News Release

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Not intended for UK- or Canada-based media

Merck KGaA, Darmstadt, Germany, to Highlight Data at ESMO 2022 with Potential for Transformative Impact on Cancer Patients

- **Late-breaking data highlight 5-year survival results from Phase II study of the investigational IAP inhibitor xevinapant in the curative setting of unresected LA SCCHN**
- **Initial results of Phase II INSIGHT 2 study of TEPMETKO plus osimertinib as second-line treatment in *EGFR*-mutant NSCLC with *MET* amplification showed encouraging signs of clinical activity with this targeted, oral, chemo-sparing regimen**
- **First-in-human results for potential best-in-class investigational ATR inhibitor M1774**

Darmstadt, Germany, September 8, 2022 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced the latest research from the Company's oncology portfolio and pipeline to be presented at this year's European Society of Medical Oncology (ESMO) Annual Meeting, September 9-13, 2022. A total of 29 abstracts, including 5 late-breaking oral presentations and 2 additional mini-oral presentations, will feature data from company- and investigator-sponsored studies across six approved or investigational medicines in multiple tumor types.

"Our ESMO 2022 data will highlight the strong potential of our innovative pipeline for patients with cancers with significant unmet needs," said Victoria Zazulina, M.D., Head of Development Unit, Oncology, for the Healthcare business of Merck KGaA, Darmstadt, Germany. "From our IAP inhibitor xevinapant, studied in a curative

setting in locally advanced head and neck cancer; through to new data in NSCLC patients with *MET* amplification and EGFR mutations; to our potentially best-in-class oral ATR inhibitor; we are focused on unlocking novel mechanisms of action that exploit the vulnerabilities of cancer."

The company's late-breaking data at the congress feature five-year overall survival (OS) results from a Phase II study of the IAP (Inhibitor of Apoptosis Protein) inhibitor xevinapant in patients with unresected locally advanced squamous cell carcinoma of the head and neck [Mini Oral #LBA33]. Patients who received xevinapant plus chemoradiotherapy (CRT) had improved efficacy outcomes compared with those who received placebo with CRT.

Additional late-breaking results include initial results from the Phase II INSIGHT 2 trial of TEPMETKO® (tepotinib) plus osimertinib in the treatment of patients with *EGFR*-mutant non-small cell lung cancer (NSCLC) with *MET* amplification (*MET*amp) after progression on first-line treatment with osimertinib [Proffered Paper #LBA52]. The confirmed overall response rate (ORR) was 54.5% (95% CI, 32.2, 75.6) in 22 patients with *MET*amp detected by FISH (MET GCN ≥5 and/or MET/CEP7 ≥2) in tissue biopsy who received tepotinib plus osimertinib and were followed for at least nine months, with six of 12 responders still on treatment. Among the 48 patients followed for at least three months, ORR was 45.8% (95% CI, 31.4, 60.8). The most common treatment-related adverse events of any grade in greater than 15% of patients were diarrhea (40.9%), peripheral edema (23.9%) and paronychia (17.0%).

Further late-breaking data to be presented at ESMO 2022 include translational data for BAVENCIO® (avelumab) characterizing genomic biomarkers in peripheral blood from patients enrolled in the Phase III JAVELIN Bladder 100 trial [Proffered Paper #LBA74].

Additional key data to be presented:

- A mini-oral presentation from the first-in-human Phase I study of M1774, the Company's potentially best-in-class potent and selective inhibitor of ataxia telangiectasia and Rad3-related (ATR), showing a favorable safety profile and pharmacologically relevant exposure in patients with advanced solid tumors

(DDRiver Solid Tumors 301) [#457MO] exemplifying the Company's commitment to advancing understanding of DNA Damage Response (DDR) inhibition mechanisms.

- Exploratory analyses from JAVELIN Bladder 100 that examine clinical outcomes in long-term responders with advanced urothelial carcinoma treated with BAVENCIO first-line maintenance for ≥12 months [#1760P]. Long-term follow-up data presented earlier this year reinforced the benefit of BAVENCIO plus best supportive care (BSC) in the first-line maintenance setting, with a continued improvement in OS versus BSC alone for patients with locally advanced or metastatic urothelial carcinoma whose tumors had not progressed on a platinum-based chemotherapy.[1]
- Results from cohorts A and C in the Phase II VISION trial demonstrated robust and durable efficacy in treatment-naïve and previously treated patients with metastatic NSCLC with *MET*ex 14-skipping. In previously treated patients, efficacy was observed regardless of prior therapies including IO and/or platinum-based CT [#985P].

Other company-sponsored events at ESMO 2022 include:

Medical Symposia:

- **From Complex to Simple: The Journey to Strategic Sequencing in the Management of mCRC** (Friday, September 9, 6:00–7:30 PM CEST, 7.3Q Quimper Auditorium, Hall 7, Level 7.3)
- **New Approaches to Optimize Treatment Outcomes in Advanced Urothelial Carcinoma** (Saturday, September 10, 1:00-2:30 PM CEST, 7.3.U Urval Auditorium, Hall 7, Level 7.3)
- **Evolution of SCCHN Treatment** (Sunday, September 11, 6:30-8:00 PM CEST, 7.3.0 Orleans Auditorium, Hall 7, Level 7.3).

Continuing Medical Education (CME):

- **Navigating Treatment Decisions in Advanced NSCLC: Update on Molecular Testing and New Targeted Treatment Options** (Friday, September 9, 10:15-11:45 AM CEST, Quimper Auditorium, Hall 7, Level 7.3)

Select presentations (all times CEST):

Title	Lead Author	Abstract	Session Title/Date/Time

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PIPELINE			
5-year overall survival (OS) in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) treated with xevinapant+chemoradiotherapy (CRT) vs placebo+CRT in a randomized, phase 2 study	J Bourhis	LBA33	Mini Oral Session: Head and Neck Cancer Saturday, 10 September 10:55 AM
A First-in-Human Phase I Study of ATR Inhibitor M1774 in Patients with Advanced Solid Tumors (DDRiver Solid Tumors 301)	TA Yap	457MO	Mini Oral Session: Developmental Therapeutics Monday, 12 September 4:55 PM
Phase 1 study of TIGIT inhibitor M6223 as monotherapy or in combination with bintrafusp alfa (BA) in patients (pts) with metastatic/locally advanced solid unresectable tumours	LL Siu	750P	Investigational immunotherapy Monday, 12 September
BAVENCIO (avelumab)			
Characterization of genomic biomarkers in peripheral blood (PB) from patients (pts) enrolled in the JAVELIN Bladder 100 trial of avelumab first-line (1L) maintenance in advanced urothelial carcinoma (aUC)	T Powles	LBA74	Proffered Paper Session 1: GU tumours, non-prostate Saturday, 10 September 11:10 AM
Avelumab versus standard second line treatment chemotherapy in metastatic colorectal cancer (mCRC) patients with microsatellite instability (MSI): the SAMCO-PRODIGE 54 randomised phase II trial	J Taïeb	LBA23	Proffered Paper Session 1: GI lower digestive Sunday, 11 September 11:15 AM
Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (aUC): results from patients with ≥12 mos of treatment in JAVELIN Bladder 100	J Aragon-Ching	1760P	Urothelial Cancer Monday, 12 September
Preliminary results from AVENANCE, an ongoing, noninterventional real-world, ambispective study of avelumab first-line (1L) maintenance treatment in patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC)	P Barthélémy	1757P	Urothelial Cancer Monday, 12 September
Avelumab added to FOLFIRI plus cetuximab followed by avelumab maintenance in patients with previously untreated RAS wild-type colorectal cancer–The phase-II FIRE-6 (AIO KRK-0118)	S Stintzing	424P	Colorectal Cancer Sunday, 11 September
TEPTMETKO (tepotinib)			
Tepotinib+osimertinib for *EGFR*-mutant(m) NSCLC after progression on first-line (1L) osimertinib due to *MET* amplification: Initial results from the INSIGHT 2 study	J Mazieres	LBA52	Proffered Paper Session: NSCLC, metastatic Sunday, 11 September 2:55 PM
Tepotinib outcomes according to prior therapies in patients with *MET*exon14 (*MET*ex14) skipping NSCLC	E Smit	985P	NSCLC, metastatic Monday, 12 September

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,

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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

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

BAVENCIO is currently approved for at least one indication for patients in more than 50 countries.

BAVENCIO Important Safety Information from the US FDA-Approved Label

BAVENCIO can cause **severe and fatal immune-mediated adverse reactions** in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes,

creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

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 Grade 2 and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis.

BAVENCIO can cause **immune-mediated colitis**. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory

immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.

BAVENCIO can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

> ***BAVENCIO in combination with INLYTA*** can cause **hepatotoxicity** with higher than expected frequencies of Grade 3 and 4 ALT and AST elevation compared to BAVENCIO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used as monotherapy. Withhold or permanently discontinue both BAVENCIO and INLYTA based on severity of AST, ALT, or total bilirubin elevation, and consider administering corticosteroids as needed. Consider rechallenge with BAVENCIO or INLYTA, or sequential rechallenge with both BAVENCIO and INLYTA, after recovery. In patients treated with BAVENCIO in combination with INLYTA in the advanced RCC trials, increased ALT and increased AST were reported in 9% (Grade 3) and 7% (Grade 4) of patients. Immune-mediated hepatitis was reported in 7% of patients including 4.9% with Grade 3 or 4 immune-mediated hepatitis. Thirty-four patients were treated with corticosteroids and one patient was treated with a non-steroidal immunosuppressant.

BAVENCIO can cause primary or secondary **immune-mediated adrenal insufficiency**. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal

insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

BAVENCIO can cause **immune-mediated hypophysitis**. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

BAVENCIO can cause **immune-mediated type I diabetes mellitus**, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 0.1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause **immune-mediated nephritis with renal dysfunction**. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade

4 increased blood creatinine. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

BAVENCIO can result in other **immune-mediated adverse reactions**. Other clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For myocarditis, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For neurological toxicities, withhold BAVENCIO for Grade 2 and permanently discontinue for Grade 3 or Grade 4.

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 Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

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Fatal and other serious **complications of allogeneic hematopoietic stem cell transplantation (HSCT)** can occur in patients who receive HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

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. Permanently 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 in a randomized trial. 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 + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

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

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

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

About TEPMETKO® (tepotinib)

TEPMETKO is a once-daily oral MET inhibitor that inhibits the oncogenic MET receptor signaling caused by *MET* (gene) alterations. Discovered and developed in-house at Merck KGaA, Darmstadt, Germany, TEPMETKO has 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.

TEPMETKO was the first oral MET inhibitor to receive a regulatory approval anywhere in the world for the treatment of advanced NSCLC harboring *MET* gene alterations, with its approval in Japan in March 2020. In February 2021, the US Food and Drug Administration granted accelerated approval to TEPMETKO, making it the first and only once-daily oral MET inhibitor approved for patients in the US with metastatic NSCLC with *MET*ex14-skipping alterations. In February 2022, the European Commission (EC) approved once-daily oral TEPMETKO as monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC)

harboring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (*MET*ex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

TEPMETKO is available in a number of countries. To meet an urgent clinical need, TEPMETKO is also available in a pilot zone of China in line with the government policy to drive early access for innovative medicines approved outside of China.

Merck KGaA, Darmstadt, Germany is also investigating the potential role of tepotinib in treating patients with NSCLC and acquired resistance due to *MET* amplification in the Phase II INSIGHT 2 study of tepotinib in combination with osimertinib in *MET* amplified, advanced or metastatic NSCLC harboring activating EGFR mutations that has progressed following first-line treatment with osimertinib.

TEPMETKO Approved Indication in the US

TEPMETKO is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal epithelial transition (MET) exon 14 skipping alterations. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information from the US FDA-Approved Label

TEPMETKO can cause **interstitial lung disease (ILD)/pneumonitis**, which can be fatal. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Immediately withhold TEPMETKO in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified. ILD/pneumonitis occurred in 2.2% of patients treated with TEPMETKO, with one patient experiencing a Grade 3 or higher event; this event resulted in death.

TEPMETKO can cause **hepatotoxicity**, which can be fatal. Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TEPMETKO, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased

transaminases or total bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue TEPMETKO. Increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST) occurred in 13% of patients treated with TEPMETKO. Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). The median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178).

TEPMETKO can cause **embryo-fetal toxicity**. Based on findings in animal studies and its mechanism of action, TEPMETKO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential or males with female partners of reproductive potential to use effective contraception during treatment with TEPMETKO and for one week after the final dose.

Avoid concomitant use of TEPMETKO with dual strong **CYP3A inhibitors** and **P-gp inhibitors** and strong **CYP3A inducers**. Avoid concomitant use of TEPMETKO with certain **P-gp substrates** where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the P-gp substrate dosage if recommended in its approved product labeling.

Fatal adverse reactions occurred in one patient (0.4%) due to pneumonitis, one patient (0.4%) due to hepatic failure, and one patient (0.4%) due to dyspnea from fluid overload.

Serious adverse reactions occurred in 45% of patients who received TEPMETKO. Serious adverse reactions in >2% of patients included pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%).

The most common adverse reactions (≥20%) in patients who received TEPMETKO were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea.

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Clinically relevant adverse reactions in <10% of patients who received TEPMETKO included ILD/pneumonitis, rash, fever, dizziness, pruritus, and headache.

Selected laboratory abnormalities (≥20%) from baseline in patients receiving TEPMETKO in descending order were: decreased albumin (76%), increased creatinine (55%), increased alkaline phosphatase (ALP) (50%), decreased lymphocytes (48%), increased alanine aminotransferase (ALT) (44%), increased aspartate aminotransferase (AST) (35%), decreased sodium (31%), decreased hemoglobin (27%), increased potassium (25%), increased gamma-glutamyltransferase (GGT) (24%), increased amylase (23%), and decreased leukocytes (23%).

The most common Grade 3 to 4 laboratory abnormalities (≥2%) in descending order were: decreased lymphocytes (11%), decreased albumin (9%), decreased sodium (8%), increased GGT (5%), increased amylase (4.6%), increased ALT (4.1%), increased AST (2.5%), and decreased hemoglobin (2%).

A clinically relevant laboratory abnormality in <20% of patients who received TEPMETKO was increased lipase in 18% of patients, including 3.7% Grades 3 to 4.

For more information about TEPMETKO, please see full Prescribing Information, and visit www.TEPMETKO.com.

About Xevinapant
Xevinapant (formerly known as Debio 1143) is an investigational first-in-class potent oral small-molecule IAP (inhibitor of apoptosis protein) inhibitor for the treatment of LA SCCHN. In preclinical studies, xevinapant restored sensitivity to apoptosis in cancer cells, thereby enhancing the effects of chemotherapy and radiotherapy. Xevinapant, the most clinically advanced IAP inhibitor, improved efficacy outcomes in combination with chemoradiotherapy (CRT), including three-year progression-free survival and five-year survival, compared with placebo plus CRT in a Phase II study in patients with unresected locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). In March 2021, Merck KGaA, Darmstadt, Germany, gained exclusive rights from Debiopharm to develop and commercialize xevinapant worldwide. Xevinapant is not approved for any use anywhere in the world.

About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across life science, healthcare and electronics. More than 60,000 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

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the intelligence of devices – the company is everywhere. In 2021, Merck KGaA, Darmstadt, Germany, generated sales of € 19.7 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 MilliporeSigma in life science, EMD Serono in healthcare and EMD Electronics in electronics. 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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[1] Powles T, Park SH, Voog E, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up results from the JAVELIN Bladder 100 trial. *J Clin Oncol* 40, 2022 (suppl 6; abstr 487).