS and bendamustine for suboptimal response, in children, adolescents and young adults with R/R cHL, prior to autologous stem cell transplantation (ASCT). These data (Abstract #927) will be featured in an oral presentation on Monday, December 3, at 3 PM PST.

Additional data include:

**Note:** All times listed are in Pacific Standard Time

### Multiple Myeloma

- **Quality-of-life Outcomes in Patients With Relapsed/Refractory Multiple Myeloma Treated With Elotuzumab Plus Pomalidomide and Dexamethasone: Results from the Phase 2 Randomized ELOQUEST-3 Study**  
  Author: Weisel  
  Abstract: #2288  
  Poster Session: 903. Outcomes Research—Non-Malignant Hematology: Poster I  
  Saturday, December 1, 6:15-8:15 PM, Hall GH

- **Elotuzumab plus Pomalidomide/Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma: Japanese Subanalysis of the Randomized Phase 2 ELOQUEST-3 Study**  
  Author: Hori  
  Abstract: #3260  
  Poster Session: 653. Myeloma: Therapy, excluding Transplantation: Poster II  
  Sunday, December 2, 6-8 PM, Hall GH

- **Treatment Sequencing in Patients With Relapsed/Refractory Multiple Myeloma After Daratumumab Treatment: Real-World Findings From a Pooled Data Analysis of PREAMBLE and the McKesson Electronic Medical Record Database**  
  Author: Vii  
  Abstract: #3284  
  Poster Session: 653. Myeloma: Therapy, excluding Transplantation: Poster II  
  Sunday, December 2, 6-8 PM, Hall GH

- **Survival in Patients With Relapsed/Refractory Multiple Myeloma: Outcomes After 4 Years of the Ongoing Multinational Observational PREAMBLE Study**  
  Author: Cook  
  Abstract: #3285  
  Poster Discussion Session: 653. Myeloma: Therapy, excluding Transplantation: Poster II  
  Sunday, December 2, 6-8 PM, Hall GH

### Classical Hodgkin and Non-Hodgkin Lymphoma

- **Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Classic Hodgkin Lymphoma: Part 3 (Concurrent Dosing) Results and Updated Progression-Free Survival Results for Parts 1 and 2 (Staggered Dosing)**  
  Author: Advani  
  Abstract: #1635  
  Poster Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Poster I  
  Saturday, December 1, 6:15-8:15 PM, Hall GH

- **Nivolumab Treatment Beyond Investigator-Assessed Progression: Extended Follow-Up in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma From the Phase 2 CheckMate 205 Study**  
  Author: Cohen  
  Abstract: #2932  
  Poster Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Poster II  
  Sunday, December 2, 6-8 PM, Hall GH

- **Nivolumab for Relapsed or Refractory Classical Hodgkin Lymphoma (cHL) After Autologous Hematopoietic Cell Transplantation (auto-HCT): Extended Follow-Up of the Phase 2 Single-Arm CheckMate 205 Study**  
  Author: Armand  
  Abstract: #2897  
  Poster Session: 624. Hodgkin Lymphoma and T/NK Cell Lymphoma—Clinical Studies: Poster II  
  Sunday, December 2, 6-8 PM, Hall GH

### Leukemia

- **Dosing Patterns of Dasatinib Use in SIMPLICITY, an Observational Study in Chronic Phase Chronic Myeloid Leukemia (CP-CML) Patients (pts) in Routine Clinical Practice**  
  Author: Cortes  
  Abstract: #1730  
  Poster Session: 632. Chronic Myeloid Leukemia: Therapy: Poster I  
  Saturday, December 1, 6:15-8:15 PM, Hall GH
• The Impact of Chronic Myeloid Leukemia Therapy Management on the Oncology Care Model
  Author: Jabbour
  Abstract: #2265
  Poster Discussion Session: 902. Health Services Research—Malignant Diseases: Poster I
  Saturday, December 1, 6:15-8:15 PM, Hall GH

• Realized and Projected Cost Savings from the Introduction of Generic Imatinib, with Minimal
  Additional Savings to Payers Through Formulary Management
  Author: Bloudek
  Abstract: #3533
  Poster Session: 902. Health Services Research—Malignant Diseases: Poster II
  Sunday, December 2, 6-8 PM, Hall GH

• Dasatinib Versus Imatinib in Patients (Pts) With Chronic Myeloid Leukemia in Chronic Phase (CML-CP)
  Who Have Not Achieved an Optimal Response to 3 Months of Imatinib Therapy: DASCERN
  Author: Cortes
  Abstract: #788
  Monday, December 3, 2:45-4:15 PM, Room 6E

• Updated 18 Month Results from DASFREE: A Study Evaluating Dasatinib Discontinuation in Patients
  (Pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) and Deep Molecular Response
  (DMR)
  Author: Shah
  Abstract: #4253
  Poster Session: 632. Chronic Myeloid Leukemia: Therapy: Poster III
  Monday, December 3, 6-8 PM, Hall GH

• Cardiovascular Hospitalization in Patients Treated with Dasatinib or Nilotinib in SIMPLICITY, an
  Observational Study of Chronic-Phase Chronic Myeloid Leukemia (CP-CML) Patients in Routine Clinical Practice
  Author: Mauro
  Abstract: #4258
  Poster Session: 632. Chronic Myeloid Leukemia: Therapy: Poster III
  Monday, December 3, 6-8 PM, Hall GH

• Prevalence of Comorbidities Relevant to the Choice of Second-Generation (2-G) Tyrosine Kinase
  Inhibitor (TKI) for the Treatment of Chronic Myeloid Leukemia (CML) in the United States Using
  Real-World Claims Databases
  Author: Jabbour
  Abstract: #4265
  Poster Session: 632. Chronic Myeloid Leukemia: Therapy: Poster III
  Monday, December 3, 6-8 PM, Hall GH

Bristol-Myers Squibb: Advancing Oncology Research

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision is to increase quality, long-term survival for patients with cancer. 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 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 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 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 BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

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

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

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

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

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

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

**IMPORTANT SAFETY INFORMATION**

**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 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. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients.

**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 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 Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients.
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 monotherapy, adrenal insufficiency occurred in 1% (20/1994) 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 monotherapy, diabetes occurred in 0.9% (17/1994) of patients.

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.

Immune-Mediated Skin Adverse Reactions

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.

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.

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, 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% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloblastic 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 inhibitor.
immune-mediated adverse reactions were rash (16%), diarrhea/colitis (37% vs 55%), rash (26%), cough (23%), and decreased appetite. 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 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 pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 017, 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 effusion, and dehydration. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥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, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in ≥2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

Serious Adverse Reactions

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 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 effusion, and dehydration. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥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, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in ≥2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia. In Checkmate 238, Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥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 reaction (≥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 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 032, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=245) were fatigue (45%), decreased appetite (27%), musculoskeletal pain (25%), dyspnea (22%), nausea (22%), diarrhea (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%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%), and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough and dyspnea at a higher incidence than investigator’s choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 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 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/collitis (6%), and hepatitis (3%).
**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.

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

**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 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.

EMPLICITI is available for injection for intravenous use in 300 mg and 400 mg vials.

**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 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.
- 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). Fatal 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). Fatal 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 (31%, 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® first received FDA approval 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® also received FDA approval for adults with Ph+ acute lymphoblastic leukemia (ALL) who are resistant or intolerant to prior therapy. Sprycel® is approved and marketed for these indications in more than 60 countries.

Sprycel® is also an FDA-approved treatment for adults with newly diagnosed Ph+ CML-CP and is approved for this indication in more than 50 countries.

Both the FDA and the European Commission approved the expansion of Sprycel®'s indication to include pediatric patients with Ph+ CML-CP in November 2017 and July 2018.

U.S. FDA-APPROVED INDICATIONS FOR SPRYCEL

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

- Ph+ CML in chronic phase

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
- Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose
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 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
Discontinuation were reported in 1094 (5.2%) SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, 1618 adult patients with chronic phase CML, and 97 pediatric patients with chronic phase CML. In the overall population of 2712 adult SPRYCEL-treated patients, 88% of patients experienced adverse reactions leading to treatment discontinuation. 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 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 SPRYCEL-treated patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation. Among the 1618 adult SPRYCEL-treated 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 SPRYCEL-treated patients with advanced phase CML or Ph+ ALL, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

**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.

**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**

- **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 dose reduction.
  - Grapefruit juice may increase plasma concentrations of SPRYCEL and should be avoided.

- **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 reduce 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.

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 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 a total of 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).

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 SPRYCEL-treated patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation.

Among the 1618 adult SPRYCEL-treated 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 SPRYCEL-treated 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 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, dyspnea, 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%)
  - 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
    - In the pediatric studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults
  - Most common adverse reactions (≥15%) in patients included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain

Please see full Prescribing Information here.

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” as that term is defined in 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 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. These risks, uncertainties and other factors include, among others, that products mentioned in this release may not receive regulatory approval for the indication described in this release. 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, 2017, as updated by our subsequent Quarterly Reports on Form 10-Q and Current Reports on Form 8-K. 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 any forward-looking statement, whether as a result of new information, future events or otherwise.

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