Pfizer Showcases Latest Progress Against Cancer at ESMO 2017

Pfizer Oncology will present data from 21 accepted Pfizer-sponsored abstracts, including one late-breaking abstract, at the European Society for Medical Oncology (ESMO) Congress being held from September 8-12, 2017, in Madrid. These data reinforce the company’s commitment to innovation in oncology and improving the outlook for people living with cancer.

At the Congress, Pfizer will share new data from 13 of our marketed therapies and investigational compounds across multiple solid and hematologic cancers and mechanisms of action. Nearly half of these presentations highlight the potential of our immuno-oncology (IO) portfolio and IO combinations, an area we believe is pivotal to the future of cancer treatment.

“Our pace of innovation continues to accelerate. We now have 17 assets in clinical development, with a goal of speeding new therapies to patients and expanding our scientific advancements to help even more people living with cancer,” said Charles Hugh-Jones, MD, FRCP, chief medical officer at Pfizer Oncology. “With a significant investment in oncology research and development that spans new mechanisms, more pathways and novel combinations, Pfizer is relentlessly pursuing approaches that will have a meaningful impact for patients.”

Key Pfizer data at the meeting include:

- An oral late-breaking abstract on final overall survival data from the PROFILE 1014 study of XALKORI® (crizotinib), highlighting the impact that biomarker driven therapies have had on patients with lung cancer.

- First-ever clinical data from a Phase 1 dose escalation study of the investigational monoclonal antibody agonists anti-OX40 and anti-4-1BB (utomilumab) in patients with solid tumors, showcasing the potential promise of novel IO combinations.

- Subgroup analyses from the PALOMA-2 trial examining neutropenia patterns and the impact of prior (neo)adjuvant endocrine therapy and/or chemotherapy on the efficacy and safety of IBRANCE® (palbociclib) plus letrozole, both in first-line ER+/HER2– advanced breast cancer. These analyses contribute to the already robust body of efficacy and safety data supporting the use of IBRANCE, the first approved CDK 4/6 inhibitor, in HR+/HER2- metastatic breast cancer.

A full listing of Pfizer’s accepted abstracts is below. Abstracts will be available on the ESMO website on August 30, 2017 at 6:05 p.m. ET/ August 31 at 0:05 a.m. CEST. Late-breaking abstracts and abstracts selected for the Press Programme will be made public at 6:05 p.m. ET/0:05 CEST on the day of the official Congress session during which they are presented.
Pfizer Abstracts

Marketed Products

• **BAVENCIO® (avelumab)**
  o Abstract #856P: Avelumab Treatment of Metastatic Urothelial Carcinoma (Muc) in the Phase 1b JAVELIN Solid Tumor Study: Updated Analysis With ≥6 Months of Follow-Up in All Patients. *Apolo AB et al*
  o Abstract #882P: Potential Impact of Avelumab+Axitinib (A+Ax) on Tumor Size (TS) Compared With Historical Data of Sunitinib (S) as Evaluated by a Modeling and Simulation (MS) Approach. *Zheng J et al*
  o Abstract #913P: Avelumab in Patients With Metastatic Adrenocortical Carcinoma (mACC): Results From the JAVELIN Solid Tumor Trial. *Le Tourneau C et al*
  o Abstract #1227P: Avelumab Treatment in Chemotherapy-naïve Patients With Distant Metastatic Merkel Cell Carcinoma (mMCC). *D’Angelo SP et al*
  o Abstract #1377TiP: JAVELIN Lung 100: Updated Design of a Phase 3 Trial of Avelumab vs Platinum Doublet Chemotherapy as First-Line (1L) Treatment for Metastatic or Recurrent PD-L1+ Non-Small Cell Lung Cancer (NSCLC). *Reck M et al*

• **BESPONSA® (inotuzumab ozogamicin)**
  o Abstract #1033P: Quantitative Assessment of Inotuzumab Ozogamicin (InO) Response Relative to Investigator’s Choice of Chemotherapy (ICC) in Adults With Relapsed or Refractory (R/R) CD22+ B-Cell Acute Lymphoblastic Leukemia (ALL). *Ana G. et al*

• **IBRANCE® (palbociclib)**

• **SUTENT® (sunitinib)**
  o Abstract #855PD: Adjuvant Sunitinib (SU) in Patients (pts) With High Risk Renal Cell Carcinoma (RCC): Safety and Therapy Management in S-TRAC Trial. *Staehler M et al*

• **XALKORI® (crizotinib)**
  o Abstract #LBA50: Overall Survival (OS) for First-Line Crizotinib Versus Chemotherapy in ALK+ Lung Cancer: Updated Results From PROFILE 1014. *Mok TS et al*

• **XTANDI® (enzalutamide)**
  o Abstract #787PD: Prognostic Associations of Prostate-Specific Antigen (PSA) Decline With Survival, Radiographic Response and Progression in Chemotherapy-Naïve Men With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Treated With Enzalutamide. *Armstrong A et al*
Investigational Compounds

- **Lorlatinib**
  - Abstract #1308PD: Preliminary Efficacy and Safety of Lorlatinib in Patients (Pts) With ROS1-Positive Non-Small Cell Lung Cancer (NSCLC). Besse B et al
  - Abstract #1343P: Efficacy and Safety of Lorlatinib in Patients (pts) With ALK-Non-Small Cell Lung Cancer (NSCLC) Previously Treated With 2nd-Generation ALK TKIs. Felip E et al
  - Abstract #1380TiP: A Randomized, Open-Label Comparison of Lorlatinib Versus Crizotinib as First-Line Treatment for Advanced Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC). Shaw A et al

- **Utomilumab (PF-05082566, 4-1BB agonistic mAb) and PF-04518600 (OX40 mAb)**
  - Abstract #1142PD: Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) Data From a Phase I Dose-Escalation Study of OX40 Agonistic Monoclonal Antibody (mAb) PF-04518600 (PF-8600) in Combination With Utomilumab, a 4-1BB Agonistic mAb. Hamid O et al

- **PF-06747775 (EGFR tyrosine kinase inhibitor)**
  - Abstract #1358P: First-in-Human Phase I Study of PF-06747775, a Third Generation Mutant Selective EGFR Tyrosine Kinase Inhibitor (TKI) in Metastatic EGFR Mutant NSCLC After Progression on a First-Line EGFR TKI. Husain H et al

- **PF-06801591 (anti-PD-1 antibody)**
  - Abstract #1183P: Safety, Efficacy, Pharmacokinetics (PK) and Pharmacodynamics (PD) of PF 06801591, an Anti-PD1 Antibody Administered Intravenously (IV) or Subcutaneously (SC). Johnson M et al

- **PF-04136309 (CCR2 inhibitor)**
  - Abstract #750P: Phase Ib Study of PF-04136309 (an Oral CCR2 Inhibitor) in Combination With Nab-Paclitaxel/Gemcitabine in First-Line Treatment of Metastatic Pancreatic Adenocarcinoma. Noel M et al

Biosimilars

- Abstract #154PD: A Randomized, Double-Blind Study of PF-05280014 (a Potential Biosimilar) Vs Trastuzumab, Both Given With Docetaxel (D) and Carboplatin (C), as Neoadjuvant Treatment for Operable Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Breast Cancer. Lammers PE et al
  - Abstract #238PD: A Randomized, Double-Blind Study of PF-05280014 (a Potential Trastuzumab Biosimilar) Vs Trastuzumab, Both in Combination With Paclitaxel, as First-Line Treatment for HER2-Positive Metastatic Breast Cancer. Pegram M et al

**About BESPONSA® (inotuzumab ozogamicin)**

BESPONSA is an antibody-drug conjugate (ADC) composed of a monoclonal antibody (mAb) targeting CD22, a cell surface antigen expressed on cancer cells in almost all B-ALL patients, linked to a cytotoxic agent. When BESPONSA binds to the CD22 antigen on B-cells, it is internalized into the cell, where the cytotoxic agent calicheamicin is released causing cell death. BESPONSA is administered as a one-hour intravenous infusion that can be given in the outpatient setting of care for appropriate patients.

BESPONSA originates from a collaboration between Pfizer and Celltech, now UCB. Under the terms of this agreement, Pfizer has sole responsibility for all commercialization, manufacturing
and clinical development activities for this molecule. Pfizer also collaborated with SFJ Pharmaceuticals Group on the registrational program (INO-VATE ALL) for BESPONSA.

**BESPONSA® (Inotuzumab Ozogamicin) Indication**

BESPONSA is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

**Important Safety Information for BESPONSA® (Inotuzumab Ozogamicin)**

**WARNING: HEPATOTOXICITY, INCLUDING HEPATIC VENO-OCCLUSIVE DISEASE (VOD) (ALSO KNOWN AS SINUSOIDAL OBSTRUCTION SYNDROME) and INCREASED RISK OF POST–HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) NON-RELAPSE MORTALITY (NRM):**

- Hepatotoxicity, including fatal and life-threatening VOD, occurred in patients who received BESPONSA. The risk of VOD was greater in patients who underwent HSCT after BESPONSA treatment. Consider identified risk factors. Monitor closely for signs and symptoms of VOD
- There was a higher post-HSCT non-relapse mortality rate in patients receiving BESPONSA, resulting in a higher Day 100 post-HSCT mortality rate

**Hepatotoxicity, Including VOD:** Hepatotoxicity, including fatal and life-threatening VOD, occurred in patients who received BESPONSA. The risk of VOD was greater in patients who underwent HSCT after BESPONSA treatment. The use of HSCT conditioning regimens containing 2 alkylating agents and last total bilirubin ≥ the upper limit of normal (ULN) before HSCT were significantly associated with an increased risk of VOD. Other risk factors for VOD in patients treated with BESPONSA included ongoing or prior liver disease, prior HSCT, increased age, later salvage lines, and a greater number of BESPONSA treatment cycles. Grade 3/4 increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin have occurred.

Monitor closely for signs and symptoms of VOD; these may include elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites. Elevation of liver tests may require dosing interruption, dose reduction, or permanent discontinuation of BESPONSA. Permanently discontinue treatment if VOD occurs. If severe VOD occurs, treat according to standard medical practice.

**Increased Risk of Post-HSCT Non-Relapse Mortality:** There was a higher post-HSCT non-relapse mortality rate in patients receiving BESPONSA, resulting in a higher Day 100 post-HSCT mortality rate. In the BESPONSA arm, the most common causes of post-HSCT non-relapse mortality included VOD and infections. Monitor closely for toxicities post HSCT, including signs and symptoms of infection and VOD.

**Myelosuppression:** Myelosuppression, and severe, life-threatening and fatal complications of myelosuppression, including hemorrhagic events and infections, have occurred with BESPONSA. Thrombocytopenia, neutropenia, and febrile neutropenia were reported.

Monitor complete blood counts prior to each dose of BESPONSA and monitor for signs and symptoms of infection, bleeding/hemorrhage, or other effects of myelosuppression during treatment and provide appropriate management. As appropriate, administer prophylactic anti
infectives during and after treatment with BESPONSA. Dose interruption, dose reduction, or permanent discontinuation may be required.

**Infusion-Related Reactions:** Infusion-related reactions have occurred in patients who received BESPONSA. Premedicate with a corticosteroid, antipyretic, and antihistamine prior to dosing. Monitor patients closely during and for at least 1 hour after the end of the infusion for the potential onset of infusion-related reactions. Interrupt the infusion and institute appropriate medical management if an infusion-related reaction occurs. For severe or life-threatening infusion reactions, permanently discontinue BESPONSA.

**QT Interval Prolongation:** Increases in QT interval have occurred. Administer BESPONSA with caution in patients who have a history of or predisposition to QTc prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances. Obtain electrocardiograms and electrolytes prior to treatment and after initiation of any drug known to prolong QTc, and periodically monitor as clinically indicated during treatment.

**Embryo-Fetal Toxicity and Nursing Mothers:** BESPONSA can cause embryo-fetal harm. Advise males and females of reproductive potential to use effective contraception during BESPONSA treatment and for at least 5 and 8 months after the last dose, respectively. Advise women against breastfeeding while receiving BESPONSA and for 2 months after the last dose.

**Adverse Reactions:** The most common (≥20%) adverse reactions observed with BESPONSA were thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinemia.

The most common (≥2%) serious adverse reactions were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, VOD, and fatigue.

Please see full [Prescribing Information](#) including BOXED WARNING for BESPONSA.

**About BAVENCIO® (Avelumab)**
Avelumab is a human antibody specific for a protein called PD-L1, or programmed death ligand-1. Avelumab is designed to potentially engage both the adaptive and innate immune systems. By binding to PD-L1, avelumab is thought to prevent tumor cells from using PD-L1 for protection against white blood cells, such as T-cells, exposing them to anti-tumor responses. Avelumab has been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro. In November 2014, Merck KGaA, Darmstadt, Germany, and Pfizer announced a strategic alliance to co-develop and co-commercialize avelumab.

**BAVENCIO® (Avelumab) Indications**
BAVENCIO is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) 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.
These indications are approved under accelerated approval based on tumor response and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

**IMPORTANT SAFETY INFORMATION FOR BAVENCIO® (AVELUMAB)**

BAVENCIO can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients, including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause immune-mediated hepatitis, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis was reported in 0.9% (16/1738) of patients, including two (0.1%) patients with Grade 5 and 11 (0.6%) with Grade 3.

BAVENCIO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO until resolution for moderate or severe (Grade 2 or 3) colitis and permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon re-initiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including seven (0.4%) with Grade 3.

BAVENCIO can cause immune-mediated endocrinopathies, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% (8/1738) of patients, including one (0.1%) with Grade 3.

**Thyroid disorders** can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders including hypothyroidism, hyperthyroidism, and thyroiditis were reported in 6% (98/1738) of patients, including three (0.2%) with Grade 3.

**Type 1 diabetes mellitus** including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients, including two cases of Grade 3 hyperglycemia.
BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% (1/1738) of patients.

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO: myocarditis with fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent doses based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% (439/1738) of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

The most common adverse reactions (all grades, ≥ 20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (50%), musculoskeletal pain (32%), diarrhea (23%), nausea (22%), infusion-related reaction (22%), rash (22%), decreased appetite (20%), and peripheral edema (20%).

**Selected treatment-emergent laboratory abnormalities** (all grades, ≥ 20%) in patients with metastatic MCC were lymphopenia (49%), anemia (35%), increased aspartate aminotransferase (34%), thrombocytopenia (27%), and increased alanine aminotransferase (20%).
The most common adverse reactions (all grades, ≥ 20%) in patients with locally advanced or metastatic urothelial cancer (UC) were fatigue (41%), infusion-related reaction (30%), musculoskeletal pain (25%), nausea (24%), decreased appetite/hypophagia (21%) and urinary tract infection (21%).

Selected laboratory abnormalities (grades 3-4, ≥ 3%) in patients with locally advanced or metastatic UC were hyponatremia (16%), gamma-glutamyltransferase increased (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

Please see full Prescribing Information for BAVENCIO.

About IBRANCE® (palbociclib) 125 mg capsules
IBRANCE is an oral inhibitor of CDKs 4 and 6, which are key regulators of the cell cycle that trigger cellular progression. In the U.S., IBRANCE is indicated for the treatment of HR+, HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women, or fulvestrant in women with disease progression following endocrine therapy. Including the U.S., IBRANCE is approved in more than 65 countries.

Important IBRANCE (palbociclib) Safety Information from the US Prescribing Information

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Based on the mechanism of action, IBRANCE can cause fetal harm. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may impair fertility in males and has the potential to cause genotoxicity. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women not to breastfeed during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

The most common adverse reactions (≥10%) of any grade reported in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).
The most frequently reported Grade ≥3 adverse reactions (≥5%) in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

Lab abnormalities of any grade occurring in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

The most common adverse reactions (≥10%) reported in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

The most frequently reported Grade ≥3 adverse reactions (≥5%) in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 1%) and leukopenia (31% vs 2%).

Lab abnormalities of any grade occurring in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 40%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (43% vs 48%), and increased alanine aminotransferase (36% vs 34%).

Avoid concurrent use of strong CYP3A inhibitors. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg/day. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of strong CYP3A inducers. The dose of sensitive CYP3A substrates with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

IBRANCE has not been studied in patients with moderate to severe hepatic impairment or in patients with severe renal impairment (CrCl <30 mL/min).

Please see full Prescribing Information for IBRANCE.
About SUTENT® (sunitinib malate)
SUTENT is an oral multi-kinase inhibitor that works by blocking multiple molecular targets implicated in the growth, proliferation and spread of cancer. Two important SUTENT targets, vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are expressed by many types of solid tumors and are thought to play a crucial role in angiogenesis, the process by which tumors acquire blood vessels, oxygen and nutrients needed for growth. SUTENT also inhibits other targets important to tumor growth, including KIT, FLT3 and RET.

SUTENT® (sunitinib malate) Indication
SUTENT® (sunitinib malate) is indicated for the treatment of advanced renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate, and progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

SUTENT Important Safety Information

Boxed Warning/Hepatotoxicity: Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Pregnancy: Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Nursing mothers: Given the potential for serious adverse reactions (ARs) in nursing infants, a decision should be made whether to discontinue nursing or SUTENT.

Cardiovascular events: Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

QT interval prolongation and Torsades de Pointes: SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsades de Pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension: Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.
**Reversible posterior leukoencephalopathy syndrome (RPLS):** There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of RPLS.

**Hemorrhagic events:** Hemorrhagic events, including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations.

**Tumor lysis syndrome (TLS):** Cases of TLS have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated.

**Thrombotic microangiopathy (TMA):** TMA, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

**Proteinuria:** Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions.

**Dermatologic toxicities:** Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started. Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

**Thyroid dysfunction:** Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice.

**Hypoglycemia:** SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of SUTENT. Assess whether antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

**Osteonecrosis of the jaw (ONJ):** ONJ has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates.

**Wound healing:** Cases of impaired wound healing have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.

**Adrenal function:** Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.
Laboratory tests: CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

CYP3A4 coadministration: Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort.

Most common ARs & most common grade 3/4 ARs (advanced RCC): The most common ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%). The most common grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

Most common grade 3/4 lab abnormalities (advanced RCC): The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) included lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).

Most common ARs & most common grade 3/4 ARs (imatinib-resistant or -intolerant GIST): The most common ARs occurring in ≥20% of patients with GIST and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (40% vs 27%), anorexia (33% vs 29%), skin discoloration (30% vs 23%), mucositis/stomatitis (29% vs 18%), asthenia (22% vs 11%), altered taste (21% vs 12%), and constipation (20% vs 14%). The most common grade 3/4 ARs (occurring in ≥4% of patients with GIST receiving SUTENT vs placebo) were asthenia (5% vs 3%), hand-foot syndrome (4% vs 3%), diarrhea (4% vs 0%), and hypertension (4% vs 0%).

Most common grade 3/4 lab abnormalities (imatinib-resistant or -intolerant GIST): The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with GIST receiving SUTENT vs placebo) included lipase (10% vs 7%), neutrophils (10% vs 0%), amylase (5% vs 3%), and platelets (5% vs 0%).

Most common ARs & most common grade 3/4 ARs (advanced pNET): The most common ARs occurring in ≥20% of patients with advanced pNET and more commonly with SUTENT than placebo (all grades, vs placebo) were diarrhea (59% vs 39%), stomatitis/oral syndromes (48% vs 18%), nausea (45% vs 29%), abdominal pain (39% vs 34%), vomiting (34% vs 31%), asthenia (34% vs 27%), fatigue (33% vs 27%), hair color changes (29% vs 1%), hypertension (27% vs 5%), hand-foot syndrome (23% vs 2%), bleeding events (22% vs 10%), and epistaxis (21%...
vs 5%), and dysgeusia (21% vs 5%). The most commonly reported grade 3/4 ARs (occurring in ≥5% of patients with advanced pNET receiving SUTENT vs placebo) were hypertension (10% vs 1%), hand-foot syndrome (6% vs 0%), stomatitis/oral syndromes (6% vs 0%), abdominal pain (5% vs 10%), fatigue (5% vs 9%), asthenia (5% vs 4%), and diarrhea (5% vs 2%).

**Most common grade 3/4 lab abnormalities (advanced pNET):** The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with advanced pNET receiving SUTENT vs placebo) included decreased neutrophils (16% vs 0%), increased glucose (12% vs 18%), increased alkaline phosphatase (10% vs 11%), decreased phosphorus (7% vs 5%), decreased lymphocytes (7% vs 4%), increased creatinine (5% vs 5%), increased lipase (5% vs 4%), increased AST (5% vs 3%), and decreased platelets (5% vs 0%).

Please see full [Prescribing Information](#) including BOXED WARNING for SUTENT.

**About XALKORI® (crizotinib)**

XALKORI is a tyrosine kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive or ROS1-positive as detected by an FDA-approved test. XALKORI has received approval for patients with ALK-positive NSCLC in more than 90 countries, including Australia, Canada, China, Japan, South Korea and the European Union.

**XALKORI® Important Safety Information**

**Hepatotoxicity:** Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1719). Transaminase elevations generally occurred within the first 2 months. Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop transaminase elevations. Permanently discontinue for ALT/AST elevation >3 times ULN with concurrent total bilirubin elevation >1.5 times ULN (in the absence of cholestasis or hemolysis); otherwise, temporarily suspend and dose-reduce XALKORI as indicated.

**Interstitial Lung Disease (Pneumonitis):** Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur. Across clinical trials (n=1719), 2.9% of XALKORI-treated patients had any grade ILD, 1.0% had Grade 3/4, and 0.5% had fatal ILD. ILD generally occurred within 3 months after initiation of treatment. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes and permanently discontinue XALKORI in patients with drug-related ILD/pneumonitis.

**QT Interval Prolongation:** QTc prolongation can occur. Across clinical trials (n=1616), 2.1% of patients had QTcF (corrected QT by the Fridericia method) 500 ms and 5.0% had an increase from baseline QTcF 60 ms by automated machine-read evaluation of ECGs. Avoid use in patients with congenital long QT syndrome. Monitor ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that prolong the QT interval. Permanently discontinue XALKORI in patients who develop QTc >500 ms or 60 ms change from baseline with Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia. Withhold XALKORI in patients who develop QTc >500 ms on at least 2 separate ECGs until recovery to a QTc -480 ms, then resume at a reduced dose.
**Bradycardia:** Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 12.7% of patients treated with XALKORI (n=1719). Avoid use in combination with other agents known to cause bradycardia. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm, re-evaluate the use of concomitant medications, and adjust the dose of XALKORI. Permanently discontinue for life-threatening bradycardia due to XALKORI; however, if associated with concomitant medications known to cause bradycardia or hypotension, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm. If concomitant medications can be adjusted or discontinued, restart XALKORI at 250 mg once daily with frequent monitoring.

**Severe Visual Loss:** Across clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (n=1719). Discontinue XALKORI in patients with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation. There is insufficient information to characterize the risks of resumption of XALKORI in patients with a severe visual loss; a decision to resume should consider the potential benefits to the patient.

**Vision Disorders:** Most commonly visual impairment, photopsia, blurred vision or vitreous floaters, occurred in 63.1% of 1719 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. 0.8% of patients had Grade 3 and 0.2% had Grade 4 visual impairment. The majority of patients on the XALKORI arms in Studies 1 and 2 (>50%) reported visual disturbances which occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact on daily activities.

**Embryo-Fetal Toxicity:** XALKORI can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to the fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 45 days (females) or 90 days (males) respectively, following the final dose of XALKORI.

**ROS1-positive Metastatic NSCLC:** Safety was evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study, and was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC. Vision disorders occurred in 92% of patients in the ROS1 study; 90% of patients had Grade 1 vision disorders and 2% had Grade 2.

**Adverse Reactions:** Safety was evaluated in a phase 3 study in previously untreated patients with ALK-positive metastatic NSCLC randomized to XALKORI (n=171) or chemotherapy (n=169). Serious adverse events were reported in 34% of patients treated with XALKORI, the most frequent were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% of patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis. Common adverse reactions (all grades) occurring in ≥25% and more commonly (≥5%) in patients treated with XALKORI vs chemotherapy were vision disorder (71% vs 10%), diarrhea (61% vs 13%), edema (49% vs 12%), vomiting (46% vs 36%), constipation (43% vs 30%), upper respiratory infection (32% vs 12%), dysgeusia (26% vs 5%), and abdominal pain (26% vs 12%). Grade 3/4 reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were QT prolongation (2% vs 0%), esophagitis (2% vs 0%), and constipation (2% vs 0%). In patients treated with XALKORI vs chemotherapy, the
following occurred: elevation of ALT (any grade [79% vs 33%] or Grade 3/4 [15% vs 2%]); elevation of AST (any grade [66% vs 28%] or Grade 3/4 [8% vs 1%]); neutropenia (any grade [52% vs 59%] or Grade 3/4 [11% vs 16%]); lymphopenia (any grade [48% vs 53%] or Grade 3/4 [7% vs 13%]); hypophosphatemia (any grade [32% vs 21%] or Grade 3/4 [10% vs 6%]). In patients treated with XALKORI vs chemotherapy, renal cysts occurred (5% vs 1%). Nausea (56%), decreased appetite (30%), fatigue (29%), and neuropathy (21%) also occurred in patients taking XALKORI.

**Drug Interactions:** Exercise caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of crizotinib. Avoid concomitant use of strong CYP3A inducers and inhibitors. Avoid concomitant use of CYP3A substrates with narrow therapeutic range in patients taking XALKORI. If concomitant use of CYP3A substrates with narrow therapeutic range is required in patients taking XALKORI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

**Lactation:** Because of the potential for adverse reactions in breastfed infants, advise females not to breastfeed during treatment with XALKORI and for 45 days after the final dose.

**Hepatic Impairment:** XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Use caution in patients with hepatic impairment.

**Renal Impairment:** Decreases in estimated glomerular filtration rate occurred in patients treated with XALKORI. Administer XALKORI at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis. No starting dose adjustment is needed for patients with mild and moderate renal impairment.

Please see full Prescribing Information for XALKORI.

For more information about XALKORI, please visit www.XALKORI.com.

**About XTANDI® (enzalutamide) capsules**
XTANDI (enzalutamide) is an androgen receptor inhibitor that blocks multiple steps in the androgen receptor signaling pathway within the tumor cell. In preclinical studies, enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors, and inhibit androgen receptor nuclear translocation and interaction with DNA. The clinical significance of this mechanism of action (MOA) is unknown.

**XTANDI® (enzalutamide) Indication**
XTANDI® (enzalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

**XTANDI® (enzalutamide) Important Safety Information**

**Contraindications**
XTANDI is not indicated for women. XTANDI can cause fetal harm and potential loss of pregnancy.

**Warnings and Precautions**
Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients
with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)** In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

**Adverse Reactions**
The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI patients from the two placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. In the bicalutamide-controlled study of chemotherapy-naive patients, the most common adverse reactions (≥ 10%) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, upper respiratory tract infection, diarrhea, and weight loss.

In the placebo-controlled study of patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naive patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the bicalutamide-controlled study of chemotherapy-naive patients, Grade 3-4 adverse reactions were reported in 38.8% of XTANDI patients and 37.6% of bicalutamide patients. Discontinuations due to adverse events were reported for 7.6% of XTANDI patients and 6.3% of bicalutamide patients.

Lab Abnormalities: In the two placebo-controlled trials, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

Infections: In the study of patients taking XTANDI who previously received docetaxel, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In the study of chemotherapy-naive patients, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls (including fall-related injuries) occurred in 9% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.
Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

**Drug Interactions**

**Effect of Other Drugs on XTANDI** Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

**Effect of XTANDI on Other Drugs** Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see full Prescribing Information for XTANDI.

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