O-8 **Final overall survival for the phase 3 KN177 study: Pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer**

T. André[1], K. Shiu[2], T. Kim[3], B. Jensen[4], L. Jensen[5], C. Punt[6], D. Smith[7], R. Garcia-Carbonero[8], J. Alcaide García[9], P. Gibbs[10], C. De la Fouchardière[11], F. Rivera Herrero[12], E. Elez[13], J. Bendell[14], D. Le[15], T. Yoshino[16], W. Zhong[17], D. Fogelman[18], P. Marinello[18], L. Diaz, Jr.[19]

[1]Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris and Sorbonne Université, Paris, France; [2]University College London NHS Foundation Trust, London, United Kingdom; [3]Asan Medical Centre, University of Ulsan, Seoul, South Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Center, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Málaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]University Hospital Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Department of Medical Oncology, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, United States; [15]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, United States; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc., Kenilworth, United States; [19]Memorial Sloan Kettering Cancer Center, New York, United States

Background: In the phase 3, randomized open-label KEYNOTE-177 (NCT02563002) study 1L pembrolizumab versus chemotherapy provided superior progression-free survival (PFS) at second interim analysis (IA2) in patients with microsatellite-instability high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal Cancer (mCRC). The study continued to final analysis of overall survival (OS), planned after 190 OS events or 12 months after IA2, whichever occurred first. We present results of the final analysis of OS, 12 months after IA2.

Methods: A total of 307 patients with MSI-H/dMMR mCRC and ECOG PS 0 or 1 were randomized 1:1 to 1L pembrolizumab 200 mg Q3W for up to 2y or investigator's choice of mFOLFOX6 or FOLFIRI Q2W ± bevacizumab or cetuximab. Treatment continued until PD, unacceptable toxicity, patient/investigator decision to withdraw, or completion of 35 cycles (pembrolizumab only). Patients receiving chemotherapy could crossover to pembrolizumab for up to 35 cycles after confirmed PD. Primary end points were OS and PFS (RECIST v1.1, central review). Secondary end points included ORR, duration of response (DOR) (RECIST v1.1, central review), and safety. For OS significance, the p-value had to meet a prespecified α of 0.0246 (one-sided). Sensitivity analyses to adjust for crossover effect were performed. Data cut-off for final analysis was Feb 19, 2021.

Results: Median (range) study follow-up was 44.5 mo (36.0-60.3) with pembrolizumab vs 44.4 mo (36.2-58.6) with chemotherapy. 56 (36%) patients crossed over from chemotherapy to pembrolizumab, with 37 more receiving anti-PD-1/PD-L1 therapies off study (60% effective crossover rate in the ITT). The HR for OS favored pembrolizumab vs chemotherapy with a trend toward reduction in the risk of death (HR 0.74; 95% CI, 0.53-1.03; P=0.0359; median not reached [NR] vs 36.7 mo); this difference did not reach statistical significance. Sensitivity analysis by the rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38), respectively. Pembrolizumab vs chemotherapy met the prespecified criteria for PFS superiority at IA2. At final analysis, median PFS was 16.5 mo vs 8.2 mo (HR 0.59; 95% CI, 0.45-0.79), but was not formally tested per analysis plan. Confirmed ORR was 45.1% (20 CR, 49 PR) vs 33.1% (6 CR, 45 PR). Median (range) DOR was NR (2.3+ to 53.5+) vs 10.6 mo (2.8 to 48.3+), respectively. Treatment-related adverse events (TRAEs) occurred in 79.7% vs 98.6% of patients; 21.6% vs 66.4%, respectively, had grade ≥3 TRAEs.

Conclusions: As 1L therapy for patients with MSI-H/dMMR mCRC, pembrolizumab vs chemotherapy provides statistically superior PFS with fewer TRAEs, and is associated with a trend toward reduced mortality that did not meet statistical significance likely due to the high crossover rate from chemotherapy to anti-PD1/PD-L1 therapies. Together these data confirm pembrolizumab as a new standard-of-care in the 1L for patients with MSI-H/dMMR mCRC.

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