Elizabeth Varki Jobes, Esq. Joins EMD Serono as Chief Compliance Officer North America

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ROCKLAND, Mass., Feb. 4, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the U.S. and Canada, today announced that Elizabeth Varki Jobes, Esq. joined the company as Senior Vice President, Chief Compliance Officer North America. In this role, Ms. Jobes will oversee the strategic direction of EMD Serono's comprehensive compliance program. She will serve as a member of EMD Serono's leadership team, as well as a member of the Global Compliance Healthcare team led by Betania Glorio, Global Compliance Officer, Healthcare, Merck KGaA, Darmstadt, Germany.

"It's an exciting time to be at EMD Serono as we prepare to introduce new therapies into practice and advance existing standards of care," said Rehan Verjee, President of EMD Serono and Global Head of Innovative Medicine Franchises, Merck KGaA, Darmstadt, Germany. "I am very pleased to welcome Elizabeth at this time given her significant experience in supporting companies like ours achieve on this mission."

compliance program supporting the launch of the first-approved gene therapy in the United States.

Previously, Ms. Jobes held leadership positions across a number of biopharmaceutical companies, including Senior Vice President, Chief Compliance Officer for Auxilium Pharmaceuticals, Inc.; Vice President, Chief Compliance Officer for Adolor (Cubist) Corporation; and Senior Director, Global Compliance for Cephalon, Inc. Ms. Jobes also spent a number of years working in the Philadelphia District Attorney's Office, first as a trial attorney, then as assistant chief and chief across various units.

She earned her J.D. from Rutgers University School of Law and her B.A. from Pennsylvania State University.

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 multiple sclerosis. Today, the business has approximately 1,300 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

Merck KGaA, Darmstadt, Germany, a vibrant science and technology company, operates across healthcare, life science and performance materials. Around 51,000 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 billion in 66 countries.

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.

Your Contact
Melissa Beglin 781-681-2609

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SITEMAP

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EMD Serono to Present Multiple Sclerosis Data on Cladribine Tablets and Evobrutinib at ACTRIMS 2019

-- Scientific presentations on cladribine tablets include analysis on durability of NEDA (no evidence of disease activity) status and safety analysis with up to 10 years of follow-up data in some patients

-- Primary safety and efficacy analysis from Phase II study of evobrutinib in patients with relapsing MS to be shared in oral presentation

ROCKLAND, Mass., Feb. 28, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, will present data at the fourth annual ACTRIMS (Americas Committee for Treatment and Research in Multiple Sclerosis) Forum taking place February 28-March 2 in Dallas, TX. These data include efficacy and safety results for cladribine tablets and evobrutinib, investigational agents for relapsing MS.

Cladribine tablets has been studied as a short-course (a maximum of 20 days of treatment over two years) oral therapy. It is thought to preferentially target lymphocytes, which may be integral to the pathological process of RMS. Data presented on cladribine tablets at ACTRIMS will include:

- An exploratory analysis of the efficacy in patients with relapsing MS stratified according to age;
- An analysis of severity and frequency of relapses in patients with relapsing MS.

"The efficacy of cladribine tablets was evaluated in the CLARITY, CLARITY EXT, and ORACLE-MS trials that included patients with RMS," said Stuart Cook, MD, Professor Emeritus at Rutgers, New Jersey Medical School. "Building on existing clinical evidence, I am pleased to present an updated safety analysis on cladribine tablets at ACTRIMS, which includes up to 10 years of follow-up data in some patients."

The integrated analysis of patients from the clinical trial program also includes two additional years of data from the long-term PREMIERE Registry.[1]

Data on evobrutinib will include an oral presentation of the primary safety and efficacy analysis from a Phase II study in patients with relapsing MS and on prevention of inflammatory macrophage differentiation. Evobrutinib is a highly-specific, oral Bruton's Tyrosine Kinase (BTK) inhibitor and the first BTK inhibitor to show clinical proof-of-concept in RMS.

"We are proud to participate in the important scientific exchange at ACTRIMS as it aligns with our commitment to advancing MS science to address patient needs with our research programs and investigational MS treatments," said John Walsh, M.D., Vice President, Neurology and Immunology, US Medical Affairs, EMD Serono.

The EMD Serono Medical Affairs Exhibit Booth at ACTRIMS 2019 will offer participants the chance to make a charitable donation to Can Do MS by participating in the construction of a neuron scaffolding. The goal is to reach a total donation of $10,000 by conference end.

Below are data abstracts from our investigational products that were accepted as posters for presentation at ACTRIMS.

Thursday, February 28

Poster #	Title	Authors	Format/Time
3634	A Real-World Study of Disease-Modifying Drug Treatment	Nicholas, J; Edwards, NC; Harlow, D; Phillips, AL	Poster Session 1 / Opening

	Treatment		PM
3658	Durability of NEDA-3 Status in Patients with Relapsing Multiple Sclerosis Receiving **Cladribine Tablets**: CLARITY Extension	Giovannoni, G, Keller, B, Jack, D	Poster Session 1 / Opening Network Event 6:00 PM-8:00 PM
3821	An Exploratory Analysis of the Efficacy of **Cladribine Tablets** in Patients with RMS Stratified According to Age above and below 45 Years in CLARITY	Giovannoni, G; Rammohan, K; Cook, S; Soelberg-Sorensen, P; Vermersch, P; Keller, B; Verdun di Cantogno, E	Poster Session 1 / Opening Network Event 6:00 PM-8:00 PM
3829	CLARITY: An Analysis of Severity and Frequency of Relapses in Patients with RMS Treated with **Cladribine Tablets** or Placebo	Schippling, S; Sormani, MP; De Stefano, N; Giovannoni, G; Galazka, A; Keller, B; Alexandri, N	Poster Session 1 / Opening Network Event 6:00 PM-8:00 PM
3948	Updated safety analysis of **Cladribine Tablets** in the treatment of patients with multiple sclerosis	Cook, S; Giovannoni, G; Leist, T; Syed, S; Nolting, A; Damian, D; Schick, R	Poster Session 1 / Opening Network Event 6:00 PM-8:00 PM
3602	Primary analysis of a randomized Phase II study to evaluate the efficacy and safety of **evobrutinib**, a BTK inhibitor, in patients with relapsing MS	Montalban, X; Arnold, DL; Weber, MS; Staikov, I; Piasecka-Stryczynska, K; Willmer, J; Martin, E; Dangond, F; Wolinsky, JS	Poster Session 1 / Opening Network Event 6:00 PM-8:00 PM

Friday, March 1

	differentiation: a potential role in MS	Bruttger, J	Lunch 11:15 AM-1:00 PM
3602	Primary analysis of a randomized Phase II study to evaluate the efficacy and safety of **evobrutinib**, a BTK inhibitor, in patients with relapsing MS	Montalban, X; Arnold, DL; Weber, MS; Staikov, I; Piasecka-Stryczynska, K; Willmer, J; Martin, E; Dangond, F; Wolinsky, JS	Session: Cutting Edge Developments in MS Research 4:00 – 5:30 **Oral Presentation**

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About Cladribine Tablets

Cladribine tablets (marketed as MAVENCLAD® outside the U.S.) is an investigational oral therapy studied as a short 8-10 day per year treatment regimen that is thought to preferentially target lymphocytes which may be integral to the pathological process of relapsing MS (RMS). Cladribine tablets is currently undergoing FDA review and is not approved for the treatment for any use in the United States. Cladribine tablets has been approved in 50 countries, including the European Union (EU), Canada, and Australia, for various relapsing MS indications.

The clinical development program for cladribine tablets includes:

- The CLARITY (Cladribine Tablets Treating MS Orally) study: a two-year Phase III placebo-controlled study designed to evaluate the efficacy and safety of cladribine tablets as a monotherapy in patients with RRMS.
- The CLARITY extension study: a Phase III placebo-controlled study following on from the CLARITY study, which evaluated the safety and exploratory efficacy of cladribine tablets over two additional years beyond the two-year CLARITY study, according to the treatment assignment scheme for years 3 and 4.

monotherapy in patients at risk of developing MS (patients who have experienced a first clinical event suggestive of MS).

- The ONWARD (Oral Cladribine Added ON to Interferon beta-1a in Patients With Active Relapsing Disease) study: a Phase II placebo-controlled study designed primarily to evaluate the safety and tolerability of adding cladribine tablets treatment to patients with relapsing forms of MS, who have experienced breakthrough disease while on established interferon-beta therapy.
- PREMIERE (Prospective Observational Long-term Safety Registry of Multiple Sclerosis) study: a long-term observational follow-up safety registry of MS patients who participated in cladribine tablets clinical studies.

In the two-year CLARITY study, the most commonly reported adverse event (AE) in patients treated with cladribine tablets was lymphopenia (26.7% with cladribine tablets and 1.8% for placebo). The incidence of infections was 48.3% with cladribine tablets and 42.5% with placebo, with 99.1% and 99.0% respectively rated mild-to-moderate by investigators. Adverse Events reported in other clinical studies were similar.[2]

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for MS, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly selective inhibitor of Bruton's Tyrosine Kinase (BTK), which is important in the development and functioning of various immune cells, including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses, such as proliferation and antibody and cytokine release. As BTK is not expressed in T cells, evobrutinib does not directly affect T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common, non-traumatic, disabling neurological disease in young adults. It is estimated that approximately 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

EMD Serono, Inc. and Multiple Sclerosis

For more than 20 years, EMD Serono has been relentlessly focused on understanding the

complex and unpredictable disease. EMD Serono is digging deeper to advance the science.

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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 1,300 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com

References

1. Cook S., Giovanonni G., et al. Updated Safety Analysis of Cladribine Tablets in the Treatment of Patients with Multiple Sclerosis. Presentation at ACTRIMS 2019.
2. Cook S, Vermersch P, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. *Multiple Sclerosis Journal* 17(5) 578–593; 2010

Your Contact
Alice McGrail +1 781-681-2886

SOURCE EMD Serono

FDA Approves MAVENCLAD® (Cladribine) Tablets as First and Only Short-Course Oral Treatment for Relapsing-Remitting and Active Secondary Progressive Multiple Sclerosis

- MAVENCLAD is the first oral MS treatment to provide two years of proven efficacy with a maximum of 20 days of treatment

- MAVENCLAD's unique mechanism may provide an important new option for patients with ongoing active disease

- MAVENCLAD demonstrated significant efficacy across key measures of disease activity

- Approval is based on clinical program consisting of more than 9,500 patient years of cladribine data and up to eight years of time on study

ROCKLAND, Mass., March 29, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved MAVENCLAD® (cladribine) tablets for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). MAVENCLAD is the first and only FDA-approved treatment for

Experience the interactive Multichannel News Release here:
https://www.multivu.com/players/English/8485951-emd-serono-mavenclad-fda-approval/

Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). The MAVENCLAD label includes a boxed warning for potential risk of malignancy and risk of teratogenicity. The label appropriately defines the relevant associated contraindications.

"Multiple sclerosis is the leading cause of non-traumatic disability in young and middle-aged adults," said Belén Garijo, CEO Healthcare and Member of the Executive Board of Merck KGaA, Darmstadt, Germany. "We feel privileged to introduce MAVENCLAD into clinical practice in the United States. MAVENCLAD opens a new way to treat MS – a treatment that requires a maximum of 20 days of oral therapy to deliver two years of efficacy to a patient. This approval is a testimony to our long-standing commitment to people living with MS."

"As an investigator in the clinical trial program, I am pleased MAVENCLAD will now be available to patients in the U.S. With short treatment courses with pills taken for no more than 10 days in a year and no injections or infusions, MAVENCLAD is an efficacious new treatment option for MS," said Thomas Leist, M.D., PhD, Director, Comprehensive Multiple Sclerosis Center at Jefferson University Hospitals, Philadelphia, PA. "Nearly one million individuals are afflicted with MS in the U.S. alone, according to a recent National MS Society sponsored study. MAVENCLAD is a welcome new oral treatment option for this heterogeneous and often unpredictable disease."

Eighty-five percent of people living with MS are initially diagnosed with RRMS, characterized by attacks of new or increasing neurological symptoms. Most people with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of neurologic function over time.[1] SPMS can be further characterized at different points as either active (with relapses and/or evidence of new magnetic resonance imaging [MRI] activity) or not active.

"The FDA approval of MAVENCLAD is excellent news for people living with RRMS and active SPMS. MAVENCLAD offers a new and effective option for some of those patients with an oral

their clinician to choose a treatment with a dosing schedule that supports their lifestyle. CMSC congratulates EMD Serono for their dedication to bring MAVENCLAD to the U.S. as the first short-course oral treatment option for the community."

In the clinical trial program, 1,976 patients received therapy for a total of 9,509 patient years, of which the mean time on study including follow-up was approximately 4.8 years and 24% of the follow-up was for eight years. MAVENCLAD demonstrated clinical efficacy across key measures of disease activity, such as annualized relapse rate (ARR), disability progression and MRI activity:

- Patients experienced a 58% relative reduction in the ARR with MAVENCLAD compared to placebo (0.14 vs. 0.33, $p<0.001$).
- 81% of patients were free of relapses after two years of short-course oral treatment with MAVENCLAD, compared to 63% of patients who received placebo ($p<0.05$).
- Patients treated with MAVENCLAD had a 33% reduction in risk of 3-month confirmed disability progression as measured by Expanded Disability Status Scale (EDSS) compared to placebo ($p<0.05$).
- Patients taking MAVENCLAD experienced a lower median number of T1-weighted gadolinium-enhanced brain lesions and new or enlarging T2 brain lesions compared to patients with placebo (0 vs. 0.33 and 0 vs. 0.67, $p<0.001$).

The most common (>20%) adverse reactions reported in the pivotal Phase III study, CLARITY, were upper respiratory tract infection, headache and lymphopenia. Serious adverse reactions reported in the clinical program included malignancies (0.27 events per 100 patient-years) in MAVENCLAD treatment arms, compared to placebo patients (0.13 events per 100 patient-years), and herpes zoster infections (2.0% vs. 0.2%) and oral herpes (2.6% vs. 1.2%).

Following the administration of two treatment courses, additional courses of MAVENCLAD are not to be administered. Re-treatment with MAVENCLAD during years three and four may further increase the risk of malignancy. The safety and efficacy of reinitiating MAVENCLAD more than two years after completing two treatment courses has not been studied.

EMD Serono is committed to helping support patients prescribed MAVENCLAD. Over the course of 16 years, the company's comprehensive patient support program in the U.S., MS LifeLines®, has had over four million touchpoints with patients, care partners, healthcare professionals and other stakeholders to support our goal of providing one-on-one assistance to U.S. patients prescribed an EMD Serono MS therapy. MS LifeLines is now expanding to help patients

are uninsured or underinsured.

The U.S. approval of MAVENCLAD follows its approval in over 50 countries, including the European Union (EU) in August 2017.

For more information on MAVENCLAD, and prescribing information including the boxed WARNINGS, visit www.MAVENCLAD.com.

About MAVENCLAD® (cladribine) Tablets (10 mg)

MAVENCLAD, approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019, is the first short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of the risk of malignancy. Patients should follow healthcare provider instructions including cancer screening, contraception and blood tests. The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. MAVENCLAD causes a dose-dependent reduction in lymphocyte counts followed by recovery.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

MAVENCLAD has been approved in over 50 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is

the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

EMD Serono, Inc. and Multiple Sclerosis

For more than 20 years, EMD Serono has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. EMD Serono is digging deeper to advance the science.

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[1] National MS Society. Secondary progressive MS (SPMS). www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS. Accessed March 2019.

Your Contact

Alice McGrail 1-781-681-2886

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MAVENCLAD® (Cladribine) Tablets Now Covered by Express Scripts

- Within a week of FDA approval, MAVENCLAD has formulary coverage with one of the leading pharmacy benefit managers in the U.S.

- MAVENCLAD is the first and only oral multiple sclerosis treatment to provide two years of proven efficacy with a maximum of 20 days of treatment

ROCKLAND, Mass., April 8, 2019 /PRNewswire/ -- EMD Serono, Inc. today announced that Express Scripts is covering on its formulary the oral multiple sclerosis (MS) therapy, MAVENCLAD® (cladribine) tablets, which was approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019. Express Scripts has over 80 million members nationally, including thousands of people living with MS.

"The Express Scripts Multiple Sclerosis Care Value Program℠ provides comprehensive care for people with multiple sclerosis, and we are proud to add MAVENCLAD to the treatment options members can access," said Steve Miller, M.D., Executive Vice President and Chief Clinical Officer, Cigna. "Combining the expertise of our specialist pharmacists, our clinical care model at our Accredo specialty pharmacy and

In addition to being listed immediately on the Express Scripts formulary, additional patient access opportunities exist for members within their custom health plan or employer benefit offerings.

"Ensuring rapid access to MAVENCLAD for patients is a high priority for us," said Rehan Verjee, President of EMD Serono and Global Head of the Innovative Medicine Franchises. "With its maximum of 20 days of oral treatment over two years, MAVENCLAD offers a new way to treat MS, and we are pleased that an industry leader like Express Scripts has recognized the importance of covering MAVENCLAD for its members."

The FDA approved MAVENCLAD for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). MAVENCLAD is the first and only FDA-approved treatment for RRMS and active SPMS that provides two years of proven efficacy with a maximum of 20 days of oral treatment, during a two-year period.

Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS, and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). The MAVENCLAD label includes a boxed warning that states it may increase the risk of malignancy, and risk of teratogenicity.

MS is a progressive, autoimmune disease affecting one million people in the U.S., and more than 2.3 million people worldwide. It is the most common non-traumatic, disabling neurological disease in young adults. Eighty-five percent of people living with MS are initially diagnosed with RRMS, characterized by attacks of new or increasing neurological symptoms. Most people with RRMS will eventually transition to a secondary progressive course in which there is a progressive worsening of neurologic function over time. SPMS can be further characterized at different points as either active (with relapses and/or evidence of new magnetic resonance imaging [MRI] activity) or not active.

EMD Serono is committed to helping support patients prescribed MAVENCLAD. The company's comprehensive patient support program, MS LifeLines, provides one-on-one assistance to U.S. patients prescribed an EMD Serono MS therapy. This includes personalized patient support like assistance with navigating insurance questions and additional resources that may be able to assist patients who are uninsured or underinsured.

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 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common, non-traumatic, disabling neurological disease in young adults. It is estimated that more than 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common. Eighty-five percent of people living with MS are initially diagnosed with relapsing-remitting MS (RRMS), characterized by attacks of new or increasing neurological symptoms. Most people with RRMS will eventually transition to a secondary progressive course (SPMS) in which there is a progressive worsening of neurologic function over time. SPMS can be further characterized at different points as either active (with relapses and/or evidence of new magnetic resonance imaging [MRI] activity) or not active.

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MAVENCLAD has been approved in over 50 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis for patients with prior or increased risk of malignancy.**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm.**

CONTRAINDICATIONS

- current malignancy.
- pregnancy, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 m after the last dose in each treatment course.
- human immunodeficiency virus (HIV).
- active chronic infections (e.g., hepatitis or tuberculosis).
- history of hypersensitivity to cladribine.
- breastfeeding while taking MAVENCLAD and for 10 days after the last dose.

DOSING CONSIDERATIONS: After the completion of 2 treatment courses, do not administer additional MAVENCLAD during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after completion of 2 treatment courses has not been studied.

ADDITIONAL WARNINGS AND PRECAUTIONS

- **Lymphopenia:** In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.

included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Monitor for infections.

- **Hematologic Toxicity**: Mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions**: Irradiation of cellular blood components is recommended.
- **Liver Injury**: Obtain liver function tests prior to treatment. Discontinue MAVENCLAD if significant injury is suspected.
- **Hypersensitivity**: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Serious hypersensitivity reactions occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue treatment. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Please see the full **Prescribing Information**, including **boxed WARNING** for additional information.

EMD Serono, Inc. and Multiple Sclerosis

For more than 20 years, EMD Serono has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. EMD Serono is digging deeper to advance the science.

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 1,300 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com

Your Contact
Alice McGrail 1-781-681-2886

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EMD Serono

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SITEMAP

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EMD Serono to Present New Data on Mavenclad®, Rebif® and the Investigational Therapy Evobrutinib at the AAN Annual Meeting 2019

EXPLORE MORE

- 20 abstracts will be presented during the AAN Annual Meeting 2019 to demonstrate EMD Serono's commitment and clinical development program in multiple sclerosis

ROCKLAND, Mass., April 30, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced that data from across its multiple sclerosis (MS) portfolio will be presented at the American Academy of Neurology (AAN) 2019 Annual Meeting, May 4-10, 2019 in Philadelphia, PA. The company will present a total of 20 abstracts (18 posters and two platform presentations), including data on MAVENCLAD® (cladribine) tablets, the investigational therapy evobrutinib (an oral, selective Bruton's Tyrosine Kinase (BTK) inhibitor) and Rebif® (interferon beta-1a).

"The wealth of data to be presented at AAN 2019 highlights our continued progress across our portfolio of marketed products and investigational agents in multiple sclerosis," said Luciano Rossetti, Head of Global Research & Development at EMD Serono. "We are very proud of our commitment to further the understanding of multiple sclerosis and enhance our clinical development program to meet the needs of patients."

- Post-hoc analysis of the CLARITY Extension study to examine the durability of no evidence of disease activity-3 (NEDA-3) in relapsing MS (RMS) patients receiving cladribine tablets
- Integrated analysis of pooled long-term safety data of cladribine tablets in patients with MS collated from the CLARITY, CLARITY Extension, ORACLE-MS studies and the PREMIERE registry
- A new analysis of the speed of onset of the MRI effect is presented. At 3 months the effect on new inflammatory lesions was apparent in the ORACLE-MS study. In the same study consistency in clinical outcomes was observed across different patient subgroups defined by patient and disease characteristics at baseline
- Abstracts from the ORACLE-MS study describe the effect of cladribine tablets on early MS
- Results from studies investigating the biological effects of cladribine tablets, including the effect on lymphocyte proliferation, and endothelial responsiveness to tumor necrosis factor and its effect on hematopoietic precursors and immune cells, to offer further insights on the potential mode of action of cladribine tablets

Key evobrutinib data will include:

- Results of analysis of the efficacy and safety of evobrutinib in patients with RMS over 48 Weeks: a randomized, placebo-controlled, phase 2 study

Key Rebif® data will include:

- Investigation from the European Interferon Beta (IFNβ) pregnancy registry and Nordic health study into the prevalence of pregnancy outcomes in IFNβ-exposed women
- Results from the IMPROVE study on the dynamics of pseudo-atrophy in RMS patients treated with interferon beta-1a as assessed by monthly brain MRI

EMD Serono will also be announcing the launch of a new, collaborative MS research network called 'MS-LINK' (**L**eadership and **I**nnovation **N**etwor**k**), an initiative that brings together a community of multiple sclerosis stakeholders to form a scientific foundation for sustainable transformation of MS care, with the shared goal of improving patient outcomes.

Below is a selection of abstracts that have been accepted for presentation at AAN 2019:

MAVENCLAD (cladribine tablets) data			
Title	**Lead Author**	**Poster**	**Presentation / Session**

relapsing multiple sclerosis receiving cladribine tablets: CLARITY Extension			ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Cladribine tablets were associated with rapid onset of improvements in MRI outcomes in the ORACLE-MS trial	Scarberry S	P3.2-061	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
The effect of cladribine tablets on delaying the time to conversion to CDMS or McDonald MS is consistent across subgroups in the ORACLE-MS study	Bowen J	P3.2-101	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Untreated Patients with Multiple Sclerosis: Prevalence and Characteristics in Denmark and in the United States	Nørgaard M	P4.2-060	11:30 - 18:30 ET, Wednesday 8 May P4: MS Epidemiology, Co-Morbidities, and Modifiable Risk Factors

sclerosis			8 May P4: MS Therapeutics: MOA and Safety
Gaps in treatment and treatment discontinuation among patients with multiple sclerosis newly-initiating once- or twice-daily oral disease-modifying drugs	Nicholas J	P3.2-102	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Lymphopenia rates in CLARITY/CLARITY Extension are consistent in patients with or without high disease activity at baseline	Cook S	P3.2-062	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Meta-analysis of real-world adherence and persistence of maintenance once- or twice-daily oral disease-modifying drugs (dimethyl fumarate, fingolimod, and teriflunomide) in multiple sclerosis	Nicholas J	P3.2-041	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
ADA genetic variants influence central inflammation and clinical characteristics in MS: implications for cladribine treatment	Stampanoni Bassi M	P4.2-044	11:30 - 18:30 ET, Wednesday 8 May

			MOA and Safety
Dissection of the distinct susceptibility of hematopoietic precursors and immune cells to cladribine	Carlini F	P4.2-045	11:30 - 18:30 ET, Wednesday 8 May P4: MS Therapeutics: MOA and Safety
Neuroblastoma cell line and lymphocytes talk for cladribine influenced apoptosis and inflammation pathways in Multiple Sclerosis (MS): an "in vitro" study	Ruggieri M	P2.2-095	11:30 - 18:30 ET, Monday 6 May P2: MS Immunology and Basic Science
Gene expression profiles of proteins involved in cladribine metabolism and their possible correlation with Epstein-Barr virus variants	Mechelli R	P2.2-096	11:30 - 18:30 ET, Monday 6 May P2: MS Immunology and Basic Science
Evobrutinib data			
Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib (M2951) in Patients with Relapsing Multiple Sclerosis over 48 Weeks: a Randomized, Placebo-Controlled, Phase 2 Study	Montalban X	Oral presentation	13:33 ET, Friday 10 May S56: MS Trials and Treatment

Differentiation: A Potential Role in Multiple Sclerosis			May P2: MS Immunology and Basic Science
Inhibition of Bruton's Tyrosine Kinase Selectively Prevents Antigen-Activation of B cells and Ameliorates B-Cell-Mediated Experimental Autoimmune Encephalomyelitis	Torke S	P2.2-063	11:30 - 18:30 ET, Monday 6 May P2: MS Immunology and Basic Science
Rebif® (interferon beta-1a)			
Pregnancy and Infant Outcomes with Interferon Beta: Data from the European Interferon Beta Pregnancy Registry and MS Preg study conducted in Finland and Sweden	Hellwig K	450	13:44 ET, Thursday 9 May S49: MS Epidemiology and Risk Stratification
Dynamics of Pseudo-Atrophy in RRMS Patients Treated with Interferon beta-1a as Assessed by Monthly Brain MRI	De Stefano N	P5.2-047	11:30 - 18:30 ET, Thursday 9 May P5: MS Neuroimaging

the first and only short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). Patients should follow healthcare provider instructions including cancer screening, contraception and blood tests. The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. MAVENCLAD causes a dose-dependent reduction in lymphocyte counts followed by recovery.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

MAVENCLAD has been approved in over 50 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis for patients with prior or increased risk of malignancy.**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm.**

CONTRAINDICATIONS

- current malignancy.
- pregnancy, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 m after the last dose in each treatment

- active chronic infections (e.g., hepatitis or tuberculosis).
- history of hypersensitivity to cladribine.
- breastfeeding while taking MAVENCLAD and for 10 days after the last dose.

DOSING CONSIDERATIONS: After the completion of 2 treatment courses, do not administer additional MAVENCLAD during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after completion of 2 treatment courses has not been studied.

ADDITIONAL WARNINGS AND PRECAUTIONS

- **Lymphopenia:** In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Monitor for infections.
- **Hematologic Toxicity**: Mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions**: Irradiation of cellular blood components is recommended.
- **Liver Injury**: Obtain liver function tests prior to treatment. Discontinue MAVENCLAD if significant injury is suspected.
- **Hypersensitivity**: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Serious hypersensitivity reactions occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue treatment. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Please see the full **Prescribing Information,** including **boxed WARNING** for additional information.

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly specific inhibitor of Bruton's tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Rebif® (interferon beta-1a)

Rebif (interferon beta-1a) is used to treat relapsing forms of MS to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS. The efficacy and safety of Rebif in controlled clinical trials beyond 2-years has not been established.

Important Safety Information:

Rebif is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

Rebif should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif. Discontinue Rebif if anaphylaxis occurs.

In controlled clinical trials, injection site reactions occurred more frequently in Rebif-treated patients than in placebo-treated and Avonex-treated patients. Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, discontinue Rebif until skin lesions are healed.

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in Rebif-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in Rebif-treated patients than in placebo and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

Cases of thrombotic microangiopathy (TMA), some fatal, have been reported with interferon beta products, including Rebif, up to several weeks or years after starting therapy. Discontinue Rebif if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including Rebif, in clinical trials and in postmarketing reports.

The most common side effects with Rebif are injection-site disorders, headaches, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

There are no adequate and well-controlled studies in pregnant women. Rebif should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rebif full prescribing information is available at http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf?Version=

the most common non-traumatic, disabling neurological disease in young adults. It is estimated that approximately 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

EMD Serono, Inc. and Multiple Sclerosis

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Contact:
Alice McGrail: +1 781 738 8791

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EMD Serono Launches MS-LINK™, a Community to Advance MS Science and Improve Patient Lives

EXPLORE MORE

- MS-LINK™ brings together first interdisciplinary community across industry, academia and advocacy with the shared goal of improving outcomes in MS
- Initial collaborations launched with the National MS Society and the University of Texas Southwestern Medical Center

ROCKLAND, Mass., May 7, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced the launch of MS-LINK™ (**L**eadership and **I**nnovation **N**etwor**k**), an initiative that brings together an interdisciplinary community of multiple sclerosis (MS) stakeholders to form a top-tier scientific research network focused on sustainable transformation of MS care. MS-LINK will focus on working cooperatively in the areas of real-world data and patient reported outcomes, as well as scientific and precision medicine, and initially includes the National MS Society and the University of Texas Southwestern Medical Center.

"Real progress in MS will not come from just one lab or one doctor, but from working together collaboratively with the brightest minds in MS to drive a true paradigm shift in how we treat and support people living with this disease," said Rehan Verjee, President of EMD Serono and

Southwestern Medical Center, our work to bring together research focusing on patient-reported outcomes, real-world data and precision medicine has only just begun, and we're excited to continue to grow the MS-LINK network in the future."

MS-LINK is comprised of two research networks. The first network – the real-world data and patient reported outcomes network (RWD/PRO) -- will generate and analyze large-scale, longitudinal data to tackle clinical questions directly impacting MS patients' daily lives and to bring patient-centered solutions to the forefront of care. The first RWD/PRO collaboration is with the University of Texas Southwestern Medical Center and will focus on analyzing magnetic resonance imaging (MRI) anomalies through 3D visual modelling and artificial intelligence to differentiate MS brain lesions from non-specific white matter lesions. These insights may not only provide clinicians with a more accurate diagnostic tool but provide a more refined clinical surveillance metric for disease surveillance. In addition, 3D research will examine the effects of MS treatment on lesion size, shape and surface features to further investigate the impact of race and ethnicity in MS.

"Being able to see and feel a 3D printed lesion in your hand is very different from looking at it on a screen, even if you're examining a 3D model," noted Darin T. Okuda, M.D., Neurology and Neurotherapeutics professor at the University of Texas Southwestern Medical Center, and project lead. "This is an important advancement for patients and healthcare professionals, and also artificial intelligence researchers, as investigating accurate 3D representations of MS brain lesions both before and after treatment has unmatched explanatory power."

The second network – the scientific and precision medicine network - will address individual patient needs by creating physician resources and conducting innovative research that considers personal variability in genes, environment and lifestyle. This network recently launched its first research collaboration with the National MS Society. Through this network, EMD Serono is funding a pilot research program to test innovative ideas or untested methods to understand the impact of aging on MS, and to gather preliminary data to determine the potential for further funding.

"We believe that everyone who wants to do something about MS can fuel progress. Partnering with EMD Serono's MS-LINK initiative will enable us to fund more research focused on

collaboration could help identify new innovative strategies for slowing down, stopping, or even reversing MS progression."

MS-LINK will continue expanding collaborations focusing on topics such as immune involvement, treatment selection, shared decision making and modifiable risk factors. New studies are set to be launched later in the year with additional MS-LINK community members.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common, non-traumatic, disabling neurological disease in young adults. It is estimated that more than 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

About MS-LINK™

MS-LINK™ is an initiative developed by EMD Serono that brings together a community of multiple sclerosis (MS) stakeholders, including industry, academia and advocacy groups, to form a top-tier scientific research network for sustainable transformation of MS care, with the shared goal of improving patient outcomes. MS-LINK is comprised of two research networks committed to working cooperatively to address key unmet needs in MS. The first is the real-world data and patient reported outcomes (RWD/PRO) network, that will generate and analyze large-scale, longitudinal data to tackle clinical questions that have a direct impact on the everyday lives of MS patients, and bring patient-centered solutions to the forefront of MS care. The second is the scientific and precision medicine network, which will address the needs of patients by creating physician resources and conducting innovative research that takes into account individual variability in genes, environment and lifestyle.

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Your Contact

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COMPLIANCE & TRANSPARENCY

THERAPEUTIC AREAS

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Positive Phase II Data Further Highlights Clinical Proof of Concept for Evobrutinib, First Oral Bruton's Tyrosine Kinase (BTK) Inhibitor to Report Positive Phase II Clinical Results in MS

-- 48-week results provide additional evidence of relapse reduction for investigational evobrutinib

-- Evobrutinib demonstrated rapid lesion reductions on MRI at week 12 that were maintained through week 48, with no new safety signals identified over 52 weeks

-- Data presented at the American Academy of Neurology 2019 Annual Meeting and simultaneously published in the NEJM

ROCKLAND, Mass., May 10, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced new 48-week results of the double-blind, randomized, placebo-controlled, Phase II study of evobrutinib in patients with relapsing multiple sclerosis (RMS). The results have been presented at the American Academy of Neurology (AAN) 2019 Annual Meeting in Philadelphia, PA with simultaneous publication in the *New England Journal of Medicine (NEJM)*. Evobrutinib is the first oral, highly selective Bruton's tyrosine kinase (BTK) inhibitor to show clinical proof of concept in RMS.

with evobrutinib compared with placebo. With evobrutinib 75 mg QD (once a day) and 75 mg BID (twice a day), rapid reductions in number of T1 Gd+ lesions were observed by week 12 of treatment. New data showed that the effect on T1 gadolinium-enhancing lesions reduction seen at week 12 was maintained through 48 weeks with evobrutinib 75 mg QD and 75 mg BID.

"These positive Phase II evobrutinib data are a great example of the strength of our pipeline and commitment to developing new, innovative treatments in multiple sclerosis," said Luciano Rossetti, Head of Global Research & Development at EMD Serono. "As a leader in autoimmune diseases and MS we are proud of this in-house discovery at EMD Serono. We look forward to continuing to investigate the potential of evobrutinib as we continue to address unmet patient needs in MS care."

With evobrutinib 75 mg BID, annualized relapse rate (ARR) (confidence interval) was 0.11 (0.04-0.25) with 79 percent of patients remaining relapse free over 48 weeks of treatment. For reference, at 24 weeks, ARR for evobrutinib 75 mg BID was 0.08 (0.01-0.30) and 0.37 (0.17-0.70) for placebo.

No treatment associated infections, infestations, or lymphopenia were observed and no new safety signals were identified over 52 weeks. The most common treatment-related TEAEs (>10%) included nasopharyngitis and increased ALT. The percentage of shifts from baseline to Grade 2 or greater in ALT were 5.7%, 3.8%, and 13% in the evobrutinib 25mg QD, 75mg QD and 75mg BID groups, respectively. The corresponding shifts in ALT in the placebo group over 24 weeks was 7.5%. All events had an onset within 24 weeks of treatment initiation and were reversible on treatment discontinuation with no clinical consequences within the 52-week study period. During the course of the study, 85 percent of patients (227 out of 267) completed 52 weeks of treatment.

"Building on our initial analysis at 24 weeks, these new data further demonstrate the potential role of evobrutinib in relapsing multiple sclerosis, subject to further clinical investigation" said Dr. Xavier Montalban, Professor of Medicine and Department Division Director, Neurology, at the University of Toronto and Director of the MS Centre at St. Michael's Hospital, Canada, and Chairman & Director Neurology-Neuroimmunology Department & Neurorehabilitation Unit, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain. "Evobrutinib is the first Bruton's tyrosine kinase inhibitor to demonstrate clinical proof of concept in multiple sclerosis. We are pleased that these 48-week data further support our

These 48-week results are a new analysis following the initial 24-week presentation of the data at the 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Berlin, Germany, on October 12, 2018.

EMD Serono presented a total of 20 abstracts (18 posters and two platform presentations) during AAN 2019. For further information on the evobrutinib 48-week abstract please see here:

- Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib in Patients with Relapsing Multiple Sclerosis over 48 Weeks: a Randomized, Placebo-Controlled, Phase 2 Study – presented at 1:33 PM ET on Friday, May 10 during the S56: MS Trials and Treatment session.

The presentation of these data read-outs showcases the breadth of EMD Serono's multiple sclerosis (MS) portfolio and further underscores its commitment to the advancement of MS treatment.

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 for your online subscription of this service as our geo-targeting requires new links in the email. You may later change your selection or discontinue this service.

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly selective inhibitor of Bruton's tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Selectivity has been *assessed in vitro*. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

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Your Contact
alice.mcgrail@emdserono.com
Phone: +1 781 738 8791

SOURCE EMD Serono

EMD Serono to Present Data at CMSC Annual Meeting Showcasing Breadth of MS Portfolio and Commitment to Understanding How MS Impacts Patients

- 20 abstracts to be presented, including data on MAVENCLAD® (cladribine) tablets, Rebif® (interferon beta-1a) and investigational therapy evobrutinib

ROCKLAND, Mass., May 28, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, will present data from its multiple sclerosis (MS) portfolio at the Consortium of Multiple Sclerosis Centers (CMSC) 2019 Annual Meeting, taking place May 28 – June 1, 2019 in Seattle, WA. The company will present a total of 20 abstracts (18 posters and two oral presentations), including new data on MAVENCLAD® (cladribine) tablets.

"We are dedicated to the continuation of research into our MS portfolio, and are excited to have a strong scientific presence at the CMSC Annual Meeting," said John Walsh, M.D., Vice President, Neurology and Immunology, U.S. Medical Affairs and Interim Head, North America Medical Affairs at EMD

Meeting attendees can learn more about EMD Serono and its support of the MS community by visiting and participating in interactive activities at the congress, including "I'm Balancing MS," at booth #101. Individuals can work with their colleagues to create an original art piece depicting the neuroimmunology of MS. For each participant, EMD Serono will make a donation to the Foundation of CMSC's Workforce of the Future, which supports initiatives for young professionals who care for people with MS including The International Organization of Multiple Sclerosis Nurses (IOMSN).

"EMD Serono has spearheaded this effort over the past two decades and their support has been instrumental in our progress," said June Halper, CEO of CMSC. "IOMSN is dedicated to sustain nursing care in MS throughout the world. Its growth and positive impact on MS care is due, in no small measure, to scholarship funding and support of its educational activities by its supporters."

In addition, EMD Serono will honor World MS Day at CMSC on May 30 by showcasing multiple pieces of artwork from the MS On My Mind (MSOMM) initiative, including a final mural created at National MS Society Walk MS events across the country. The mural incorporates personalized messages from Walk MS attendees and will come together for the first time at CMSC. CMSC attendees can visit booth #236 to meet MSOMM creative director, Lydia Emily Archibald, and see her artwork inspired by submissions from those impacted by MS.

Below is a selection of abstracts that have been accepted for presentation at CMSC 2019:

MAVENCLAD® (cladribine) tablets data			
Title	**Lead Author**	**Poster**	**Presentation/ Session**
Severity and frequency of relapses in patients with relapsing-remitting MS treated with Cladribine Tablets in CLARITY and placebo in CLARITY Extension	Schippling S	DXT55	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session

above and below 45 years; CLARITY and CLARITY Extension			6:45 PM – 8:15 PM PT Poster Session
Rationale and feasibility of a phase IV study (CLASSIC MS) assessing long-term efficacy outcomes for patients with multiple sclerosis treated with Cladribine Tablets in the phase III trials	Boyko A	DXT35	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
The effects of cladribine tablets on reduction in MRI lesions are consistent across subgroups in the ORACLE-MS study	Leist T	Oral Presentation	Friday May 31 3:20 PM - 3:40 PM PT Washington State Convention Center 611-612
Relapse outcomes in CLARITY EXT patients treated with cladribine tablets or placebo were comparable regardless of the between-trial bridging intervals	Rammohan K	DXT56	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing-remitting multiple sclerosis: tolerability and quality-of-life outcomes	Singer B	DXT57	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
CLARITY Extension: Long-term efficacy of cladribine tablets in patients with high disease activity at baseline following switch to placebo	Vermersch P	DXT31	Thursday May 30 6:45 PM – 8:15 PM PT

Updated safety analysis of cladribine tablets in the treatment of patients with multiple sclerosis	Cook S	DXT58	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Durability of NEDA-3 status in patients with relapsing multiple sclerosis receiving cladribine tablets: CLARITY Extension	Giovannoni G	DXT01	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Evobrutinib data			
Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib (M2951) in Patients With Relapsing MS Over 48 Weeks: a Phase II Study	Montalban X	Oral Presentation	Friday May 31 3:40 PM - 4:00 PM PT Washington State Convention Center 611-612
Inhibition of Bruton's tyrosine kinase prevents inflammatory macrophage differentiation: a potential role in multiple sclerosis	Alankus YB	NDM05	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Rebif® (interferon beta-1a) data			
Real-world infection rates and lymphocyte counts in patients ≥50 years with relapsing-remitting MS treated with subcutaneous interferon beta-1a or dimethyl fumarate	Hayward B	DXT68	Thursday May 30 6:45 PM – 8:15 PM PT

Cumulative data from the European Interferon Beta Pregnancy Registry	Hellwig K	DXT66	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Dynamics of pseudoatrophy in relapsing-remitting MS patients treated with interferon beta-1a as assessed by monthly brain MRI	Battaglini M	DXT61	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
MAGNIMS score–assessed disease activity predicts long-term activity-free status and disability progression in subcutaneous interferon beta-1a–treated patients	Sormani MP	DXT02	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
HEOR data			
Comorbidity and concomitant medication use among patients with multiple sclerosis newly initiating disease-modifying drugs	Nicholas J	DXT33	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Gaps in treatment and treatment discontinuation among patients with multiple sclerosis newly initiating once- or twice-daily oral disease-modifying drugs	Nicholas J	DXT34	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session
Clinical and economic burden of non-adherence to oral disease-modifying drugs in	Nicholas J	DXT38	Thursday May 30

			Poster Session
Relapses, healthcare resource use, and costs among patients with multiple sclerosis taking maintenance (once-or twice-daily) oral disease-modifying drugs and experiencing lapses in therapy	Nicholas J	DXT32	Thursday May 30 6:45 PM – 8:15 PM PT Poster Session

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About MAVENCLAD®

MAVENCLAD, approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019, is the first and only short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and**

in patients treated with MAVENCLAD.

- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm.**

CONTRAINDICATIONS

- Current malignancy.
- Pregnancy, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 m after the last dose in each treatment course.
- Human immunodeficiency virus (HIV).
- Active chronic infections (e.g., hepatitis or tuberculosis).
- History of hypersensitivity to cladribine.
- Breastfeeding while taking MAVENCLAD and for 10 days after the last dose.

DOSING CONSIDERATIONS: After the completion of 2 treatment courses, do not administer additional MAVENCLAD during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after completion of 2 treatment courses has not been studied.

ADDITIONAL WARNINGS AND PRECAUTIONS

- **Lymphopenia:** In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Monitor for infections.
- **Hematologic Toxicity**: Mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.

- **Liver Injury**: Obtain liver function tests prior to treatment. Discontinue MAVENCLAD if significant injury is suspected.
- **Hypersensitivity**: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Serious hypersensitivity reactions occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue treatment. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Please see the full **Prescribing Information,** including **boxed WARNING** for additional information.

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly specific inhibitor of Bruton's tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Rebif® (interferon beta-1a)

Rebif (interferon beta-1a) is used to treat relapsing forms of MS to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS. The efficacy and safety of Rebif in controlled clinical trials beyond 2-years has not been established.

interferon beta, human albumin, or any other component of the formulation.

Rebif should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif if hepatic injury occurs.

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif. Discontinue Rebif if anaphylaxis occurs.

In controlled clinical trials, injection site reactions occurred more frequently in Rebif-treated patients than in placebo-treated and Avonex-treated patients. Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, discontinue Rebif until skin lesions are healed.

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in Rebif-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in Rebif-treated patients than in placebo and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

Cases of thrombotic microangiopathy (TMA), some fatal, have been reported with interferon beta products, including Rebif, up to several weeks or years after starting therapy. Discontinue Rebif if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including

The most common side effects with Rebif are injection-site disorders, headaches, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

There are no adequate and well-controlled studies in pregnant women. Rebif should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rebif full prescribing information is available at http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf?Version=

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common non-traumatic, disabling neurological disease in young adults. It is estimated that more than 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

EMD Serono, Inc. and Multiple Sclerosis

For more than 20 years, EMD Serono has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. EMD Serono is digging deeper to advance the science.

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 1,300 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com

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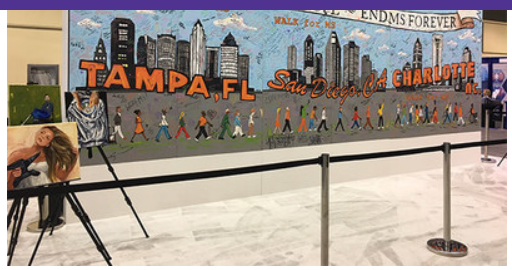
EMD Serono Makes Multiple Sclerosis Visible This World MS Day and Beyond

- MS On My Mind initiative uncovers emotional and physical impact MS has among individuals through artwork showcased at CMSC Annual Meeting

(1)

ROCKLAND, Mass., May 30, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, joins the global multiple sclerosis (MS) community in recognition of World MS Day, an initiative created by the Multiple Sclerosis International Federation (MSIF) to raise awareness of this challenging disease that affects more than 2.3 million people worldwide. In support of this year's World MS Day theme, "My Invisible MS" (#MyInvisibleMS), EMD Serono is making MS visible through tailored initiatives and contributions aimed at shining a light on the impact of MS – both for patients and their caregivers.

One such initiative is MS On My Mind (MSOMM), which is part of the company's #MSInsideOut global campaign aimed at providing a deeper understanding of MS around the world. MSOMM raises awareness of the emotional and multi-faceted impact MS has on individuals and aims to uncover findings that might help fuel actionable solutions to address patient and caregiver



submissions, top themes emerged among patients and caregivers such as extreme fatigue, the inability to perform and maintain physical activity and concern about the future.

"Our company is deeply committed to MS and better understanding both the visible and unseen ways the disease can affect patients," said Andrew Paterson, Global Head of Neurology & Immunology at Merck KGaA, Darmstadt, Germany. "We are inspired by the patients and caregivers who have advanced this understanding and who made aspects of their MS visible by sharing their experience."

This year, World MS Day falls within the same week as the Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting in Seattle, WA. EMD Serono is showcasing several paintings and murals developed by MSOMM creative director and MS patient Lydia Emily Archibald at the meeting. Lydia Emily used her talents to bring the invisible symptoms of MS to life through compelling artwork. Her commitment and passion for advocacy work continue to inspire and motivate the MS community.

"Although we all have different day-to-day lives and responsibilities, we are impacted by MS in very similar ways," said Ms. Archibald. "MS might strike in the form of frustration and struggle yet trigger moments of sincere gratitude and accomplishment. All MSOMM submissions to date have been equally compelling and relatable. I am honored to have had the opportunity to bring peoples' stories to life."

Globally, Merck KGaA, Darmstadt, Germany is supporting MSIF's Informed Decision-Making Program by donating €1 (up to €50,000) for every post shared publicly in social media including combined use of the hashtags #MSInsideOut and #MyInvisibleMS until June 8. The Informed Decision-Making Program supports several initiatives of MS patient groups around the world that aim to provide reliable, accessible and up-to-date information, so people know they are making the best decision for their MS and their lives.

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About World MS Day 2019

World MS Day is officially marked on 30 May each year. Events and campaigns take place throughout the month of May. It brings the global MS community together to share stories, raise awareness and campaign with and for everyone affected by multiple sclerosis. World MS Day 2019 will take place on 30 May. The 2019 campaign will be called 'My Invisible MS' (#MyInvisibleMS) and the theme is Visibility. In 2009, the MS International Federation (MSIF) and its members initiated the first World MS Day. Together we have reached hundreds of thousands of people around the world, with a campaign focusing on a different theme each year. MSIF provides a toolkit of free resources to help everyone to take part in World MS Day. Anyone can use these tools, or make their own, to create positive change in the lives of more than 2.3 million people around the world.

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Your Contact

alice.mcgrail@emdserono.com

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Massachusetts-based Business Sectors of Merck KGaA, Darmstadt, Germany Named 'Best Places to Work' by Boston Business Journal

- EMD Serono, MilliporeSigma and EMD Performance Materials make prestigious Massachusetts top employer list for 2019

Rockland, Massachusetts, June 20, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that its Massachusetts-based business sectors, EMD Serono, MilliporeSigma and EMD Performance Materials, have been named to the *Boston Business Journal*'s annual "Best Places to Work" list. Companies were selected based on survey responses provided by employees.

This is the 17th year that the *Boston Business Journal* has published its "Best Places to Work" list, and the first time that all three Massachusetts-based U.S. businesses of Merck KGaA, Darmstadt, Germany have won the award together. The company won in the extra-large company category and was one of only nine winning extra-large companies. "Best Places to Work" honors the area's leading employers that go beyond the norm to foster a meaningful and enjoyable work environment and is based on internal employee survey results.

large (250 to 999 employees) and extra-large (1,000 employees and over). The three businesses of Merck KGaA, Darmstadt, Germany have approximately 2,900 employees in Massachusetts.

The *Boston Business Journal*'s "Best Places to Work" surveys and the subsequent scoring of responses were provided in partnership with Quantum Workplace.

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 52,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of €14.8 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 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.

Your Contact
Melissa.beglin@emdserono.com

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EMD Serono's Embracing Carers™ Launches 'Time Counts' to Raise 1 Million Minutes of Support for Caregivers

• 'Time Counts' launches as a social media-led video series asking individuals to collectively give 1 million minutes to better support caregivers

• Embracing Carers™, a global initiative led by EMD Serono, raises awareness about the often-overlooked needs of caregivers and develops practical support solutions collaboratively with global caregiving organizations

ROCKLAND, Mass., July 16, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical company of Merck KGaA, Darmstadt, Germany in the U.S. and Canada, today announced that its Embracing Carers™ initiative has launched 'Time Counts,' a social media-led video series asking friends and families of caregivers to collectively give 1 million minutes of their time to better support caregivers around the world.

"Caregivers are critical contributors not only to a patient's health, but also for health systems, which would be greatly disadvantaged without the millions of hours of their silent work," said Belén Garijo, Member of the Executive Board and CEO Healthcare at Merck KGaA, Darmstadt,

visible, recognized and considered a global health priority."

Embracing Carers™ recognizes that caregivers dedicate so much of their time to supporting a loved one that their own basic health-related activities are often selflessly sacrificed. For example, 54% of unpaid caregivers don't have time to book or attend their own medical appointments, while 58% find it difficult to sleep on a regular basis, according to a 2017 Embracing Carers™ international online survey conducted by EMD Serono.[1]

'Time Counts' by Embracing Carers™ hopes to assuage these time constraints by aiming to raise 1 million minutes of time to provide caregivers with support in their role. By sharing caregiver stories via social media, 'Time Counts' will encourage individuals to give time to help with specific tasks, such as grocery shopping, cooking a meal or checking-in to connect and let them know support is available.

An advocate of 'Time Counts', actor Sean Hayes, famed for his Emmy-winning performance as Jack McFarland on NBC's *Will & Grace*, shared his story of caregiving for his mother during her battle with Alzheimer's disease and encourages viewers to help the caregivers in their own lives by giving their most valuable support of all – time. Sean has partnered with Embracing Carers™ to create a video message to announce 'Time Counts', which asks viewers to visit www.embracingcarers.com and participate. The aim is that through 'Time Counts', individuals will give time back to caregivers so they can better address their own health and wellbeing.

"The International Alliance of Carer Organizations (IACO) is proud to be a strategic advisor for the Embracing Carers™ initiative that has become a global force in creating awareness and recognition of caregivers since 2017," said Nadine Henningsen, IACO Board Chair. "Through innovative campaigns like 'Time Counts' we can build on this momentum to ensure caregivers are recognized and supported in their vital role."

For more information on Embracing Carers™, visit www.embracingcarers.com.

About Embracing Carers™

Launched in 2017, Embracing Carers™ is a global initiative led by EMD Serono in collaboration with leading carer organizations around the world to increase awareness and discussion about the often-overlooked needs of caregivers. The Embracing Carers™ global advisors include Caregiver Action Network, Carers Australia, Carers Canada, Carers UK, Carers Worldwide,

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About the Embracing Carers™ International Survey

The Embracing Carers™ online survey was conducted by Censuswide on behalf of EMD Serono. It questioned 3,516 unpaid caregivers aged 18-75 years including 2,106 respondents aged 35-55 in Australia, France, Germany, Italy, Spain, UK and the US between 27 July and 8 August, 2017.

About the International Alliance of Carer Organizations (IACO)

Incorporated in 2012, the International Alliance of Carer Organizations (IACO) is a global coalition of 15-member nations committed to building a global understanding and respect for the vital role of family caregivers. Recognized as an official NGO by the United Nations, IACO works to improve the quality of life and support the needs of caregivers, through international partnerships and advocacy that strengthens and honors the voice of caregivers. To learn more, visit www.internationalcarers.org.

[1] Embracing Carers™ International Survey. Censuswide 27 July – 8 August, 2017

Your Contact
Melissa Beglin +1 781 681 2609

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EMD Serono to Showcase Scientific Leadership at ECTRIMS 2019 with New Data Across Multiple Sclerosis Medicines

-Company to present 39 abstracts, including data on MAVENCLAD® (cladribine) tablets, Rebif® (interferon beta-1a) and investigational evobrutinib

-Long-term data and real-world evidence further characterize effectiveness of MAVENCLAD and support clinical trial findings

ROCKLAND, Mass., Aug. 28, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced that it will present data on its approved and investigational multiple sclerosis (MS) treatments at the 35th Congress of the European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS). During ECTRIMS, taking place from September 11-13, 2019, in Stockholm, Sweden, EMD Serono will present 39 abstracts, including new long-term safety and efficacy data on MAVENCLAD® (cladribine) tablets and new long-term efficacy data for interferon beta (IFN β) therapies, including Rebif® (interferon beta-1a). Data will also be presented further elucidating the proposed mechanism of action for investigational therapy evobrutinib, the first oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor to demonstrate clinical proof of concept in relapsing multiple sclerosis (RMS).

term safety and efficacy data for MAVENCLAD, long-term efficacy data for interferon beta therapies, including Rebif, and data further elucidating evobrutinib's proposed unique mechanism of action and its potential as a novel therapeutic approach in MS," said Luciano Rossetti, Head of Global R&D for EMD Serono. "These data reinforce the important role of our currently-available treatments and offer further insights on our investigational treatment, as we continue our unwavering commitment to address the needs of the MS community."

Key MAVENCLAD data include:

- A *post hoc* analysis evaluating five-year disease stability in patients enrolled in the CLARITY and CLARITY EXTENSION trials
- Results from an exploratory analysis of real-world data from an Italian MS registry assessing time-to-treatment change after MAVENCLAD, which examined efficacy of MAVENCLAD on relapse rate and disability progression at five years after starting treatment
- Results from up to 10 years of follow-up from the PREMIERE safety registry, which further support the long-term benefit-risk profile of MAVENCLAD
- New data further illustrating how MAVENCLAD is thought to preferentially target key immune cells involved with MS and its potential qualitative effect on the immune system

Key Rebif data include:

- Results using a new *post hoc* exploratory statistical methodology, which examined changes in disability status over time using eight years of data from the PRISMS study

Key evobrutinib data include:

- Three analyses that investigate the potential role of evobrutinib, the first oral, highly selective BTK inhibitor to demonstrate clinical proof of concept in RMS, in inhibiting pathogenic B-cells and promoting myelin repair

Additional EMD Serono activities at ECTRIMS 2019:

- Panel discussion and networking event on September 11 bringing together Patient Advocacy Groups, people living with MS and multi-disciplinary experts to have a conversation about family planning with MS (6:00 – 7:30 PM, Epicenter, Stockholm)

with MS and the company's ongoing commitment to MS research and development through the Grant for Multiple Sclerosis Innovation (GMSI)

- Satellite symposium events on September 11 (12:30 – 1:30 PM, Hall A Stockholmsmässan) and September 12 (6:15 – 7:15 PM, Hall A Stockholmsmässan) covering key learnings on managing disease progression in MS, including monitoring methods, recent advancements in MS immune targeting and the importance of innovative registry studies
- #MSInsideOut Experience, including the MS House and virtual reality (VR), at EMD Serono booth B40 that will immerse visitors into a day-in-the-life of an MS patient, educating them on symptoms of MS and how they affect the human body in different settings

Below is a selection of abstracts that have been accepted for presentation at ECTRIMS 2019:

MAVENCLAD® (cladribine) tablets Presentations			
Title	**Authors**	**Abstract No. / Poster No.**	**Presentation Date/Time/Session**
Reduction of risk of secondary progressive multiple sclerosis within two years of treatment with Cladribine Tablets: An analysis of the CLARITY study	Vermersch P, Giovannoni G, Soelberg-Sorensen P, Rammohan K, Cook S, Keller B, Roy S	A-1026-0005-00522	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Long-term disease stability assessed by the Expanded Disability Status Scale in patients treated with Cladribine Tablets in the CLARITY and CLARITY Extension studies	Giovannoni G, Comi G, Rammohan K, Rieckmann P, Vermersch P, Dangond F, Keller B, Jack D	A-1026-0033-00521	ePoster
The CLARITY Study:	Vermersch P, Rammohan	A-1026-0031-	Session Title:

Received Disease-Modifying Therapies Prior to Treatment with Cladribine Tablets			09.11.2019 Presenting Time: 5:15-7:15 PM
Updated safety of cladribine tablets in the treatment of patients with multiple sclerosis: Integrated safety analysis and post-approval data	Cook S, Giovannoni G, Leist T, Comi G, Syed S, Nolting A, Damian D, Schick R	A-1026-0033-00523	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
An analysis of the relationship between cladribine dose and risk of malignancies in patients with multiple sclerosis	Cook S, Giovannoni G, Leist T, Comi G, Nolting A, Sylvester E, Jack D, Damian D, Galazka A	A-1026-0033-01927	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Long term, registry-based, prospective, post-authorization safety study evaluating adverse events of special interest in patients with highly active relapsing multiple sclerosis newly started on oral cladribine – CLARION	Butzkueven H, Korhonen P, Hillert J, Trojano M, Aydemir A, Magyari M, Khanfir H, Pinuaga C, Sabidó M, CLARION Study group	A-1026-0033-00518	ePoster
Incidence of any malignancies in patients treated for multiple	Magyari M, Foch C, Nørgaard M, Boutmy E, Veres K, Sabidó M	A-1026-0034-01799	Scientific Session 2: Safety assessment in the post-approval phase - real world

			09.11.2019 Presenting Time: 3:01-3:13 PM
Increase of naïve B cells M2 macrophages and reduction of memory B/T cells during immune repopulation at 96 weeks in CLARITY assessed by Immune cell deconvolution	Giovannoni G, Leist T, Soelberg-Sorensen P, Kalatskaya I, Boschert U, DeMartino J, Rolfe A	A-1026-0031-00511	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM
Long-term effectiveness in patients previously enrolled in the Cladribine Tablets pivotal trials: a Real-World Evidence analysis using data from the Italian Multiple Sclerosis Registry (CLARINET-MS)	Patti F, Visconti A, Capacchione A, Trojano M on behalf of the CLARINET-MS study group	A-1026-0031-00516	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Comparative effectiveness of Cladribine tablets vs other drugs in relapsing-remitting multiple sclerosis: an approach merging randomized controlled trial with real life data	Signori A, Saccà F, Lanzillo R, Maniscalco GT, Signoriello E, Repice A, Annovazzi P, Baroncini D, Clerico M, Binello E, Cerqua R, Mataluni G, Perini P, Bonavita S, Lavorgna L, Zarbo IR, Laroni A, Gutierrez LP, Gioia SL, Frigeni B, Barcella V, Frau J, Cocco E, Fenu G, Clerici VT,	A-1026-0031-00187	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM

	A, Pontecorvo S, Grasso R, Barone S, Barrilà C, Russo CV, Esposito S, Ippolito D, Landi D, Visconti A, Sormani MP		
CD4+ T cells and CD19+ B cells respond differentially to cladribine treatment in vitro depending on their activation status. Role of deoxycytidine kinase	Carlini F, Ivaldi F, Boschert U, Visconti A, de Rosbo NK, Uccelli A	P1353	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Studying the effect of cladribine on microglia survival, proliferation, activation and cytokine release	Eixarch H, Calvo-Barreiro L, Fissolo N, Boschert U, Comabella M, Montalban X, Espejo C	P610	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Effects of 2-chlorodeoxyadenosine (Cladribine) on Microglial cells and Astrocytes	Aybar F, Perez MJ, Pasquini JM, Correale J	P623	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Understanding the mechanisms of action of Cladribine in innate immune cells in MS	C. Rodríguez-Mogeda, S. Van der Pol, A.J. Van het Hof, HE. De Vries	P984	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM
Year 1 Performance of	Lyons M, Lott N, Morgan K	A-1026-0037-	ePoster

patients taking MAVENCLAD (cladribine tablets) in UK			
Cladribine is not mutagenic to mitochondrial DNA and RNA in leukemic cell lines	Järvinen E, Tienari PJ, Battersby BJ	P698	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Cladribine modify functional properties of murine microglia	Jørgensen LØ, Hyrlov KH, Elkjær ML, Pedersen AE, Svenningsen ÅF, Illes Z	A-1026-0031-01729	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM
Safety data from the non-interventional, prospective study CLEVER (CLadribine Tablets – EValuation of thERapy satisfaction) and CLADQoL (CLADribine Tablets – evaluation of Quality of Life)	Penner, I-K, Ziemssen T, Nolting A, Hübschen M, Richter J, Schel E, Wagner T, Mueller B, Posevitz-Fejfar A	A-1026-0031-01026	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Non-interventional, prospective study CLEVER (CLadribine Tablets – EValuation of thERapy satisfaction)	Ziemssen T, Grothe C, Reifschneider G, Morgenbesser T, Richter J, Schel E, Wagner T, Müller B, Posevitz-Fejfar A	A-1026-0031-01164	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM

CLADQoL (CLADribine Tablets - evaluation of Quality of Life)	Schel E, Wagner T, Müller B, Posevitz-Fejfar A		
Cladribine tablets versus other disease-modifying oral treatments in multiple sclerosis (MS) in achieving no evidence of radiological and clinical disease activity (NEDA) - network meta-analysis (NMA)	Bartosik-Psujek H, Kaczyński Ł, Górecka M, Rolka M, Wójcik R, Kaczor M P, Zięba P	A-1026-0037-01912	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM
Cladribine tablets: Observational evaluation of effectiveness, safety, and patient reported outcomes in suboptimally controlled patients previously taking injectable disease-modifying drugs for relapsing forms of multiple sclerosis (CLICK-MS)	Miravalle A A, Katz J, Sloane J, Hayward B, Walsh J S, Harlow D E	A-1026-0033-01906	ePoster
Risk reduction of EDSS progression in patients with relapsing multiple sclerosis treated with cladribine tablets in the CLARITY study: post-hoc analysis including	Thrower B, Fox E J, Damian D, Lebson L, Dangond F	A-1026-0031-01938	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM

In depth analysis of B cells in multiple sclerosis patients after treatment with cladribine	Marsh-Wakefield F, Juillard P, Ashhurst T, McGuire H, Byrne SN, Hawke S, Grau GE	P1225	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM.
FIMS Study: Exploration of Factors which Influence treatment decisions of patients with Multiple Sclerosis	Bardsley B, Cinc E, Heriot E, Lazarus K-J, McMurtrie M, Haynes J, Coleman E, Macdonell R	P676	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
Markers of premature immunosenescence in the peripheral blood of multiple sclerosis subjects vs. healthy controls	Clénet ML, Daigneault A, Laurent C, Jamann H, Mamane V, Ouedraogo O, Carmena Moratalla A, Duquette P, Rousseau MC, Arbour N and Larochelle C	A-1026-0029-01320	Session Title: Poster Session 1 Session Date: 09.11.2019 Presenting Time: 5:15-7:15 PM
MAVENCLAD® (cladribine) tablets Late-Breaker Presentation			
Cladribine decreases CD95 expressing CD4+ and CD8+ cells in lymphoid organs in naïve marmosets (Callithrix jacchus)	Kap Y, Boschert U, t'Hart B	A-1026-0000-02694	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Rebif® (interferon beta-1a) Presentations			
Effect of Interferon β-1a Treatment on Serum Neurofilament Light	Kuhle J, Leppert D, Comi G, De Stefano N, Kappos	A-1026-0035-00622	Session Title: Poster Session 3 Session Date:

Demyelinating Event in the REFLEX trial			12:15-2:15 PM
Pharmacodynamic biomarkers of interferon β-1a: Assessment in patients receiving long-term treatment with subcutaneous interferon β-1a in REFLEX and REFLEXION	Freedman MS, Wojcik J, D'Antonio M, Hyvert Y, Stinchi S, D'Urso V, Dangond F	A-1026-0033-00634	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Efficacy of subcutaneous interferon β-1a in patients with a first clinical demyelinating event: the REbif FLEXible dosing in early multiple sclerosis (REFLEX) study – outcomes in patients stratified by the 2017 McDonald criteria	Freedman MS, Kappos L, Comi G, De Stefano N, Roy S, Issard D	A-1026-0031-00626	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Post-hoc Analysis to Evaluate the Effects of Subcutaneous Interferon β-1a in Subgroups of Patients from the PRISMS Study with Early Onset vs Late Onset Disease	Freedman MS, Brod S, Wray S, Singer B, Dangond F, Issard D, Harlow D, Jack D	A-1026-0031-00628	ePoster
Assessing the duration of EDSS improvement	Signori A, Bovis F, Carmisciano L, Alexandri	A-1026-0035-00443	Session Title: Poster Session 3

applied to the long term extension of the PRISMS study			Presenting Time: 12:15-2:15 PM
Effectiveness of subcutaneous interferon beta-1a 22/44 µg versus teriflunomide in newly treated patients with multiple sclerosis. A study in a French nationwide cohort of Multiple Sclerosis: Observatoire Francais de la sclérose en plaques (OFSEP)	Rollot F, Foch C, Laplaud D, Boutmy E, Marhardt K, Sabido S	A-1026-0034-00636	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM
Prevalence of infant outcomes at birth after exposure to interferon beta prior to or during pregnancy: A register-based cohort study in Finland and Sweden among women with MS	Vattulainen P, Burkill S, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Myhr K-M, Montgomery S, Korhonen P, the European Interferon Beta Pregnancy Study Group and the Nordic MS Pregnancy & Interferon Beta study group	A-1026-0009-01725	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Systematic mapping of the global educational offerings for multiple sclerosis patients on the topic of disease progression	Bharadia T, Kesselring J, Boyko A, Sumelahti M-L on behalf of the MS in the 21st Century initiative, and Alexandri N	A-1026-0005-01837	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM

multiple sclerosis			Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Evobrutinib (Bruton's Tyrosine Kinase Inhibitor) Presentations			
Bruton's tyrosine kinase (BTK) inhibition promotes myelin repair in two different models of demyelination	Aigrot M S, Martin E, Grenningloh R, Stankoff B, Lubetzki C, Boschert U, Zalc B	A-1026-0025-01553	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM
Inhibition of Bruton's Tyrosine Kinase Selectively Prevents Antigen-Activation of B cells and Ameliorates B cell-Mediated Experimental Autoimmune Encephalomyelitis	Torke S, Häusler D, Grenningloh R, Boschert U, Brück W and Weber M S	A-1026-0031-01785	Session Title: Poster Session 2 Session Date: 09.12.2019 Presenting Time: 5:15-7:15 PM
Effect of evobrutinib, a Bruton's tyrosine kinase inhibitor, on immune cell and immunoglobulin levels over 48 weeks in a phase 2 study in relapsing multiple sclerosis	Montalban X, Shaw J, Syed S, Dangond F, Martin E C, Grenningloh R, Weber MS, on behalf of the Evobrutinib Phase 2 Study Group	A-1026-0031-01645	Session Title: Poster Session 3 Session Date: 09.13.2019 Presenting Time: 12:15-2:15 PM

MAVENCLAD, approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019, is the first and only short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). Patients should follow healthcare provider instructions including cancer screening, contraception and blood tests. The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. MAVENCLAD causes a dose-dependent reduction in lymphocyte counts followed by recovery.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

MAVENCLAD has been approved in over 60 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis for patients with prior or increased risk of malignancy.**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm.**

CONTRAINDICATIONS

- Current malignancy.

course.

- Human immunodeficiency virus (HIV).
- Active chronic infections (e.g., hepatitis or tuberculosis).
- History of hypersensitivity to cladribine.
- Breastfeeding while taking MAVENCLAD and for 10 days after the last dose.

DOSING CONSIDERATIONS: After the completion of 2 treatment courses, do not administer additional MAVENCLAD during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after completion of 2 treatment courses has not been studied.

ADDITIONAL WARNINGS AND PRECAUTIONS

- **Lymphopenia:** In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Monitor for infections.
- **Hematologic Toxicity**: Mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions**: Irradiation of cellular blood components is recommended.
- **Liver Injury**: Obtain liver function tests prior to treatment. Discontinue MAVENCLAD if significant injury is suspected.
- **Hypersensitivity**: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Serious hypersensitivity reactions occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue treatment. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Please see the full **Prescribing Information,** including **boxed WARNING** for additional information.

About Rebif® (interferon beta-1a)

Rebif (interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It is used to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS. The efficacy and safety of Rebif in controlled clinical trials beyond 2-years has not been established.

IMPORTANT SAFETY INFORMATION:

Rebif is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

Rebif should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif if hepatic injury occurs.

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif. Discontinue Rebif if anaphylaxis occurs.

injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, discontinue Rebif until skin lesions are healed.

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in Rebif-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in Rebif-treated patients than in placebo and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

Cases of thrombotic microangiopathy (TMA), some fatal, have been reported with interferon beta products, including Rebif, up to several weeks or years after starting therapy. Discontinue Rebif if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including Rebif, in clinical trials and in postmarketing reports.

The most common side effects with Rebif are injection-site disorders, headaches, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

There are no adequate and well-controlled studies in pregnant women. Rebif should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please see the full Prescribing Information for additional information: http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf?Version=

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly selective inhibitor of Bruton's tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and

suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common, non-traumatic, disabling neurological disease in young adults. It is estimated that approximately 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

EMD Serono, Inc. and Multiple Sclerosis

For more than 20 years, EMD Serono has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. EMD Serono is digging deeper to advance the science.

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 1,300 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com

Your Contact
alice.mcgrail@emdserono.com
Phone: +1 781 738 8791

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EMD Serono Initiates Pivotal Phase III Program for Investigational Evobrutinib in Relapsing Multiple Sclerosis

EXPLORE MORE

- EVOLUTION RMS 1 and 2 pivotal Phase III trials will investigate the efficacy and safety of evobrutinib in relapsing multiple sclerosis

- Evobrutinib is the first oral, highly selective Bruton's Tyrosine Kinase inhibitor to show clinical proof of concept in relapsing multiple sclerosis

- Decision to initiate Phase III program based on effect seen with evobrutinib on magnetic resonance imaging endpoints at 24 weeks and annualized relapse rate over 48 weeks in Phase II

- Unique collaboration with Accelerated Cure Project for Multiple Sclerosis provided guidance on patient-reported outcomes measures and clinical study design

ROCKLAND, Mass., Sept. 10, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced the initiation of two global pivotal Phase III trials (EVOLUTION RMS 1 and 2) studying the efficacy and safety of evobrutinib, an oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor in adult patients with relapsing multiple sclerosis (RMS).

could address MS pathobiology in a fundamentally new way," said Luciano Rossetti, Head of Global R&D for EMD Serono. "Evobrutinib, which was developed in our own laboratories, is an oral, highly selective BTK inhibitor that has shown clinical proof of concept in RMS. Progressing this molecule into Phase III is an important step for us and the MS community, with an opportunity to further advance on benefit-risk considerations for RMS patients."

Evobrutinib is entering Phase III trials following the results of the Phase II clinical trial, which met its primary endpoint over 24 weeks of treatment, where the total cumulative number of T1 gadolinium-enhancing (Gd+) lesions was reduced with evobrutinib compared with placebo. The reduction of T1 Gd+ lesions was observed at 12 weeks, the first time point at which magnetic resonance imaging (MRI) data was available, and maintained through 48 weeks with evobrutinib 75 mg QD (once a day) and 75 mg BID (twice a day). Further data show that the effect on relapse reduction observed at Week 24 was maintained through 48 weeks.

In the Phase II trial, the most commonly observed adverse events of any grade associated with evobrutinib included nasopharyngitis and increases in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lipase. All events had an onset within 24 weeks of treatment initiation and were reversible on treatment discontinuation with no clinical consequences within the 52-week safety period. During the course of the study, 85% of patients (227 out of 267) completed 52 weeks of treatment.

EVOLUTION RMS 1 and 2 are multicenter, randomized, parallel group, double-blind, active-controlled studies comparing evobrutinib twice-daily with interferon beta-1a given intramuscularly once a week. The primary endpoint of both studies is annualized relapse rate (ARR) at Week 96. Secondary endpoints include time to first occurrence of 12- and 24-week confirmed Expanded Disability Status Scale (EDSS) Progression and total number of Gd+ T1 lesions and new or enlarging T2 lesions assessed by MRI.

As part of the company's commitment to patient-focused drug development, EMD Serono collaborated with the Accelerated Cure Project (ACP) for Multiple Sclerosis and its iConquerMS people-powered research network to capture and integrate the perspectives of people affected by MS into the design and implementation of the clinical trials. Through this innovative collaboration, a council of individuals living with MS provided feedback and insights on t

relevance of PRO measures to the real-world patient experience and insights on patient-facing materials. This engagement largely focused on the two PROs included as secondary endpoints: change from baseline in Patient Reported Outcomes Measurement Information System (PROMIS) MS Physical Function (PF) and the PROMIS MS Fatigue Scores at 96 Weeks.

"Even with the most effective therapies for RMS, more than 50% of patients experience clinical or subclinical disease activity, therefore a need still exists for novel oral therapies that address MS pathobiology differently," noted Dr. Xavier Montalban, Professor of Medicine and Department Division Director, Neurology, at the University of Toronto, Director of the MS Centre at St. Michael's Hospital, Canada, Chairman & Director Neurology-Neuroimmunology Department & Neurorehabilitation Unit, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain and principal investigator for the EVOLUTION RMS 2 trial. "We look forward to seeing the outcomes of this clinical program following the promising Phase II results."

Trial recruitment is currently underway with the goal of 1,900 patients enrolled. The target completion is in June 2023.

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly selective inhibitor of Bruton's tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. The global Phase III clinical development program evaluating evobrutinib in MS includes two pivotal studies, EVOLUTION RMS 1 and 2. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common, non-traumatic, disabling neurological disease in young adults. It is estimated that approximately 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the l

EMD Serono, Inc. and Multiple Sclerosis

For more than 20 years, EMD Serono has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. EMD Serono is digging deeper to advance the science.

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 1,300 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com

Your Contact
alice.mcgrail@emdserono.com
Phone: +1 781 738 8791

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CHMP Adopts Positive Opinion for BAVENCIO® (avelumab) Plus Axitinib for First-Line Treatment of Patients with Advanced Renal Cell Carcinoma

- Opinion based on Phase III data showing combination lowered risk of disease progression or death by 31% and improved objective response rate compared with sunitinib1

- Decision by the European Commission anticipated in fourth quarter of 2019

Rockland, MA and New York, US, September 20, 2019 – 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) in combination with axitinib for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC). The opinion was based on positive findings from the Phase III JAVELIN Renal 101 study, which demonstrated a significant extension in median progression-free survival (PFS) and a clinically meaningful improvement in objective response rate (ORR) for the combination across all prognostic risk groups compared with sunitinib.[1] The CHMP positive opinion will be reviewed by the European Commission (EC), with

"Today's positive CHMP opinion is a significant step toward potentially transforming the treatment landscape and bringing much needed options to people living with advanced renal cell carcinoma in Europe. We believe that the combination of BAVENCIO plus axitinib has the potential to help address a significant need for patients with advanced renal cell carcinoma for first-line treatments with a benefit across all prognostic risk groups, and we look forward to a decision from the European Commission," said Luciano Rossetti, Head of Global R&D for EMD Serono.

In 2018, an estimated 136,500 new cases of kidney cancer were diagnosed in Europe, and approximately 54,700 people died from the disease.[2] RCC is the most common form of kidney cancer, accounting for about 3% of all cancers in adults.[2] Approximately 20% to 30% of patients are first diagnosed with RCC at the advanced stage, and 30% of patients treated for an earlier stage go on to develop metastases.[3,4] About half of patients living with advanced RCC do not go on to receive additional treatment after first-line therapy,[5,6] for reasons that may include poor performance status or adverse events from their initial treatment.[5,7,8] The five-year survival rate for patients with metastatic RCC is approximately 12%.[9]

"Kidney cancer represents a significant burden in Europe, where incidence rates are among the highest in the world," said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. "Pfizer has been a leader in the development of kidney cancer treatments for more than a decade, and it is a privilege to continue our efforts to bring a new treatment option to this community."

The U.S. Food and Drug Administration (FDA) approved BAVENCIO in combination with axitinib for the first-line treatment of patients with advanced RCC in May 2019.[10] A supplemental application for BAVENCIO in combination with axitinib in unresectable or metastatic RCC was submitted in Japan in January 2019.

About the JAVELIN Renal 101 Study

The Phase III JAVELIN Renal 101 study is a randomized, multicenter, open-label study of BAVENCIO in combination with axitinib in 886 patients with untreated advanced or metastatic RCC. The major efficacy outcome measures were PFS as assessed by a Blinded Independent Central Review (BICR) using RECIST v1.1 and overall survival (OS) in the first-line treatment of patients with advanced RCC who have PD-L1-positive tumors (PD-L1 expression level ³1%). If

OS irrespective of PD-L1 expression, objective response, time to response (TTR), duration of response (DOR) and safety are included as secondary endpoints. The study is continuing for OS.

About the JAVELIN Clinical Development Program

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and more than 10,000 patients evaluated across more than 15 different tumor types. In addition to RCC, these tumor types include gastric/gastro-esophageal junction cancer, head and neck cancer, Merkel cell carcinoma, non-small cell lung cancer and urothelial carcinoma.

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.[11-13] BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[13-15] In November 2014, EMD Serono and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indication in the US

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

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 Grade 5, 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

hepatitis occurred with BAVENCIO as a single agent in 0.9% of patients, including two (0.1%) patients with Grade 5, 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 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.

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 and for subsequent infusions 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-

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.

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

Axitinib Important Safety Information from the US FDA-Approved Label
Hypertension including **hypertensive crisis** has been observed with axitinib. Blood pressure should be well controlled prior to initiating axitinib. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue axitinib if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of axitinib, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed with axitinib and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported with axitinib. Axitinib has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

may require permanent discontinuation of axitinib.

Gastrointestinal perforation and fistula, including death, have occurred with axitinib. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported with axitinib. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of axitinib on **wound healing** have been conducted. Stop axitinib at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed with axitinib. If signs or symptoms occur, permanently discontinue treatment.

Proteinuria has been observed with axitinib. Monitor for proteinuria before initiation of, and periodically throughout, treatment with axitinib. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with axitinib. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. Axitinib has not been studied in patients with severe hepatic impairment.

Axitinib can cause **fetal harm**. Advise patients of the potential risk to the fetus and to use effective contraception during treatment.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

Please see full Prescribing Information for axitinib.

(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%).

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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 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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 52,000 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

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 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 September 20, 2019. 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 new indication in the European Union for BAVENCIO in combination with axitinib for the treatment of patients with advanced renal cell carcinoma, 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

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 and uncertainties regarding whether the other primary endpoint of JAVELIN Renal 101 will be met; 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 in combination with axitinib in any other jurisdictions or in any jurisdictions for any other potential indications for BAVENCIO or combination therapies; whether and when the pending applications in the European Union and Japan for BAVENCIO in combination with axitinib may be approved 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 in combination with axitinib 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 or combination therapies, including BAVENCIO in combination with axitinib; 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, 2018, 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. Motzer R, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma. *The New England Journal of Medicine*. 2019;380:1103-1115.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356-387.
3. Ljungberg B, Campbell S, Cho H. The epidemiology of renal cell carcinoma. *Eur Urol*. 2011;60:615-621.

6. Eggers H, Ivanyi P, Hornig M, Grunwald V. Predictive factors for second-line therapy in metastatic renal cell carcinoma: a retrospective analysis. *J Kidney Cancer VHL*. 2017;4(1):8-15.
7. Motzer R, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *The New England Journal of Medicine*. 2018;378:1277-1290.
8. Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: A randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. *Eur Urol*. 2015;68;837-847.
9. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2014;32:2765-2772.
10. Ridge C, Pua B, Madoff D. Epidemiology and staging of renal cell carcinoma. *Semin Intervent Radiol.* 2014;31(1):3-8.
11. BAVENCIO Prescribing Information. Rockland, MA: EMD Serono Inc.; 2019.
12. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. *Cancer Control.* 2014;21(3):231-237.
13. Dahan R, Sega E, Engelhardt J, et al. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell.* 2015;28(3):285-295.
14. 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.
15. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. *Immunotherapy.* 2012;4(5):511-527.
16. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. *Expert Opin Biol Ther.* 2017;17(4):515-523.

New Data at ESMO 2019 for EMD Serono Highlight Focused Clinical Development and Commitment to Patient Care

EXPLORE MORE

- **New subgroup analyses for first-line treatment of advanced renal cell carcinoma with BAVENCIO®* (avelumab) in combination with axitinib**
- **Three-year overall survival data for patients treated first-line with ERBITUX® (cetuximab) plus FOLFOX-4 in metastatic colorectal cancer**
- **Data across several therapeutic agents showcase progress of early- to late-stage pipeline, including tepotinib†, and novel combinations**

Rockland, Massachusetts, September 23, 2019 – EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, today announced that new data representing several key therapeutic agents from its diverse oncology pipeline will be presented at the 2019 European Society for Medical Oncology (ESMO) Congress, September 27–October 1, in Barcelona, Spain.

Spanning multiple tumor types, data being presented include new evidence supporting approved treatments BAVENCIO®* (avelumab) and ERBITUX® (cetuximab), and new research from EMD Serono's, early pipeline, including novel combinations and the investigational targeted therapy tepotinib†, recently granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA) in patients with metastatic non-small cell lung cancer

Ministry of Health, Labour and Welfare (MHLW), which granted SAKIGAKE 'fast-track' designation for tepotinib in advanced NSCLC harboring *MET* exon 14 skipping alterations.

"Our presence at ESMO underscores our commitment to research and development in highly focused areas within immuno-oncology, precision medicine and DNA damage response," said Luciano Rossetti, Global Head of Research & Development for EMD Serono. "We believe that by applying cutting-edge science in our clinical programs we are getting closer to making a difference in patient outcomes."

New data for BAVENCIO® will include two poster discussions from the Phase III JAVELIN Renal 101 study evaluating efficacy of first-line treatment with avelumab in combination with axitinib compared with sunitinib in two clinically relevant subgroups of patients with advanced renal cell carcinoma (RCC): those with sarcomatoid histology and those who did not undergo upfront cytoreductive nephrectomy. Results from JAVELIN Renal 101 supported the recent US FDA approval and the positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for BAVENCIO® plus axitinib for first-line treatment of adult patients with advanced RCC.

ERBITUX® data further reinforce the impact of primary tumor location on three-year overall survival among patients from China with *RAS* wild-type metastatic colorectal cancer (mCRC) treated with first-line FOLFOX-4 with or without cetuximab from the Phase III TAILOR trial. Additionally, a pooled analysis of patient-level data explores the effect on overall survival of cetuximab in combination with chemotherapy dosed once every two weeks, compared with once-weekly dosing, for first-line treatment in patients with *RAS* wild-type mCRC. These two sets of results underscore the clinical benefit of cetuximab and add to the growing body of evidence supporting its role in combination with chemotherapy in first-line *RAS* wild-type mCRC.

New research will be presented from across the company's earlier pipeline, including a pooled analysis of safety data across Phase I and II studies in advanced solid tumors for the investigational oral MET inhibitor tepotinib.

A number of investigator-sponsored studies (ISS) and collaborative research studies (CRS) exploring EMD Serono's pipeline will also be presented at this year's congress, including a late-breaking oral presentation on results from a randomized Phase II study of M6620‡, an

compared with gemcitabine alone in platinum-resistant high-grade serous ovarian cancer. The study is sponsored by the National Cancer Institute (NCI) under its Cooperative Research and Development Agreement with Merck KGaA, Darmstadt, Germany for M6620, and these results are the first-ever randomized data to be presented for an ATR inhibitor.

**The combination of BAVENCIO® and axitinib is approved for the first-line treatment of advanced RCC only in the United States and Argentina. There is no guarantee that avelumab in combination with axitinib will be approved for RCC by any other health authority worldwide.*

†Tepotinib is the recommended International Nonproprietary Name (INN) for the MET kinase inhibitor (MSC2156119J). Tepotinib is currently under clinical investigation and not approved for any use anywhere in the world.

‡M6620 is currently under clinical investigation and not approved for any use anywhere in the world.

Notes to Editors

Key EMD Serono, ISS and CRS abstracts scheduled for presentation are listed below.

Title	Lead Author	Abstract #	Presentation Date / Time (CEST)	Location
BAVENCIO® (avelumab)				
Poster Discussions				
Efficacy and biomarker	TK. Choueiri	4823	Sunday, September	Hall 2 – Pamplona

sarcomatoid subgroup from the phase 3 JAVELIN Renal 101 trial of first-line avelumab plus axitinib (A + Ax) vs sunitinib (S) for advanced renal cell carcinoma (aRCC)			PM (3:15 PM lecture time)	Poster Board No. 910PD
Primary renal tumour shrinkage in patients (pts) who did not undergo cytoreductive nephrectomy (CN): subgroup analysis from the phase 3 JAVELIN Renal 101 trial of first-line avelumab	L. Albiges	4174	Sunday, September 29, 2019, 3:00–3:15 PM (3:15 PM lecture time)	Hall 2 – Pamplona Auditorium Poster Board No. 908PD

sunitinib (S) for advanced renal cell carcinoma (aRCC)				

Poster Sessions

Long-term avelumab treatment in patients with advanced non-small cell lung cancer (NSCLC): post-hoc analysis from JAVELIN Solid Tumor	B. Hrinczenko	4256	Saturday, September 28, 2019, 12:00–1:00 PM	Hall 4 - Poster Area Poster Board No. 1493P
Assessing the impact of subsequent immunotherapy treatment on overall survival: a post-hoc analysis of the phase 3	F. Barlesi	5113	Saturday, September 28, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 1492P

avelumab vs docetaxel in patients with platinum-treated NSCLC				
Randomized phase 3 trial of avelumab + axitinib vs sunitinib as first-line treatment for advanced renal cell carcinoma: JAVELIN Renal 101 Japanese subgroup analysis	M. Uemura	1451	Monday, September 30, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 956P
Health-related quality of life in patients with metastatic Merkel cell carcinoma receiving second-line or later avelumab treatment: 36-month follow-up data	SP. D'Angelo	3152	Monday, September 30, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 1320P

Poster Session				
Impact of primary tumor side on 3-year survival outcomes of first-line (1L) FOLFOX-4 ± cetuximab in patients with RAS wild-type (wt) metastatic colorectal cancer (mCRC) in the phase 3 TAILOR trial	S. Qin	4455	Sunday, September 29, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 591P
The cost of adverse event management in patients with RAS wild-type metastatic colorectal cancer treated with first-line cetuximab and panitumumab: an Italian healthcare	K. Patterson	1212	Sunday, September 29, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 596P

Non-inferiority on overall survival of every- 2-weeks vs weekly schedule of cetuximab for the first-line treatment of RAS wild-type metastatic colorectal cancer	S. Kasper	2589	Sunday, September 29, 2019, 12:00 – 1:00 PM	Hall 4 – Poster Area Poster Board No. 584P
Tepotinib				
Poster Session				
Safety Profile of Tepotinib in Patients with Advanced Solid Tumors: Pooled Analysis of Phase I and II Data	T. Decaens	3930	Saturday, September 28, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 479P
Drug-drug interaction	J. Heuer	5373	Saturday, September	Hall 4 – Poster

CYP3A and P-gp substrates			PM	Poster Board No. 480P
Bioavailability of tepotinib: impact of omeprazole and food	J. Heuer	5455	Saturday, September 28, 2019, 12:00-1:00 PM	Hall 4 – Poster Area Poster Board No. 481P
Combinations				
M6620 Oral Session				
Randomized Phase 2 Study of ATR inhibitor M6620 in Combination with Gemcitabine versus Gemcitabine alone in Platinum Resistant High	PA. Konstantinopoulos	1547 LBA60	Friday, September 27, 2019, 4:45–5:00 PM	Hall 2 – Pamplona Auditorium

(HGSOC) (NCT02595892)				
Poster Session				
Phase 1b, open-label, dose-escalation study of M9241 (NHS-IL12) plus avelumab in patients (pts) with advanced solid tumors	J. Strauss	4062	Monday, September 30, 2019, 12:00–1:00 PM	Hall 4 – Poster Area Poster Board No. 1264P
Avelumab-cetuximab-radiotherapy versus standards of care in locally advanced squamous cell carcinoma of head and neck: safety phase of randomized trial GORTEC 2017-01 (REACH)	Y. Tao	4934	Saturday, September 28, 2019, 8:45–9:45 AM (9:05 AM lecture time)	Hall 5 – Bilbao Auditorium Poster Board No. 1118PD

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.[1-3] BAVENCIO® has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[3-5] In November 2014, Merck KGaA, Darmstadt, Germany and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO®.

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and about 10,000 patients evaluated across more than 15 different tumor types. These tumor types include RCC, gastric/gastro-esophageal junction cancer, head and neck cancer, Merkel cell carcinoma, non-small cell lung cancer, and urothelial carcinoma.

BAVENCIO Approved Indications in the US

BAVENCIO® (avelumab) in combination with INLYTA® (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 (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in more than 45 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

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

including one (0.1%) patient with Grade 5, 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 Grade 5, and 11 (0.6%) with Grade 3.

> *BAVENCIO in combination with INLYTA* 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 INLYTA 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 INLYTA, 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. Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Hepatotoxicity led to permanent discontinuation in 6.5% and immune-mediated hepatitis led to permanent discontinuation of either BAVENCIO or axitinib in 5.3% of patients.

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.

(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 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%

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 and for subsequent infusions 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% of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO in combination with INLYTA 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 INLYTA for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with INLYTA 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.

Clinical chemistry and hematology laboratory values abnormalities have been reported with BAVENCIO and also BAVENCIO in combination with INLYTA including but not limited to grade 3-4 lymphopenia, anemia, elevated cholesterol and liver enzymes.

INLYTA Important Safety Information from the US FDA-Approved Label

Hypertension including **hypertensive crisis** has been observed with INLYTA. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed with INLYTA and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported with INLYTA. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed with INLYTA and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred with INLYTA. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported with INLYTA. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed with INLYTA. If signs or symptoms occur, permanently discontinue treatment.

dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

INLYTA can cause **fetal harm**. Advise patients of the potential risk to the fetus and to use effective contraception during treatment.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

For more information and full Prescribing Information, visit www.INLYTA.com.

ADVERSE REACTIONS (BAVENCIO + INLYTA)

Fatal adverse reactions occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving BAVENCIO in combination with INLYTA. 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 INLYTA (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 INLYTA (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%),

count decreased (27% vs 80%), blood bilirubin increased (21% vs 23%), and hemoglobin decreased (21% vs 65%).

About ERBITUX® (cetuximab)

ERBITUX® is an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR). As a monoclonal antibody, the mode of action of ERBITUX® is distinct from standard non-selective chemotherapy treatments in that it specifically targets and binds to the EGFR. This binding inhibits the activation of the receptor and the subsequent signal-transduction pathway, which results in reducing both the invasion of normal tissues by tumor cells and the spread of tumors to new sites. It is also believed to inhibit the ability of tumor cells to repair the damage caused by chemotherapy and radiotherapy and to inhibit the formation of new blood vessels inside tumors, which appears to lead to an overall suppression of tumor growth. Based on *in vitro* evidence, ERBITUX® also targets cytotoxic immune effector cells towards EGFR-expressing tumor cells (antibody-dependent cell-mediated cytotoxicity [ADCC]).

ERBITUX® has already obtained market authorization in over 100 countries worldwide for the treatment of RAS wild-type metastatic colorectal cancer and for the treatment of squamous cell carcinoma of the head and neck. Merck KGaA, Darmstadt, Germany licensed the right to market ERBITUX®, a registered trademark of ImClone LLC, outside the U.S. and Canada from ImClone LLC, a wholly owned subsidiary of Eli Lilly and Company, in 1998.

ERBITUX® Important Safety Information from the US FDA-Approved Label

The US Prescribing Information for ERBITUX® includes BOX WARNINGS for infusion reactions and cardiopulmonary arrest. Very commonly (≥25%) reported side effects with ERBITUX® include cutaneous adverse reactions (including acne-like skin rash, pruritus, and nail changes), headache, diarrhea, infection and hypomagnesemia.

WARNING: INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: ERBITUX® can cause serious and fatal infusion reactions [see Warnings and Precautions (5.1), Adverse Reactions (6)]. Immediately interrupt and permanently discontinue ERBITUX® for serious infusion reactions [see Dosage and Administration (2.4)].

Cardiopulmonary Arrest: Cardiopulmonary arrest or sudden death occurred in patients with squamous cell carcinoma of the head and neck receiving ERBITUX® with radiation therapy or a

cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX® administration [see Warnings and Precautions (5.2, 5.6)].

Please see full US Prescribing Information available at www.accessdata.fda.gov

About Tepotinib

Tepotinib, discovered in-house at Merck KGaA, Darmstadt, Germany, is an investigational oral MET inhibitor that is designed to inhibit the oncogenic MET receptor signaling caused by *MET* (gene) alterations, including both *MET* exon 14 skipping mutations and *MET* amplifications, or MET protein overexpression. It has been designed to have a highly selective mechanism of action, with the potential to improve outcomes in aggressive tumors that have a poor prognosis and harbor these specific alterations.

Tepotinib is currently being investigated in NSCLC and Merck KGaA, Darmstadt, Germany is actively assessing the potential of investigating tepotinib in combination with novel therapies and other tumor indications.

References

1. Dolan DE and Gupta S. Cancer Control 2014;21:231–7.
2. Dahan R, et al. Cancer Cell 2015;28:285–95.
3. Boyerinas B, et al. Cancer Immunol Res 2015;3:1148–57.
4. Kohrt HE, et al. Immunotherapy 2012;4:511–27.
5. Hamilton G and Rath B. Expert Opin Biol Ther 2017;17:515–23.

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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

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 multiple sclerosis. Today, the business has approximately 1,300 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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 52,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 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 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.

EMD SERONO

COMPLIANCE & TRANSPARENCY

THERAPEUTIC AREAS

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SITEMAP

LEGAL STATEMENT

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New Data for BAVENCIO® (avelumab) for Advanced Cancers to Be Presented at ESMO 2019

Not intended for UK-based media

- Analyses from the Phase III JAVELIN Renal 101 study support efficacy of BAVENCIO plus axitinib across multiple subgroups of patients with advanced renal cell carcinoma (RCC)
- Abstracts highlight data on BAVENCIO as a monotherapy and in combination in multiple advanced cancers

ROCKLAND, Massachusetts and NEW YORK, Sept. 27, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced the presentation of multiple analyses from the JAVELIN clinical development program assessing BAVENCIO® (avelumab) alone or as part of combination regimens for the treatment of advanced cancers, including renal cell carcinoma (RCC), metastatic Merkel cell carcinoma (mMCC) and some other solid tumors at the European Society for Medical Oncology (ESMO) Congress 2019 in Barcelona, Spain.

"These data at ESMO underscore the clinical activity of treatment with BAVENCIO across multiple tumor types and patient populations," said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. "Furthermore, these

"The immunotherapy era has led to vast progress in the treatment of cancer, yet we know that many patients with advanced or aggressive cancers still need additional treatment options," said Luciano Rossetti, Head of Global R&D for EMD Serono. "We are committed to continued research of BAVENCIO as we seek to further advance treatment options for patients with certain cancers."

Data to be presented at ESMO include three subgroup analyses of the Phase III JAVELIN Renal 101 study (NCT02684006), a randomized, multicenter, open-label study of BAVENCIO in combination with axitinib in 886 patients with untreated advanced RCC from patients across all International Metastatic RCC Database Consortium (IMDC) risk groups. This study, results of which were published in *The New England Journal of Medicine* in February 2019, demonstrated that BAVENCIO in combination with axitinib significantly improved progression-free survival (PFS) compared with sunitinib in patients with advanced RCC, with a generally acceptable safety tolerability profile, including serious adverse events.[1]

Results from new analyses of JAVELIN Renal 101 being presented at ESMO, which assessed the effect of BAVENCIO in combination with axitinib in subgroups including patients who did not undergo cytoreductive nephrectomy, patients with sarcomatoid histology, and Japanese patients, are consistent with findings from the overall JAVELIN Renal 101 study population and provide a better understanding of the combination in a broad range of patients with advanced RCC. In May 2019, the U.S. Food and Drug Administration (FDA) approved BAVENCIO in combination with axitinib for the first-line treatment of patients with advanced RCC.[2] The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending approval of BAVENCIO in combination with axitinib for the first-line treatment of adult patients with advanced RCC in September 2019.

Presentation #908PD: Phase III JAVELIN Renal 101 Study Subgroup Analysis of Patients with Advanced RCC who did not Undergo Upfront Cytoreductive Nephrectomy

- Sunday, September 29, 15:20 – 15:20: Pamplona Auditorium (Hall 2)

A post-hoc analysis of JAVELIN Renal 101 evaluated patients with advanced RCC who did not undergo prior surgery to remove as much of the visible tumors on the kidneys as possible (cytoreductive nephrectomy), which comprised 20.2% of participants in the study. The findings

the primary renal tumor versus sunitinib (≥30% shrinkage for best percent change in renal target lesions from baseline in 34.5% versus 9.7%, respectively).[3] The majority of patients with advanced RCC undergo nephrectomy before starting systemic treatment,[4] and those who do undergo nephrectomy may experience complications or delays in treatment.[5] These results are the first of their kind to report the efficacy of an immunotherapy plus a tyrosine kinase inhibitor in patients with advanced RCC when there is still a primary tumor present.[3]

Presentation #910PD: Phase III JAVELIN Renal 101 Study Subgroup Analysis of Patients with Advanced RCC with Sarcomatoid Histology

- Sunday, September 29, 15:20 – 15:20: Pamplona Auditorium (Hall 2)

A post-hoc analysis of JAVELIN Renal 101 in patients with advanced RCC with sarcomatoid histology, an aggressive subtype of RCC[6] that carries the worst prognosis for patients with renal tumors,[7,8] included 12.2% of participants in the trial. The results presented at ESMO showed that BAVENCIO plus axitinib improved PFS and objective response rate (ORR) versus sunitinib in patients with advanced RCC with sarcomatoid histology (median PFS: 7.0 months versus 4.0 months, HR 0.57 [95% CI, 0.325-1.003]; median ORR: 46.8% versus 21.3%). These findings provide insight into the biology of sarcomatoid histology and treatment with this immunotherapy in this subgroup of patients.[9]

Presentation #956P: Phase III JAVELIN Renal 101 Study Subgroup Analysis of Japanese Patients with Advanced RCC

- Monday, September 30, 12:20 - 12:20: Poster Area (Hall 4)

An analysis assessing the efficacy and safety of Japanese patients with advanced RCC (n=67) in JAVELIN Renal 101 study showed that BAVENCIO in combination with axitinib improved median PFS compared to sunitinib in Japanese patients with advanced RCC regardless of PD-L1 expression (16.6 months versus 11.2 months, respectively; HR, 0.66; [95% CI, 0.30-1.46]). Common treatment-emergent adverse events (grade ≥3) in each arm included hand-foot syndrome (9% versus 9%), hypertension (30% versus 18%), and platelet count decreased (0% versus 32%).[10] A supplemental application for BAVENCIO in combination with axitinib in unresectable or metastatic RCC was submitted in Japan in January 2019.

- An analysis of health-related quality of life (HRQoL) from the Phase II JAVELIN Merkel 200 study, in which patients with mMCC, an aggressive form of skin cancer with poor outcomes,[11] treated with BAVENCIO reported stable or improved HRQoL across various time points (presentation #1320P).[12]
- Interim results from the Phase Ib JAVELIN IL-12 study evaluating BAVENCIO in combination with M9241, EMD Serono's investigational IL-12 fusion protein containing an anti-DNA antibody, in patients with solid tumors, which informed the recommended dosing for Phase II of this study (presentation #1224P).[13]
- Post-hoc analyses from the JAVELIN Solid Tumor Phase I trial (presentation #1493P)[14] and Phase III JAVELIN Lung 200 study (presentation #1492P)[15] that further elucidate the effects of BAVENCIO in patients with advanced non-small cell lung cancer.

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.[16-18] BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[18-20] In November 2014, EMD Serono and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indications

BAVENCIO® (avelumab) 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 (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

treatment.

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 Grade 5, 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 Grade 5, 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 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 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,

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 and for subsequent infusions 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% 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.

Axitinib Important Safety Information from the US FDA-Approved Label

Hypertension including **hypertensive crisis** has been observed with axitinib. Blood pressure should be well controlled prior to initiating axitinib. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue axitinib if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of axitinib, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed with axitinib and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported with axitinib. Axitinib has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Cardiac failure has been observed with axitinib and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with axitinib. Management of cardiac failure may require permanent discontinuation of axitinib.

Gastrointestinal perforation and fistula, including death, have occurred with axitinib. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported with axitinib. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of axitinib on **wound healing** have been conducted. Stop axitinib at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed with axitinib. If signs or symptoms occur, permanently discontinue treatment.

dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with axitinib. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. Axitinib has not been studied in patients with severe hepatic impairment.

Axitinib can cause **fetal harm**. Advise patients of the potential risk to the fetus and to use effective contraception during treatment.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

Please see full Prescribing Information for axitinib.

ADVERSE REACTIONS (BAVENCIO + AXITINIB)

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%),

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 **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%).

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

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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 52,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 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 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

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 September 27, 2019. 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 new indication approved in the U.S. for BAVENCIO in combination with axitinib for the treatment of patients with advanced renal cell carcinoma, 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 and axitinib; 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 and uncertainties regarding whether the other primary endpoint of JAVELIN Renal 101 will be met; 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 in combination with axitinib in any other jurisdictions or in any jurisdictions for any other potential indications for BAVENCIO or combination therapies; whether and when the pending applications in the European Union and Japan for BAVENCIO in combination with axitinib may be approved and whether and when regulatory authorities in any jurisdictions where any other applications are pending or may be

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 or combination therapies, including BAVENCIO in combination with axitinib; 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, 2018, 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. Motzer R, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019; 380:1103-1115.
2. BAVENCIO Prescribing Information. Rockland, MA: EMD Serono Inc.; 2019.
3. Albiges L, et al. Primary renal tumour shrinkage in patients (pts) who did not undergo upfront cytoreductive nephrectomy (uCN): subgroup analysis from the phase 3 JAVELIN Renal 101 trial of first-line avelumab + axitinib (A + Ax) vs sunitinib (S) for advanced renal cell carcinoma (aRCC). *Annals of Oncology.* 2019. TBD.
4. Culp S. Cytoreductive nephrectomy and its role in the present-day period of targeted therapy. *Ther Adv Urol*. 2015;7(5):275-285.
5. Silberstein J, et al. Systemic classification and prediction of complications after nephrectomy in patients with metastatic renal cell carcinoma (RCC). *BJU Int*. 2012;110(9):1276-1282.
6. Pichler, Renate et al. "Renal Cell Carcinoma with Sarcomatoid Features: Finally New Therapeutic Hope?" *Cancers*. 2019;11(3):422.
7. Al-Juhaishi, T et al. "Survival outcomes in sarcomatoid renal cell carcinoma." *Journal of Clinical Oncology.* 2018;36:15_suppl
8. American Cancer Society. Survival Rates for Kidney Cancer https://amp.cancer.org/cancer/kidney-cancer/detection-diagnosis-staging/survival-rates.html. Accessed September 2019.
9. Choueiri T, et al. Efficacy and biomarker analysis of patients (pts) with advanced renal cell carcinoma (aRCC) with sarcomatoid histology (sRCC): subgroup analysis from the phase 3

10. Uemura M, et al. Randomized phase 3 trial of avelumab + axitinib vs sunitinib as first-line treatment for advanced renal cell carcinoma: JAVELIN Renal 101 Japanese subgroup analysis. *Annals of Oncology.* 2019. TBD.
11. Becker, J.C., Merkel cell carcinoma, *Annals of Oncology*. 2010: 21, 7_suppl:vii81–vii85
12. D'Angelo S, et al. Health-related quality of life in patients with metastatic Merkel cell carcinoma receiving second-line or later avelumab treatment: 36-month follow up data. *Annals of Oncology.* 2019. TBD.
13. Strauss J, et al. Phase 1b, open-label, dose-escalation study of M9241 (NHS-IL12) plus avelumab in patients (pts) with advanced solid tumors. *Annals of Oncology.* 2019. TBD.
14. Hrinczenko B, et al. Long-term avelumab treatment in patients with advanced non-small cell lung cancer (NSCLC): post hoc analyses from JAVELIN Solid Tumor. *Annals of Oncology*. 2019. TBD.
15. Barlesi F, et al. Assessing the impact of subsequent checkpoint inhibitor (CPI) treatment on overall survival: post hoc analyses from the phase 3 JAVELIN Lung 200 study of avelumab vs docetaxel in platinum-treated locally advanced/metastatic non-small cell lung cancer (NSCLC). *Annals of Oncology.* 2019. TBD.
16. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. *Cancer Control.* 2014;21(3):231-237.
17. Dahan R, Sega E, Engelhardt J, et al. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell.* 2015;28(3):285-295.
18. 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.
19. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. *Immunotherapy.* 2012;4(5):511-527.
20. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. *Expert Opin Biol Ther.* 2017;17(4):515-523.

Your Contacts

EMD Serono Inc.

Media

Noelle Piscitelli

+1-781-427-4351

Investor Relations

+49-6151-72-3321

Jessica Smith
+1-212-733-6213
Investor Relations
Ryan Crowe
+1-212-733-8160

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EMD Serono Announces JAMA Publication of Phase II Results of Sprifermin for Osteoarthritis Structure Modification

- Multi-year analysis indicates investigational sprifermin increased cartilage thickness in patients with knee osteoarthritis (OA), compared with placebo in the Phase II FORWARD trial

- Dose-dependent structural changes indicate potential of sprifermin to have a structure-modifying effect in OA

- Post-hoc, exploratory analysis of the FORWARD trial, to be featured as an oral presentation at the American College of Rheumatology (ACR) Annual Meeting, supports further investigation of sprifermin as a potential disease-modifying OA treatment in a targeted at-risk patient population

- There are currently no approved OA therapies for preventing or slowing disease progression

ROCKLAND, Mass., Oct. 8, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the U.S. and Canada, today announced that results from FORWARD, a five-year, multicenter Phase II study of sprifermin, a recombinant human fibroblast growth factor-18, in patients with symptomatic radiographic knee osteoarthritis (OA) were published online in the *Journal of the American Medical Association* (JAMA). Published results, based on the two-year primary outcome and the three-year follow-up analysis from the

"The publication of these clinical data assessing therapeutic intervention for osteoarthritis in the *Journal of the American Medical Association* and at the upcoming American College of Rheumatology Annual Meeting are noteworthy," said Luciano Rossetti, Head of Global R&D for EMD Serono. "This represents an area of significant medical need, as osteoarthritis is a degenerative condition with no approved treatment options that directly target structural disease progression."

In this study of 549 patients, the primary endpoint, defined as the change in total femorotibial joint cartilage thickness from baseline at two years with sprifermin compared to placebo as measured by quantitative magnetic resonance imaging (MRI), was met. At the two-year treatment point, a mean increase in cartilage thickness was observed in the two sprifermin groups receiving the highest doses compared with the placebo group. For the groups receiving 100µg sprifermin, administered as an intra-articular injection every six months or every 12 months, the total difference in cartilage thickness was statistically significant at +0.05 mm (95% CI: 0.03-0.07) and at +0.04 mm (95% CI 0.03-0.07) respectively, compared to placebo. Two-year changes in cartilage thickness with sprifermin at a dose of 30µg every six months or every 12 months showed no significant differences versus placebo. In the three-year follow-up analysis, the statistically significant difference (+0.05 mm) in cartilage thickness, observed between sprifermin and placebo for patients who received 100µg of sprifermin every six months, was maintained.

Secondary endpoints evaluated in the trial included changes in cartilage thickness as measured by MRI in the medial and lateral compartments, as well as changes in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) core over two years. Total WOMAC scores decreased (indicating reduced symptoms) by approximately 50% compared to baseline in all treatment groups, including placebo. Statistically significant treatment effects of increased cartilage thickness were observed in the medial and lateral femorotibial compartments, including the central medial and central lateral regions, in the highest sprifermin dose group. Consistent increases in cartilage volume were observed over two years.

Adverse events were reported in more than 90% of participants across all treatment groups but were mostly mild or moderately severe and considered unrelated to treatment by the site

respiratory infection, nasopharyngitis), vascular disorders (hypertension) and nervous system disorders (headache).

Additionally, a post-hoc, exploratory analysis from the Phase II FORWARD trial that will be featured as an oral presentation at the upcoming 2019 American College of Rheumatology (ACR) Annual Meeting on Tuesday, November 12, 2019 evaluated cartilage thickness changes and symptomatic outcomes in a subgroup of OA patients with both greater pain and thinner cartilage, as measured by joint space width, at baseline who are at higher risk of further structural and symptomatic progression. In this 'at-risk' subgroup, WOMAC score improvements increased over the three-year period and were significant at Year 3 (18 months after last injection) in favor of sprifermin compared to placebo (mean difference in WOMAC pain score for sprifermin 100µg every six months versus placebo: -8.75 [95% CI -22.42, 4.92]). These results support further investigation of sprifermin as a potential OA treatment for higher-risk patient populations.

The Company is evaluating external partnership opportunities for its OA portfolio, including sprifermin, with the goal of finding the right partner to advance the development of structurally-modifying treatments to change the course of OA. By pursuing alternative paths to internally driven development, the Company plans to further focus its efforts in inflammatory neurology and immunology (N&I) diseases with potentially overlapping inflammatory mechanisms like multiple sclerosis (MS) and systemic lupus erythematosus (SLE).

There are approximately 237 million people worldwide living with symptomatic and activity-limiting OA[1], the third most rapidly rising condition associated with disability globally.[2] OA most commonly affects the knee joints.[3] Symptomatic knee OA is associated with physical disability, reduced quality of life and increased mortality in older adults.[3,4] Currently, OA therapies primarily target symptoms and there are no approved structure-modifying OA treatments for preventing or slowing disease progression.

About Sprifermin

Sprifermin is in clinical development to investigate its potential as a treatment for OA in the knee. It is a truncated recombinant human FGF-18 protein thought to induce chondrocyte proliferation and increased extra-cellular matrix (ECM) production, with the potential of promoting cartilage growth and repair. Sprifermin is currently in Phase II studies.

a five-year, multicenter, dose-finding, randomized Phase II study of sprifermin administered intra-articularly in patients with knee osteoarthritis (OA) conducted across 10 sites. Eligible participants were aged 40–85 years with symptomatic radiographic knee osteoarthritis and Kellgren-Lawrence grade 2 or 3. Enrolment began July 2013 and ended May 2014; last participant visit for the data reported here was May 2017. The primary outcome at two years and a follow-up analysis at three years are reported.

About Osteoarthritis

There are approximately 237 million people worldwide living with symptomatic and activity-limiting OA[1], the third most rapidly rising condition associated with disability globally. By the end stage of the disease, total knee replacement is often necessary. OA is likely to be the number one cause of total hip and knee replacement in the US. Currently there are no approved drugs for preventing or slowing disease progression.

References

1. GBD Collaborators et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1545–602
2. Osteoarthritis Research Society International. Osteoarthritis: a serious disease. https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa-serious-disease.pdf [Accessed September 2019]
3. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-1330.
4. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. BMJ. 2011;342:d1165.

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 1,300 employees around the

Your Contact
alice.mcgrail@emdserono.com
Phone: +1 781 738 8791

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This site contains information that is intended for US residents only. Canadian residents should consult the EMD Inc. website at www.emdserono.ca for information on products and services approved in Canada.

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Exploratory Analysis Reports Efficacy and Safety of BAVENCIO® (avelumab) Over Three Years in Previously Treated Metastatic Merkel Cell Carcinoma

- 32% of patients were alive at three years; median duration of response was 40.5 months1

- Data represent the longest prospective follow-up for an immune checkpoint inhibitor in patients with mMCC,1 a rare and aggressive type of skin cancer2

Rockland, MA and New York, US, October 22, 2019 – EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced three-year results from Part A of the pivotal Phase II JAVELIN Merkel 200 trial regarding long-term overall survival and durable responses in patients with previously treated metastatic Merkel cell carcinoma (mMCC) who received avelumab (BAVENCIO®).[1] In this exploratory analysis, the overall survival (OS) rate at three years was 32%; the median duration of response (DOR) was 40.5 months; and the objective response rate (ORR) was 33.0%, which was unchanged from the one-year analysis.[1] These data will be presented at the First International Symposium on Merkel Cell Carcinoma in Tampa, Florida on October 21-22, 2019.

200 trial, up to one-third of patients with this disease who received avelumab were alive at three years," said Sandra P. D'Angelo, M.D., study global principal investigator, medical oncologist at Memorial Sloan Kettering Cancer Center. "The durability of clinical response and survival outcomes from avelumab treatment in this setting with three years of follow-up underscore the benefits of this medicine in the treatment of patients with metastatic Merkel cell carcinoma."

Results from the Phase II, open-label, single-arm, multicenter JAVELIN Merkel 200 study supported the U.S. Food and Drug Administration (FDA) accelerated approval of BAVENCIO for mMCC in 2017. The analysis presented today shows that with a minimum follow-up of 36 months and a median follow-up of 40.8 months (range: 36.4–49.7), the ORR was 33.0% (95% CI: 23.3%, 43.8%) and median DOR was 40.5 months (95% CI: 18.0, NE). Among the 11.4% (10/88) of patients with complete responses (CR), half (n=5) had an ongoing response at the data cutoff. Progression-free survival (PFS) rates were 26% (95% CI: 17%, 36%) at two years and 21% (95% CI: 12%, 32%) at three years. Median OS was 12.6 months (95% CI: 7.5, 17.1), and OS rates were 36% (95% CI: 26%, 46%) at two years and 32% (95% CI: 23%, 42%) at three years.[1] An analysis of OS compared to historical control data was not part of this analysis.

No unanticipated adverse events (AEs) or late infusion-related reactions occurred with long-term treatment. Treatment-related AEs of any grade occurred in 77.3% of patients (grade ≥3 in 11.4%); 21.6% had an immune-related AE of any grade (grade ≥3 in 4.5%).[1]

About JAVELIN Merkel 200

JAVELIN Merkel 200 is a Phase II, open-label, single-arm, multicenter study. Part A included 88 patients with Stage IV mMCC whose disease had progressed on or after chemotherapy administered for distant metastatic disease. The primary endpoint in Part A was best overall response (BOR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC); secondary endpoints included IRC-assessed DOR and PFS by RECIST 1.1; OS; and safety and tolerability. Part B included 116 patients with mMCC who were treatment-naïve to systemic therapy in the metastatic setting. For Part B, the major efficacy outcome measure was durable response, defined as objective response (complete response or partial response) with a duration of at least six months; secondary outcome measures included BOR, DOR, PFS and OS. Patients received BAVENCIO 10

About Merkel Cell Carcinoma

Metastatic MCC is a rare and aggressive disease in which cancer cells form in the top layer of the skin, close to nerve endings.[2,3] MCC, which is also known as neuroendocrine carcinoma of the skin or trabecular cancer, often starts in those areas of skin that are most often exposed to the sun, including the head, neck and arms.[4,5] Risk factors for MCC include sun exposure and infection with Merkel cell polyomavirus.[6] Caucasian males older than 50 are at increased risk.[7] MCC is often misdiagnosed as other skin cancers and grows at an exponential rate on chronically sun-damaged skin.[5,8]

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.[9-11] BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[11-13] In November 2014, EMD Serono and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indications

In the US, the FDA granted accelerated approval for BAVENCIO for the treatment of (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in more than 50 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

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

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 Grade 5, 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 Grade 5, 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.

(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 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%

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 and for subsequent infusions 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% 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.

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%).

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 carcinoma (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%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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 axtinib (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%).

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

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 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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 56,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 billion in 66 countries.

Darmstadt, Germany operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials. Since its founding 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 October 22, 2019. 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), 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

whether and when any drug applications may be filed for BAVENCIO in any jurisdictions for potential indications for BAVENCIO or combination therapies or other product candidates; whether and when regulatory authorities in any jurisdictions where applications are pending or may be submitted for BAVENCIO or combination therapies or other product candidates 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 or combination therapies or other product candidates; 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, 2018, 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. D'Angelo S, et al. First International Symposium on Merkel Cell Carcinoma 2019. NCT02155647.
2. Becker, J.C., Merkel cell carcinoma, *Annals of Oncology*. 2010:21, 7_suppl:vii81–vii85.
3. American Cancer Society. What is Merkel cell carcinoma? http://www.cancer.org/cancer/skincancer-merkelcell/detailedguide/skin-cancer-merkel-cell-carcinoma-what-is-merkel-cell-carcinoma. Last accessed September 2019.
4. Schadendorf D et al. Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. *European Journal of Cancer.* 2017;71:53–69.
5. Nghiem P, et al. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. *Future Oncology.* 2017;13(14):1263–1279.
6. Villani A, et al. Merkel Cell Carcinoma: Therapeutic Update and Emerging Therapies. *Dermatol Ther (Heidelb).* 2019;9(2):209-222.
7. American Cancer Society. Key Statistics for Merkel Cell Carcinoma. http://www.cancer.org/cancer/merkel-cell-skin-cancer/about/key-statistics.html. Last accessed September 2019.

9. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. *Cancer Control.* 2014;21(3):231-237.
10. Dahan R, Sega E, Engelhardt J, et al. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell.* 2015;28(3):285-295.
11. 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.
12. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. *Immunotherapy.* 2012;4(5):511-527.
13. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. *Expert Opin Biol Ther*. 2017;17(4):515-523.

Your Contacts

EMD Serono Inc.

Media Noelle Piscitelli +1 781 427 4351

Investor Relations +49 6151 72 3321

Pfizer Inc., New York, USA

Media Jessica Smith +1 212 733 6213

Investor Relations Ryan Crowe +1 212 733 8160

European Commission Approves BAVENCIO® (avelumab) Plus Axitinib Combination for First-Line Treatment of Patients With Advanced Renal Cell Carcinoma

Not intended for UK-based media

-- EU approval based on JAVELIN Renal 101 trial results demonstrating significant improvement in progression-free survival with BAVENCIO in combination with axitinib compared with sunitinib

-- Combination regimen approved across all IMDC prognostic risk groups and irrespective of PD-L1 expression

ROCKLAND, Massachusetts and NEW YORK, Oct. 28, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced that the European Commission (EC) has approved BAVENCIO® (avelumab) in combination with axitinib for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC). The approval was based on positive interim results from the Phase III JAVELIN Renal 101 study, which demonstrated that BAVENCIO in combination with axitinib significantly lowered risk of disease progression or death by 31% (HR: 0.69 [95% CI: 0.574–0.825; p<0.0001]) and nearly doubled objective response rate

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk groups. Improvement in progression-free survival (PFS) was observed across pre-specified subgroups in patients receiving the treatment combination.[1] EMD Serono and Pfizer have a global strategic alliance to jointly develop and commercialize BAVENCIO.

"There is a high incidence of kidney cancer in Europe, and for the most common type, renal cell carcinoma, we continue to need additional treatment options, particularly for patients with advanced disease, where outcomes are poorest," said Professor James Larkin, Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust and Professor at the Institute of Cancer Research (ICR). "We've seen a demonstrated efficacy benefit and safety and tolerability profile for avelumab in combination with axitinib across all prognostic risk groups in patients with advanced renal cell carcinoma, so today's approval in Europe brings an important option that can help healthcare professionals optimize treatment strategies across risk stratification."

In 2018, an estimated 136,500 new cases of kidney cancer were diagnosed in Europe, and approximately 54,700 people died from the disease.[2] Many patients living with advanced RCC do not go on to receive additional treatment after first-line therapy,[3,4] for reasons that may include poor performance status or adverse events from their initial treatment.[3,5,6] The five-year survival rate for patients with advanced RCC is approximately 12%.[7]

"This first European approval of an anti-PD-L1 as part of a combination treatment for advanced renal cell carcinoma builds on our commitment to bringing innovative treatment options to patients with hard-to-treat cancers through our extensive JAVELIN clinical trial program," said Rehan Verjee, Global Head of Innovative Medicine Franchises for the Biopharma business of Merck KGaA, Darmstadt, Germany, and President, EMD Serono. "RCC is the most common form of kidney cancer, accounting for 90% of diagnoses. We are now working to make BAVENCIO in combination with axitinib available for patients with advanced renal cell carcinoma as quickly as possible."

"The European Commission approval of BAVENCIO in combination with axitinib has the potential to bring even more patients with advanced renal cell carcinoma a new first-line treatment, and it allows us to continue to deliver on our more than decade-long passion to do more for patients with kidney cancer," said Andy Schmeltz, Global President, Pfizer Oncology. "We thank all of the researchers, doctors, advocates, patients and their families who helped get us here today, and we will continue in our fight against this advanced cancer."

2019. A supplemental application for BAVENCIO in combination with axitinib in unresectable or metastatic RCC was submitted in Japan in January 2019.

Additionally, with this approval, the posology section of the Summary of Product Characteristics for BAVENCIO has been updated. The recommended dose of BAVENCIO as monotherapy is 800 mg administered intravenously over 60 minutes every 2 weeks. Administration of BAVENCIO should continue according to the recommended schedule until disease progression or unacceptable toxicity. The recommended dose of BAVENCIO in combination with axitinib is 800 mg administered intravenously over 60 minutes every 2 weeks and axitinib 5 mg orally taken twice daily (12 hours apart) with or without food until disease progression or unacceptable toxicity.[1]

Data from JAVELIN Renal 101 Study Supporting Approval

This approval was based on interim data from the Phase III JAVELIN Renal 101 study, a randomized, multicenter, open-label study of BAVENCIO in combination with axitinib in 886 patients with untreated advanced or metastatic RCC with a clear cell component. The study included patients across risk groups (International Metastatic Renal Cell Carcinoma Database Consortium [IMDC]: 21% favorable, 62% intermediate and 16% poor; Memorial Sloan Kettering Cancer Center [MSKCC]: 22% favorable, 65% intermediate and 11% poor). The primary efficacy endpoints were progression-free survival (PFS) as assessed by a Blinded Independent Central Review (BICR) using RECIST v1.1 and overall survival (OS) in the first-line treatment of patients with advanced RCC who have PD-L1-positive tumors (PD-L1 expression level ≥1%). PFS based on BICR assessment per RECIST v1.1 and OS irrespective of PD-L1 expression, objective response (OR), time to response (TTR), duration of response (DOR) and safety are included as secondary endpoints. The study is continuing for OS.

In the analysis, BAVENCIO in combination with axitinib significantly improved median PFS compared with sunitinib by more than five months in patients irrespective of PD-L1 expression (13.3 months [95% CI: 11.1–15.3] vs. 8.0 months [95% CI: 6.7–9.8]). With a median follow-up for OS of 19 months, data for the trial's other primary endpoint of OS were immature, with 27% of deaths, and the trial is continuing as planned. The hazard ratio for OS in patients treated with BAVENCIO in combination with axitinib compared with sunitinib was 0.80 (95% CI: 0.616, 1.027) at the interim analysis.

(25.2%), cough (23.7%), headache (21.3%), dyspnea (20.9%), and arthralgia (20.9%).

About the JAVELIN Clinical Development Program

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and more than 10,000 patients evaluated across more than 15 different tumor types. In addition to RCC, these tumor types include gastric/gastro-esophageal junction cancer, head and neck cancer, Merkel cell carcinoma, non-small cell lung cancer and urothelial carcinoma.

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, EMD Serono and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indications in the US

BAVENCIO® (avelumab) 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 (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in 50 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

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

including one (0.1%) patient with Grade 5, 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 Grade 5, 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.

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% 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.

subsequent infusions 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% 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.

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%).

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%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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 axtinib (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%).

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

Axitinib Important Safety Information from the US FDA-Approved Label
Hypertension including **hypertensive crisis** has been observed with axitinib. Blood pressure should be well controlled prior to initiating axitinib. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the

considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed with axitinib and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported with axitinib. Axitinib has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Cardiac failure has been observed with axitinib and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with axitinib. Management of cardiac failure may require permanent discontinuation of axitinib.

Gastrointestinal perforation and fistula, including death, have occurred with axitinib. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported with axitinib. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of axitinib on **wound healing** have been conducted. Stop axitinib at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed with axitinib. If signs or symptoms occur, permanently discontinue treatment.

Proteinuria has been observed with axitinib. Monitor for proteinuria before initiation of, and periodically throughout, treatment with axitinib. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with axitinib. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. Axitinib has not been studied in patients with severe hepatic impairment.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

Please see full Prescribing Information for axitinib.

ADVERSE REACTIONS (BAVENCIO + AXITINIB)
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%).

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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%).

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.

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

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 56,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 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 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 October 28, 2019. Pfizer assumes no

This release contains forward-looking information about BAVENCIO (avelumab), including a new indication approved in the European Union for BAVENCIO in combination with axitinib for the treatment of patients with advanced renal cell carcinoma, 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 and axitinib; 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 in combination with axitinib in any other jurisdictions or in any jurisdictions for any other potential indications for BAVENCIO or combination therapies; whether and when the pending application in Japan for BAVENCIO in combination with axitinib may be approved 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 in combination with axitinib 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 or combination therapies, including BAVENCIO in combination with axitinib; 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, 2018, 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.

1. BAVENCIO® (avelumab) EU SmPC. Available from: http://www.ema.europa.eu/ema/. Accessed October 2019.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356-387.
3. Eggers H, Ivanyi P, Hornig M, Grünwald V. Predictive factors for second-line therapy in metastatic renal cell carcinoma: a retrospective analysis. *J Kidney Cancer VHL*. 2017;4(1):8-15.
4. Motzer R, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *The New England Journal of Medicine*. 2018;378:1277-1290.
5. Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: A randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. *Eur Urol*. 2015;68;837-847.
6. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2014;32:2765-2772.
7. Ridge C, Pua B, Madoff D. Epidemiology and staging of renal cell carcinoma. *Semin Intervent Radiol*. 2014;31(1):3-8.
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. FcγRs 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	Friederike Segeberg	+49 6151 72 6328
Investor Relations		+49 6151 72-3321

Pfizer Inc., New York, USA

	Lisa O'Neill	+44 7929 339 560
Investor Relations	Ryan Crowe	+1 212 733 8160

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YOUR REQUESTS

EMD Serono and Pfizer Provide Update on Phase III JAVELIN Gastric 100 Trial

EXPLORE MORE

Not intended for UK-based media

ROCKLAND, Mass. and NEW YORK, Nov. 8, 2019 /PRNewswire/ -- EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced topline results of the Phase III JAVELIN Gastric 100 study evaluating avelumab as first-line maintenance therapy following induction chemotherapy in patients with unresectable, locally advanced or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) cancer versus continuation of chemotherapy or best supportive care. While the study showed clinical activity for avelumab in this setting, it did not meet the primary endpoints of superior overall survival compared with the standard of care in the overall intent-to-treat population (n=499; HR: 0.91; 95% CI: 0.74, 1.11) or the PD-L1–positive population (n=54; HR: 1.13; 95% CI: 0.57, 2.23).

"Advanced gastric cancer is a hard-to-treat tumor, and there is a key unmet need for additional treatments. Additionally, it is rarely immunogenic, and to date no immune checkpoint inhibitor has demonstrated superiority to the current standard of care with chemotherapy," said Prof. Dr. Markus Möhler, Head of GI Oncology, Senior Physician Gastroenterology & Endosonography, Johannes-Gutenberg University, Mainz, Germany and coordinating

advancing our understanding and potential treatment options of this challenging disease."

No new safety signals were observed, and the safety profile for avelumab in this trial was consistent with that observed in the overall JAVELIN clinical development program. A detailed analysis of the Phase III JAVELIN Gastric 100 study is being conducted to better understand the results, and findings will be shared with the scientific community.

About JAVELIN Gastric 100

JAVELIN Gastric 100 (NCT02625610) is a Phase III, multicenter, randomized, open-label trial investigating maintenance therapy with avelumab in patients with HER2-negative advanced (unresectable, locally advanced or metastatic) adenocarcinoma of the stomach or of the gastroesophageal junction (GEJ) who have not yet received chemotherapy for the treatment of metastatic or locally advanced disease, in an overall population unselected for PD-L1 expression. A total of 805 patients were enrolled to receive induction (initial) chemotherapy with oxaliplatin and either 5-fluorouracil (5-FU) or capecitabine for 12 weeks. Of these, 499 patients whose disease had not progressed at the end of the 12 weeks of chemotherapy treatment were randomly assigned to receive either avelumab as a maintenance treatment or continuation of the same chemotherapy regimen until disease progression. Patients unfit for further chemotherapy received best supportive care. The primary endpoints are overall survival in all randomized patients or in the PD-L1+ population (≥1%).

About Gastric Cancer

Globally, gastric cancer is the third most common cause of cancer death.[1] The standard first-line option for patients with HER2-negative disease is chemotherapy,[2] yet patients with advanced disease can experience resistance, leading to a poor prognosis.[3] Over the past decade, there have been limited advancements in treatment,[4] and the median overall survival for patients at the advanced stage is less than one year.[5] In recognition of the significant need, the Merck KGaA, Darmstadt, Germany-Pfizer alliance initiated a Phase III trial to assess a novel first-line maintenance approach in advanced gastric cancer, to understand the potential of checkpoint inhibitor treatment following confirmed response or stabilization of disease on induction chemotherapy.

About the JAVELIN Clinical Development Program

The clinical development program for BAVENCIO, known as JAVELIN, involves more than 10,000 patients evaluated across more than 15 different tumor types. In addition to

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.[6-8] 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) 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 (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in 50 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

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 Grade 5, 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.

(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 Grade 5, 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 hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid

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 and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including

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.

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 carcinoma (UC) were fatigue (41%), infusion-related reaction (30%), musculoskeletal pain (25%), nausea (24%), decreased appetite/hypophagia (21%), and urinary tract infection (21%).

lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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 axtinib (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%).

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

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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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 56,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 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 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.

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 November 8, 2019. 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 results of the Phase III JAVELIN Gastric 100 study evaluating avelumab as first-line maintenance therapy following induction chemotherapy in patients with unresectable, locally advanced or metastatic HER2-negative gastric or gastroesophageal junction cancer, 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; 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 any potential indications for BAVENCIO or combination therapies; whether and when regulatory authorities in any jurisdictions where any such applications are

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 or combination therapies; 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, 2018, 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. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;0:1–31.

2. Digklia A, et al. Advanced gastric cancer: Current treatment landscape and future perspectives. *World J Gastroenterol*. 2016;22(8):2403-2414.

3. Shi WJ, Gao JB. Molecular mechanisms of chemoresistance in gastric cancer. *World J Gastrointest Oncol*. 2016;8(9):673-81.

4. Apicella M, et al. Targeted therapies for gastric cancer: failures and hopes from clinical trials. *Oncotarget.* 2017;8(34):57654-57669.

5. Shah MA. Update on metastatic gastric and esophageal cancers. *J Clin Oncol.* 2015;33:1760–9.

6. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. *Cancer Control.* 2014;21(3):231-237.

8. 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	Jessica Smith	+1 212 733 6213
Investor Relations	Ryan Crowe	+1 212 733 8160

SOURCE EMD Serono

FDA Accepts sBLA and Grants Priority Review for BAVENCIO® (avelumab) Plus INLYTA® (axitinib) for the Treatment of Advanced Renal Cell Carcinoma

Not intended for UK-based media

Rockland, MA and New York, NY, February 11, 2019 – EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced that the US Food and Drug Administration (FDA) has accepted for Priority Review the supplemental Biologics License Application (sBLA) for BAVENCIO® (avelumab) in combination with INLYTA® (axitinib)* for patients with advanced renal cell carcinoma (RCC). The application has been given a target action date in June 2019.

"The combination of BAVENCIO with INLYTA builds on Pfizer's significant heritage in advancing standards of care for patients with advanced RCC and has the potential to make a meaningful impact for the lives of patients," said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. "We look forward to working with the FDA to

"Our alliance is focused on the development of potential new treatment options for patients with cancers that have high unmet medical needs, including the broad spectrum of people living with advanced RCC," said Luciano Rossetti, M.D., Executive Vice President, Head of Global Research & Development at the Biopharma business of Merck KGaA, Darmstadt, Germany. "This regulatory milestone, which closely follows the acceptance of our application in Japan, represents an important step forward for science and for patients."

The submission is based on data from the pivotal Phase III JAVELIN Renal 101 trial, which were presented in a Presidential Symposium at the European Society of Medical Oncology (ESMO) 2018 Congress in Munich. In December 2017, the FDA granted Breakthrough Therapy Designation for BAVENCIO in combination with INLYTA for treatment-naïve patients with advanced RCC.

Despite available therapies, the outlook for patients with advanced RCC remains poor.[1] Approximately 20% to 30% of patients are first diagnosed at the metastatic stage.[2] The five-year survival rate for patients with metastatic RCC is approximately 12%.[1]

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and more than 9,000 patients evaluated across more than 15 different tumor types. In addition to RCC, these tumor types include breast, gastric/gastro-esophageal junction, and head and neck cancers, Merkel cell carcinoma, non-small cell lung cancer, and urothelial carcinoma.

*The combination of BAVENCIO and INLYTA is under clinical investigation for advanced RCC, and there is no guarantee this combination will be approved for advanced RCC by any health authority worldwide. In the US, INLYTA is approved as monotherapy for the treatment of advanced RCC after failure of one prior systemic therapy. INLYTA is also approved by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced RCC after failure of prior treatment with SUTENT® (sunitinib) or a cytokine.

Your Contacts
News Release EMD Serono Inc.
Media Lisa Buffington +1 781 681 2340
Investor Relations +49 6151 72 3321

About Renal Cell Carcinoma

RCC is the most common form of kidney cancer, accounting for about 2% to 3% of all cancers in adults.[3,4] The most common type of RCC is clear cell carcinoma, accounting for approximately 70% of all cases.[3] In 2019, an estimated 73,820 new cases of kidney cancer will be diagnosed in the US.[5]

About BAVENCIO® (avelumab)

Avelumab is a human anti-programmed death ligand-1 (PD-L1) antibody. Avelumab 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, avelumab has been shown to release the suppression of the T cell-mediated antitumor immune response in preclinical models.[6-8] Avelumab has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[8-10] In November 2014, Merck KGaA, Darmstadt, Germany, and Pfizer announced a strategic alliance to co-develop and co-commercialize avelumab.

Approved Indications

In the US, the FDA granted accelerated approval for avelumab (BAVENCIO®) for the treatment of (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in more than 45 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

Important Safety Information from the US FDA-Approved Label

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 reinitiation 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.

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% (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 1,738 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

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 carcinoma (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%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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

About INLYTA® (axitinib)

INLYTA is an oral therapy that is designed to inhibit tyrosine kinases, including vascular

INLYTA is approved for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. INLYTA is also approved by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.

INLYTA Important Safety Information

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming **pregnant** while receiving INLYTA.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

For more information and full Prescribing Information, visit www.INLYTA.com.

About SUTENT® (sunitinib malate)

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

SUTENT is indicated in the US for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate; the treatment of advanced RCC; the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy; and the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

SUTENT Important Safety Information

Boxed Warning/Hepatotoxicity has been observed in clinical trials and postmarketing experience. Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. Fatal liver failure has been observed. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. Interrupt SUTENT for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have signs and symptoms of liver failure.

Cardiovascular events, including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death have occurred. Monitor patients for signs and symptoms of congestive heart failure. Discontinue SUTENT for clinical manifestations of congestive heart failure. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Baseline and periodic evaluations of left ventricular ejection fraction should also be considered while these patients are receiving SUTENT.

seen in <0.1% of patients. Monitor patients that are at a higher risk for developing QT interval prolongation, including those with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Consider monitoring of electrocardiograms and electrolytes. Concomitant treatment with strong CYP3A4 inhibitors may increase sunitinib plasma concentrations and dose reduction of SUTENT should be considered.

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.

Hemorrhagic events, including tumor-related hemorrhage, and viscus perforation (both with fatal events) have occurred. These events may occur suddenly, and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Perform serial complete blood counts (CBCs) and physical examinations.

Cases of **tumor lysis syndrome (TLS)** (some fatal) have been reported. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated.

Thrombotic microangiopathy (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 and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt treatment for 24-hour urine protein ≥3 grams. Discontinue for repeat episodes of protein ≥3 grams despite dose reductions or nephrotic syndrome.

Dermatologic toxicities: Severe cutaneous reactions have been reported, including cases of necrotizing fasciitis, 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

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

Hypoglycemia may occur. SUTENT can result in symptomatic hypoglycemia, which may lead to a 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 treatment with SUTENT. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

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

Impaired wound healing has occurred with SUTENT. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Embryo fetal toxicity and reproductive potential
Females - SUTENT can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with SUTENT and for 4 weeks following the final dose.
Males - Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with SUTENT and for 7 weeks after the last dose.
Male and female infertility - based on findings in animals, male and female fertility may be compromised by treatment with SUTENT

least 4 weeks after the last dose.

Venous thromboembolic events: In patients treated with SUTENT (N=7527) for GIST, advanced RCC, adjuvant treatment of RCC and pNET, 3.5% of patients experienced a venous thromboembolic event; 2.2% Grade 3-4.

There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of **reversible posterior leukoencephalopathy syndrome (RPLS)**. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating healthcare provider.

Pancreatic function: In a trial of patients receiving adjuvant treatment for RCC, 1 patient (<1%) on SUTENT and none on placebo experienced pancreatitis.

CYP3A4 inhibitors and inducers: 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 (adjuvant RCC): The **most common ARs** reported in ≥20% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (all grades, vs placebo) were mucositis/stomatitis (61% vs 15%), diarrhea (57% vs 22%), fatigue/asthenia (57% vs 34%), hand-foot syndrome (50% vs 10%), hypertension (39% vs 14%), altered taste (38% vs 6%), nausea (34% vs 15%), dyspepsia (27% vs 7%), abdominal pain (25% vs 9%), hypothyroidism/TSH increased (24% vs 4%), rash (24% vs 12%), hair color changes (22% vs 2%). The **most common grade 3/4 ARs** reported in ≥5% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (vs placebo) were hand-foot syndrome (16% vs <1%), fatigue/asthenia (8% vs 2%), hypertension (8% vs 1%), and mucositis/stomatitis (6% vs 0%).

Most common grade 3/4 lab abnormalities (adjuvant RCC): The **most common grade 3/4 lab abnormalities** (occurring in ≥ 2% of patients receiving SUTENT) included neutropenia (13%), thrombocytopenia (5%), leukopenia (3%), lymphopenia (3%), elevated

Most common ARs & most common grade 3/4 ARs (advanced RCC): The **most common ARs** reported 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** reported 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** reported 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** reported 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% vs0%).

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

Most common ARs & most common grade 3/4 ARs (advanced pNET): The **most common ARs** reported 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%), epistaxis (21% vs 5%), and dysgeusia (21% vs 5%). The **most common grade 3/4 ARs** reported 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 and Medication Guide, for SUTENT® (sunitinib malate) at www.SUTENT.com.

Alliance between Merck KGaA, Darmstadt, Germany, and Pfizer Inc., New York, US
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.

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 multiple sclerosis. Today, the business has approximately 1,300 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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 51,000 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 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.

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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. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. 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 February 11, 2019. 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 new indication for BAVENCIO in combination with INLYTA (axitinib) for the treatment of patients with advanced renal cell carcinoma, 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 further analyses of existing clinical data and uncertainties regarding whether the other primary endpoint of JAVELIN Renal 101 will be met; 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 in combination with INLYTA for the potential new

and Japan for BAVENCIO in combination with INLYTA for the potential new indication may be approved and whether and when regulatory authorities in any jurisdictions where any other applications are pending or may be submitted for BAVENCIO or combination therapies 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 and/or other matters that could affect the availability or commercial potential of BAVENCIO or combination therapies, including BAVENCIO in combination with INLYTA for the potential new indication; 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, 2017, 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. National Cancer Institute: SEER Stat Fact Sheets: Kidney and renal pelvis. Available from: http://seer.cancer.gov/statfacts/html/kidrp.html. Accessed February 2019.

2. Ljungberg B, Campbell S and Cho H. The Epidemiology of Renal Cell Carcinoma. Eur Urol. 2011;60:615-621.

3. American Cancer Society. What is kidney cancer? Available from: https://www.cancer.org/cancer/kidney-cancer/about.html. Accessed February 2019.

4. Escudier B, Porta C, Schmidinger M et al Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25(Suppl3):iii49-iii56.

5. American Cancer Society. Cancer facts and figures 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-

6. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. Cancer Control. 2014;21(3):231-237.

7. Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. Cancer Cell. 2015;28(3):285-295.

8. 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.

9. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. Immunotherapy. 2012;4(5):511-527.

10. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. Expert Opin Biol Ther. 2017;17(4):515-523.

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SITEMAP

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FDA Approves BAVENCIO® (avelumab) Plus INLYTA® (axitinib) Combination for Patients with Advanced Renal Cell Carcinoma

Not intended for UK-based media

BAVENCIO is the first anti-PD-L1 in combination with INLYTA approved by FDA for first-line treatment of patients with advanced renal cell carcinoma (RCC)

Phase III study showed combination significantly lowered risk of disease progression or death by 31% and extended progression-free survival by 5.4 months for patients with advanced RCC compared with sunitinib

Combination approved based on Phase III data in an overall population that included patients regardless of PD-L1 expression and across favorable, intermediate and poor prognostic groups

Rockland, MA and New York, US, May 14, 2019 – EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced that the US Food and Drug Administration (FDA) has approved BAVENCIO® (avelumab) in combination with INLYTA® (axitinib) for the first-line treatment of patients with advanced renal cell carcinoma (RCC). This is the first FDA approval for an anti-PD-L1 therapy as part of a combination regimen for patients with advanced RCC. The approval of BAVENCIO in combination with INLYTA was based on positive results from the Phase III JAVELIN Renal 101 study (NCT02684006), in which the combination significantly improved median progression-free survival (PFS) compared with sunitinib by more than five months in the intent-to-treat (ITT) patient population (HR: 0.69 [95% CI: 0.56–0.84]; 2-sided p-value=0.0002; median PFS for BAVENCIO in combination with INLYTA: 13.8 months [95% CI: 11.1-NE]; sunitinib: 8.4 months [95% CI: 6.9-11.1]). The ITT population included patients regardless of PD-L1 expression and across IMDC (International Metastatic Renal Cell Carcinoma Database) prognostic risk groups (favorable 21%, intermediate 62% and poor 16%).[1]

"As we look to continue to improve outcomes for people with advanced RCC, new treatment approaches have the potential to benefit patients," said Robert J. Motzer, M.D., Jack and Dorothy Byrne Chair in Clinical Oncology, Memorial Sloan Kettering Cancer Center, New York, US, and principal investigator for JAVELIN Renal 101. "With today's FDA approval of avelumab in combination with axitinib, we can now offer patients with advanced RCC a first-line treatment option that combines a PD-L1 immunotherapy with a well-known VEGFR TKI to provide a significant reduction in the risk of disease progression or death and doubling of the response rate compared with sunitinib."

RCC is a type of cancer where PD-L1 expression may contribute to inhibition of the immune response against the tumor.[2] It is also a highly vascular tumor, in which vascular endothelial growth factor (VEGF) plays a key role.[3]

"A kidney cancer diagnosis is life-changing for both patients and their loved ones, and having a treatment strategy for their disease quickly becomes a priority," said Dena Battle, President, KCCure. "The approval of new treatments such as BAVENCIO in combination with INLYTA gives patients with advanced RCC much-needed options."

at the advanced stage, and 30% of patients treated for an earlier stage go on to develop metastases.[4,5] About half of patients living with advanced RCC do not go on to receive additional treatment after first-line therapy,[6,7] for reasons that may include poor performance status or adverse events from their initial treatment.[6,8,9]

"Today's approval of BAVENCIO in combination with INLYTA builds on Pfizer's long heritage in bringing innovation to the RCC community with the hopes of making a significant and meaningful impact on the lives of patients," said Andy Schmeltz, Global President, Pfizer Oncology. "For more than 12 years, Pfizer has led the field in its commitment to developing new treatments for patients with advanced kidney cancer."

"With today's FDA approval of BAVENCIO in combination with INLYTA, we feel privileged that we can offer patients with first-line advanced renal cell carcinoma a new treatment option," said Rehan Verjee, President, EMD Serono, and Global Head of Innovative Medicine Franchises, Merck KGaA, Darmstadt, Germany.

In JAVELIN Renal 101, the objective response rate (ORR) was doubled in the ITT population with BAVENCIO in combination with INLYTA versus sunitinib (51.4% [95% CI: 46.6-56.1] vs. 25.7% [95% CI: 21.7-30.0]). With a median overall survival (OS) follow-up of 19 months, data for the trial's other primary endpoint of OS were immature, with 27% of deaths in the ITT population, and the trial is continuing as planned. The most common adverse reactions (≥20%) were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain and headache. Serious adverse reactions occurred in 35% of patients receiving BAVENCIO in combination with INLYTA. The incidence of major adverse cardiovascular events (MACE) was higher with BAVENCIO in combination with INLYTA versus sunitinib.[1] Findings from the study have been published in The New England Journal of Medicine.[10]

The European Medicines Agency (EMA) validated the Type II variation application for BAVENCIO in combination with INLYTA in advanced RCC in March 2019, and a supplemental application for BAVENCIO in combination with INLYTA in unresectable or metastatic RCC was submitted in Japan in January 2019.

spectrum of patient access and reimbursement support services intended to help US patients prescribed BAVENCIO receive appropriate access. CoverOne may be reached by phone at 844-8COVER1 (844-826-8371) or online at www.CoverOne.com.

Pfizer is committed to ensuring that patients who are prescribed INLYTA have access to this innovative therapy. Patients in the US have access to Pfizer Oncology Together™, which offers personalized support and financial assistance resources to help patients access their prescribed Pfizer Oncology medications. For more information, please call 1-877-744-5675 or visit PfizerOncologyTogether.com.

In an effort to streamline the patient enrollment process, EMD Serono and Pfizer have partnered to create a single enrollment form for the BAVENCIO and INLYTA combination for patients with advanced RCC that can be processed through both CoverOne and Pfizer Oncology Together. Each program will independently conduct the access and reimbursement activities for the product for which it is responsible.

Your Contacts
News Release EMD Serono Inc.
Media Noelle Piscitelli +1 781 427 4351
Investor Relations +49 6151 72 3321

Pfizer Inc., New York, USA
Media Jessica Smith +1 212 733 6213
Investor Relations Ryan Crowe +1 212 733 8160

About Renal Cell Carcinoma

In 2019, an estimated 73,820 new cases of kidney cancer will be diagnosed in the US, and approximately 14,770 people will die from the disease.[11] RCC is the most common form of kidney cancer, accounting for about 2% to 3% of all cancers in adults.[12,13] Approximately 20% to 30% of patients with kidney cancer are first diagnosed at the advanced stage.4 The five-year survival rate for patients with metastatic RCC is approximately 12%.[14]

About the JAVELIN Renal 101 study

The Phase III JAVELIN Renal 101 study is a randomized (1:1), multicenter, open-label study of BAVENCIO in combination with INLYTA in 886 patients with untreated advanced RCC regardless

outcome measures were PFS as assessed by a Blinded Independent Central Review (BICR) using RECIST v1.1 and OS in patients with PD-L1-positive tumors using a clinical trial assay (PD-L1 expression level ≥1%). If PFS was statistically significant in patients with PD-L1-positive tumors, it was then tested in the ITT population. The hazard ratio for PFS in patients with PD-L1-positive tumors was HR 0.61 (95% CI: 0.48, 0.79). PFS and OS in the ITT population, overall response and safety are included as secondary endpoints. The study is continuing for OS.

About the JAVELIN Clinical Development Program

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and about 10,000 patients evaluated across more than 15 different tumor types. In addition to RCC, these tumor types include gastric/gastro-esophageal junction cancer, head and neck cancer, Merkel cell carcinoma, non-small cell lung cancer, and urothelial carcinoma.

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.15-17 BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.17-19 In November 2014, EMD Serono and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indication in the US

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

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 Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

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 Grade 5, and 11 (0.6%) with Grade 3.

BAVENCIO in combination with INLYTA 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 INLYTA 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 INLYTA, 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 hyperthyroidism with medical management. Withhold BAVENCIO for severe

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 INLYTA: 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 and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion

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 INLYTA 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 INLYTA for Grade 3-4 cardiovascular events. MACE occurred in 7% of patients with advanced RCC treated with BAVENCIO in combination with INLYTA 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.

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

INLYTA Important Safety Information from the US FDA-Approved Label
Hypertension including **hypertensive crisis** has been observed with INLYTA. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Hemorrhagic events, including fatal events, have been reported with INLYTA. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed with INLYTA and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred with INLYTA. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported with INLYTA. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed with INLYTA. If signs or symptoms occur, permanently discontinue treatment.

Proteinuria has been observed with INLYTA. Monitor for proteinuria before initiation of, and periodically throughout, treatment with INLYTA. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

INLYTA can cause **fetal harm**. Advise patients of the potential risk to the fetus and to use effective contraception during treatment.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

For more information and full Prescribing Information, visit www.INLYTA.com.

ADVERSE REACTIONS (BAVENCIO + INLYTA)

Fatal adverse reactions occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving BAVENCIO in combination with INLYTA. 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 INLYTA (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 INLYTA (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%).

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

and is striving to find new ways to treat cancer.

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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 1,300 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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 52,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 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 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.

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. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. 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 May 14, 2019. 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 new indication approved in the U.S. for BAVENCIO in combination with INLYTA (axitinib) for the treatment of patients with advanced renal cell carcinoma, 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 and INLYTA; 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 and uncertainties regarding whether the other primary endpoint of JAVELIN Renal 101 will be met; 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

combination therapies; whether and when the pending applications in the European Union and Japan for BAVENCIO in combination with INLYTA may be approved 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 in combination with INLYTA 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 or combination therapies, including BAVENCIO in combination with INLYTA; 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, 2018, 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. BAVENCIO Prescribing Information. Rockland, MA: EMD Serono Inc.; 2019.
2. Weinstock M and McDermott D. Targeting PD-1/PD-L1 in the treatment of metastatic renal cell carcinoma. Therapeutic Advances in Urology. 2015;7(6):365-377.
3. Roskoski R Jr. Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. Pharmacological Research. 2017;120:116-132.
4. Ljungberg B, Campbell S and Cho H. The Epidemiology of renal cell carcinoma. European Urology. 2011;60:615-621.
5. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. World Journal of Urology. 2018;36(12):1943-1952.
6. Eggers H, Ivanyi P, Hornig M and Grünwald V. Predictive Factors for Second-Line Therapy in Metastatic Renal cell Carcinoma: A Retrospective Analysis. Journal of Kidney Cancer and VHL. 2017;4(1):8-15.
7. Motzer R, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. The New England Journal of Medicine. 2018;378:1277-1290.
8. Eichelberg C, et al. SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. European Urology. 2015;68:837-847.
9. Motzer R, et al. Phase II Randomized Trial Comparing Sequential First-Line Everolimus and Second-Line Sunitinib Versus First-Line Sunitinib and Second-Line Everolimus in Patients With Metastatic Renal Cell Carcinoma. Journal of Clinical Oncology. 2014;32:2765-2772.

https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html. Accessed May 2019.
12. American Cancer Society: What is Kidney Cancer? Available from: https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html. Accessed May 2019.
13. Ljungberg B, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. European Urology. 2019 Feb.
14. National Cancer Institute: SEER Cancer Stat Fact Sheets: Kidney and Renal Pelvis. Available from: https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed May 2019.
15. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. Cancer Control. 2014;21(3):231-237.
16. Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. Cancer Cell. 2015;28(3):285-295.
17. 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 Immunology Research. 2015;3(10):1148-1157.
18. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. Immunotherapy. 2012;4(5):511-527.
19. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. Expert Opinion on Biological Therapy. 2017;17(4):515-523.

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GLUCOPHAGE® (metformin hydrochloride) Notification to HCPs and Patients

GLUCOPHAGE® (metformin hydrochloride) was previously commercialized by Bristol-Myers Squibb (BMS) in the U.S., and BMS has decided to discontinue commercialization. Merck KGaA, Darmstadt, Germany licensed to BMS the rights to the product when it was originally approved in the U.S.; today, the rights to GLUCOPHAGE are in the process of transferring to EMD Serono in the U.S.

Due to the company's strategic focus and resourcing, EMD Serono decided not to commercialize GLUCOPHAGE in the U.S. at this time. Patients currently taking GLUCOPHAGE should speak directly with their healthcare team about the treatment plan that best meets their needs.

As the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the U.S. and Canada, we are focused exclusively on specialty care conditions including multiple sclerosis, oncology, fertility and HIV-associated wasting. We continue to explore and seek to develop potential new medicines in oncology, immuno-oncology, neurology and immunology.

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Merck KGaA, Darmstadt, Germany and GSK Announce Global Alliance to Jointly Develop and Commercialize M7824, a Novel Immunotherapy with Potential in Multiple Difficult-to-Treat Cancers

(3)

Eight high priority immuno-oncology clinical development studies ongoing or expected to commence in 2019, including studies in non-small cell lung and biliary tract cancers

Merck KGaA, Darmstadt, Germany will receive an upfront payment of €300 million and is eligible for potential development milestone payments of up to €500 million triggered by data from the M7824 lung cancer program, plus future approval and commercial milestones of up to €2.9 billion for a total potential deal value of up to €3.7 billion

Darmstadt, Germany, February 5, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, and GSK, a science-led global healthcare company, today announced that the companies have entered into a global strategic alliance to jointly develop and

for multiple difficult-to-treat cancers. This includes a Phase II trial to investigate M7824 compared with pembrolizumab as a first-line treatment in patients with PD-L1 expressing advanced non-small cell lung cancer (NSCLC).

M7824 is designed to simultaneously target two immuno-suppressive pathways, transforming growth factor-β (TGF-β) trap and an anti-programmed cell death ligand-1 (PD-L1), that are commonly used by cancer cells to evade the immune system. Bifunctional antibodies aim to increase efficacy above and beyond that achieved with individual therapies or combinations of individual therapies.1 M7824 has the potential to offer new ways to fight difficult-to-treat cancers beyond the established PD-1/PD-L1 class. In addition to use as a single agent, M7824 is also being considered for use in combination with other assets from the pipelines of both companies.

"Our bifunctional fusion protein M7824 has the potential to bring new answers to patients living with cancer. Together with GSK we aim to drive a paradigm shift in the treatment of cancer as the leader in this novel class of immunotherapies," said Belén Garijo, Member of the Executive Board and CEO Healthcare of Merck KGaA, Darmstadt, Germany. "GSK clearly emerged as the ideal partner due to their strong commitment to oncology, and the complementary talent and capabilities they will bring to our alliance. We now look forward to harnessing the full potential of M7824 across a broad range of cancer indications as we continue to advance our oncology portfolio."

"Despite recent medical advances, many patients with difficult-to-treat cancers don't currently benefit from immuno-oncology therapies leaving them with limited treatment options. M7824 brings together two different biological functions in a single molecule and we have observed encouraging clinical results in treating certain cancer patients, particularly those people with non-small cell lung cancer," said Hal Barron, Chief Scientific Officer and President R&D, GSK. "I'm excited by the potential impact this first-in-class immunotherapy could have on the lives of cancer patients."

Merck KGaA, Darmstadt, Germany will receive an upfront payment of €300 million and is eligible for potential development milestone payments of up to €500 million triggered by data from the M7824 lung cancer program. Merck KGaA, Darmstadt, Germany will also be eligible for further payments upon successfully achieving future approval and commercial milestones of up to €2.9 billion. The total potential deal value is up to €3.7 billion. Both companies will jointly

This alliance reflects the strategic approach of Merck KGaA, Darmstadt, Germany to oncology R&D, identifying those opportunities that can progress the company's highly promising clinical stage assets as efficiently and rapidly as possible, whether through internal expertise and capabilities or external collaborations.

For GSK, this alliance is a further step in the company's priority to strengthen its pharmaceuticals pipeline. This follows the company's recent acquisition of TESARO, an oncology-focused company based in Waltham, Massachusetts. GSK's approach to oncology is focused on innovation in the areas of immuno-oncology, cell therapy, cancer epigenetics and, most recently, genetic medicine.

With this alliance, both companies have the leadership position in this new class of immunotherapies, specifically leveraging TGF-β biology.

**Bintrafusp alfa is the proposed International Nonproprietary Name (INN) for the bifunctional immunotherapy M7824. Bintrafusp alfa is currently under clinical investigation and not approved for any use anywhere in the world.*

Your Contact

Media Relations
friederike.segeberg@emdgroup.com
Phone: +49 6151 72-6328

Investor Relations
investor.relations@emdgroup.com
Phone: +49 6151 72-3321

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localized blocking of the two immuno-suppressive pathways – targeting both pathways aims to control tumor growth by potentially restoring and enhancing anti-tumor responses. M7824 is currently in Phase I studies for solid tumors, as well as a randomized Phase II trial to investigate M7824 compared with pembrolizumab as a first-line treatment in patients with PD-L1 expressing advanced NSCLC. The multicenter, randomized, open-label, controlled study is evaluating the safety and efficacy of M7824 versus pembrolizumab as a monotherapy treatment.

To-date, nearly 700 patients have been treated with M7824 across more than 10 tumor types in Phase I studies. Encouraging data from the ongoing Phase I studies indicates M7824's potential safety and clinical anti-tumor activity across multiple types of difficult-to-treat cancers, including advanced NSCLC, human papillomavirus-associated cancers, biliary tract cancer (BTC) and gastric cancer. In addition, in pre-clinical studies M7824 demonstrated superior anti-tumor activity, compared with anti-PD-L1 alone or with anti-PD-L1 and TGF-β trap when co-administered. In total, eight high priority immuno-oncology clinical development studies are ongoing or expected to commence in 2019, including studies in non-small cell lung and biliary tract cancers.

References

1. Lan Y, et al. Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-β. Science Translational Medicine. 2018 Jan; 10(424).

GSK – one of the world's leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For further information please visit www.gsk.com.

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 51,000 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 billion in 66 countries.

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Merck KGaA, Darmstadt, Germany Data at ASCO 2019 Showcase Multiple Innovative Molecules with Potential to Impact Unmet Needs in Cancer Care

Not intended for UK-based media

New biomarker analyses for BAVENCIO®* (avelumab) in combination with axitinib in first-line renal cell carcinoma (RCC)

Data presented across several modalities and mechanisms showcase the scientific innovation and diversity of the company's pipeline, which includes bintrafusp alfa‡ (M7824) and tepotinib†

Darmstadt, Germany, May 15, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that data across several modalities and mechanisms targeting difficult-to-treat cancers will be presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, May 31–June 4, Chicago, IL, US. New data will be presented for BAVENCIO®* (avelumab) and ERBITUX® (cetuximab), including rational combinations with chemotherapy, radiation therapy and other targeted agents to try to identify new ways to

and who have been treated first-line with BAVENCIO® (avelumab) in combination with axitinib. Abstracts also showcase the scientific innovation and diversity of Merck KGaA, Darmstadt, Germany's pipeline, with results from a number of high-priority clinical development programs, including tepotinib†, bintrafusp alfa‡ (M7824) and the company's comprehensive DNA Damage Response (DDR) portfolio. Merck KGaA, Darmstadt, Germany operates its biopharmaceutical business in the U.S. and Canada as EMD Serono.

"At this year's ASCO meeting we continue to demonstrate the breadth and depth of our oncology and immuno-oncology portfolio. We will present examples of the latest precision medicine and biomarker research and some of the most exciting mechanisms being investigated today, including tepotinib and our first-in-class bifunctional fusion protein immunotherapy, bintrafusp alfa," said Luciano Rossetti, Global Head of Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "Merck KGaA, Darmstadt, Germany's oncology pipeline has significant promise in the near term through our late-stage priority programs, and our early pipeline includes several potentially groundbreaking modalities. We look forward to sharing the latest science with the global oncology community."

For BAVENCIO® (avelumab), Merck KGaA, Darmstadt, Germany, will share data from five studies across tumor types including Merkel cell carcinoma, RCC, hepatocellular carcinoma and urothelial carcinoma. This includes an oral presentation of biomarker analyses of baseline tumor samples from the Phase III JAVELIN Renal 101 trial in previously untreated patients with advanced RCC. The trial indicated that PD-L1 expression (≥1% immune cells) was associated with the longest progression-free survival (PFS) in the avelumab plus axitinib arm and the shortest PFS in the sunitinib arm (HR, 0.63; 95% CI, 0.49, 0.81). An analysis of relevant gene expression signatures (GES) indicated that in the avelumab plus axitinib arm, PFS was enhanced in immune GES–positive patients vs those in the negative group (HR, 0.63; 95% CI, 0.46, 0.86; 2-sided p=0.004), and vs those in an independent dataset (JAVELIN Renal 100; Choueiri, Lancet Oncol, 2018) (HR, 0.46; 95% CI, 0.20, 1.05; 2-sided p=0.064). The combination demonstrated a safety and tolerability profile consistent with the known safety profiles of each drug alone. The most common adverse reactions (≥20%) were diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache. Serious adverse reactions occurred in 35% of patients receiving BAVENCIO® (avelumab) in combination with axitinib. The incidence of major

ERBITUX® (cetuximab) data from a retrospective analysis of overall survival (OS) by subsequent therapy in patients with RAS wild-type metastatic colorectal cancer from the Phase III EPIC study will be presented, to evaluate the effect of post-study therapies (with ERBITUX®, without ERBITUX®, or no subsequent therapy) on OS.

A number of the molecules to be featured were discovered in-house at Merck KGaA, Darmstadt, Germany. This includes tepotinib, an oral MET inhibitor designed to inhibit the oncogenic MET receptor signaling caused by MET (gene) alterations, and bintrafusp alfa, a bifunctional fusion protein designed to simultaneously target two immuno-suppressive pathways. Merck KGaA, Darmstadt, Germany's partnership with GSK to jointly develop and commercialize bintrafusp alfa, announced in February 2019, is part of the company's strategic approach to oncology R&D. Together, Merck KGaA, Darmstadt, Germany, and GSK aim to rapidly and efficiently progress this molecule, which represents a potential step change in the treatment of cancer.

For tepotinib, promising updated results from the ongoing Phase II VISION study in 85 patients with non-small cell lung cancer (NSCLC) with MET exon 14 skipping mutations (identified by liquid biopsy [LBx] or tumor biopsy [TBx]) will be shared. Results show an overall response rate (ORR) of 51.4% for LBx patients (independent review committee [IRC]-assessed) or 63.9% (investigator-assessed). The ORR for TBx patients was 41.5% (IRC-assessed) or 58.5% (investigator-assessed). Median duration of response was 9.8 (IRC-assessed) or 17.1 months (investigator-assessed) for LBx patients and 12.4 (IRC-assessed) or 14.3 months (investigator-assessed) for TBx patients. Any grade treatment-related adverse events (TRAEs) reported by ≥10% of 69 patients evaluable for safety were peripheral edema (47.8%), diarrhea (18.8%), nausea (15.9%) and asthenia (10.1%). No Grade 4 or 5 TRAEs were observed. TRAEs led to permanent discontinuation in two (2.9%) patients (one interstitial lung disease, one diarrhea and nausea). These data continue to mature, and an updated data cut from the VISION study will be given as an oral presentation at the ASCO meeting on Monday, June 3.

For bintrafusp alfa, a trial-in-progress poster will be shared on the open-label study of bintrafusp alfa vs pembrolizumab as a first-line treatment in patients with PD-L1-expressing advanced NSCLC.

Merck KGaA, Darmstadt, Germany takes a personalized approach to R&D, and precision medicine has long been a priority. Abstracts being presented at ASCO also include biomarker

**The combination of BAVENCIO and axitinib is approved for the first-line treatment of advanced RCC only in the United States. There is no guarantee that avelumab in combination with axitinib will be approved for RCC by any other health authority worldwide.*

[†]Tepotinib is the recommended International Nonproprietary Name (INN) for the MET kinase inhibitor (MSC2156119J). Tepotinib is currently under clinical investigation and not approved for any use anywhere in the world.

[‡]Bintrafusp alfa is the proposed International Nonproprietary Name (INN) for the bifunctional immunotherapy M7824. Bintrafusp alfa is currently under clinical investigation and not approved for any use anywhere in the world.

Notes to Editors
Key Merck KGaA, Darmstadt, Germany-supported abstracts slated for presentation are listed below. In addition, a number of investigator-sponsored studies have been accepted (not listed).

BAVENCIO® (avelumab)

Oral Session

Title Biomarker analyses from JAVELIN Renal 101: avelumab + axitinib (A+Ax) vs sunitinib (S) in advanced renal cell carcinoma (aRCC)
Lead Author T.K. Choueiri
Abstract # 101
Presentation Date / Time (CDT) Sat, Jun 1, 8:00 AM – 9:30 AM (8:12 AM – 8:24 AM lecture time)
Location Hall D1

Poster Sessions

Title 5-factor prognostic model for survival of patients with metastatic urothelial carcinoma receiving 3 different post-platinum PD-L1 inhibitors

Presentation Date / Time (CDT) Mon, Jun 3, 1:15 PM – 4:15 PM
Location Hall A

Title First-line avelumab + axitinib in patients with advanced hepatocellular carcinoma: results from a phase 1b trial (VEGF Liver 100)
Lead Author M. Kudo
Abstract # 4072
Presentation Date / Time (CDT) Mon, Jun 3, 8:00 AM – 11:00 AM
Location Hall A

Title Integrative molecular analysis of metastatic Merkel cell carcinoma to identify predictive biomarkers of response to avelumab
Lead Author S. Georges
Abstract # 9569
Presentation Date / Time (CDT) Mon, Jun 3, 1:15 PM – 4:15 PM
Location Hall A

Bintrafusp Alfa

Poster Session

Title Randomized open-label study of M7824 vs pembrolizumab as first-line (1L) treatment in patients with PD-L1 expressing advanced non-small cell lung cancer (NSCLC)
Lead Author L. Paz-Ares
Abstract # TPS9114
Presentation Date / Time (CDT) Sun, Jun 2, 8:00 AM – 11:00 AM
Location Hall A

Discovery

Poster Session

Lead Author P.K. Shah
Abstract # 2567
Presentation Date / Time (CDT) Sun, Jun 2, 8:00 AM – 11:00 AM
Location Hall A

ERBITUX® (cetuximab)

Poster Session

Title Retrospective Analysis of Overall Survival (OS) by Subsequent Therapy in Patients With RAS-Wild-type (wt) Metastatic Colorectal Cancer (mCRC) Receiving Cetuximab ± Irinotecan
Lead Author P.K. Shah
Abstract # 2567
Presentation Date / Time (CDT) Sun, Jun 2, 8:00 AM – 11:00 AM
Location Hall A

Tepotinib

Oral Session

Title Phase II study of tepotinib in NSCLC patients with METex14 mutations
Lead Author P.K. Paik
Abstract # 9005
Presentation Date / Time (CDT) Mon, Jun 3, 8:00 AM – 11:00 AM (9:24 AM – 9:36 AM lecture time)
Location Hall B1

Your Contact
Brenda.Mulligan@emdserono.com
Phone: +1 978 821 5345

About Tepotinib
Tepotinib, discovered in-house at Merck KGaA, Darmstadt, Germany, is an investigational oral MET inhibitor that is designed to inhibit the oncogenic MET receptor signaling caused by MET (gene) alterations, including both MET exon 14 skipping mutations and MET amplifications, or MET protein overexpression. It has been designed to have a highly selective mechanism of action, with the potential to improve outcomes in aggressive tumors that have a poor prognosis and harbor these specific alterations.

Tepotinib is currently being investigated in NSCLC and Merck KGaA, Darmstadt, Germany, is actively assessing the potential of investigating tepotinib in combination with novel therapies and other tumor indications.

About Bintrafusp Alfa (M7824)
Bintrafusp alfa is an investigational bifunctional immunotherapy that is designed to combine a TGF-β trap with the anti-PD-L1 mechanism in one fusion protein. Bintrafusp alfa is designed to combine co-localized blocking of the two immuno-suppressive pathways – targeting both pathways aims to control tumor growth by potentially restoring and enhancing anti-tumor responses. Bintrafusp alfa is currently in Phase I studies for solid tumors, as well as a randomized Phase II trial to investigate bintrafusp alfa compared with pembrolizumab as a first-line treatment in patients with PD-L1 expressing advanced NSCLC. The multicenter, randomized, open-label, controlled study is evaluating the safety and efficacy of bintrafusp alfa versus pembrolizumab as a monotherapy treatment.

To date, nearly 700 patients have been treated with bintrafusp alfa across more than 10 tumor types in Phase I studies. Encouraging data from the ongoing Phase I studies indicates bintrafusp alfa's potential safety and clinical anti-tumor activity across multiple types of difficult-to-treat cancers, including advanced NSCLC, human papillomavirus-associated cancers, biliary tract cancer and gastric cancer. In addition, in pre-clinical studies bintrafusp alfa demonstrated superior anti-tumor activity, compared with anti-PD-L1 alone or with anti-PD-L1 and TGF-β trap when co-administered. In total, eight high-priority immuno-oncology clinical development studies are ongoing or expected to commence in 2019, including studies in non-small cell lung and biliary tract cancers.

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.[1-3] BAVENCIO has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[3-5] In November 2014, Merck KGaA, Darmstadt, Germany, and Pfizer announced a strategic alliance to co-develop and co-commercialize BAVENCIO.

BAVENCIO Approved Indications in the US
BAVENCIO® (avelumab) in combination with INLYTA® (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 (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease

response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in more than 45 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

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 Grade 5, 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 Grade 5, and 11 (0.6%) with Grade 3.

> *BAVENCIO in combination with INLYTA* 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 INLYTA 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 INLYTA, 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. Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Hepatotoxicity led to permanent discontinuation in 6.5% and immune-mediated hepatitis led to permanent discontinuation of either BAVENCIO or axitinib in 5.3% of patients.

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

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% 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 INLYTA: 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 and for subsequent infusions 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% of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO in combination with INLYTA can cause **major adverse cardiovascular events (MACE)** including severe and fatal events. Consider baseline and periodic evaluations of left

of patients with advanced RCC treated with BAVENCIO in combination with INLYTA 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.

Clinical chemistry and hematology laboratory values abnormalities have been reported with BAVENCIO and also BAVENCIO in combination with INLYTA including but not limited to grade 3-4 lymphopenia, anemia, elevated cholesterol and liver enzymes.

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

INLYTA Important Safety Information from the US FDA-Approved Label
Hypertension including **hypertensive crisis** has been observed with INLYTA. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed with INLYTA and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported with INLYTA. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed with INLYTA and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred with INLYTA. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported with INLYTA. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Proteinuria has been observed with INLYTA. Monitor for proteinuria before initiation of, and periodically throughout, treatment with INLYTA. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

INLYTA can cause **fetal harm**. Advise patients of the potential risk to the fetus and to use effective contraception during treatment.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

For more information and full Prescribing Information, visit www.INLYTA.com.

ADVERSE REACTIONS (BAVENCIO + INLYTA)
Fatal adverse reactions occurred in 1.8% of patients with **advanced renal cell carcinoma (RCC)** receiving BAVENCIO in combination with INLYTA. 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 INLYTA (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 INLYTA (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%).

About Erbitux® (cetuximab)
Erbitux® is a IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR). As a monoclonal antibody, the mode of action of Erbitux® is distinct from standard non-selective chemotherapy treatments in that it specifically targets and binds to the EGFR. This binding inhibits the activation of the receptor and the subsequent signal-transduction pathway,

inside tumors, which appears to lead to an overall suppression of tumor growth. Based on in vitro evidence, Erbitux® also targets cytotoxic immune effector cells towards EGFR expressing tumor cells (antibody dependent cell-mediated cytotoxicity, ADCC).

Very commonly reported side effects with Erbitux® include acne-like skin rash, mild to moderate infusion-related reactions and hypomagnesemia.

Erbitux® has already obtained market authorization in 114 countries world-wide for the treatment of RAS wild-type metastatic colorectal cancer and for the treatment of squamous cell carcinoma of the head and neck (SCCHN). Merck KGaA, Darmstadt, Germany, licensed the right to market Erbitux®, a registered trademark of ImClone LLC, outside the U.S. and Canada from ImClone LLC, a wholly-owned subsidiary of Eli Lilly and Company, in 1998.

References

1. Dolan DE, et al. Cancer Control 2014;21:231–7.
2. Dahan R, et al. Cancer Cell 2015;28:285–95.
3. Boyerinas B, et al. Cancer Immunol Res 2015;3:1148–57.
4. Kohrt HE, et al. Immunotherapy 2012;4:511–27.
5. Hamilton G, et al. Expert Opin Biol Ther 2017;17:515–23.

About Merck KGaA, Darmstadt, Germany

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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 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.

Merck KGaA, Darmstadt, Germany Presents Updated Results for Investigational Therapy Tepotinib Demonstrating Durable Clinical Response in Patients with Advanced NSCLC with METex14 Skipping Mutations

ASCO Abstract # Tepotinib (MET kinase inhibitor): 9005

Not intended for UK-based media

Alterations of the MET signaling pathway are present in 3-5% of non-small cell lung cancer patients and correlate with poor prognosis

New interim data from Phase II VISION study (all lines of treatment) show tepotinib induced objective responses, as assessed by independent review, in 50.0% of patients identified by liquid biopsy (LBx) and 45.1% of patients identified by tissue biopsy (TBx)

Safety results for tepotinib are consistent with those reported in previous studies; most treatment-related adverse events (TRAEs) were Grade 1 and 2, and no Grade 4 or 5 TRAEs were observed

Darmstadt, Germany, June 3, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, which operates its biopharmaceutical business as EMD Serono in the US and Canada, today presented updated results from the potentially registrational Phase II VISION study, showing durable anti-tumor clinical activity for the investigational targeted therapy tepotinib* across different lines of treatment in advanced non-small cell lung cancer (NSCLC) patients harboring MET exon 14 skipping mutations detected by liquid biopsy (LBx) or tissue biopsy (TBx). Data were shared in an oral presentation today at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL, US.

"Tepotinib has been designed to potentially improve outcomes in aggressive tumors that have a poor prognosis and harbor these specific alterations," said Luciano Rossetti, Global Head of Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "Tepotinib is an important part of our strategic focus on precision medicine, and both the proportion of patients responding and the duration of anti-tumor clinical activity demonstrate the potential of this investigational therapy."

Discovered in-house at Merck KGaA, Darmstadt, Germany, tepotinib is an investigational, highly potent and selective[1] oral MET kinase inhibitor that is designed to inhibit the oncogenic signaling caused by MET (gene) alterations, including both MET exon 14 skipping mutations and MET amplifications, or MET protein overexpression. Alterations of the MET signaling pathway are found in various cancer types, including 3-5% of NSCLC cases, and correlate with aggressive tumor behavior and poor clinical prognosis.[2-4]

"Patients with this NSCLC molecular subtype lack treatment options that have the potential to significantly improve clinical outcomes," said Paul K. Paik, M.D., primary study investigator and Clinical Director, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center. "It is noteworthy to see data that are consistent with tepotinib's previously reported efficacy findings in this patient population, and that also provide valuable new insight into its durable clinical activity across various treatment lines."

response rate (ORR) of 50.0% for LBx-identified patients as assessed by Independent Review Committee (IRC), and 55.3% as assessed by investigators. The ORR for TBx-identified patients was 45.1% and 54.9%, respectively. The overall median duration of response (DOR) was 12.4 months and 17.1 months among LBx-identified patients, as assessed by IRC and investigators, respectively, while among TBx-identified patients, 15.7 and 14.3 months were observed, respectively.

Most treatment-related adverse events (TRAEs) were Grade 1 and 2. No Grade 4 or 5 TRAEs were observed. Any grade TRAEs reported by ≥10% of 87 patients evaluable for safety were peripheral edema (48.3%), nausea (23.0%) diarrhea (20.7%) and increased blood creatinine (12.6%). Other relevant TRAEs of any grade include increased lipase (4.6%), fatigue (3.4%) and vomiting (3.4%). TRAEs led to permanent discontinuation in four patients (two patients due to peripheral edema, one due to interstitial lung disease, one due to diarrhea and nausea). The use of both liquid and tissue biopsies to identify patients for the VISION trial is intended to support improved patient selection and is consistent with the company's focus on patient-centric drug development.

Tepotinib is currently being investigated in NSCLC in two different settings: in NSCLC harboring MET alterations (MET exon 14 skipping mutations and MET amplifications) as monotherapy, as well as in combination with the tyrosine kinase inhibitor (TKI) osimertinib in epidermal growth factor receptor (EGFR) mutated MET amplified NSCLC having acquired resistance to prior EGFR TKI. Additional information on these clinical trials can be found at ClinicalTrials.gov using the identifiers NCT02864992 and NCT03940703, respectively. Merck, KGaA, Darmstadt, Germany is also actively assessing the potential of investigating tepotinib in combination with novel therapies for other tumor indications.

**Tepotinib is the recommended International Nonproprietary Name (INN) for the MET kinase inhibitor (MSC2156119J). Tepotinib is currently under clinical investigation and not approved for any use anywhere in the world.*

Notes to Editors
Tepotinib oral session

Title: Phase II study of tepotinib in NSCLC patients with METex14 mutations
Lead Author: P.K. Paik

9:36 AM lecture time)

Location: Hall B1

Your Contact

Brenda.Mulligan@emdgroup.com

Phone: +1 978 821 5345

About Non-Small Cell Lung Cancer

With 2 million cases diagnosed annually, lung cancer (including trachea, bronchus, and lung) is the most common type of cancer worldwide, and the leading cause of cancer-related death, with 1.7 million mortality cases worldwide.[5] Alterations of the MET signaling pathway, including MET exon 14 skipping mutations and MET amplifications, occur in 3-5% of NSCLC cases.[2-4]

About Tepotinib

Tepotinib, discovered in-house at Merck KGaA, Darmstadt, Germany, is an investigational oral MET inhibitor that is designed to inhibit the oncogenic MET receptor signaling caused by MET (gene) alterations, including both MET exon 14 skipping mutations and MET amplifications, or MET protein overexpression. It has been designed to have a highly selective mechanism of action, with the potential to improve outcomes in aggressive tumors that have a poor prognosis and harbor these specific alterations.

Tepotinib is currently being investigated in NSCLC and Merck KGaA, Darmstadt, Germany is actively assessing the potential of investigating tepotinib in combination with novel therapies and in other tumor indications.

References

1. Bladt, F et al. Clin Cancer Res 2013;19:2941-2951.
2. Reungwetwattana T, et al. Lung Cancer 2017;103:27-37.
3. Mo HN, et al. Chronic Dis Transl Med 2017; 3(3):148-153.
4. Lutterbach B, et al. Cancer Res 2007;67:2081–8.
5. Bray F, et al. CA Cancer J Clin. Global cancer statistics 2018: GLOBOCAN estimates of

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Merck KGaA, Darmstadt, Germany to Expand US Biopharmaceutical R&D Facility to Advance Innovative Clinical Pipeline

(2)

Not intended for UK-based media

Merck KGaA, Darmstadt, Germany investing $70 million in U.S. Research & Development Hub

Expansion of R&D footprint to accelerate science and innovation in Oncology, Immuno-oncology and Immunology globally

Merck KGaA, Darmstadt, Germany, which operates its biopharmaceutical business as EMD Serono in the U.S. and Canada, today announced a $70 million investment to expand its state

accommodate approximately 400 new and current R&D employees focused on advancing science in oncology, immuno-oncology and immunology.

"Our talented and passionate R&D teams based in Billerica have been highly engaged in advancing a number of pipeline compounds," said Luciano Rossetti, Head of Global Research & Development at the Biopharma business of Merck KGaA, Darmstadt, Germany. "We continue to strengthen our innovation footprint in both the U.S. and Darmstadt, Germany where our global R&D headquarters are located, with the goal of delivering transformational value to patients around the world."

With this latest project, Merck KGaA, Darmstadt, Germany will have invested more than $150 million in infrastructure to advance biopharmaceutical R&D in the state of Massachusetts in recent years, with more than 150 new jobs added to its growing U.S. R&D Hub in Billerica since 2011. The town of Billerica played a critical role in bringing this latest building expansion project to fruition, working collaboratively with Company officials to underscore the benefits of expanding the state-of-the-art R&D facility.

"The continued investment of Merck KGaA, Darmstadt, Germany in Massachusetts is a testament to the state's global leadership in life sciences," said Travis McCready, President and CEO of the Massachusetts Life Sciences Center. "In working collaboratively with the town of Billerica, the company's campus expansion over the past decade has not only helped attract and retain top talent in the area, but more importantly, contributed to improving the lives of people with serious medical needs."

When construction is completed in 2021, the building will offer wet labs, office space and a cafeteria for the campus. Consistent with previous projects, the building will be constructed to the highest environmental and employee wellness standards by seeking LEED® and WELL certifications. LEED is a preeminent program for the design, construction and operation of high-performance green buildings. WELL is a building standard focused on enhancing people's health and wellness through built environments.

The healthcare business of Merck KGaA, Darmstadt, Germany employs approximately 3,500 R&D professionals across four global R&D hubs: Darmstadt, Germany; Boston, U.S.; Tokyo, Japan; and Beijing, China. Merck KGaA, Darmstadt, Germany invests approximately 20% of total sales in R&D discovery and development each year.

in R&D, manufacturing and corporate roles across almost 60 sites country-wide. Within the state of Massachusetts, more than 2,800 professionals work across 10 locations.

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For further information: Amber.Chase@emdserono.com Phone: +1 774-257-8629

Merck KGaA, Darmstadt, Germany, Announces FDA Breakthrough Therapy Designation for Investigational Therapy Tepotinib in Patients with Metastatic NSCLC with METex14 Skipping Alterations

EXPLORE MORE

Investigational oral MET inhibitor has previously received SAKIGAKE 'fast-track' regulatory designation in Japan

MET exon 14 skipping alterations and MET amplifications are present in 3-5% of non-small cell lung cancer patients and correlate with poor prognosis

The designation is based on data from the ongoing VISION study, which showed preliminary clinical evidence for tepotinib in metastatic NSCLC harboring METex14 skipping alterations

Not intended for UK-based media

US and Canada, today announced that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for the investigational targeted therapy tepotinib* in patients with metastatic non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping alterations who progressed following platinum-based cancer therapy.

"Tepotinib was associated with robust objective responses with durability that has not previously been seen in patients with metastatic NSCLC harboring MET exon 14 skipping alterations, selected by either tissue or liquid biopsy approaches," said Luciano Rossetti, Global Head of Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "This breakthrough therapy designation further underscores the potential of tepotinib, and we aim to advance this program and deliver this medicine as quickly as possible to NSCLC patients who may benefit."

Lung cancer is the most common type of cancer worldwide, with 2 million cases diagnosed annually.[1] Alterations of the MET signaling pathway are found in various cancer types, including 3-5% of NSCLC cases, and correlate with aggressive tumor behavior and poor clinical prognosis.[2-4]

Discovered in-house at Merck KGaA, Darmstadt, Germany, tepotinib is an investigational oral MET kinase inhibitor that is designed to be highly potent and selective[5] and to inhibit the oncogenic signaling caused by MET (gene) alterations, including both MET exon 14 skipping alterations and MET amplifications, or MET protein overexpression.

In March 2018, tepotinib's potential was recognized by the Japanese Ministry of Health, Labour and Welfare (MHLW), which granted SAKIGAKE 'fast-track' designation for tepotinib in advanced NSCLC harboring MET exon 14 skipping alterations. SAKIGAKE designation promotes research and development in Japan, aiming at early practical application for innovative pharmaceutical products, medical devices and regenerative medicines.

Tepotinib is also being investigated in the INSIGHT 2 study (NCT03940703) in combination with the tyrosine kinase inhibitor (TKI) osimertinib in epidermal growth factor receptor (EGFR) mutated, MET amplified, locally advanced or metastatic NSCLC having acquired resistance to prior EGFR TKI.

The Breakthrough Therapy Designation is based on data from the ongoing VISION study (NCT02864992), showing preliminary clinical evidence that tepotinib may offer an improvement

treatment.

Results from an interim analysis of the ongoing VISION study in 73 efficacy-evaluable patients with NSCLC with MET exon 14 skipping alterations identified by LBx or TBx testing demonstrate overall objective response rate (ORR) of 50.0% for LBx-identified patients as assessed by Independent Review Committee (IRC), and 55.3% as assessed by investigators. The ORR for TBx-identified patients was 45.1% and 54.9%, respectively. The overall median duration of response (DOR) was 12.4 months and 17.1 months among LBx-identified patients, as assessed by IRC and investigators, respectively, while among TBx-identified patients, 15.7 and 14.3 months were observed, respectively.

Most treatment-related adverse events (TRAEs) were Grade 1 and 2. No Grade 4 or 5 TRAEs were observed. Any grade TRAEs reported by ≥10% of 87 patients evaluable for safety were peripheral edema (48.3%), nausea (23.0%) diarrhea (20.7%) and increased blood creatinine (12.6%). Other relevant TRAEs of any grade include increased lipase (4.6%), fatigue (3.4%) and vomiting (3.4%). TRAEs led to permanent discontinuation in four patients (two patients due to peripheral edema, one due to interstitial lung disease, one due to diarrhea and nausea).

Results from this study were presented in an oral presentation at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting.[6] The use of both LBx and TBx to identify patients for the VISION study is intended to support improved patient selection and is consistent with the company's focus on patient-centric drug development.

**Tepotinib is the recommended International Nonproprietary Name (INN) for the MET kinase inhibitor (MSC2156119J). Tepotinib is currently under clinical investigation and not approved for any use anywhere in the world.*

Your Contacts

Media Relations
friederike.segeberg@emdgroup.com
Phone: +49 6151 72-6328

Investor Relations
investor.relations@emdgroup.com
Phone: +49 6151 72-3321

drugs which are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). The FDA's granting of the Breakthrough Therapy Designation for advanced NSCLC does not alter the standard regulatory requirement to establish the safety and effectiveness of a drug through adequate and well-controlled studies to support approval.

About Non-Small Cell Lung Cancer

With 2 million cases diagnosed annually, lung cancer (including trachea, bronchus and lung) is the most common type of cancer worldwide, and the leading cause of cancer-related death, with 1.7 million mortality cases worldwide.1 Alterations of the MET signaling pathway, including MET exon 14 skipping alterations and MET amplifications, occur in 3-5% of NSCLC cases.[2-4]

About Tepotinib

Tepotinib, discovered in-house at Merck KGaA, Darmstadt, Germany, is an investigational oral MET inhibitor that is designed to inhibit the oncogenic MET receptor signaling caused by MET (gene) alterations, including both MET exon 14 skipping alterations and MET amplifications, or MET protein overexpression. It has been designed to have a highly selective mechanism of action, with the potential to improve outcomes in aggressive tumors that have a poor prognosis and harbor these specific alterations.

Tepotinib is currently being investigated in NSCLC and Merck KGaA, Darmstadt, Germany is actively assessing the potential of investigating tepotinib in combination with novel therapies and in other tumor indications.

References

1. Bray F, et al. CA Cancer J Clin. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492 PMID:30207593.

2. Reungwetwattana T, et al. Lung Cancer 2017;103:27-37.

3. Mo HN, et al. Chronic Dis Transl Med 2017; 3(3):148-153.

4. Lutterbach B, et al. Cancer Res 2007;67:2081–8.

6. Paik P, et al. J Clin Oncol 2019;37: (suppl; abstr 9005).

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 52,000 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 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 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.

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Pivotal Phase III Data for BAVENCIO® (avelumab) Plus INLYTA® (axitinib) in Advanced Renal Cell Carcinoma Published in New England Journal of Medicine

Not intended for UK-based media

JAVELIN Renal 101 shows significant improvement in progression-free survival with a hazard ratio of 0.69 in patients regardless of PD-L1 expression

US FDA has granted Priority Review to BAVENCIO plus INLYTA for patients with advanced renal cell carcinoma

Data at 2019 Genitourinary Cancers Symposium reinforce consistency of PFS and ORR benefits across broad population of patients with advanced RCC, including all prognostic risk groups, and show increased time to progression on next-line therapy

Rockland, MA and New York, NY, February 16, 2019 – EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the US and Canada, and Pfizer Inc. (NYSE: PFE) today announced the publication of results from an interim analysis of the pivotal JAVELIN Renal 101 trial online in the New England Journal of Medicine.[1] The combination of BAVENCIO® (avelumab) and INLYTA® (axitinib)* significantly extended median progression-free survival (PFS) by more than five months compared with SUTENT® (sunitinib) as a first-line treatment for patients with advanced renal cell carcinoma (RCC), irrespective of PD-L1 expression (HR: 0.69 [95% CI: 0.56–0.84]; BAVENCIO+INLYTA: 13.8 months [95% CI: 11.1-NE]; SUTENT: 8.4 months [95% CI: 6.9-11.1]; p<0.001). Further, the objective response rate (ORR) was doubled with BAVENCIO+INLYTA versus SUTENT in this population (51.4% [95% CI: 46.6-56.1] vs. 25.7% [95% CI: 21.7-30.0]). The study is continuing for the other primary endpoint of overall survival (OS).

"There is a significant need for patients with advanced RCC to prolong the time until the disease worsens beyond what tyrosine kinase inhibitors alone offer," said Robert J. Motzer, M.D., Jack and Dorothy Byrne Chair in Clinical Oncology, Memorial Sloan Kettering Cancer Center, New York, US, and principal investigator for JAVELIN Renal 101. "The magnitude and consistency of PFS and response rates seen thus far across populations in the JAVELIN Renal 101 study suggest that many different types of patients, including those with a favorable prognosis, could potentially derive benefit from this particular combination."

Additional data presented today at the 2019 Genitourinary Cancers Symposium reinforce the consistency of the PFS and ORR results across patient subgroups, including patients with favorable, intermediate and poor prognoses as well as those with PD-L1-positive or negative tumors. In subgroup analyses, approximately two-thirds of patients with favorable risk (66% of patients using the Memorial Sloan Kettering Cancer Center risk model and 68% with the International Metastatic Renal Cell Carcinoma Database Consortium risk model) achieved a complete or partial response with BAVENCIO+INLYTA. Median PFS for these patients is not yet estimable. BAVENCIO+INLYTA also extended median PFS2, defined as the time from randomization to disease progression on next-line therapy (HR: 0.56 [95% CI: 0.42-0.74]; NE [95% CI: 19.9-NE] vs. 18.4 months [95% CI: 15.7-23.6]) and increased median duration of response by more than four months (95% CI: 2.9-5.1) in the overall population.

"In this study, the combination of avelumab plus axitinib not only prolonged the initial response in treated patients compared to sunitinib, but for patients who went on to subsequent therapy,

senior and co-corresponding author of JAVELIN Renal 101, and presenter. “Together with the progression-free survival results and objective response rates, these findings show the potential of this combination regimen to be an important new treatment option for patients with advanced RCC.”

The Phase III JAVELIN Renal 101 study is evaluating the combination of BAVENCIO+INLYTA compared with SUTENT in 886 patients with previously untreated advanced RCC. BAVENCIO+INLYTA significantly reduced the risk of disease progression or death by 39% in patients with PD-L1-positive (≥1%) tumors, a primary endpoint (HR: 0.61 [95% CI: 0.47–0.79], p<0.001; median PFS: 13.8 months [95% CI: 11.1-NE] vs. 7.2 months [95% CI: 5.7-9.7]). In the overall population, which was tested after achieving statistical significance for the primary endpoint, the risk was reduced by 31%. The confirmed ORR in patients with PD-L1-positive tumors was 55.2% (95% CI: 49.0-61.2) with BAVENCIO+INLYTA vs. 25.5% (95% CI: 20.6-30.9) with SUTENT.

In the BAVENCIO+INLYTA arm, 20.8% of patients received subsequent anticancer drug therapies, compared with 39.2% in the SUTENT arm. In the SUTENT arm, about two-thirds (66.7%) of patients who received subsequent anticancer therapy were known to have been treated with an anti–PD-1/PD-L1 agent.

Adverse events of grade 3 or higher during treatment (treatment-emergent adverse events [TEAEs]) occurred in 71.2% of patients in the BAVENCIO+INLYTA arm and 71.5% in the SUTENT arm); grade 3 or higher TEAEs that occurred in more than 5% of patients receiving the combination were hypertension (25.6%), diarrhea (6.7%), increased alanine aminotransferase level (6.0%) and hand–foot syndrome (5.8%). In the combination arm, 9.0% of patients experienced grade 3 or higher immune-related adverse events. Grade 5 events occurred in three patients in the BAVENCIO+INLYTA arm (myocarditis, necrotizing pancreatitis, sudden death; n=1 each); and in one patient in the SUTENT arm (intestinal perforation). There were fewer discontinuations due to adverse events that occurred during treatment with BAVENCIO+INLYTA, compared with SUTENT (7.6% vs. 13.4%).

On February 11, 2019, the alliance announced that the US Food and Drug Administration (FDA) accepted for Priority Review the supplemental Biologics License Application (sBLA) for BAVENCIO in combination with INLYTA for patients with advanced RCC. The application has been given a target action date in June 2019. A supplemental application for

combination with INLYTA for treatment-naïve patients with advanced RCC. Despite available therapies, the outlook for patients with advanced RCC remains poor.[2]

*The combination of BAVENCIO and INLYTA is under clinical investigation for advanced RCC, and there is no guarantee this combination will be approved for advanced RCC by any health authority worldwide. In the US, INLYTA is approved as monotherapy for the treatment of advanced RCC after failure of one prior systemic therapy. INLYTA is also approved by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced RCC after failure of prior treatment with SUTENT or a cytokine.

Your Contacts
News Release Merck
Media Relations: noelle.piscitelli@emdserono.com +1 781 427 4351
Investor Relations: investor.relations@merckgroup.com +49 6151 72-3321

Pfizer
Media Relations: jessica.m.smith@pfizer.com +1 212 733 6213
Investor Relations: ryan.crowe@pfizer.com +1 212 733 8160

About Renal Cell Carcinoma

RCC is the most common form of kidney cancer, accounting for about 2% to 3% of all cancers in adults.[3,4] The most common type of RCC is clear cell carcinoma, accounting for approximately 70% of all cases.[3] In 2019, an estimated 73,820 new cases of kidney cancer will be diagnosed in the US, and approximately 14,770 people will die from the disease.[5] Approximately 20% to 30% of patients are first diagnosed at the metastatic stage.[6] The five-year survival rate for patients with metastatic RCC is approximately 12%.[2]

About the JAVELIN Clinical Development Program

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and more than 9,000 patients evaluated across more than 15 different tumor types. In addition to RCC, these tumor types include breast, gastric/gastro-esophageal junction, and head and neck cancers, Merkel cell carcinoma, non-small cell lung cancer, and urothelial carcinoma.

About BAVENCIO® (avelumab)

Avelumab is a human anti-programmed death ligand-1 (PD-L1) antibody. Avelumab 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, avelumab has been shown to release the suppression of the T cell-mediated antitumor immune response in preclinical models.[7-9] Avelumab has also been shown to induce NK cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro.[9-11] In November 2014, Merck KGaA, Darmstadt, Germany, and Pfizer announced a strategic alliance to co-develop and co-commercialize avelumab.

Approved Indications

In the US, the FDA granted accelerated approval for avelumab (BAVENCIO®) for the treatment of (i) adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (mMCC) and (ii) patients with locally advanced or metastatic urothelial carcinoma (mUC) 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 rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is currently approved for patients with MCC in more than 45 countries globally, with the majority of these approvals in a broad indication that is not limited to a specific line of treatment.

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% (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 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 reinitiation 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 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% (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

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 1,738 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.

(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 carcinoma (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%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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

About INLYTA® (axitinib)

INLYTA is an oral therapy that is designed to inhibit tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors 1, 2 and 3; these receptors can influence tumor growth, vascular angiogenesis and progression of cancer (the spread of tumors). In the US, INLYTA is approved for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. INLYTA is also approved by the European Medicines Agency (EMA) for use in the EU in adult patients with advanced RCC after failure of prior treatment with sunitinib or a cytokine.

INLYTA Important Safety Information

Hypertension including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose.

evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

For more information and full Prescribing Information, visit www.INLYTA.com.

About SUTENT® (sunitinib malate)

Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET).

disease progression on or intolerance to imatinib mesylate; the treatment of advanced RCC; the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy; and the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease.

SUTENT Important Safety Information

Boxed Warning/Hepatotoxicity has been observed in clinical trials and postmarketing experience. Hepatotoxicity may be severe, and in some cases fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. Fatal liver failure has been observed. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. Interrupt SUTENT for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have signs and symptoms of liver failure.

Cardiovascular events, including myocardial ischemia, myocardial infarction, left ventricular ejection fraction declines to below the lower limit of normal and cardiac failure including death have occurred. Monitor patients for signs and symptoms of congestive heart failure. Discontinue SUTENT for clinical manifestations of congestive heart failure. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. Baseline and periodic evaluations of left ventricular ejection fraction should also be considered while these patients are receiving SUTENT.

SUTENT can cause **QT Prolongation** 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. Monitor patients that are at a higher risk for developing QT interval prolongation, including those with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Consider monitoring of electrocardiograms and electrolytes. Concomitant treatment with strong CYP3A4 inhibitors may increase sunitinib plasma concentrations and dose reduction of SUTENT should be considered.

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.

tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Perform serial complete blood counts (CBCs) and physical examinations.

Cases of **tumor lysis syndrome (TLS)** (some fatal) have been reported. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated.

Thrombotic microangiopathy (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 and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt treatment for 24-hour urine protein ≥3 grams. Discontinue for repeat episodes of protein ≥3 grams despite dose reductions or nephrotic syndrome.

Dermatologic toxicities: Severe cutaneous reactions have been reported, including cases of necrotizing fasciitis, 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, discontinue SUTENT treatment. If a diagnosis of SJS or TEN is suspected, treatment must not be restarted.

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

Hypoglycemia may occur. SUTENT can result in symptomatic hypoglycemia, which may lead to a loss of consciousness or require hospitalization. Reductions in blood glucose levels may be

adjusted to minimize the risk of hypoglycemia.

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

Impaired wound healing has occurred with SUTENT. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Embryo fetal toxicity and reproductive potential
Females - SUTENT can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with SUTENT and for 4 weeks following the final dose.
Males - Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with SUTENT and for 7 weeks after the last dose.
Male and female infertility - based on findings in animals, male and female fertility may be compromised by treatment with SUTENT

Lactation: Because of the potential for serious adverse reactions in breastfed infants from SUTENT, advise a lactating woman not to breastfeed during treatment with SUTENT and for at least 4 weeks after the last dose.

Venous thromboembolic events: In patients treated with SUTENT (N=7527) for GIST, advanced RCC, adjuvant treatment of RCC and pNET, 3.5% of patients experienced a venous thromboembolic event; 2.2% Grade 3-4.

There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of **reversible posterior leukoencephalopathy syndrome (RPLS)**. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension.

Pancreatic function: In a trial of patients receiving adjuvant treatment for RCC, 1 patient (<1%) on SUTENT and none on placebo experienced pancreatitis.

CYP3A4 inhibitors and inducers: 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 (adjuvant RCC): The **most common ARs** reported in ≥20% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (all grades, vs placebo) were mucositis/stomatitis (61% vs 15%), diarrhea (57% vs 22%), fatigue/asthenia (57% vs 34%), hand-foot syndrome (50% vs 10%), hypertension (39% vs 14%), altered taste (38% vs 6%), nausea (34% vs 15%), dyspepsia (27% vs 7%), abdominal pain (25% vs 9%), hypothyroidism/TSH increased (24% vs 4%), rash (24% vs 12%), hair color changes (22% vs 2%). The **most common grade 3/4 ARs** reported in ≥5% of patients receiving SUTENT for adjuvant treatment of RCC and more commonly than in patients given placebo (vs placebo) were hand-foot syndrome (16% vs <1%), fatigue/asthenia (8% vs 2%), hypertension (8% vs 1%), and mucositis/stomatitis (6% vs 0%).

Most common grade 3/4 lab abnormalities (adjuvant RCC): The **most common grade 3/4 lab abnormalities** (occurring in ≥ 2% of patients receiving SUTENT) included neutropenia (13%), thrombocytopenia (5%), leukopenia (3%), lymphopenia (3%), elevated alanine aminotransferase (2%), elevated aspartate aminotransferase (2%), hyperglycemia (2%), and hyperkalemia (2%).

Most common ARs & most common grade 3/4 ARs (advanced RCC): The **most common ARs** reported 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

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** reported 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** reported 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% vs0%).

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** reported 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%), epistaxis (21% vs 5%), and dysgeusia (21% vs 5%). The **most common grade 3/4 ARs** reported 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%

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 and Medication Guide, for SUTENT® (sunitinib malate) at www.SUTENT.com.

Alliance between Merck KGaA, Darmstadt, Germany, and Pfizer Inc., New York, US
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.

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 multiple sclerosis. Today, the business has approximately 1,300 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

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 51,000 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 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.

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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. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. 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

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Pfizer Disclosure Notice

The information contained in this release is as of February 11, 2019. 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 new indication for BAVENCIO in combination with INLYTA (axitinib) for the treatment of patients with advanced renal cell carcinoma, 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 further analyses of existing clinical data and uncertainties regarding whether the other primary endpoint of JAVELIN Renal 101 will be met; 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 in combination with INLYTA for the potential new indication in any other jurisdictions or in any jurisdictions for any other potential indications for BAVENCIO or combination therapies; whether and when the pending applications in the U.S. and Japan for BAVENCIO in combination with INLYTA for the potential new indication may be approved and whether and when regulatory authorities in any jurisdictions where any other applications are pending or may be submitted for BAVENCIO or combination therapies 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 and/or other matters that could affect the availability or commercial potential of BAVENCIO or combination therapies, including BAVENCIO in combination with INLYTA for the potential new indication; and competitive developments.

10-K for the fiscal year ended December 31, 2017, 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. Motzer RJ, Rini B, Albiges L, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. NEJM. February 16, 2019. Published online ahead of print.

2. National Cancer Institute: SEER Stat Fact Sheets: Kidney and renal pelvis. Available from: http://seer.cancer.gov/statfacts/html/kidrp.html. Accessed February 2019.

3. American Cancer Society. What is kidney cancer? Available from: https://www.cancer.org/cancer/kidney-cancer/about.html. Accessed February 2019.

4. Escudier B, Porta C, Schmidinger M et al Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annal Oncol. 2014; 25(Suppl3):iii49-iii56.

5. American Cancer Society. Cancer facts and figures 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed February 2019.

6. Ljungberg B, Campbell S and Cho H. The Epidemiology of Renal Cell Carcinoma. Eur Urol. 2011;60:615-621.

7. Dolan DE, Gupta S. PD-1 pathway inhibitors: changing the landscape of cancer immunotherapy. Cancer Control. 2014;21(3):231-237.

8. Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. Cancer Cell. 2015;28(3):285-295.

9. 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.

10. Kohrt HE, Houot R, Marabelle A, et al. Combination strategies to enhance antitumor ADCC. Immunotherapy. 2012;4(5):511-527.

11. Hamilton G, Rath B. Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. Expert Opin Biol Ther. 2017;17(4):515-523.

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