Original Investigation

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Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer

The KEYNOTE-062 Phase 3 Randomized Clinical Trial

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Abstract

Importance: Safe and effective therapies for untreated, advanced gastric/gastroesophageal junction (G/GEJ) cancer remain an unmet need.

Objective: To evaluate the antitumor activity of pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy alone in patients with untreated, advanced G/GEJ cancer with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of 1 or greater.

Design, setting, and participants: The phase 3 KEYNOTE-062 randomized, controlled, partially blinded interventional trial enrolled 763 patients with untreated, locally advanced/unresectable or metastatic G/GEJ cancer with PD-L1 CPS of 1 or greater from 200 centers in 29 countries between September 18, 2015, and May 26, 2017.

Interventions: Patients were randomized 1:1:1 to pembrolizumab 200 mg, pembrolizumab plus chemotherapy (cisplatin 80 mg/m2/d on day 1 plus fluorouracil 800 mg/m2/d on days 1 to 5 or capecitabine 1000 mg/m2 twice daily), or chemotherapy plus placebo, every 3 weeks.

Main outcomes and measures: Primary end points were overall survival (OS) and progression-free survival (PFS) in patients with PD-L1 CPS of 1 or greater or 10 or greater.

Results: A total of 763 patients were randomized to pembrolizumab (n = 256), pembrolizumab plus chemotherapy (n = 257), or chemotherapy (n = 250). The median (range) age of all patients in the study cohort was 62 (20-87) years; 554 of 763 (72.6%) were men. At final analysis, after a median (range) follow-up of 29.4 (22.0-41.3) months,

pembrolizumab was noninferior to chemotherapy for OS in patients with CPS of 1 or greater (median, 10.6 vs 11.1 months; hazard ratio [HR], 0.91; 99.2% CI, 0.69-1.18). Pembrolizumab monotherapy was not superior to chemotherapy in patients with CPS of 1 or greater. Pembrolizumab prolonged OS vs chemotherapy in patients with CPS of 10 or greater (median, 17.4 vs 10.8 months; HR, 0.69; 95% CI, 0.49-0.97), but this difference was not statistically tested. Pembrolizumab plus chemotherapy was not superior to chemotherapy for OS in patients with CPS of 1 or greater (12.5 vs 11.1 months; HR, 0.85; 95% CI, 0.70-1.03; P = .05) or CPS of 10 or greater (12.3 vs 10.8 months; HR, 0.85; 95% CI, 0.62-1.17; P = .16) or for PFS in patients with CPS of 1 or greater (6.9 vs 6.4 months; HR, 0.84; 95% CI, 0.70-1.02; P = .04). Grade 3 to 5 treatment-related adverse event rates for pembrolizumab, pembrolizumab plus chemotherapy, and chemotherapy were 17%, 73%, and 69%, respectively.

Conclusions and relevance: This phase 3 randomized clinical trial found that among patients with untreated, advanced G/GEJ cancer, pembrolizumab was noninferior to chemotherapy, with fewer adverse events observed. Pembrolizumab or pembrolizumab plus chemotherapy was not superior to chemotherapy for the OS and PFS end points tested.

Trial registration: ClinicalTrials.gov Identifier: NCT02494583.

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Conflict of interest statement

Conflict of Interest Disclosures: Dr Shitara reported grants from Dainippon Sumitomo Pharma, Daiichi Sankyo, Chugai Pharma, Medi Science; grants and personal fees from Taiho

Pharmaceutical, Merck Pharmaceutical, grants and personal fees from Ono Pharmaceutical, Astellas, Eli Lilly and Company, personal fees from Bristol-Myers Squibb, Takeda Pharmaceuticals, Pfizer, Novartis, AbbVie, Yakult, and GlaxoSmithKline outside the submitted work. Dr Van Cutsem reported other from Merck during the conduct of the study; grants from Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Merck, Merck KGaA, Novartis, Roche, Servier; personal fees from Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Halozyme, GlaxoSmithKline, Incyte, Ipsen, Lilly, Merck, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, and Taiho outside the submitted work. Dr Bang reported other from AstraZeneca, Novartis, Genentech/Roche, Merck Sharp & Dohme, Merck Serono, Bayer, Bristol-Myers Squibb, Eli Lilly, Taiho, Daiichi Sankyo, Astellas, BeiGene, GreenCross, Samyang Biopharm, Hanmi, and Genexine; and other from Merck Sharp & Dohme, AstraZeneca, Novartis, Genentech/Roche, Merck Serono, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Eli Lilly, Boehringer Ingelheim, MacroGenics, Boston Biomedical, Five Prime, Curis, Taiho, Takeda, Ono, Daiichi Sankyo, Astellas, BeiGene, Green Cross, CKD Pharma, and Genexine outside the submitted work. Dr Fuchs reported personal fees from Agios, Amylin Pharmaceuticals, Bain Capital, CytomX Therapeutics, Daiichi Sankyo, Eli Lilly, Entrinsic Health, EvolveImmune Therapeutics, Genentech, Merck, Taiho, and Unum Therapeutics outside the submitted work; Dr Fuchs also serves as a director for CytomX Therapeutics and owns unexercised stock options for CytomX and Entrinsic Health and is a cofounder of EvolveImmune Therapeutics and has equity in this private company. Dr Wyrwicz reported personal fees from Merck Sharp & Dohme during the conduct of the study. Dr K. Lee reported grants to his institution from Merck Sharp & Dohme during the conduct of the study; grants to his institution from Ono Pharmaceutical, Merck KGaA, AstraZeneca, and Pfizer outside the submitted work. Dr Garrido reported grants from Pfizer; personal fees from Merck Sharp & Dohme and Bayer; and grants and personal fees from Bristol-Myers Squibb outside the submitted work. Dr Chung reported grants from Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Merck Serono, Bristol-Myers Squibb/ONO, Taiho, Amgen, and BeiGene; personal fees from Merck-Serono, Lilly, and Foundation Medicine; and other from Taiho, Celltrion, Merck Sharp & Dohme, Lilly, Quintiles, Bristol-Myers Squibb, Merck Serono, Gloria, BeiGene, Amgen, and ZymeWork outside the submitted work. Dr Braghiroli reported other from Merck Sharp & Dohme during the conduct of the study; and personal fees from Merck Sharp & Dohme, Roche, and Bayer outside the submitted work. Dr Karaseva reported grants from Merck Sharp & Dohme during the conduct of the study. Dr Caglevic reported personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Boehringer Ingelheim, Andes Biotechnologies, and Lilly and nonfinancial support from Roche outside the submitted work, and participation in clinical trials for Merck Sharp & Dohme, Medivation, AstraZeneca, Roche, Astellas Pharma, Bristol-Myers Squibb, and Andes Biotechnologies. Dr Villanueva reported personal fees from Merck Sharp & Dohme during the conduct of the study. Dr Goekkurt reported personal fees from Merck Sharp & Dohme, Bristol-Myers Squibb, and Servier outside the submitted work. Dr Satake reported grants and personal fees from Ono Pharmaceutical, Taiho Pharmaceutical, and Takeda; personal fees from Bayer, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Merck Bio Pharma, Merck Sharp & Dohme, Sanofi, and Yakult Honsha outside the submitted work. Dr Enzinger reported personal fees from Astellas, Celgene, Daiichi

Sankyo, Five Prime, Lilly, Loxo, Merck, Taiho, and Zymeworks outside the submitted work. Dr Alsina reported personal fees from Lilly, Servier, Merck Sharp & Dohme, and Bristol-Myers Squibb outside the submitted work. Dr Benson reported grants from Merck during the conduct of the study; grants from Astellas, Celgene, Infinity Pharmaceuticals, Taiho Pharmaceutical, Rafael Pharmaceuticals, Medimmune/AstraZeneca, Xencor, and SynCore; grants and personal fees from NCCN, Bristol-Myers Squibb, Merck Sharpe and Dohme, ECOG-ACRIN, Amgen; personal fees from Guardant, Terumo, Lexicon, ACCC, Imedex, Artemida Pharma, Array (Pfizer), and Eisai outside the submitted work. Dr Chao reported grants, personal fees, and other from Merck during the conduct of the study; grants from Brooklyn ImmunoTherapeutics; personal fees and other from Lilly, Foundation Medicine, and Daiichi Sankyo, Macrogenics, and Amgen; personal fees from Boston Biomedical, AstraZeneca, Taiho Pharmaceutical, and Ono Pharmaceutical outside the submitted work. Dr Ko reported grants from Merck during the conduct of the study; grants from Roche/Genentech, Merrimack, Celgene, Bristol-Myers Squibb, Apexigen, Abgenomics, Astellas, and Halozyme and personal fees from Erytech and Imugene outside the submitted work. Dr Wainberg reported grants from Novartis and Plexxikon and personal fees from Merck, Lilly, Array, EMD Serono, Five Prime, and Molecular Templates outside the submitted work. Dr Kher reported being an employee of Merck & Co. Dr Kang reported other from Merck & Co during the conduct of the study; in addition, Dr Kang had a patent to MK 3475. Dr Tabernero reported personal fees and other from Array Biopharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Chugai, Genentech, Genmab A/S, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, Merck Sharp & Dohme, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, F. Hoffmann-La Roche, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX SAS, and Roche Diagnostics outside the submitted work. No other disclosures were reported.