News Release

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Not intended for UK-based media

Merck KGaA, Darmstadt, Germany, Advances Oncology Portfolio and Pipeline with New and Long-term Data in Multiple Cancers at ESMO 2020

- **New analyses from Phase III JAVELIN Bladder 100 study of BAVENCIO®* assess efficacy across subgroups, patient-reported outcomes and exploratory biomarkers in advanced urothelial cancer**
- **Overall efficacy data, and analyses of brain metastases and HRQoL for tepotinib† from largest ongoing study in NSCLC harboring *MET*ex14 skipping**
- **Long-term follow-up data for novel bifunctional fusion protein targeting TGF-β/PD-L1, bintrafusp alfa‡ in NSCLC and BTC demonstrate continued durability of response**

Darmstadt, Germany, September 14, 2020 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced more than 30 abstracts will be presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020 from September 19-21. The abstracts span the Company's clinical program in oncology across several innovative modalities and mechanisms that have the potential to advance treatment across a range of tumor types including biliary tract, lung and urothelial (bladder) cancers.

"Our oncology ambition is to discover innovative therapies with transformative results. The data being presented in urothelial cancer demonstrate this approach in action, where we are seeing promising results for a new first-line maintenance therapeutic option with BAVENCIO® in this form of cancer," said Luciano Rossetti, Global Head of Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "In addition, long-term follow-up data in advanced lung

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cancer from two of our in-house developed mechanisms—our oral MET inhibitor, tepotinib, and our first-in-class bifunctional fusion protein immunotherapy targeting TGF-β/PD-L1, bintrafusp alfa—continue to show sustained impact in one of the leading causes of cancer mortality."

Key data highlights at ESMO

Avelumab (BAVENCIO®)

Phase III JAVELIN Bladder 100 (Presentations #699O; 704MO; 745P). Primary results from the JAVELIN Bladder 100 study demonstrated an overall survival (OS) benefit for BAVENCIO vs. best supportive care in the first-line maintenance treatment of advanced urothelial carcinoma, making BAVENCIO the first and only immunotherapy to significantly prolong OS in this setting. Three new abstracts from the JAVELIN Bladder 100 study will be presented at ESMO:

- An oral presentation during the Proffered Paper 1 – GU, non-prostate session scheduled on September 19, 2020 at 5:28pm–5:40pm CEST/11:28am-11:40am EDT, will highlight associations between clinical outcomes and exploratory biomarkers (Presentation #699O)
- Two other abstracts provide more information on prespecified subgroup analyses, as well as patient-reported outcomes.

Phase III JAVELIN Head and Neck 100 (Presentation #910O). Primary results from this Phase III study will be presented. The study is a demonstration of our commitment to develop options for patients with squamous cell carcinoma of the head and neck, and the results increase understanding in the field of the role of immunotherapy.

Tepotinib

Phase II VISION (Presentations: #1283P; 1286P; 1347P). Three posters from the largest study in patients with non-small cell lung cancer (NSCLC) harboring *MET*ex14 skipping treated with tepotinib—an oral, once-daily, highly selective MET inhibitor. Data presented will highlight:

- Durable clinical activity that has been consistent across clinically relevant subgroups both in treatment-naïve and in previously treated patients as well as in patients with brain metastases as assessed by liquid biopsy or tissue biopsy (Poster #1283P)
- Health-related quality of life (HRQoL) has been shown to be maintained, with clinically meaningful delays in the time to deterioration of cough, dyspnea, and chest pain (Poster #1286P)
- A safety profile consisting of mostly mild to moderate adverse events with few treatment discontinuations.

INSIGHT 2 (NSCLC): The INSIGHT 2 study assessing the combination of osimertinib and tepotinib in patients with EGFR-mutant NSCLC that has developed resistance to first-line osimertinib treatment due to *MET* amplification is ongoing and actively recruiting patients (Poster #1415TiP).

Bintrafusp alfa (M7824)

Data from the INTR@PID clinical trial program for first-in-class bintrafusp alfa, an investigational bifunctional fusion protein targeting both TGF-β and PD-L1 pathways, show promising and durable responses across multiple tumor types including NSCLC and biliary tract cancer (BTC) with a manageable safety profile in Phase I expansion cohorts.

Two long-term follow-up studies assessing efficacy and safety from the INTR@PID clinical trial program will be presented as posters at ESMO 2020:

- **INTR@PID Solid Tumor 001 three-year long-term follow-up for 2L treatment of NSCLC** (Poster #1272P)
- **INTR@PID Solid Tumor 008 28-month long-term follow-up in patients with pretreated biliary tract cancer** (Poster #73P)

In addition, preliminary analysis will be presented in a mini-oral presentation (#616MO) from a trial conducted by the National Cancer Institute (NCI), the Quick Efficacy Seeking Trial (QuEST) investigating a triple combination therapy (BN-brachyury [BVax] + bintrafusp alfa + N-803) in castration-resistant prostate cancer. Available on demand from September 18 at ESMO.org.

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**BAVENCIO is under clinical investigation for the first-line maintenance treatment of advanced UC and not yet approved in any markets outside of the US.*

†Tepotinib is the International Nonproprietary Name (INN) for the MET kinase inhibitor MSC2156119J. Tepotinib is currently under clinical investigation in NSCLC and not yet approved in any markets outside of Japan.

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

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. 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) is indicated in the US for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy. BAVENCIO is also indicated for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

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

Avelumab is currently approved for patients with MCC in 51 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 fatal, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

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

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

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

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

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

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

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer antihyperglycemics or insulin in patients with severe or life-threatening (Grade ≥3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% of patients, including two cases of Grade 3 hyperglycemia.

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during

treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% of patients.

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO as a single agent or in 489 patients who received *BAVENCIO in combination with axitinib*: myocarditis including fatal cases, pancreatitis including fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

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

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

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

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%).

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

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

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

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

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

Selected laboratory abnormalities (all grades, ≥20%) worsening from baseline in patients with advanced RCC receiving BAVENCIO in combination with axitinib (vs

sunitinib) were blood triglycerides increased (71% vs 48%), blood creatinine increased (62% vs 68%), blood cholesterol increased (57% vs 22%), alanine aminotransferase increased (ALT) (50% vs 46%), aspartate aminotransferase increased (AST) (47% vs 57%), blood sodium decreased (38% vs 37%), lipase increased (37% vs 25%), blood potassium increased (35% vs 28%), platelet count decreased (27% vs 80%), blood bilirubin increased (21% vs 23%), and hemoglobin decreased (21% vs 65%).

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

About Tepotinib
Tepotinib is an oral MET inhibitor that is designed to inhibit the oncogenic MET receptor signaling caused by *MET* (gene) alterations. Discovered and developed in-house at Merck KGaA, Darmstadt, Germany, 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. In March 2020, tepotinib became the first oral MET inhibitor indicated for the treatment of advanced NSCLC harboring *MET* gene alterations to receive a regulatory approval globally, with the Japanese Ministry of Health, Labour and Welfare (MHLW) approval for the treatment of patients with unresectable, advanced or recurrent NSCLC with *MET*ex14 skipping alterations. In September 2019, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation for tepotinib in patients with metastatic NSCLC harboring *MET*ex14 skipping alterations whose disease progressed following platinum-based cancer therapy. Tepotinib is also being investigated in the Phase II INSIGHT 2 study in combination with osimertinib in *MET* amplified, advanced or metastatic NSCLC harboring activating *EGFR* mutations that has progressed following first-line treatment with osimertinib.

About Bintrafusp Alfa
Bintrafusp alfa (M7824), discovered in-house at Merck KGaA, Darmstadt, Germany and currently in clinical development through a strategic alliance with GSK, is a potential first-in-class investigational bifunctional fusion protein designed to simultaneously block two immunosuppressive pathways, TGF-β and PD-L1, within the tumor microenvironment. This bifunctional approach is thought to control tumor growth by potentially restoring and enhancing anti-tumor responses. In preclinical studies, bintrafusp alfa has demonstrated antitumor activity both as monotherapy and in combination with chemotherapy. Based on its mechanism of action, bintrafusp alfa offers a potential targeted approach to addressing the underlying pathophysiology of difficult-to-treat cancers.

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

to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.