Efficacy of Pembrolizumab Monotherapy for Advanced Gastric/Gastroesophageal Junction Cancer with Programmed Death Ligand 1 Combined Positive Score ≥10

Zev A. Wainberg,[1] Charles S. Fuchs,[2] Josep Tabernero,[3] Kohei Shitara,[4] Kei Muro,[5] Eric Van Cutsem,[6] Yung-Jue Bang,[7] Hyun Cheol Chung,[8] Kensei Yamaguchi,[9] Eniko Varga,[10] Jen-Shi Chen,[11] Daniel Hochhauser,[12] Peter Thuss-Patience,[13] Salah-Eddin Al-Batran,[14] Marcelo Garrido,[15] Uma Kher,[16] Chie-Schin Shih,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Joseph Chao[17]

[1]Department of the Division of Hematology Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA USA; [2]Department of Medical Oncology, Yale Cancer Center, Smilow Cancer Hospital, New Haven, CT, USA; [3]Department of Medical Oncology, Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain; [4]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan; [5]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [6]University Hospitals and KU Leuven, Leuven, Belgium; [7]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea; [8]Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [9]Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital of JFCR, Tokyo, Japan; [10]Department of Oncology, Debreceni Egyetem Klinikai Központ, Debrecen, Hungary; [11]Department of Hematology, Oncology, Linkou Chang Gung Memorial Hospital and Chang Gung University, Tao-Yuan, Taiwan; [12]Department of Medical Oncology, UCL Cancer Institute, London,

United Kingdom; [13]Department of Hematology, Oncology, and Tumor Immunology, Charité–University Medicine Berlin, Campus Virchow-Klinikum, Berlin, Germany; [14]Deparment of Tumor Diseases, Institut für Klinisch-Onkologische, Frankfurt, Germany; [15]Department of Hematology and Medical Oncology, Pontificia Universidad Católica de Chile, Santiago, Chile; [16]Department of Medical Oncology, Merck & Co., Inc., Kenilworth, NJ, USA; [17]Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Funding

This study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Corresponding author:
Zev A. Wainberg, MD
GI Oncology Program
David Geffen School of Medicine at UCLA
10945 Le Conte Avenue
Los Angeles, CA 90095
Phone: 310-633-8400
Email: zwainberg@mednet.ucla.edu

Disclosure of Potential Conflicts of Interest

Dr. Wainberg reports advisory/consultancy for AstraZeneca, Bayer, Daiichi, FivePrime, Lilly, Merck, and Molecular Therapeutics; research grant/funding (to his institution) from AstraZeneca, Daiichi, FivePrime, Lilly, and Merck; and

travel/accommodations/expenses for Bayer, Daiichi, Lilly, Merck, and Molecular Therapeutics.

Dr. Fuchs reports consulting for Agios, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi-Sankyo, Eli Lilly, Entrinsic Health, Evolveimmune Therapeutics, Genentech, Merck, Taiho, and Unum Therapeutics. He also serves as a director for CytomX Therapeutics and owns unexercised stock options for CytomX and Entrinsic Health. He is a co-founder of EvolveImmune Therapeutics and has equity in this private company. He has provided expert testimony for Amylin Pharmaceuticals and Eli Lilly.

Dr. Tabernero reports consultancy for Array Biopharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer-Ingelheim, Chugai, F. Hoffmann-La Roche Ltd, Foundation Medicine, Genentech Inc, Genmab A/S, HalioDX SAS, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, Roche Diagnostics, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, and VCN Biosciences.

Dr. Shitara reports an advisory role for AbbVie Inc, Astellas Pharma, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Merck, Novartis, Ono Pharmaceutical, Pfizer Inc, Taiho Pharmaceutical, and Takeda Pharmaceuticals; research funding for Astella Pharma, Chugai Pharma, Dainippon Sumitomo Pharma, Daiichi Sankyo, Eli Lilly and Company, Medi Science, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical; and honoraria (lecture fee) for AbbVie Inc, Novartis, and Yakult.

Dr. Muro reports research funding (to his institution) from Daiichi Sankyo, Mediscience Planning, MSD, Parexel International, Pfizer, Sanofi, Solasia Pharma, and Sumitomo Dainippon Pharma; honoraria for speaking from Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical, Takeda Pharmaceutical, and Sanofi; and advisory/consultancy for Amgen, AstraZeneca, and Ono Pharmaceutical Co., Ltd.

Dr. Van Cutsem reports consulting/advisory role for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, Halozyme, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, Taiho; and grants (to his institution) from Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, Merck KGaA, Novartis, Roche, and Servier.

Dr. Bang reports consulting/advisory for Astellas, AstraZeneca, Bayer, BeiGene, BMS, Daiichi-Sankyo, Eli Lilly, Genentech/Roche, Genexine, GreenCross, Hammi, Merck-Serono, MSD, Novartis, Samyang Biopharm, and Taiho; grants (to the institution for clinical trials) from Astellas, AstraZeneca, Bayer, BeiGene, Boehringer-Ingelheim, Bostin Biomedical, BMS, CKD Pharma, Curis, Daiichi-Sanyko, Eli Lilly, FivePrime, Genentech/Roche, Genexine GreenCross, GSK, MacroGenics, Merck Serono, MSD, Novartis, Ono, Pfizer, Taiho, and Takeda.

Dr. Chung reports research support from Amgen, BeiGene, BMS/Ono, GSK, Lilly, MSD, Merck-Serono, and Taiho; honoraria from Lilly and Merck-Serono; and consultancy for Amgen, BeiGene, BMS, Celltrion, Gloria, Lilly, Merck-Serono, MSD, Quintiles, Taiho, and Zymework.

Dr. Yamaguchi reports consulting/advisory for Bristol-Myers Squibb and Daiichi Sankyo; speakers' bureau for Bristol-Myers Squibb, Chugai Pharma, Daiichi Sankyo, Lilly, Merck Serono, Ono Pharmaceutical, Sanofi, Taiho Pharmaceutical, and Takeda; and research funding (institution) from Boehringer Ingelheim, Chugai Pharma, Daiichi Sankyo, Eisai, Gilead Sciences, Lilly, MSD Oncology, Ono Pharmaceutical, Sumitomo Dainippon Pharma, Taiho Pharmaceutical, and Yakult Honsha.

Dr. Varga reports no conflict of interest.

Dr. Chen reports no conflict of interest.

Dr. Hochhauser reports stock or other ownership in Novartis and Roche; research funding from Merck Serono; and travel, accommodations, and expenses from Merck.

Dr. Thuss-Patience reports advisory board for BMS, Lilly, Merck Serono, MSD, Pfizer, Roche, and Servier; and study support from Merck Serono.

Dr. Al-Batran reports no conflict of interest.

Dr. Garrido reports no conflict of interest.

Dr. Kher is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Dr. Shih is an employee of and a stockholder in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Dr. Shah is an employee of and a stockholder in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Dr. Bhagia is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ.

Dr. Chao reports personal fees from Amgen, AstraZeneca, Boston Biomedical, Daiichi-Sankyo, Foundation Medicine, Macrogenics, Merck, Ono Pharmaceutical, and Taiho Pharmaceutical; and grants from Brooklyn Immunotherapeutics and Merck.

Article type: Research article–clinical trial: immunotherapy

Subcategory: immunotherapy and cytokines: preclinical, clinical trials, and hematologic malignancies

Translational relevance (≤150 words): 128
Abstract (≤250 words, including subheadings): 249
Words (≤5000 words): 3224
References (≤50): 26
Tables/Figures (≤6): 3/3

Running head: Efficacy of pembrolizumab for CPS ≥10 G/GEJ cancer

Key words (≤5): gastrointestinal cancers; biomarkers; immunotherapy; clinical trials

Translational relevance (128/150 words)

Pembrolizumab monotherapy demonstrated a clinically meaningful survival benefit and durable antitumor activity in patients with PD-L1 combined positive score (CPS) ≥10 gastric or gastroesophageal junction cancer from KEYNOTE-059 cohort 1 (n = 46; third-line or beyond setting), KEYNOTE-061 (n = 53; second-line setting), and KEYNOTE-062 (n = 92; first-line setting). We observed numerically higher overall survival medians, response rates, and durations of response with pembrolizumab monotherapy than with chemotherapy in patients whose tumors expressed CPS ≥10 across lines of therapy. Responsiveness to immune checkpoint inhibitors and the role of pembrolizumab in the treatment paradigm of gastric cancer are still being determined, and this study adds to the existing body of evidence that the immunohistochemical PD-L1 CPS is one clinically relevant biomarker that can lead to improved clinical efficacy.

Abstract (249/250 words)

Purpose: Pembrolizumab demonstrated efficacy in PD-L1–positive (combined positive score [CPS] ≥1) advanced gastric/gastroesophageal junction (G/GEJ) cancer in the first-, second-, and third-line setting in KEYNOTE-062, KEYNOTE-061, and KEYNOTE-059, respectively. To better delineate the specificity of CPS as a predictor of clinical outcomes, we analyzed pembrolizumab efficacy in patients with CPS≥10 in these trials.

Experimental Design: Included were patients with CPS≥10 tumors from KEYNOTE-059 cohort 1 (pembrolizumab, n=46; post hoc), KEYNOTE-061 (pembrolizumab, n=53; chemotherapy, n=55; post hoc), and KEYNOTE-062 (pembrolizumab, n=92; chemotherapy, n=90; primary). Efficacy outcomes were OS, PFS, ORR, and DOR.

Results: In KEYNOTE-059 median follow-up was 6 months, median OS was 8 months (95% CI, 5.8-11.1), ORR was 17%, and median (range) DOR was 21 months (3+-35+). In KEYNOTE-061 median follow-up was 9 months, median OS (pembrolizumab vs chemotherapy) was 10 versus 8 months (HR, 0.64; 95% CI, 0.41-1.02), median PFS was 3 months versus 3 months (HR, 0.86; 95% CI, 0.56-1.33), ORR was 25% versus 9%, and median (range) DOR was not reached (4-26+ months) versus 7 months (3-7). In KEYNOTE-062, median follow-up was 11 months, median OS (pembrolizumab vs chemotherapy) was 17 months versus 11 months (HR, 0.69; 95% CI, 0.49-0.97), median PFS was 3 months versus 6 months (HR, 1.09, 95% CI; 0.79-1.49), ORR was 25% versus 38%, and median (range) DOR was 19 months (1+-34+) versus 7 months (2+-30+).

Conclusions: This comprehensive analysis showed consistent improvements toward more favorable clinical outcomes with pembrolizumab across lines of therapy in patients with CPS≥10 G/GEJ cancer.

Introduction

Gastric cancer ranks fifth among the most commonly diagnosed cancers worldwide and accounts for more than 1 million new cases and approximately 800,000 deaths per year (1). Evidence suggests that the programmed death 1 (PD-1) pathway may have prognostic significance in gastric cancer, with several studies demonstrating a relationship between expression of PD-L1 and overall survival (OS) (2-4). Although the prevalence of immunohistochemical PD-L1 expression varies between studies, most indicate that a significant proportion (range, 25%-65%) of patients with gastric cancer overexpress PD-L1, regardless of scoring method (2,5). Current first-line standard-of-care therapy for patients with unresectable locally advanced, recurrent, or metastatic disease remains combination chemotherapy with a fluoropyrimidine and a platinum-based agent, with trastuzumab added to the regimen for patients with HER2–positive disease (6). Various agents are recommended for use in second-line therapy, including chemotherapies and immunotherapies. The anti–PD-1 inhibitor pembrolizumab is approved for the treatment of patients with gastric cancer and is among the preferred regimens as second-line therapy for patients with microsatellite instability-high (MSI-H) or mismatch protein repair–deficient (dMMR) gastric cancer. Based on results from KEYNOTE-059, pembrolizumab is also approved as third-line or later therapy for patients with tumors that have a PD-L1 combined positive score (CPS) ≥1 (7). The ability of PD-L1 expression to predict response to immune checkpoint inhibitors beyond the approved use of third-line pembrolizumab for gastric cancer expressing CPS ≥1 remains unclear.

Pembrolizumab has demonstrated antitumor activity in patients with PD-L1–positive advanced gastric or gastroesophageal junction (GEJ) cancer in phase 2 and 3 trials (8-10). In cohort 1 of the global, single-arm, multicohort, phase 2 KEYNOTE-059

study, patients with advanced gastric or GEJ cancer whose disease progressed after ≥2 lines of therapy received pembrolizumab monotherapy (8). Among the 148 patients with CPS ≥1 tumors that were either microsatellite stable or had unknown MMR/dMMR status, 23 patients had a response, for an objective response rate (ORR) of 15.5%. The median duration of response (DOR) among these patients was 16.3 months (range, 1.6+ to 17.3+), and safety was manageable. Although the ORR was higher in patients with PD-L1–positive tumors (15.5%) than in patients with PD-L1–negative tumors (6.4%), the responses observed in the PD-L1–negative population indicated an incomplete separation of responders from nonresponders based on CPS ≥1 (8).

In the randomized, open-label, phase 3 KEYNOTE-061 study, patients with advanced gastric or GEJ cancer whose disease progressed after first-line therapy received pembrolizumab or paclitaxel (9). Among the 395 patients with CPS ≥1 tumors, pembrolizumab did not significantly prolong survival compared with paclitaxel (median OS, 9.1 vs 8.3 months; HR, 0.82; 95% CI, 0.66-1.03; one-sided *P* = 0.0421). Although there was also no improvement in progression-free survival (PFS) or response rates, pembrolizumab monotherapy did offer more durable responses and a favorable safety profile compared with paclitaxel.

The randomized phase 3 KEYNOTE-062 study enrolled patients with advanced gastric or GEJ cancer who had not previously received therapy for advanced disease (10). Among the 506 patients with CPS ≥1 tumors, OS with pembrolizumab was noninferior to that with cisplatin plus 5-fluorouracil (5-FU) or capecitabine (HR, 0.91; 99.2% CI, 0.69-1.18; prespecified noninferiority margin, 1.2). Pembrolizumab did not improve PFS or ORR but demonstrated a better tolerability profile than chemotherapy.

The predictive value of PD-L1 in gastric cancer is unclear given that multiple studies with immune checkpoint inhibitors other than pembrolizumab have demonstrated similar responses in patients regardless of PD-L1 status. In addition, the absence of a standard PD-L1 immunohistochemistry (IHC) assay and scoring method across studies makes cross-study comparisons difficult. In the phase 1/2 CheckMate-032 study of patients with chemotherapy-refractory advanced esophagogastric cancer, responses were observed with nivolumab alone and with nivolumab in combination with ipilimumab regardless of PD-L1 status (defined as tumor proportion score [TPS] with a cutoff of 1% using PD-L1 IHC 28-8 pharmDx [Agilent Technologies]) (11). Response rates were numerically higher in patients with PD-L1–positive tumors, but the sample sizes were small. The phase 3 ATTRACTION-2 study randomly assigned patients with advanced gastric or GEJ cancer who had previously received two or more lines of therapy to receive nivolumab or placebo (12). In an exploratory analysis evaluating PD-L1 expression (defined as TPS with a cutoff of 1%) and OS, median OS was numerically higher with nivolumab than with placebo regardless of PD-L1 positivity. Outcomes based on PD-L1 status were also evaluated with avelumab in patients with gastric cancer in the phase 1b JAVELIN Solid Tumor trial (13), the phase 3 JAVELIN Gastric 300 trial (14), and the phase 3 JAVELIN Gastric 100 trial (15). There were no significant differences in outcomes among patients with PD-L1–positive or –negative tumors. For all three studies, PD-L1–positive was defined as ≥1% of tumor cells using PD-L1 IHC 73-10 pharmDx. However, exploratory analysis using 22C3 pharmDx suggested a survival benefit with maintenance avelumab over chemotherapy in patients with CPS ≥1 tumors (HR, 0.72; 95% CI, 0.49-1.05) (15,16).

In addition to measuring PD-L1 expression on tumor cells and before the development of CPS, pembrolizumab studies assessed response by mononuclear inflammatory cell density score (MIDS). The CheckMate-032, ATTRACTION-2, and JAVELIN Gastric studies did not evaluate MIDS, which might have provided different results, highlighting the need to continue exploring patient subgroups likely to respond to PD-1/PD-L1 inhibitors.

Among the limited PD-L1 data available for patients with gastric or GEJ cancer, the open-label phase 1b KEYNOTE-012 study (NCT01848834) evaluated the antitumor activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic adenocarcinoma of the stomach or GEJ (17). PD-L1 expression was measured in 35 patients with available biopsy samples at baseline using TPS and MIDS. When response was evaluated using TPS, ORR was 24% for patients with TPS 0%, 0% for patients with TPS 1% to 49%, and 33% for patients with TPS ≥50%. When response was evaluated using MIDS, ORR was 0% for MIDS 0, 25% for MIDS 1, 12% for MIDS 2, 44% for MIDS 3, and 0% for MIDS 4. Although conclusions are limited because of the small numbers of patients, these findings do not demonstrate an association between response and high PD-L1 expression using TPS though there may be an association between high MIDS and response. The study provided evidence of the importance of measuring PD-L1 expression in immune cells, as opposed to tumor cells exclusively, in patients with gastric cancer based on analysis of the results and on the use of CPS. In the CheckMate-649 study in patients with gastric or GEJ cancer or esophageal adenocarcinoma, nivolumab plus chemotherapy provided statistically significant improvements in OS and PFS compared with chemotherapy alone in patients with CPS ≥5 tumors (18). A statistically significant OS benefit was also shown in patients with CPS ≥1 tumors

and in the all–randomly assigned population, showing an enrichment of OS benefit as the CPS cutoff increased (18).

A recent meta-analysis of randomized controlled trials of PD-1/PD-L1 inhibitors in patients with advanced solid tumors, including three trials in patients with gastric or GEJ cancer, suggested that enriching for PD-L1 status by increasing the minimum proportion of stained cells can increase efficacy in a dose-response relationship (19). Based on the experience with pembrolizumab in gastric cancer clinical trials, CPS ≥10 was chosen for further evaluation in this analysis to better delineate the specificity of CPS as a predictor of clinical outcomes with pembrolizumab monotherapy. Herein, we characterize clinical outcomes with pembrolizumab monotherapy across lines of therapy in patients with CPS ≥10 advanced gastric or GEJ cancer by analyzing patients with CPS ≥10 tumors enrolled in cohort 1 of KEYNOTE-059 (post hoc analysis), in KEYNOTE-061 (post hoc analysis), and in KEYNOTE-062 (primary analysis).

Methods

Study design

The designs of KEYNOTE-059 cohort 1, KEYNOTE-061, and KEYNOTE-062 have been described (8-10). In brief, all three trials evaluated the efficacy of pembrolizumab 200 mg administered intravenously every 3 weeks for up to 35 cycles (~2 years) for locally advanced, unresectable, or metastatic gastric or GEJ adenocarcinoma. In KEYNOTE-059, patients were enrolled regardless of PD-L1 expression status. In KEYNOTE-061, patients were randomly assigned 1:1 to receive pembrolizumab monotherapy or standard-dose paclitaxel administered intravenously. Initially, patients were enrolled regardless of PD-L1 expression status,

but enrollment was then restricted to those with CPS ≥1 tumors (9). In KEYNOTE-062, patients were randomly assigned (1:1:1) to receive pembrolizumab monotherapy, pembrolizumab plus chemotherapy (standard-dose cisplatin plus 5-FU or capecitabine administered intravenously or orally, respectively), or placebo plus chemotherapy (hereafter referred to as chemotherapy); patients were required to have CPS ≥1 tumors (10). The present analysis of KEYNOTE-062 includes only those patients enrolled in the pembrolizumab monotherapy and chemotherapy groups.

PD-L1 expression was assessed in archival or newly collected tumor samples using PD-L1 IHC 22C3 pharmDx (Agilent Technologies) (8-10) and was measured using CPS (defined as the number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] as a proportion of the total number of tumor cells multiplied by 100) (20). Samples were not reanalyzed for this analysis. For all three trials, the primary analysis populations were patients with CPS ≥1 tumors. Analysis of outcomes in patients with CPS ≥10 was post hoc for KEYNOTE-059 and KEYNOTE-061 but was part of the prespecified primary analysis for KEYNOTE-062.

The study protocols and all amendments were approved by the institutional review board or ethics committee at each participating institution. The studies were conducted in accordance with the protocol and its amendments and with Good Clinical Practice guidelines. All patients provided written informed consent before enrollment.

Outcomes and statistical considerations

For the present analysis, we evaluated clinical outcomes in all patients with CPS ≥10 tumors who received ≥1 dose of study drug. Results were analyzed for each of the trials separately (ie, results were not pooled across trials). Efficacy end points included OS, PFS, ORR (complete response [CR] plus partial response [PR]), and DOR. Response was assessed by central review per RECIST v1.1. The Kaplan-Meier method was used to calculate OS, PFS, and DOR. Hazard ratios and their associated 95% CIs were calculated using stratified Cox proportional hazards models with Efron's method of tie handling. In KEYNOTE-059, ORR was calculated using the Clopper-Pearson method. In KEYNOTE-061 and KEYNOTE-062, treatment differences in OS and PFS were assessed using the log-rank test with hazard ratios estimated using a stratified Cox regression model. Response rate was compared using the Miettinen and Nurminen method. In KEYNOTE-062, the prespecified hypotheses included OS analysis of pembrolizumab versus chemotherapy in patients with PD-L1 CPS ≥10 with a planned enrollment for 80% power to detect a hazard ratio of 0.58 at alpha = 0.75% (one-sided). Full details of the statistical analysis have been published (10).

Data cutoff dates for this analysis were August 8, 2018, for KEYNOTE-059, October 26, 2017, for KEYNOTE-061, and March 26, 2019, for KEYNOTE-062.

All three trials are registered with ClinicalTrials.gov (NCT02335411 [KEYNOTE-059], NCT02370498 [KEYNOTE-061], NCT02494583 [KEYNOTE-062]).

Results

All patients enrolled in KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 had evaluable tumor samples for PD-L1 status with the exception of two patients each in KEYNOTE-059 cohort 1 and KEYNOTE-061; 31% (46 of 148), 18% (108 of 592), and 36% (182 of 506), respectively, had CPS ≥10 tumors (Table 1). Follow-up duration is reported in Table 1. Baseline characteristics for patients with CPS ≥10 tumors were generally comparable between the pembrolizumab and chemotherapy groups in KEYNOTE-061 and KEYNOTE-062 (Table 2).

Overall and progression-free survival in the CPS ≥10 population

In KEYNOTE-059, median OS was 8 months (95% CI, 5.8-11.1). OS rates were 33% at 12 months and 15% at 24 months (Figure 1A). In KEYNOTE-061, median OS was 10 months (95% CI, 5.9-17.3) with pembrolizumab and 8 months (95% CI, 5.1-9.9) with chemotherapy (HR, 0.64; 95% CI, 0.41-1.02). The OS rates for pembrolizumab and chemotherapy were 45% versus 23% at 12 months and 35% versus 18% at 18 months, respectively (Figure 1B). In KEYNOTE-062, median OS was 17 months (95% CI, 9.1-23.1) with pembrolizumab and 11 months (95% CI, 8.5-13.8) with chemotherapy (HR 0.69; 95% CI, 0.49-0.97). The OS rates for pembrolizumab and chemotherapy were 57% versus 47% at 12 months and 39% versus 22% at 24 months, respectively (Figure 1C). Kaplan-Meier curves showed improved OS in the CPS ≥10 population compared with the CPS ≥1 population from the original studies (Figure 1A-C).

In KEYNOTE-059, median PFS was 2 months (95% CI, 2.0-3.4) (Figure 2A). In KEYNOTE-061, median PFS was 3 months (95% CI, 1.4-3.1) with pembrolizumab and 3 months (95% CI, 2.7-4.1) with chemotherapy (HR, 0.86; 95% CI, 0.56-1.33) (Figure 2B). In KEYNOTE-062, median PFS was 3 months (95% CI, 1.6-5.4) with pembrolizumab and 6 months (95% CI, 5.4-6.9) with chemotherapy (HR, 1.09; 95% CI, 0.79-1.49) (Figure 2C). Kaplan-Meier curves of PFS in the CPS ≥10 population compared with the CPS ≥1 population from the original studies are shown in Figure 2A-C.

Response in the CPS ≥10 population

In KEYNOTE-059, the confirmed ORR was 17% (n = 8); one patient achieved CR and seven achieved PR (Table 3). The median DOR was 21 months (range, 3+ to 35+) (Figure 3A); five responders (71%) had a response duration ≥6 months. In KEYNOTE-061, confirmed ORR was 25% (n = 13) for pembrolizumab-treated patients; five patients achieved CR and 8 PR (Table 3). In chemotherapy-treated patients, the ORR was 9% (n = 5); one patient achieved CR and four achieved PR. The median DOR was not reached (range, 4 to 26+ months) for pembrolizumab and was 7 months (range, 3 to 7) for chemotherapy (Figure 3B); 10 responders (77%) treated with pembrolizumab and one responder (53%) treated with chemotherapy had a response duration ≥6 months. In KEYNOTE-062, confirmed ORR was 25% (n = 23) for pembrolizumab-treated patients; seven patients achieved CR and 16 achieved PR (Table 3). In chemotherapy-treated patients, the ORR was 38% (n = 34); four patients achieved CR and 30 achieved PR. The median DOR was 19 months (range, 1+ to 34+) for pembrolizumab and 7 months (range, 2+ to 30+) for chemotherapy (Figure 3C); 18 responders (82%) treated with pembrolizumab and 16

responders (53%) treated with chemotherapy had a response duration ≥6 months. Kaplan-Meier curves showed DOR in the CPS ≥10 population compared with the CPS ≥1 population from the original studies.

Discussion

In the primary analysis of patients with CPS ≥1 gastric or GEJ cancer who were enrolled in KEYNOTE-059 cohort 1, KEYNOTE-061, and KEYNOTE-062, pembrolizumab monotherapy demonstrated promising antitumor activity. In KEYNOTE-061 and KEYNOTE-062, pembrolizumab was associated with an improved safety profile, but it did not significantly improve survival outcomes compared with chemotherapy (8-10). The current analysis in patients with CPS ≥10 tumors revealed durable responses and elongation of the tails of the Kaplan-Meier OS curves with pembrolizumab monotherapy across lines of therapy. However, pembrolizumab monotherapy did not numerically improve PFS in this analysis of KEYNOTE-061 or KEYNOTE-062 or ORR in KEYNOTE-062 compared with chemotherapy. The relationship between OS and PFS in clinical trials of immune checkpoint inhibitors has been investigated in several tumor types, including gastric cancer; differences in PFS and OS benefit as well as direction of outcomes are likely attributable to the mechanism of action, specific disease, and population under study (21).

In addition to other factors including MSI and HER2 status, PD-L1 expression can provide important guidance for patient selection in clinical practice and is used to select patients eligible for pembrolizumab therapy. Based on a recent meta-analysis showing an expression–response relationship between PD-L1 and OS, we evaluated

whether an increase in PD-L1 positivity from CPS ≥1 to CPS ≥10 resulted in improved responses to pembrolizumab (19). In comparing the current analysis of CPS ≥10 tumors, in which patient numbers are small, with previously reported data in patients with CPS ≥1 tumors, we observed numerically higher median OS, ORR, and DOR with pembrolizumab therapy by increasing the CPS cutoff from ≥1 to ≥10. In KEYNOTE-059, median OS increased from 6 months to 8 months, and the 12-month OS rate increased from 24% to 33%, the ORR increased from 16% to 17%, and the DOR increased from 16 to 21 months (8). In KEYNOTE-061, median OS increased from 9 to 10 months, and the 12-month OS rate increased from 40% to 45%, the 18-month OS rate increased from 26% to 35%, the ORR increased from 16% to 25%, and the DOR increased from 18 months to not reached (9,22). In KEYNOTE-062, median OS increased from 11 to 17 months, and the 12-month OS rate increased from 47% to 57%, the 24-month OS rate increased from 27% to 39%, the ORR increased from 15% to 25%, and the DOR increased from 14 to 19 months (10). In KEYNOTE-061, the hazard ratio for OS decreased from 0.82 for CPS ≥1 to 0.64 for CPS ≥10 (9), and in KEYNOTE-062, the hazard ratio for OS decreased from 0.91 for CPS ≥1 to 0.69 for CPS ≥10 (10). In KEYNOTE-062, the combination of pembrolizumab and chemotherapy was not superior to chemotherapy for OS in patients with CPS ≥1 or CPS ≥10 tumors (10). Thus, increasing the CPS cutoff to CPS ≥10 in patients with gastric or GEJ cancer may provide greater treatment benefit for patients eligible to receive pembrolizumab monotherapy.

The clinical benefit of using higher PD-L1 cutoffs with pembrolizumab has also been evaluated in other tumor types. Evidence from the phase 3 KEYNOTE-181 study in patients with advanced/metastatic esophageal cancer demonstrated a significant

benefit with a high CPS cutoff. Among 222 patients with CPS ≥10 tumors, second-line pembrolizumab monotherapy significantly improved OS versus chemotherapy (HR, 0.69; 95% CI, 0.52-0.93; *P* = 0.0074) (23). In the phase 3 KEYNOTE-048 trial in patients with untreated, locally incurable, recurrent or metastatic head and neck squamous cell carcinoma, pembrolizumab monotherapy demonstrated a greater survival benefit than cetuximab plus chemotherapy in the population with CPS ≥20 tumors (HR, 0.61; 95% CI, 0.45-0.83; *P* = 0.0007) than in the population with CPS ≥1 tumors (HR, 0.78; 95% CI, 0.64-0.96; *P* = 0.0086) (24). In the single-arm phase 2 KEYNOTE-052 study in patients with locally advanced and unresectable or metastatic urothelial cancer, response to pembrolizumab monotherapy increased with increasing CPS cutoff (CPS ≥1, 11%; CPS >1 to <10, 20%; CPS ≥10, 39%) (25). In patients with advanced recurrent ovarian cancer enrolled in the phase 2 KEYNOTE-100 study, higher PD-L1 expression also correlated with higher response to pembrolizumab monotherapy (CPS ≥1, 5.7%; CPS ≥10, 10.0%) (26).

Limitations of the current analysis include the post hoc nature of KEYNOTE-059 cohort 1 and KEYNOTE-061 and the small patient numbers within each subgroup. Furthermore, biomarker enrichment can predict response, but prevalence can decrease with higher CPS enrichment. Taken together, definitive conclusions cannot be made from this analysis.

In this analysis, these data suggest that pembrolizumab monotherapy given as first-line (KEYNOTE-062), second-line (KEYNOTE-061), and third-line and beyond (KEYNOTE-059) therapy showed a clinically meaningful median and long-term survival benefit in patients with CPS ≥10 gastric or GEJ tumors and more durable responses compared with chemotherapy. This study adds to the existing body of evidence that the immunohistochemical PD-L1 CPS is one clinically relevant

biomarker that can lead to improved clinical efficacy and validates the importance of refining the PD-L1 CPS biomarker companion diagnostic as we attempt to define the optimal role of pembrolizumab in gastric cancer. Although evidence from the current analysis and in other tumor types has validated scoring of PD-L1 expression using tumor and immune cells (ie, CPS) to predict response to pembrolizumab, large and prospective trials are needed to validate the optimal CPS cutoff for patients with gastric or GEJ cancer.

Acknowledgments

The authors thank the patients and their families and all investigators and site personnel. The authors also thank Eric Rubin, MD, of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and/or editorial assistance was provided by Holly C. Cappelli, PhD, CMPP, and Brian Szente, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, U.S.A.

Author Contributions

Conception, design, or planning of the study: ZAW, CSF, JT, KS, EVC, EV, SS

Acquisition of data: ZAW, CSF, JT, KS, KM, EVC, YJB, HCC, EV, JSC, DH, PTP, SEAB, MG, CSS,

Analysis of data: ZAW, JT, EV, MG, PB

Interpretation of the results: ZAW, CSF, JT, KS, EVC, YJB, HCC, KY, EV, JSC, PTP, MG, UK, CSS, SS, JC

Drafting of the manuscript: ZAW, HCC, KY, EV

Critically reviewing or revising of the manuscript for important intellectual content: ZAW, CSF, JT, KS, KM, EVC, YJB, KY, EV, JSC, DH, PTP, SEAB, MG, UK, CSS, PB, SS, JC

Final approval of the version to be published: All authors

Data Sharing

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin 2018;68:394-424.

2. Zhang M, Dong Y, Liu H, Wang Y, Zhao S, Xuan Q, et al. The clinicopathological and prognostic significance of PD-L1 expression in gastric cancer: a meta-analysis of 10 studies with 1,901 patients. Sci Rep 2016;6:37933.

3. Gu L, Chen M, Guo D, Zhu H, Zhang W, Pan J, et al. PD-L1 and gastric cancer prognosis: a systematic review and meta-analysis. PLoS One 2017;12:e0182692.

4. Liu YX, Wang XS, Wang YF, Hu XC, Yan JQ, Zhang YL, et al. Prognostic significance of PD-L1 expression in patients with gastric cancer in East Asia: a meta-analysis. OncoTargets Ther 2016;9:2649-54.

5. Kawazoe A, Kuwata T, Kuboki Y, Shitara K, Nagatsuma AK, Aizawa M, et al. Clinicopathological features of programmed death ligand 1 expression with tumor-infiltrating lymphocyte, mismatch repair, and Epstein-Barr virus status in a large cohort of gastric cancer patients. Gastric Cancer 2017;20:407-15.

6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: gastric cancer (Version 3.2020). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed October 15, 2020.

7. Fashoyin-Aje L, Donoghue M, Chen H, He K, Veeraraghavan J, Goldberg KB, et al. FDA approval summary: pembrolizumab for recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma expressing PD-L1. Oncologist 2019;24:103-9.

8. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric

and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 2018;4:e180013.

9. Shitara K, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018;392:123-33.

10. Shitara K, Van Cutsem E, Bang YJ, Fuchs CS, Wyrwicz L, Lee KW, et al. Efficacy and safety ofpembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: the KEYNOTE-062 phase 3 randomized clinical trial. JAMA Oncol 2020;6:1-10.

11. Janjigian YY, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, et al. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. J Clin Oncol 2018;36:2836-44.

12. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:2461-71.

13. Chung HC, Arkenau HT, Lee J, Rha SY, Oh DY, Wyrwicz L, et al. Avelumab (anti-PD-L1) as first-line switch-maintenance or second-line therapy in patients with advanced gastric or gastroesophageal junction cancer: phase 1b results from the JAVELIN Solid Tumor trial. JImmunother Cancer 2019;7:30.

14. Bang YJ, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol 2018;29:2052-60.

15. Moehler MH, Dvorkin M, Ozguroglu M, Ryu MH, Muntean AS, Lonardi S, et al. Results of the JAVELIN Gastric 100 phase 3 trial: avelumab maintenance following

first-line (1L) chemotherapy (CTx) vs continuation of CTx for HER2− advanced gastric or gastroesophageal junction cancer (GC/GEJC). J Clin Oncol 2020;38(suppl). Abstract 278.

16. Helwick C. No survival benefit for maintenance avelumab in advanced gastric or gastroesophageal junction cancer. ASCO Post https://www.ascopost.com/issues/march-10-2020/no-survival-benefit-for-maintenance-avelumab-in-advanced-gastric-or-gastroesophageal-junction-cancer/. Accessed October 15, 2020.

17. Muro K, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. Lancet Oncol 2016;17:717-26.

18. Moehler M, Shitara K, Garrido M, Salman P, Shen L, Wyrwicz L, et al. Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. Ann Oncol 2020;31:S1191. Abstract LBA6_PR.

19. Liu X, Guo CY, Tou FF, Wen XM, Kuang YK, Zhu Q, et al. Association of PD-L1 expression status with the efficacy of PD-1/PD-L1 inhibitors and overall survival in solid tumours: a systematic review and meta-analysis. Int J Cancer 2020;147:116-27.

20. Kulangara K, Zhang N, Corigliano E, Guerrero L, Waldroup S, Jaiswal D, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. Arch Pathol Lab Med 2019;143:330-7.

21. Hess LM, Brnabic A, Mason O, Lee P, Barker S. Relationship between progression-free survival and overall survival in randomized clinical trials of targeted and biologic agents in oncology. J Cancer 2019;10:3717-27.

22. Fuchs CS, Ozguroglu M, Bang YJ, Di Bartolomeo M, Mandala M, Ryu MH, et al. Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: phase 3 KEYNOTE-061 trial. J Clin Oncol 2018;36(suppl). Abstract 4062.

23. Kojima T, Shah MA, Muro K, Francois E, Adenis A, Hsu CH, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. J Clin Oncol 2020 Oct 7 Epub ahead of print. doi 10.1200/jco.20.01888.

24. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394:1915-28.

25. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:1483-92.

26. Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol 2019;30:1080-7.

Tables

Table 1. Incidence of PD-L1–positive tumors and follow-up of patients with CPS ≥10 tumors.

Incidence	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab	Pembrolizumab	Chemotherapy	Pembrolizumab	Chemotherapy
Patients with CPS ≥1, *n*/*N* (%)	148/259 (57)	196/296 (66)	199/296 (67)	256/256 (100)	250/250 (100)
Patients with CPS ≥10, *n*/*N* (%)	46/259 (18)	53/296 (18)	55/296 (19)	92/256 (36)	90/250 (36)
Median follow-up (range), months	6 (<1-38)	10 (<1-28)	8 (1-27)	17 (<1-38)	11 (1-35)

Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand 1.

Table 2. Baseline characteristic of patients with CPS ≥10 tumors.

Characteristic	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab *n* = 46	Pembrolizumab *n* = 53	Chemotherapy *n* = 55	Pembrolizumab *n* = 92	Chemotherapy *n* = 90
Median age, years (range)	63 (30-79)	66 (35-79)	60 (37-76)	59 (20-81)	65 (31-82)
Male, *n* (%)	34 (74)	35 (66)	35 (64)	64 (70)	64 (71)
Race, *n* (%)					
White	38 (83)	34 (64)	38 (69)	58 (63)	58 (64)
Asian	3 (7)	17 (32)	13 (24)	27 (29)	23 (26)
Black	1 (2)	1 (2)	1 (2)	2 (2)	1 (1)
American Indian or Alaska Native	0	1 (2)	2 (4)	3 (3)	5 (6)
Multiple	1 (2)	0	1 (2)	1 (1)	3 (3)
Missing	3 (7)	0	0	0	0
ECOG PS, *n* (%)					
0	25 (54)	24 (45)	24 (44)	47 (51)	34 (38)
1	21 (46)	29 (55)	31 (56)	45 (49)	56 (62)
No. of previous therapies for metastatic disease, *n* (%)					
2	21 (46)	–	–	–	–
3	14 (30)	–	–	–	–

Characteristic	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab *n* = 46	Pembrolizumab *n* = 53	Chemotherapy *n* = 55	Pembrolizumab *n* = 92	Chemotherapy *n* = 90
4	8 (17)	–	–	–	–
≥5	3 (7)	–	–	–	–
Tumor site, *n* (%)[a]					
Stomach	22 (48)	35 (66)	35 (64)	68 (74)	69 (77)
GEJ	23 (50)	18 (34)	20 (36)	24 (26)	20 (22)
MSI-H, *n* (%)	2 (4)	8 (15)	5 (9)	11 (12)	10 (11)

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction. MSI-H, microsatellite instability-high.

[a]In KEYNOTE-062, one patient (1.1%) had a tumor site of “missing.”

Table 3. Response summary in patients with CPS ≥10 tumors.

	KEYNOTE-059	KEYNOTE-061		KEYNOTE-062	
	Pembrolizumab ***n* = 46**	**Pembrolizumab** ***n* = 53**	**Chemotherapy** ***n* = 55**	**Pembrolizumab** ***n* = 92**	**Chemotherapy** ***n* = 90**
ORR, *n* (%)	8 (17)	13 (25)	5 (9)	23 (25)	34 (38)
CR	1 (2)	5 (9)	1 (2)	7 (8)	4 (4)
PR	7 (15)	8 (15)	4 (7)	16 (17)	30 (33)
SD	9 (20)	12 (23)	28 (51)	23 (25)	39 (43)
PD	24 (52)	23 (43)	11 (20)	29 (32)	8 (9)
Not available[a]	5 (11)	5 (9)	11 (20)	17 (19)	9 (10)
Median time to response, months, (range)	2 (2-4)	2 (1-3)	2 (1-4)	1 (1-7)	2 (1-7)
Median DOR, months, (range)	21 (3+ to 35+)	NR (4 to 26+)	7 (3 to 7)	19 (1+ to 34+)	7 (2+ to 30+)

Abbreviations: CI, confidence interval; CPS, combined positive score; CR, complete response; DOR, duration of response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Indicates patients without an evaluable assessment or patients who had a baseline assessment but no post-baseline assessment as of the data cutoff date (due to missing, discontinuing, or death before the first post-baseline assessment).

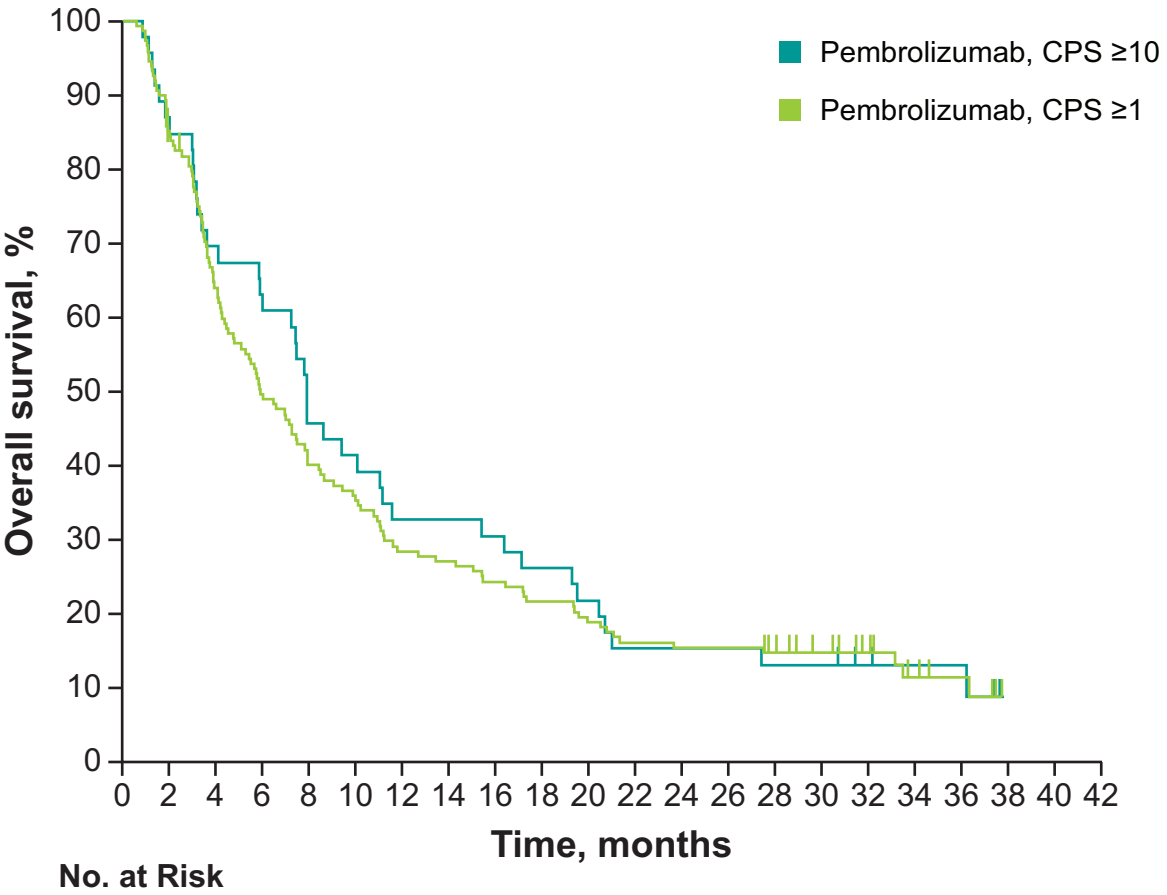
FIGURE LEGENDS

Figure 1. Kaplan-Meier estimates of OS in patients with CPS ≥1 and CPS ≥10 tumors. (**A**) Patients receiving third-line and beyond pembrolizumab in KEYNOTE-059 cohort 1. (**B**) Patients receiving second-line pembrolizumab or chemotherapy in KEYNOTE-061. (**C**) Patients receiving first-line pembrolizumab or chemotherapy in KEYNOTE-062. CPS, combined positive score; OS, overall survival.

Figure 2. Kaplan-Meier estimates of PFS in patients with CPS ≥1 and CPS ≥10 tumors. (**A**) Patients receiving third-line and beyond pembrolizumab in KEYNOTE-059 cohort 1. (**B**) Patients receiving second-line pembrolizumab or chemotherapy in KEYNOTE-061. (**C**) Patients receiving first-line pembrolizumab or chemotherapy in KEYNOTE-062. CPS, combined positive score; PFS, progression-free survival.

Figure 3. Kaplan-Meier estimates of DOR in patients with CPS ≥1 and CPS ≥10 tumors. (**A**) Patients receiving third-line and beyond pembrolizumab in KEYNOTE-059 cohort 1. (**B**) Patients receiving second-line pembrolizumab or chemotherapy in KEYNOTE-061. (**C**) Patients receiving first-line pembrolizumab or chemotherapy in KEYNOTE-062. CPS, combined positive score; DOR, duration of response.

A

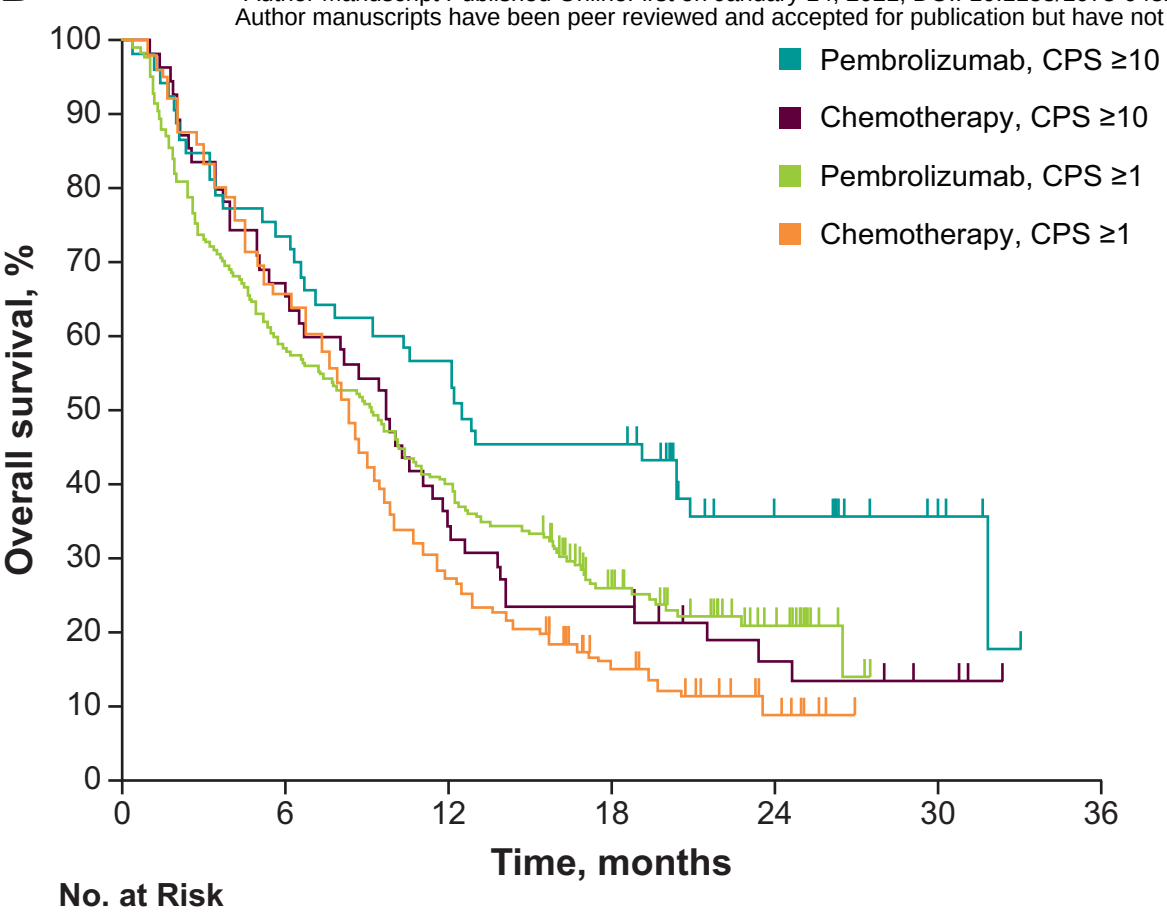


No. at Risk

148	124	93	71	58	51	41	39	35	31	27	23	22	22	18	15	10	6	4	0	0	0
46	39	32	28	21	19	15	15	14	12	10	7	7	7	6	6	4	3	3	0	0	0

B

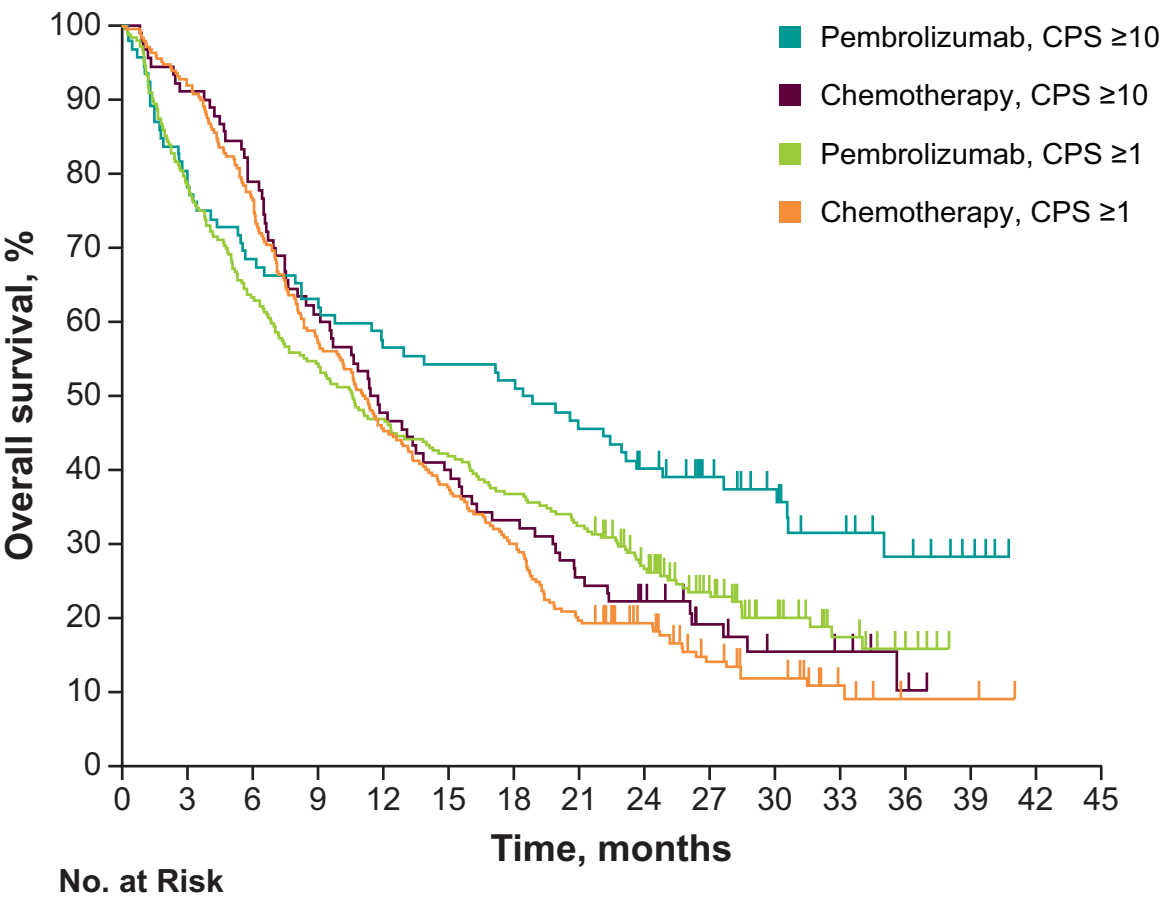
Author Manuscript Published OnlineFirst on January 14, 2021; DOI: 10.1158/1078-0432
Author manuscripts have been peer reviewed and accepted for publication but have not



No. at Risk

53	34	24	13	6	0	0
55	33	13	7	4	0	0
196	114	78	39	14	0	0
199	130	54	23	7	0	0

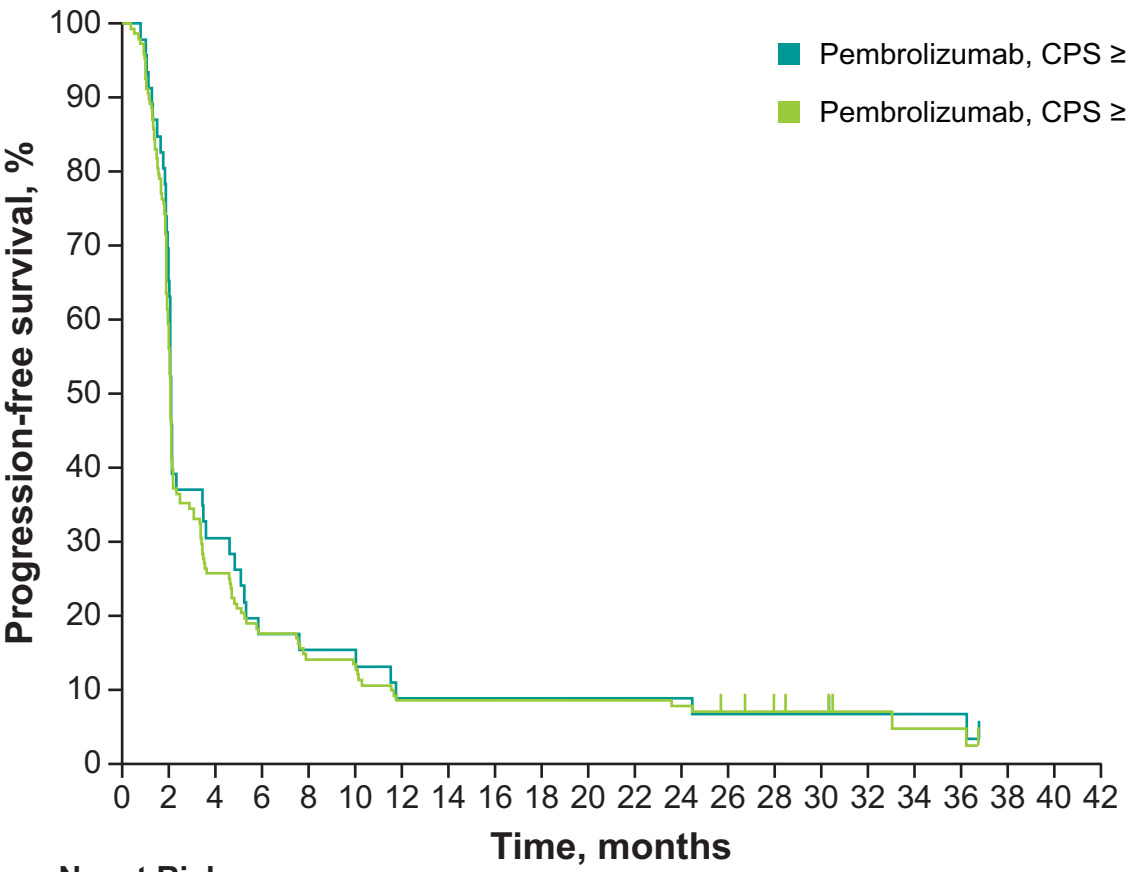
C



No. at Risk

92	71	62	56	52	50	45	40	32	22	13	9	4	0	0	0
90	82	70	53	42	33	28	20	16	8	7	3	0	0	0	0
256	201	162	139	120	107	94	83	59	38	23	12	4	0	0	0
250	230	192	144	114	94	75	49	38	21	15	6	2	2	0	0

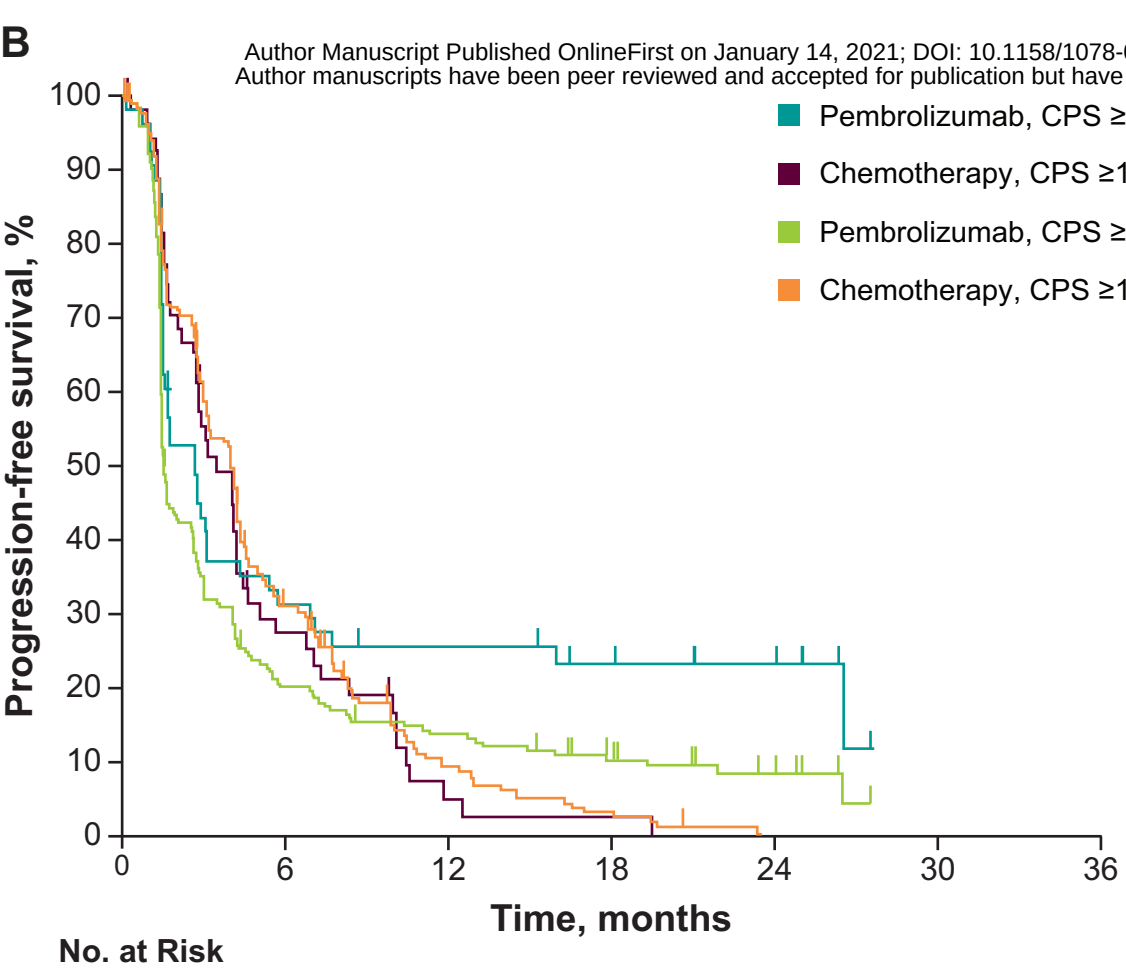
A



No. at Risk

46	32	14	8	7	7	4	4	4	4	4	4	4	3	3	3	2	2	2	0	0	0
148	88	38	26	20	19	12	12	12	12	12	12	11	9	7	6	3	2	2	0	0	0

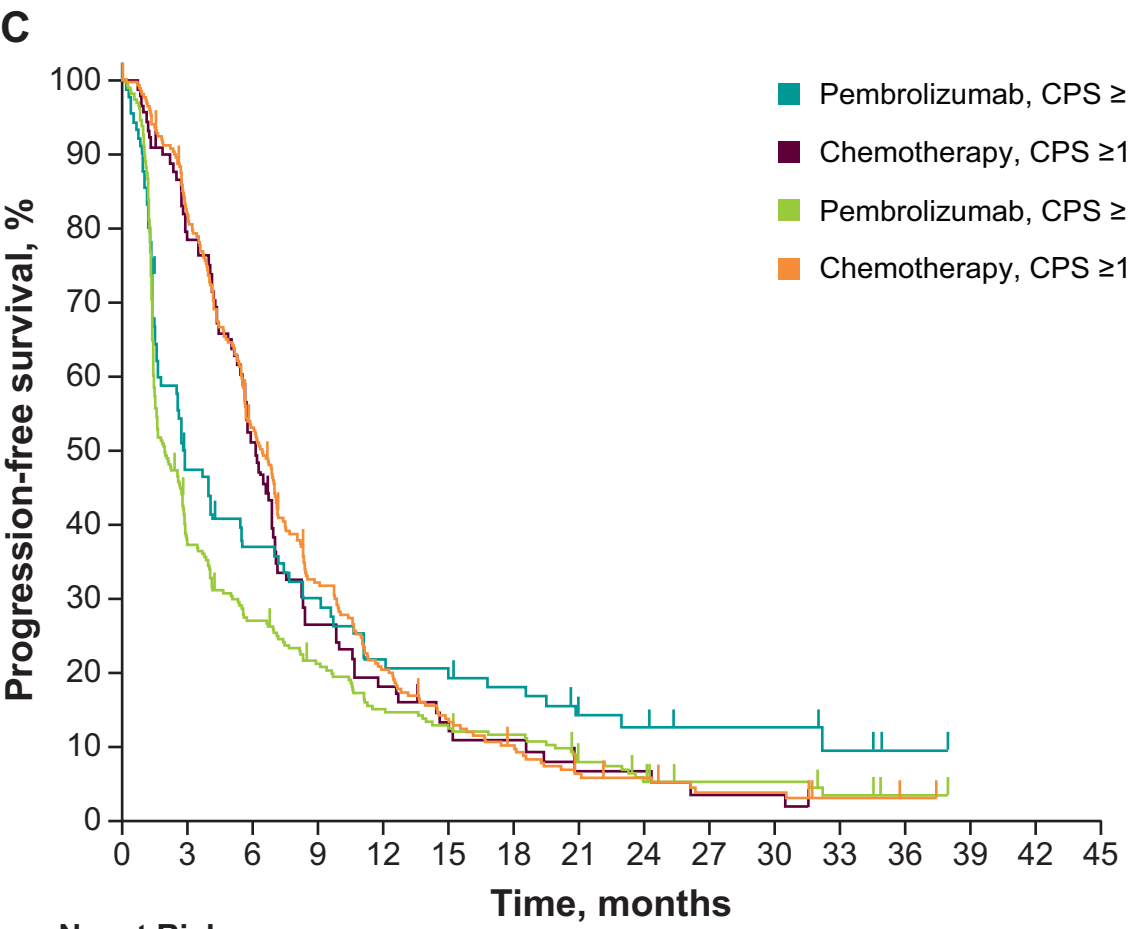
B



No. at Risk

53	16	12	9	5	0	0
55	13	2	1	0	0	0
196	38	25	15	7	0	0
199	57	15	4	0	0	0

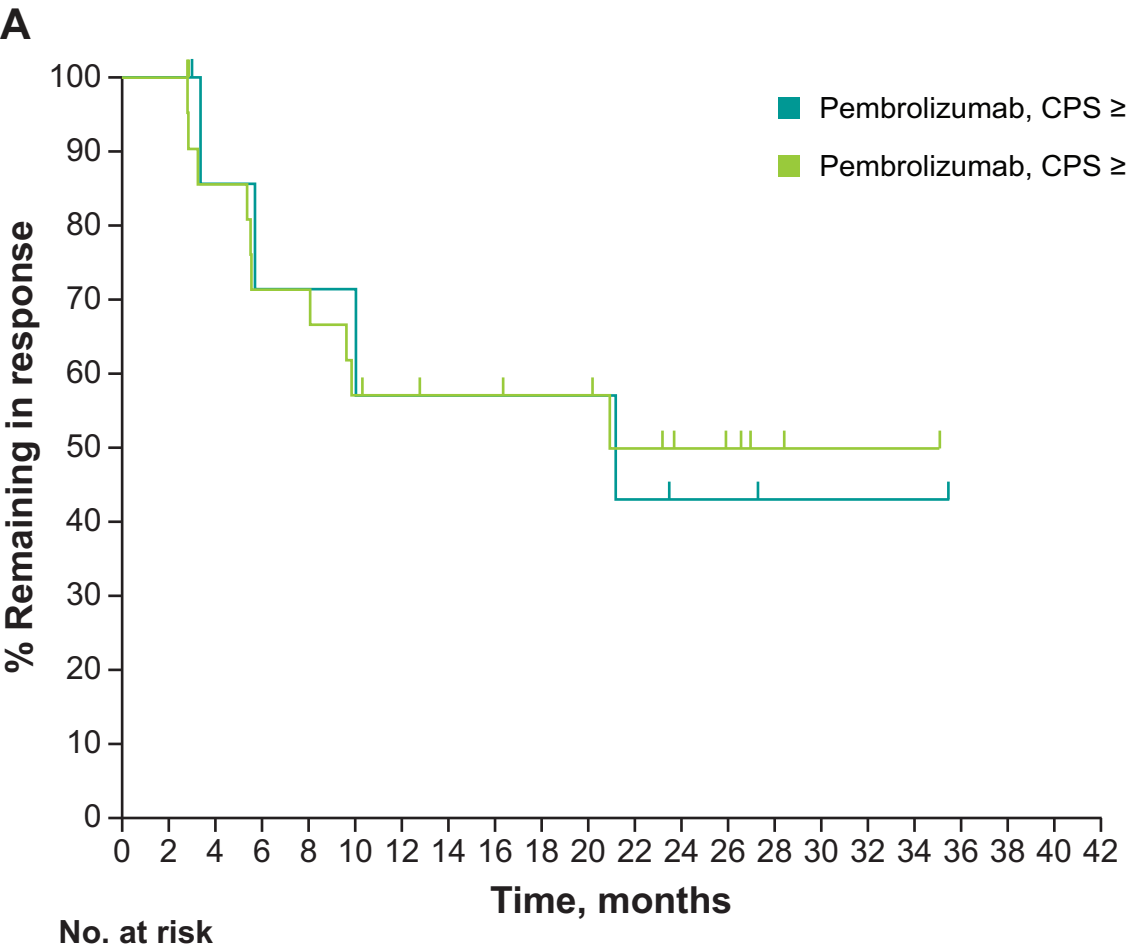
C



No. at Risk

92	41	31	25	18	17	14	9	8	5	5	3	1	0	0	0	
90	69	44	22	15	10	8	4	4	2	2	0	0	0	0	0	
256	93	65	48	34	29	25	15	9	6	6	3	1	0	0	0	
250	200	126	73	46	30	21	11	9	5	5	2	1	0	0	0	

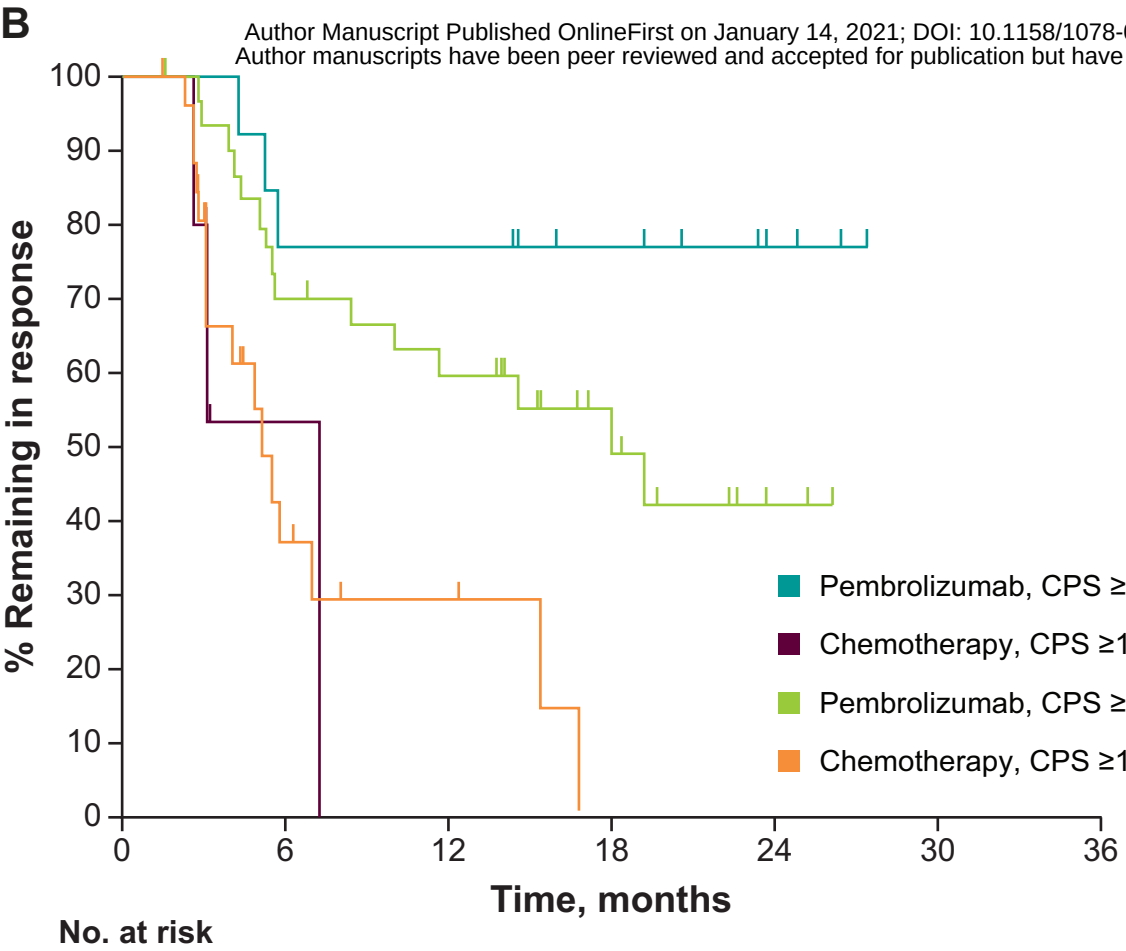
A



No. at risk

8	8	6	5	5	4	4	4	4	4	4	3	2	2	1	1	1	1	0	0	0	0
23	23	18	15	15	12	11	10	10	9	9	7	5	4	2	1	1	1	0	0	0	0

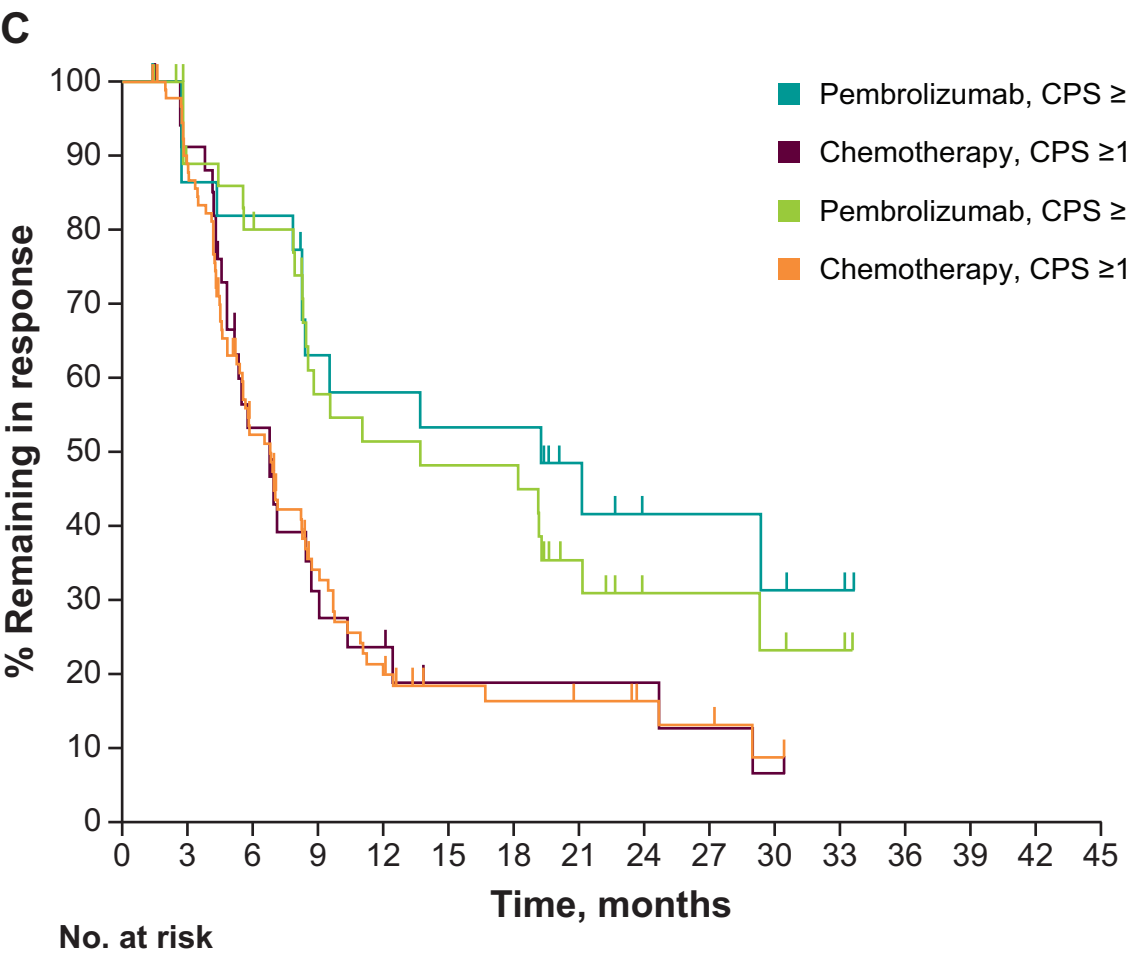
B



No. at risk

13	10	10	7	2	0	0
5	1	0	0	0	0	0
31	21	17	8	2	0	0
27	6	3	0	0	0	0

C



No. at risk

23	19	18	13	12	11	11	7	4	4	3	2	0	0	0	0
34	30	16	8	6	3	3	3	3	2	1	0	0	0	0	0
38	30	27	18	16	15	15	8	4	4	3	2	0	0	0	0
93	80	43	24	14	9	8	7	5	4	2	0	0	0	0	0

AACR American Association for Cancer Research

Clinical Cancer Research

Efficacy of Pembrolizumab Monotherapy for Advanced Gastric/Gastroesophageal Junction Cancer with Programmed Death Ligand 1 Combined Positive Score {greater than or equal to}10

Zev A. Wainberg, Charles S. Fuchs, Josep Tabernero, et al.

Clin Cancer Res Published OnlineFirst January 14, 2021.