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ESMO Abstract #
M7824 (TGF β-trap/anti-PD-L1): 10480, 1463P, 757P, 643P, 642P, 661P, 1931P

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Merck KGaA, Darmstadt, Germany, Presents Updated Results for Bifunctional Immunotherapy M7824 at ESMO 2018 Congress

- **New data include first disclosure of results for M7824 in advanced squamous cell carcinoma of the head and neck, biliary tract cancer and esophageal cancers**
- **Updated data also being presented include non-small cell lung cancer and gastric cancer**
- **M7824 is a bifunctional immunotherapy designed to bring together transforming growth factor-β and anti-PD-L1 mechanisms**

Darmstadt, Germany, October 22, 2018 – Merck KGaA, Darmstadt, Germany, the vibrant science and technology company which operates its healthcare business in the U.S. and Canada as EMD Serono, today announced new and updated results from expansion cohorts of two ongoing M7824 Phase I clinical trials (NCT02517398 and NCT02699515) at the ESMO (European Society for Medical Oncology) 2018 Congress in Munich, October. New data presented include the first presentation of results for M7824 in advanced squamous cell carcinoma of the head and neck (SCCHN), biliary tract cancer (BTC) and esophageal cancers (esophageal squamous cell carcinoma [ESCC] and esophageal adenocarcinoma [EAC]). In addition, updated data for M7824 in non-small cell lung cancer (NSCLC) and gastric cancer add to the growing evidence for M7824's clinical anti-tumor activity in a number of challenging cancers.

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News Release

"We are excited to share encouraging updated and new data for M7824, including four additional difficult-to-treat cancers," said Luciano Rossetti, Executive Vice President, Head of Global Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "The results we've seen to date will enable us to target those tumors and settings with the highest potential to impact people living with cancer, as we move into the next stage of our development program with this bifunctional immunotherapy."

New data from an ongoing Phase I expansion cohort (32 patients, NCT02517398) showed signs of promising early clinical activity in patients with refractory metastatic second-line SCCHN, especially in HPV-positive SCCHN patients. As presented during the Proffered Paper Head and Neck cancers session, the overall response rate (ORR) was 15.6%, with a numerically higher ORR in HPV-positive patients (36.4%, 4/11 patients experienced a partial response), with two additional delayed responses resulting in a 54.5% clinical response rate for the HPV-positive population. At ASCO 2018, data from the dose escalation cohort of a Phase I, open-label study in advanced HPV-associated cancers (including SCCHN) were presented in collaboration with the National Cancer Institute, which showed that M7824 delivered an ORR of 41.7% in HPV-positive tumors. These new data from the SCCHN expansion cohort add to the evidence of encouraging activity in HPV-positive tumors. A total of 11 patients (34.4%) experienced Grade 3 treatment-related adverse events (TRAEs) and no Grade 4 or 5 TRAEs were seen. The most common TRAEs were rash (18.8%), asthenia (15.6%), pruritus (15.6%), hypothyroidism (15.6%), increased alanine aminotransferase (12.5%), increased aspartate aminotransferase (12.5%) and skin neoplasm (12.5%).

Updated results (now with longer follow-up and independent review committee [IRC] assessed data) from an ongoing Phase I trial (NCT02517398) in patients with previously treated, advanced NSCLC, demonstrated an ORR of 37.0% (10/27 patients) and progression free survival of 9.5 months in patients with PD-L1+ tumors (≥1%). In patients with high PD-L1+ expressing tumors (cut-off of ≥80% using the 73-10 assay; ≥80% cut-off with 73-10 assay is most comparable to ≥50% cut-off with the 22C3 test based on internal comparability studies), ORR was 85.7% (6/7 patients). Grade 3 TRAEs occurred in 23 patients (28.8%) and Grade 4 TRAEs occurred in 2 patients (2.5%): hypokalemia and decreased blood magnesium and

News Release

increased amylase and lipase levels. The most common TRAEs were pruritus (21.3%), maculopapular rash (18.8%), decreased appetite (12.5%), asthenia (11.3%) and rash (10.0%).

New data from an ongoing expansion cohort (NCT02699515) in Asian patients with BTC who had progressed after platinum-based first-line treatment, demonstrated clinical activity with M7824 treatment. The ORR among the total of 30 patients was 20%, as assessed by IRC. Responses were observed across all PD-L1 levels and duration of response ranged from 8.3 months to 13.9+ months. Grade 3 or higher TRAEs were experienced by 10 patients (33.3%). The most common TRAEs were rash (10%) and lipase increase (10%). Three deaths due to adverse events were reported: one due to septic shock (bacteremia, etiology unknown) and two due to interstitial lung disease (ILD; reported term: interstitial pneumonitis). Both patients with ILD were Japanese, which is consistent with the higher incidence of drug-induced ILD observed among Japanese patients compared with the non-Japanese population.[1]

Three additional posters featuring new data from two cohorts of ongoing Phase I studies in patients with ESCC and advanced EAC (studies NCT02699515 and NCT02517398 respectively) and updated data in gastric cancer (NCT02699515) were also presented. These data provide further indications of the potential of M7824 in cancers with significant unmet needs.

To date more than 650 patients with various types of solid tumors have been treated across the program with M7824. The safety profile is consistent with that observed with other PD-1/PD-L1 inhibitors. Previously described rash/skin lesions (keratoacanthomas, SCC, hyperkeratosis) associated with transforming growth factor-β (TGF-β) inhibiting therapies have also been observed.

Merck KGaA, Darmstadt, Germany, has recently initiated a 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 monotherapy treatment.

News Release

M7824 is an investigational bifunctional immunotherapy that brings together a TGF-β trap and 'fuses' it with the anti-PD-L1 mechanism. Designed to simultaneously block the two immunosuppressive pathways, M7824 is thought to control tumor growth by potentially restoring and enhancing anti-tumor responses. M7824 is an important part of a novel combination approach that seeks to harness the power of the immune system and address the tremendously complex nature of difficult-to-treat tumors.

Notes to Editors

Accepted abstracts supported by Merck KGaA, Darmstadt, Germany slated for presentation are listed below. In addition, a number of investigator-sponsored studies were accepted (not listed).

Title	Lead Author	Abstract #	Presentation Date / Time (CEST)	Location
M7824 (TGF β-trap/anti-PD-L1)				
Proffered Paper Session				
M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients (pts) with advanced SCCHN: results from a phase 1 cohort	BC Cho	1048O	Mon, Oct 22, 2:45 – 4:15 PM (3:00 PM lecture time)	ICM, Room 14B
Poster Sessions				
Updated results of M7824 (MSB0011359C), a bifunctional fusion protein targeting TGF-β and PD-L1, in second-line (2L) NSCLC	L Paz-Ares	1463P	Sat, Oct 20, 12:30 – 1:30 PM	Hall A3 – Poster Area Networking Hub
Assessment of PD1/ PD-L1 colocalization in hepatocellular carcinoma (HCC) using brightfield double labeling and quantitative digital image analysis	T Mrowiec	1931P	Sun, Oct 21, 12:45 – 1:45 PM	Hall A3 – Poster Area Networking Hub
M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in Asian patients with pretreated biliary tract cancer: preliminary results from a phase 1 trial	C Yoo	757P	Sun, Oct 21, 12:45 – 1:45 PM	Hall A3 – Poster Area Networking Hub
M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with post-platinum esophageal adenocarcinoma (EAC): preliminary results from a phase 1 cohort	B Tan	643P	Sun, Oct 21, 12:45 – 1:45 PM	Hall A3 – Poster Area Networking Hub

News Release

Phase 1 study results from an esophageal squamous cell carcinoma (ESCC) cohort treated with M7824 (MSB0011359C), a bifunctional fusion protein targeting transforming growth factor β (TGF-β) and PD-L1	CC Lin	642P	Sun, Oct 21, 12:45 – 1:45 PM	Hall A3 – Poster Area Networking Hub
Updated results from a phase 1 trial of M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with pretreated recurrent or refractory gastric cancer	YJ Bang	661P	Sun, Oct 21, 12:45 – 1.45 PM	Hall A3 – Poster Area Networking Hub

About M7824
M7824 is an investigational bifunctional immunotherapy that is designed to bring together a TGF-β trap and 'fuse' it with the anti-PD-L1 mechanism. M7824 is designed to simultaneously block the two immunosuppressive 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.

About Biliary Tract Cancer (BTC)
BTC is a collective term for a group of rare and aggressive gastrointestinal cancers, made up of intrahepatic cholangiocarcinoma (iCC), extrahepatic cholangiocarcinoma (eCC), and gallbladder carcinoma (GBC).[2,3,4] Surgery is the only curative treatment, but most patients present with advanced disease and therefore have a limited survival.[4] Approximately 140,000 cases of BTC are estimated to occur annually world-wide.[5] However, incidence of BTC varies in different parts of the world: the incidence of cholangiocarcinomas is rising in the Western world, with reports of up to 2 in 100,000. By contrast, in Asian countries, the incidence is much higher.[3] GBC also has an incidence of 2 in 100,000, but is much more prevalent in parts of South America.[3] Collectively these cancers present late in the majority of patients and long-term outcomes for resectable patients are poor with median survival in the advanced setting less than 1 year.[4,6,7,8]

About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, is a leading science and technology company in healthcare, life science and performance materials. Almost 53,000 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 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 holds the global rights to the "Merck" name and brand except in the United States and Canada, where the company operates as EMD Serono, MilliporeSigma and EMD Performance Materials.

News Release

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