



# European Medicines Agency Validates the Marketing Authorization Application for Avelumab for the Treatment of Metastatic Merkel Cell Carcinoma

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If approved, avelumab, an investigational anti-PD-L1 IgG1, could be the first treatment indicated for patients with metastatic Merkel cell carcinoma. The Marketing Authorization Application is based on Phase II data from the JAVELIN Merkel 200 study demonstrating meaningful tumor responses in patients with metastatic disease that progressed after prior chemotherapy. JAVELIN Merkel 200 is the largest reported anti-PD-L1/PD-1 antibody study in this patient population.

Merck KGaA, Darmstadt, Germany, and Pfizer Inc. (NYSE: PFE) today announced that the European Medicines Agency (EMA) has validated for review Merck KGaA, Darmstadt, Germany's Marketing Authorization Application (MAA) for avelumab, for the proposed indication of metastatic Merkel cell carcinoma (MCC), a rare and aggressive skin cancer, which impacts approximately 2,500 Europeans a year.[1],[2] Validation of the MAA confirms that submission is complete and begins the EMA's centralized review process.\* If approved, avelumab, an investigational fully human anti-PD-L1 IgG1 monoclonal antibody, could be the first approved treatment indicated for metastatic MCC in the EU. Patients with metastatic MCC face a very poor prognosis, with less than 20 percent surviving beyond five years.[3]

"While early-stage Merkel cell carcinoma can be generally managed with surgery, there are significant unmet needs in metastatic disease, where treatment options are severely

limited," said Luciano Rossetti, M.D., Executive Vice President, Global Head of Research & Development at the biopharma business of Merck KGaA, Darmstadt, Germany, which in the US and Canada operates as EMD Serono. "We are pleased that the EMA is initiating its review of avelumab, as this means we are one step closer to bringing a much-needed new treatment option to European patients."

"This is the first of what we hope will be many regulatory milestones for avelumab," said Chris Boshoff, M.D., Ph.D., Senior Vice President and Head of Immuno-oncology, Early Development and Translational Oncology, Pfizer Global Product Development. "We are committed to evaluating avelumab in a number of hard-to-treat cancers, and we believe it may have potential to be an important treatment option for patients with metastatic Merkel cell carcinoma."

The avelumab metastatic MCC MAA submission is supported by data from JAVELIN Merkel 200, a multicenter, single-arm, open-label, Phase II study of 88 patients with metastatic MCC whose disease had progressed after at least one chemotherapy treatment.[1] The JAVELIN Merkel 200 study represents the largest data set of any anti-PD-L1/PD-1 antibody reported in this patient population. These data were recently published in the Lancet Oncology.[1]

Avelumab received an Orphan Drug Designation (ODD) from the European Commission for MCC. To qualify for an ODD in the EU, a medicine must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; the prevalence of the condition in the EU must not be more than 5 in 10,000, or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and it must be for a disease where no satisfactory treatment is currently available.[4]

The clinical development program for avelumab, known as JAVELIN, involves at least 30 clinical programs and over 2,900 patients evaluated across more than 15 different tumor types. In addition to metastatic MCC, these cancers include breast, gastric/gastro-esophageal junction, head and neck, Hodgkin's lymphoma, melanoma, mesothelioma, non-small cell lung, ovarian, renal cell carcinoma and urothelial (primarily bladder).

\*Avelumab is not approved for any indication in any market. This marks the first acceptance of an EU market authorization application to review the safety and efficacy results for the investigational product avelumab.

## References

Kaufman HL et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel

cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncology* 2016;17(10);1374-85. IMMOMEC (European Commission). Merkel Cell Carcinoma. <http://www.immomec.eu/project/objectives/background/merkel-cell-carcinoma/>. Last accessed October 2016. Lemos B, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: Analysis of 5,823 cases as the basis of the first consensus staging system for this cancer. *Journal of the American Academy of Dermatology* 2010;63:751-761. European Medicines Agency. Orphan designation. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_c) Last accessed October 2016. National Cancer Institute. Merkel cell carcinoma treatment-patient version (PDQ®). <http://www.cancer.gov/types/skin/patient/merkel-cell-treatment-pdq>. Last accessed October 2016. 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 October 2016. Desch L and Kuntsfeld R. Merkel cell carcinoma: chemotherapy and emerging new therapeutic options. *Journal of Skin Cancer*. 2013(2013):327150. <http://dx.doi.org/10.1155/2013/327150> Heath M, Jaimes N and Lemos B. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *Journal of the American Academy of Dermatology*. 2008;58:375-81. <http://www.pnlab.org/clinical/documents/ClinCharacteristics.pdf> Poulsen M. Merkel cell carcinoma of skin: diagnosis and management strategies. *Drugs Aging*. 2005;22(3):219-29. Swann MH and Yoon J. Merkel cell carcinoma. *Seminars in Oncology*. 2008;34(1):51-56. NCCN Merkel Cell Carcinoma Guidelines version 1. 2017. [http://www.nccn.org/professionals/physician\\_gls/PDF/mcc.pdf](http://www.nccn.org/professionals/physician_gls/PDF/mcc.pdf). Last accessed October 2016.

### About Metastatic Merkel Cell Carcinoma (MCC)

Metastatic MCC is a rare and aggressive disease in which cancer cells form in the top layer of the skin, close to nerve endings.[1],[5] 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 and neck, and arms.[6] Risk factors for MCC include sun exposure and having a weak immune system (i.e., solid organ transplant recipients, people with HIV/AIDS and people with other cancers, such as chronic lymphocytic leukemia, are at higher risk). Caucasian males older than 50 are at increased risk.[5] MCC is often misdiagnosed for other skin cancers and grows at an exponential rate on chronically sun-damaged skin. [7]-[10] Current treatment options for MCC include surgery, radiation and chemotherapy.[8] Treatment for Metastatic or Stage IV MCC is generally palliative.

## About Avelumab

Avelumab (also known as MSB0010718C) is an investigational, fully human anti-PD-L1 IgG1 monoclonal antibody. By inhibiting PD-L1 interactions, avelumab is thought to enable the activation of T-cells and the adaptive immune system. By retaining a native Fc-region, avelumab is thought to potentially engage the innate immune system and induce antibody-dependent cell-mediated cytotoxicity (ADCC). In November 2014, Merck KGaA, Darmstadt, Germany, and Pfizer announced a strategic alliance to co-develop and co-commercialize avelumab. In the JAVELIN Merkel 200 trial, treatment-related adverse events (AEs) occurred in 62 (70%) of 88 patients including fatigue and infusion-related reactions. Five grade 3 treatment-related AEs were reported in four of 88 patients and include two patients with lymphopenia and three patients with isolated laboratory abnormalities (elevated blood creatine phosphokinase, blood cholesterol, and hepatic aminotransferase).[1] There were no grade 4 treatment-related AEs or deaths related to treatment.[1] No patients in the trial discontinued treatment with avelumab permanently due to AEs; however, AEs leading to temporary treatment discontinuation of avelumab were anemia, diarrhea, and increased ALT in one patient each.[1]

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 Inc. The global strategic alliance between Merck KGaA, Darmstadt, Germany, and Pfizer Inc., New York, US, enables the companies to benefit from each other's strengths and capabilities and further explore the therapeutic potential of avelumab, an investigational anti-PD-L1 antibody initially discovered and developed by Merck KGaA, Darmstadt, Germany. The immuno-oncology alliance will jointly develop and commercialize avelumab and advance Pfizer's PD-1 antibody. The alliance is focused on developing high-priority international clinical programs to investigate avelumab, as a monotherapy, as well as combination regimens, and is striving to find new ways to treat cancer.

## About Merck KGaA, Darmstadt, Germany

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Merck KGaA, Darmstadt, Germany, is a leading science and technology company in healthcare, life science and performance materials. Around 50,000 employees work to

further develop technologies that improve and enhance life - from biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, to liquid crystals for smartphones and LCD televisions. In 2015, Merck KGaA, Darmstadt, Germany, generated sales of €12.85 billion in 66 countries.

Founded in 1668, Merck KGaA, Darmstadt, Germany, is the world's oldest pharmaceutical and chemical company. The founding family remains the majority owner of the publicly listed corporate group. Merck KGaA, Darmstadt, Germany, operates as EMD Serono, MilliporeSigma and EMD Performance Materials in the United States and Canada.

For further details and press materials about Merck KGaA, Darmstadt, Germany, in oncology products please visit [www.emdgroup.com/emd/media/media\\_center\\_oncology.html](http://www.emdgroup.com/emd/media/media_center_oncology.html).

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#### Pfizer Disclosure Notice

The information contained in this release is as of October 31, 2016. 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 avelumab (MSB0010718C), including a potential indication for avelumab for the treatment of metastatic Merkel cell carcinoma (the "Potential Indications"), Pfizer's and Merck KGaA, Darmstadt, Germany's immuno-oncology alliance involving anti-PD-L1 and anti-PD-1 therapies, 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, the uncertainties inherent in research and development, including the ability to meet anticipated clinical study commencement and completion dates as well as the possibility of unfavorable study results; risks associated with interim data; the risk that clinical trial data are subject to differing interpretations, and, even when we view data as sufficient to support the safety and/or effectiveness of a product candidate, regulatory authorities may not share our views and may require additional data or may deny approval altogether; whether and when drug applications may be filed in other jurisdictions for the Potential Indication or whether and when drug applications may be filed in any jurisdictions for any other potential indications for avelumab, combination therapies or other product candidates; whether and when the MAA for the Potential Indication or any such applications may be approved by regulatory authorities, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of avelumab, 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, 2015, 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 <http://www.sec.gov> and <http://www.pfizer.com>.

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