Pfizer Logo

BAVENCIO® (avelumab) Receives Positive CHMP Opinion for First-Line Maintenance Treatment of Locally Advanced or Metastatic Urothelial Carcinoma

Friday, December 11, 2020 - 07:40am

Not intended for UK-based media

Rockland, MA and New York, US, December 11, 2020 – EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending approval of BAVENCIO® (avelumab) as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy. The CHMP positive opinion will now be reviewed by the European Commission (EC), with a decision expected in early 2021.

The opinion was based on positive findings from the Phase III JAVELIN Bladder 100 trial, results of which were published in *The New England Journal of Medicine* in September.[1] BAVENCIO is the only immunotherapy to significantly prolong overall survival (OS) in locally advanced or metastatic UC in the first-line setting in a Phase III trial.

“Patients living with locally advanced or metastatic urothelial carcinoma in Europe are in urgent need of more treatment options that have the potential to extend their lives,” said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. “The overall survival results from JAVELIN Bladder 100 show the potential benefits of a first-line maintenance approach with BAVENCIO as a significant advancement for patients with locally advanced or metastatic urothelial carcinoma.”

Bladder cancer is the tenth most common cancer worldwide.[2] In Europe alone, nearly 200,000 people are diagnosed with bladder cancer each year and more than 60,000 patients die from the disease, despite available treatments.[3] UC, which accounts for about 90% of all bladder cancers, becomes harder to treat as it advances, spreading through the layers of the bladder wall.[4,5] For patients with advanced UC, the five-year survival rate is 5%.[6] About 4% of bladder cancers are diagnosed at an advanced stage.[7]

“BAVENCIO is the only immunotherapy treatment to demonstrate in the first-line setting the ability to help patients with locally advanced or metastatic urothelial carcinoma live longer,” said Danny Bar-Zohar, M.D., Global Head of Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. “Now with this positive opinion, we have come a big step closer to being able to offer a new option that may shift the treatment paradigm for patients in Europe.”

In June 2020, the US Food and Drug Administration (FDA) approved BAVENCIO for the maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy. Additional regulatory applications have been submitted in Japan and other countries.

JAVELIN Bladder 100 (NCT02603432) is a Phase III, multicenter, multinational, randomized, open-label, parallel-arm study investigating first-line maintenance treatment with BAVENCIO plus best supportive care (BSC) versus BSC alone in patients with locally advanced or metastatic UC. A total of 700 patients whose disease had not progressed after platinum-based induction chemotherapy as per RECIST v1.1 were randomly assigned to receive either BAVENCIO plus BSC or BSC alone. The primary endpoint was OS in the two primary populations of all patients and patients with PD-L1+ tumors.

About BAVENCIO® (avelumab)
BAVENCIO is a human anti-programmed death ligand-1 (PD-L1) antibody. BAVENCIO has been shown in preclinical models to engage both the adaptive and innate immune functions. By blocking the interaction of PD-L1 with PD-1 receptors, BAVENCIO has been shown to release the suppression of the T cell-mediated antitumor immune response in preclinical models.[8-10] In November 2014, Merck KGaA, Darmstadt, Germany and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indications
BAVENCIO® (avelumab) is indicated in the US for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy. BAVENCIO is also indicated for the treatment of patients with locally advanced or metastatic 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.

BAVENCIO in combination with axitinib is indicated in the US for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

In the US, the FDA granted accelerated approval for BAVENCIO for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

BAVENCIO is currently approved for patients in 50 countries for at least one use.

BAVENCIO Important Safety Information from the US FDA-Approved Label
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% of patients, including one (0.1%) patient with fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause **hepatotoxicity and 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 occurred with BAVENCIO as a single agent in 0.9% of patients, including two (0.1%) patients with fatal, and 11 (0.6%) with Grade 3.

BAVENCIO in combination with axitinib can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold BAVENCIO and axitinib for moderate (Grade 2) hepatotoxicity and permanently discontinue the combination for severe or life-threatening (Grade 3 or 4) hepatotoxicity. Administer corticosteroids as needed. In patients treated with BAVENCIO in combination with axitinib, Grades 3 and 4 increased ALT and AST occurred in 9% and 7% of patients, respectively, and immune-mediated hepatitis occurred in 7% of patients, including 4.9% with Grade 3 or 4.

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 until resolution. Permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon reinitiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% 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% 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 control 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% 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 antihyperglycemics 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% 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% 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 as a single agent

or in 489 patients who received *BAVENCIO in combination with axitinib*: myocarditis including fatal cases, pancreatitis including fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions. 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% of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO in combination with axitinib can cause **major adverse cardiovascular events (MACE)** including severe and fatal events. Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue BAVENCIO and axitinib for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with axitinib compared to 3.4% treated with sunitinib. These events included death due to cardiac events (1.4%), Grade 3-4 myocardial infarction (2.8%), and Grade 3-4 congestive heart failure (1.8%).

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.

A fatal adverse reaction (sepsis) occurred in one (0.3%) patient with locally advanced or metastatic urothelial carcinoma (UC) receiving BAVENCIO plus best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

The most common adverse reactions (all grades, ?20%) in patients with locally advanced or metastatic UC receiving BAVENCIO plus BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 13%), musculoskeletal pain (24% vs 15%), urinary tract infection (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving BAVENCIO, the most common adverse reactions (all grades, ?20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Selected laboratory abnormalities (all grades, ?20%) in patients with locally advanced or metastatic UC receiving BAVENCIO plus BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), blood potassium increased (24% vs 16%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

Fatal adverse reactions occurred in 1.8% of patients with advanced renal cell carcinoma (RCC) receiving BAVENCIO in combination with axitinib. These included sudden cardiac death (1.2%), stroke (0.2%),

myocarditis (0.2%), and necrotizing pancreatitis (0.2%).

The most common adverse reactions (all grades, ?20%) in patients with advanced RCC receiving BAVENCIO in combination with axitinib (vs sunitinib) were diarrhea (62% vs 48%), fatigue (53% vs 54%), hypertension (50% vs 36%), musculoskeletal pain (40% vs 33%), nausea (34% vs 39%), mucositis (34% vs 35%), palmar-plantar erythrodysesthesia (33% vs 34%), dysphonia (31% vs 3.2%), decreased appetite (26% vs 29%), hypothyroidism (25% vs 14%), rash (25% vs 16%), hepatotoxicity (24% vs 18%), cough (23% vs 19%), dyspnea (23% vs 16%), abdominal pain (22% vs 19%), and headache (21% vs 16%).

Selected laboratory abnormalities (all grades, ?20%) worsening from baseline in patients with advanced RCC receiving BAVENCIO in combination with axitinib (vs sunitinib) were blood triglycerides increased (71% vs 48%), blood creatinine increased (62% vs 68%), blood cholesterol increased (57% vs 22%), alanine aminotransferase increased (ALT) (50% vs 46%), aspartate aminotransferase increased (AST) (47% vs 57%), blood sodium decreased (38% vs 37%), lipase increased (37% vs 25%), blood potassium increased (35% vs 28%), platelet count decreased (27% vs 80%), blood bilirubin increased (21% vs 23%), and hemoglobin decreased (21% vs 65%).

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%).

Please see full US Prescribing Information and Medication Guide available at http://www.BAVENCIO.com.

About EMD Serono, Inc.
EMD Serono - the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada - is engaged in the discovery, research and development of medicines for patients with difficult to treat diseases. The business is committed to transforming lives by developing and delivering meaningful solutions that help address the therapeutic and support needs of individual patients. Building on a proven legacy and deep expertise in neurology, fertility and endocrinology, EMD Serono is developing potential new oncology and immuno-oncology medicines while continuing to explore potential therapeutic options for diseases such as psoriasis, lupus and MS. Today, the business has approximately 1,500 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com.

About Merck KGaA, Darmstadt, Germany-Pfizer Alliance
Immuno-oncology is a top priority for Merck KGaA, Darmstadt, Germany and Pfizer. The global strategic alliance between Merck KGaA, Darmstadt, Germany and Pfizer enables the companies to benefit from each other’s strengths and capabilities and further explore the therapeutic potential of BAVENCIO, an anti-PD-L1 antibody initially discovered and developed by Merck KGaA, Darmstadt, Germany. The immuno-oncology alliance is jointly developing and commercializing BAVENCIO. The alliance is focused on developing high-priority international clinical programs to investigate BAVENCIO as a monotherapy as well as combination regimens, and is striving to find new ways to treat cancer.

All Merck KGaA, Darmstadt, Germany, press releases are distributed by e-mail at the same time they become available on the EMD Group Website. In case you are a resident of the USA or Canada please go to www.emdgroup.com/subscribe to register again for your online subscription of this service as our newly introduced geo-targeting requires new links in the email. You may later change your selection or discontinue this

service

About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 57,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2019, Merck KGaA, Darmstadt, Germany, generated sales of € 16.2 billion in 66 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials. Since its founding in 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.

Pfizer Inc.: Breakthroughs that change patients' lives
At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Pfizer Disclosure Notice

The information contained in this release is as of December 11, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about BAVENCIO (avelumab), including a potential indication as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy in the EU for BAVENCIO, the alliance between Merck KGaA, Darmstadt, Germany and Pfizer involving BAVENCIO and clinical development plans, including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of BAVENCIO; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; risks associated with interim data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the

design of and results from our clinical studies; whether and when any drug applications may be filed for BAVENCIO for first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma in any additional jurisdictions or in any jurisdictions for any other potential indications for BAVENCIO or combination therapies; whether and when the EC may approve the application for BAVENCIO as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy and whether and when regulatory authorities in any jurisdictions where any other applications are pending or may be submitted for BAVENCIO or combination therapies, including BAVENCIO for locally advanced or metastatic urothelial carcinoma may approve any such applications, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy, and, if approved, whether they will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of BAVENCIO, including BAVENCIO for locally advanced or metastatic urothelial carcinoma; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2019, and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

References

1. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial cancer. *N Engl J Med*. 2020;383:1218-1230.
2. Bray F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal.* 2018;68(6):394-424.
3. Cancer Today. Estimated number of new cases in 2018, Europe, both sexes, all ages. https://gco.iarc.fr/today/online-analysis-tables. Accessed September 2020.
4. Cancer.net. Bladder cancer: introduction. https://www.cancer.net/cancer-types/bladder-cancer/introduction . Accessed August 2020.
5. American Cancer Society. What is bladder cancer? https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html. Accessed September 2020.
6. SEER. Cancer stat facts: bladder cancer. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed September 2020.
7. Cancer.net. Bladder cancer: statistics. https://www.cancer.net/cancer-types/bladder-cancer/statistics. Accessed September 2020.
8. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. *Cancer Control*. 2014;21(3):231-237.
9. Dahan R, Sega E, Engelhardt J, et al. Fc?Rs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell*. 2015;28(3):285-295.

10. Boyerinas B, Jochems C, Fantini M, et al. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (MSB0010718C) on human tumor cells. *Cancer Immunol Res.* 2015;3(10):1148-1157.

Your Contacts EMD Serono, Inc. Media Noelle Piscitelli +1 781 427 4351 Investor Relations +49 6151 72 3321 Pfizer Inc., New York, USA Media Dervila Keane (EU) +44 792 933 9560 Steve Danehy +353 86 2110834 +1 212 733 1538 Investor Relations Bryan Dunn +1 212 733 8917