clinical trial updates

Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non–Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study

Gilberto de Castro Jr, MD, PhD[1]; Iveta Kudaba, MD[2]; Yi-Long Wu, MD[3]; Gilberto Lopes, MD[4]; Dariusz M. Kowalski, MD, PhD[5]; Hande Z. Turna, MD[6]; Christian Caglevic, MD[7]; Li Zhang, MD[8]; Boguslawa Karaszewska, MD[9]; Konstantin K. Laktionov, MD[10]; Vichien Srimuninnimit, MD[11]; Igor Bondarenko, MD[12]; Kaoru Kubota, MD, PhD[13]; Rinee Mukherjee, PhD[14]; Jianxin Lin, MS[14]; Fabricio Souza, MD[14]; Tony S.K. Mok, MD[15]; and Byoung Chul Cho, MD, PhD[16]

abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

We report 5-year results from the phase III KEYNOTE-042 study (ClinicalTrials.gov identifier: NCT02220894). Eligible patients with locally advanced/metastatic non–small-cell lung cancer (NSCLC) without *EGFR/ALK* alterations and with programmed death ligand-1 (PD-L1) tumor proportion score (TPS) ≥ 1% received pembrolizumab 200 mg once every 3 weeks for 35 cycles or chemotherapy (carboplatin + paclitaxel or pemetrexed) for 4-6 cycles with optional maintenance pemetrexed. Primary end points were overall survival (OS) in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1% groups. Patients who completed 35 cycles of pembrolizumab with ≥ stable disease could begin second-course pembrolizumab upon progression. One thousand two hundred seventy-four patients were randomly assigned (pembrolizumab, n = 637; chemotherapy, n = 637). Median follow-up time was 61.1 (range, 50.0-76.3) months. OS outcomes favored pembrolizumab (*v* chemotherapy) regardless of PD-L1 TPS (hazard ratio [95% CI] for TPS ≥ 50%, 0.68 [0.57 to 0.81]; TPS ≥ 20%, 0.75 [0.64 to 0.87]; TPS ≥ 1%, 0.79 [0.70 to 0.89]), with estimated 5-year OS rates with pembrolizumab of 21.9%, 19.4%, and 16.6%, respectively. No new toxicities were identified. Objective response rate was 84.3% among 102 patients who completed 35 cycles of pembrolizumab and 15.2% among 33 patients who received second-course pembrolizumab. First-line pembrolizumab monotherapy continued to show durable clinical benefit versus chemotherapy after 5 years of follow-up in PD-L1–positive, locally advanced/metastatic NSCLC without *EGFR/ALK* alterations and remains a standard of care.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

KEYNOTE-042 is a randomized phase III study that showed significantly longer overall survival (OS) with pembrolizumab monotherapy versus platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic non–small-cell lung cancer (NSCLC) with programmed death ligand-1 (PD-L1) tumor proportion score (TPS) ≥ 50%, ≥ 20%, and ≥ 1%.[1]

We present the outcomes from the KEYNOTE-042 study after approximately 5 years of follow-up and ad hoc analyses in patients who completed 35 cycles of pembrolizumab and in those who began a second course of pembrolizumab monotherapy.

METHODS

Study Design

The KEYNOTE-042 (ClinicalTrials.gov identifier: NCT02220894) study design has been described previously.[1] The study Protocol (MK-3475-042, online only) was approved by institutional review boards or independent ethics committees at participating institutions.

Patients were randomly assigned 1:1 to pembrolizumab 200 mg once every 3 weeks intravenously or carboplatin area under the curve of 5 or 6 mg/mL/min plus investigator's choice of paclitaxel 200 mg/m^2 once every 3 weeks for six cycles or pemetrexed 500 mg/m^2, followed by optional pemetrexed 500 mg/m^2 once every

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	ITT Population: Pembrolizumab TPS ≥ 1% (n = 637)	ITT Population: Chemotherapy TPS ≥ 1% (n = 637)	Completed 35 Cycles of Pembrolizumab (n = 102)
Age, years, median (range)	63.0 (25-89)	63.0 (31-90)	62.0 (33-81)
Men	450 (70.6)	452 (71.0)	73 (71.6)
Region of enrollment			
East Asia	185 (29.0)	185 (29.0)	26 (25.5)
European Union	149 (23.4)	137 (21.5)	26 (25.5)
Latin America	136 (21.4)	133 (20.9)	26 (25.5)
Other	167 (26.2)	182 (28.6)	24 (23.5)
ECOG performance status			
0	197 (30.9)	192 (30.1)	52 (51.0)
1	439 (68.9)	445 (69.9)	50 (49.0)
2	1 (0.2)	0	0
Smoking status			
Current	125 (19.6)	146 (22.9)	22 (21.6)
Former	370 (58.1)	351 (55.1)	61 (59.8)
Never	142 (22.3)	140 (22.0)	19 (18.6)
Tumor histology			
Squamous	242 (38.0)	249 (39.1)	26 (25.5)
Nonsquamous	395 (62.0)	388 (60.9)	76 (74.5)
Disease status			
Metastatic	568 (89.2)	556 (87.3)	87 (85.3)
Locally advanced	69 (10.8)	81 (12.7)	15 (14.7)
Brain metastasis	35 (5.5)	35 (5.5)	14 (13.7)
PD-L1 tumor proportion score			
≥ 50%	299 (46.9)	300 (47.1)	66 (64.7)
20%-49%	114 (17.9)	105 (16.5)	14 (13.7)
1%-19%	224 (35.2)	232 (36.4)	22 (21.6)
Prior treatment			
Radiotherapy	74 (11.6)	82 (12.9)	17 (16.7)
Neoadjuvant therapy	3 (0.5)	7 (1.1)	0
Adjuvant therapy	18 (2.8)	12 (1.9)	3 (2.9)

NOTE. Values are presented as No. (%) unless otherwise noted.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death ligand-1; TPS, tumor proportion score.

3 weeks for nonsquamous NSCLC. Treatment continued for up to 35 cycles of pembrolizumab (approximately 2 years), or until confirmed complete response (CR) per RECIST v1.1, disease progression (PD), intolerable toxicity, investigator's decision, or patient withdrawal.

Patients randomly assigned to pembrolizumab were eligible for second-course pembrolizumab (up to 17 cycles) upon PD per investigator assessment if they had stopped initial treatment after confirmed CR or completed 35 cycles of pembrolizumab while in SD or better, and had not received any anticancer treatment since the last pembrolizumab dose.

End Points

Primary end points were OS (time from random assignment to death from any cause) in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%. Secondary end points were progression-free survival (PFS; time from random assignment to documented PD or death due to any cause) and objective response rate (proportion of patients with radiologically confirmed CR or partial response [PR]), both assessed per RECIST v1.1 by blinded independent central review (BICR), and safety. Exploratory end points included PFS2 (time from random assignment to second/subsequent PD on next-line treatment or death from any cause).

Assessments

PD-L1 expression was assessed centrally using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). No alpha was assigned to this analysis and no adjustments made for multiplicity.

RESULTS

The intent-to-treat (ITT) population included 1,274 patients with PD-L1 TPS ≥ 1% (n = 637 per treatment group; Table 1, Data Supplement, online only). Median (range) time from random assignment to database cutoff (April 28, 2021) was 61.1 (50.0-76.3) months. Of patients assigned to pembrolizumab, 46.2% had received subsequent anticancer therapy (5.0% received anti–PD-[L]1 therapy), compared with 49.3% (23.1% received anti–PD-[L]1) in the chemotherapy group (Data Supplement).

Efficacy Outcomes in the ITT Population

Key primary and secondary outcomes including OS (Data Supplement), PFS (Data Supplement), and tumor response are summarized in Table 2. Kaplan-Meier estimates of 5-year OS rates ranged from 16.6%-21.9% with pembrolizumab compared with 8.5%-10.1% with chemotherapy. Similar OS benefits of pembrolizumab versus chemotherapy were observed in key patient subgroups also, as shown in the Data Supplement.

At data cutoff, hazard ratio (HR, 95% CI; for pembrolizumab *v* chemotherapy) for PFS2 was 0.64 (0.54 to 0.76) in patients with PD-L1 TPS ≥ 50%, 0.67 (0.58 to 0.78) in patients with TPS ≥ 20%, and 0.74 (0.65 to 0.83) in patients with TPS ≥ 1% (Data Supplement).

In an exploratory analysis of patients with PD-L1 TPS 1%-49%, HR for OS for pembrolizumab versus chemotherapy was 0.88 (95% CI, 0.75 to 1.04). The estimated 5-year OS rates were 11.9% and 7.4% in the pembrolizumab and chemotherapy groups, respectively (Data Supplement).

TABLE 2. Key Efficacy Outcomes

Outcome	ITT Population						Completed 35 Cycles of Pembrolizumab[a] (PD-L1 TPS ≥ 1%) (n = 102)
	PD-L1 TPS ≥ 50%		PD-L1 TPS ≥ 20%		PD-L1 TPS ≥ 1%		
	Pembrolizumab (n = 299)	Chemotherapy (n = 300)	Pembrolizumab (n = 413)	Chemotherapy (n = 405)	Pembrolizumab (n = 637)	Chemotherapy (n = 637)	
OS							
Months, median (95% CI)	20.0 (15.9 to 24.2)	12.2 (10.4 to 14.6)	18.0 (15.5 to 21.5)	13.0 (11.6 to 15.3)	16.4 (14.0 to 19.6)	12.1 (11.3 to 13.3)	NR
HR (95% CI)	0.68 (0.57 to 0.81)		0.75 (0.64 to 0.87)		0.79 (0.70 to 0.89)		—
5-year rate,[b] % (95% CI)	21.9 (17.3 to 26.9)	9.8 (6.6 to 13.7)	19.4 (15.6 to 23.4)	10.1 (7.2 to 13.5)	16.6 (13.7 to 19.6)	8.5 (6.4 to 11.0)	61.8 (50.1 to 71.5)[e]
PFS[c]							
Months, median (95% CI)	6.5 (5.9 to 8.6)	6.5 (6.2 to 7.6)	6.2 (5.4 to 7.8)	6.9 (6.3 to 8.2)	5.6 (4.3 to 6.2)	6.8 (6.4 to 7.9)	31.9[d] (25.6 to NR)
HR (95% CI)	0.86 (0.72 to 1.02)		0.94 (0.81 to 1.09)		1.03 (0.91 to 1.16)		—
5-year rate,[b] % (95% CI)	9.2 (5.9 to 13.4)	2.1 (0.7 to 5.0)	7.8 (5.2 to 11.1)	1.6 (0.5 to 3.9)	6.9 (4.9 to 9.4)	1.2 (0.5 to 2.7)	NR[e]
Tumor response							
ORR,[c] % (95% CI)	39.1 (33.6 to 44.9)	32.3 (27.1 to 37.9)	33.2 (28.6 to 37.9)	29.1 (24.8 to 33.8)	27.3 (23.9 to 31.0)	26.7 (23.3 to 30.3)	84.3 (75.8 to 90.8)
Best overall response, No. (%)							
CR	3 (1.0)	1 (0.3)	3 (0.7)	1 (0.2)	4 (0.6)	3 (0.5)	3 (2.9)
PR	114 (38.1)	96 (32.0)	134 (32.4)	117 (28.9)	170 (26.7)	167 (26.2)	83 (81.4)
SD	89 (29.8)	132 (44.0)	145 (35.1)	195 (48.1)	246 (38.6)	332 (52.1)	15 (14.7)
PD	55 (18.4)	26 (8.7)	77 (18.6)	31 (7.7)	133 (20.9)	48 (7.5)	1 (1.0)
NE[f]	5 (1.7)	3 (1.0)	7 (1.7)	5 (1.2)	11 (1.7)	9 (1.4)	0
NA[g]	33 (11.0)	42 (14.0)	47 (11.4)	56 (13.8)	73 (11.5)	78 (12.2)	0
DOR, months, median (range)	28.1 (2.1+ to 70.0+)	10.8 (1.8+ to 63.5+)	27.7 (2.1+ to 70.0+)	10.8 (1.8+ to 63.5+)	26.5 (2.1+ to 70.0+)	8.4 (1.8+ to 63.5+)	47.4 (4.4 to 70.0+)
DOR ≥ 60 months,[b] %	28.4	16.0	26.0	16.6	27.0	13.4	—
Time to response, months, median (range)	2.1 (1.3-18.5)	2.1 (1.3-32.4)	2.1 (1.3-18.5)	2.1 (1.3-32.4)	2.1 (1.3-26.7)	2.1 (1.3-32.4)	2.1 (1.4-26.7)

NOTE. + indicates no PD by the time of last assessment.

Abbreviations: CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan-Meier; NA, no assessment; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; SD, stable disease; TPS, tumor proportion score.

[a]Median (range) time from random assignment to database cutoff among patients with PD-L1 TPS ≥ 1% who completed 35 cycles of pembrolizumab was 61.7 (50.5-75.2) months.

[b]Rate estimates on the basis of the KM method.

[c]Per RECIST v1.1 by blinded independent central review.

[d]Includes patients who completed 35 cycles of pembrolizumab and did not have PD by blinded independent central review or were not censored at last disease assessment before completion of cycle 35.

[e]OS and PFS rate 4 years after completion of 35 cycles, ie, approximately 6 years after random assignment.

[f]Postbaseline assessment(s) available but not evaluable or CR/PR/SD < 6 weeks from random assignment.

[g]No postbaseline assessment available for response evaluation.

TABLE 3. Exposure-Adjusted AE Rates for Treatment-Related AEs That Occurred in ≥ 10% of Patients in Either Treatment Group

AE	Pembrolizumab	Chemotherapy
Hypothyroidism	69 (10.8)	2 (0.3)
Fatigue	51 (8.0)	103 (16.7)
Decreased appetite	40 (6.3)	108 (17.6)
Anemia	35 (5.5)	234 (38.0)
Nausea	31 (4.9)	185 (30.1)
Vomiting	15 (2.4)	97 (15.8)
Constipation	8 (1.3)	69 (11.2)
Neutropenia	5 (0.8)	89 (14.5)
Decreased WBCs	3 (0.5)	75 (12.2)
Alopecia	2 (0.3)	136 (22.1)
Decreased neutrophil count	2 (0.3)	89 (14.5)
Decreased platelet count	2 (0.3)	66 (10.7)

Observation Period, months	0-12	12-24	24-48	> 48	0-12	12-24	24-48	> 48
Exposed at the start of interval, No.	636	204	113	0	615	72	26	3
Total exposure,[a] person-months	4,426.8	1,829.6	139.1	0	3,309.6	507.2	224.5	29.6
Total events (rate per 100 person-months)[b]	1,344 (30.4)	203 (11.1)	16 (11.5)	0	3,884 (117.4)	185 (36.5)	24 (10.7)	2 (6.8)
Hypothyroidism	72 (1.6)	17 (0.9)	2 (1.4)	0	2 (0.1)	0	0	0
Fatigue	55 (1.2)	3 (0.2)	0	0	153 (4.6)	4 (0.8)	1 (0.5)	0
Decreased appetite	40 (0.9)	5 (0.3)	1 (0.7)	0	178 (5.4)	1 (0.2)	0	0
Anemia	36 (0.8)	6 (0.3)	0	0	294 (8.9)	15 (3.0)	2 (0.9)	0
Nausea	41 (0.9)	4 (0.2)	0	0	349 (10.6)	26 (5.1)	3 (1.3)	0
Vomiting	14 (0.3)	1 (0.1)	0	0	141 (4.3)	7 (1.4)	0	0
Constipation	21 (0.5)	2 (0.1)	0	0	84 (2.5)	2 (0.4)	1 (0.5)	0
Neutropenia	6 (0.1)	2 (0.1)	0	0	171 (5.2)	6 (1.2)	2 (0.9)	0
Decreased WBCs	1 (0.0)	3 (0.2)	0	0	212 (6.4)	11 (2.2)	1 (0.5)	0
Alopecia	3 (0.1)	0	0	0	137 (4.1)	0	0	0
Decreased neutrophil count	2 (0.1)	0	0	0	216 (6.5)	11 (2.2)	6 (2.7)	2 (6.8)
Decreased platelet count	1 (0.0)	1 (0.1)	0	0	137 (4.1)	9 (1.8)	0	0

NOTE. Values are presented as No. (%) unless noted otherwise.

Abbreviation: AE, adverse event.

[a]Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.

[b]Data show AEs and include multiple occurrences of events.

Safety

In the as-treated population (PD-L1 TPS ≥ 1%), incidence of treatment-related adverse events (AEs) was 63.8% in the pembrolizumab group and 90.2% in the chemotherapy group (Data Supplement). There were no new fatal treatment-related AEs in either treatment group; all were previously reported.[1] Immune-mediated AEs and infusion reactions occurred in 27.5% and 7.6% of patients in the pembrolizumab and chemotherapy groups, respectively (Data Supplement). Exposure-adjusted treatment-related AE (Table 3) and immune-mediated AEs and infusion reaction rates (Data Supplement) generally decreased over time in both treatment groups.

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

Among patients randomly assigned to the pembrolizumab group, 102 (16.0%) with PD-L1 TPS ≥ 1% completed 35 cycles of treatment (Table 1). Objective response rate was 84.3% (Table 2). At data cutoff, 34/102 patients (33.3%) had died. Median OS from the time of completing 35 cycles was not reached. The estimated 4-year OS rate after completion of 35 cycles (ie, approximately 6 years after

random assignment) was 61.8%. At data cutoff, 41 patients (40.2%) were alive without PD and subsequent therapy.

Treatment-related AEs occurred in 81.4% of patients, with grade 3-5 events in 11.8%. Immune-mediated AEs and infusion reactions occurred in 40.2% of patients. Grade 3 events occurred in 5.9% (colitis, n = 3; severe skin reaction, n = 2; hypophysitis, n = 1); none were of grade 4 or 5 severity.

Outcomes in Patients Who Received Second-Course Pembrolizumab

Upon assessment of PD, 33 eligible patients received second-course pembrolizumab (Data Supplement). Median time from random assignment to database cutoff was 63.7 (range, 52.0-75.2) months. Five patients (15.2%) had PR and 20 (60.6%) had SD, for a disease control rate of 75.8% (Data Supplement). At data cutoff, two patients (6.1%) were alive without PD and subsequent therapy.

DISCUSSION

With > 5 years of follow-up, first-line pembrolizumab monotherapy was associated with substantially longer OS, durable response, and prolonged PFS2 compared with platinum-based chemotherapy in patients with PD-L1–positive locally advanced/metastatic NSCLC with no *EGFR/ALK* alterations. Longer-term follow-up continues to show a manageable safety profile of pembrolizumab with fewer treatment-related AEs than chemotherapy and no new safety signals. More than half of the patients who completed 35 cycles of pembrolizumab were alive 4 years after completing treatment (approximately 6 years after random assignment), and a high disease control rate was observed in patients who received a second course of pembrolizumab.

Consistent with previous analysis,[1] higher PD-L1 TPS was associated with greater efficacy of pembrolizumab. Estimated 5-year OS rates in the pembrolizumab groups were ≥ two-fold higher than in the chemotherapy groups. The long-term OS benefits observed here are similar to those reported in KEYNOTE-024[2] and KEYNOTE-001.[3] OS benefit of pembrolizumab versus chemotherapy was also observed in a subgroup analysis of patients with PD-L1 TPS 1%-49%, albeit the upper limit of 95% CI for HR included 1.00. Overall, our data support pembrolizumab monotherapy as a treatment option for patients with lower PD-L1 TPS. Other treatment options for these patients include immunotherapies with/without chemotherapy, including the combination of pembrolizumab plus chemotherapy.[4-6] Ultimately, the choice of treatment will depend upon individual characteristics and patient and physician preferences.

In KEYNOTE-042, patients randomly assigned to chemotherapy were not permitted to cross over to pembrolizumab on study; however, approximately 50% of patients in the chemotherapy group received subsequent antitumor therapy off-study, including 23% who received anti–PD-(L)1 therapy (*v* 5% in the pembrolizumab group), which may have influenced efficacy outcomes in the chemotherapy group. However, the higher PFS2 HRs with pembrolizumab versus chemotherapy across the PD-L1 TPS groups suggest that there is no benefit to delaying treatment with first-line pembrolizumab.

In conclusion, first-line pembrolizumab monotherapy continues to show long-term OS benefit and durable responses versus chemotherapy, regardless of PD-L1 TPS in patients with PD-L1–positive locally advanced/metastatic NSCLC without *EGFR/ALK* alterations. With 5-year OS rates of up to 22%, these data support the continued use of pembrolizumab monotherapy as a standard-of-care treatment for previously untreated PD-L1–positive advanced/metastatic NSCLC.

AFFILIATIONS

[1]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil
[2]Latvian Oncology Center, Riga East Clinical University, Riga, Latvia
[3]Guangdong Lung Cancer Institute, Guangdong Provinicial People's Hospital and Guangdong Academy of Medical Sciences, Guandong, China
[4]Department of Medical Oncology, Sylvester Comprehensive Cancer Center at the University of Miami, FL
[5]Department of Lung Cancer and Chest Tumours, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[6]Department of Internal Medicine, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey
[7]Cancer Research Department, Instituto Oncológico Fundación Arturo López Pérez, Santiago, Chile
[8]Peking Union Medical College Hospital, Beijing, China
[9]Przychodnia Lekarska KOMED, Konin, Poland
[10]Federal State Budgetary Institution, "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia
[11]Department of Medicine, Siriraj Hospital, Bangkok, Thailand
[12]Oncology and Medical Radiology Department, Dnipro State Medical Academy, Dnipro, Ukraine
[13]Department of Pulmonary Medicine and Oncology, Nippon Medical School Hospital, Tokyo, Japan
[14]Merck & Co, Inc, Rahway, NJ
[15]Clinical Oncology, State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Shatin, Hong Kong, China
[16]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

CORRESPONDING AUTHOR

Gilberto de Castro Jr, MD, PhD, Instituto do Câncer do Estado de São Paulo, Medical Oncology, Av Dr Arnaldo, 251—5th floor, São Paulo, SP, 01246-000, Brazil; e-mail: gilberto.castro@usp.br.

PRIOR PRESENTATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02885.

DATA SHARING STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (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 United States and European Union, 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.

AUTHOR CONTRIBUTIONS

Conception and design: Yi-Long Wu, Gilberto Lopes, Tony S.K. Mok, Byoung Chul Cho

Provision of study materials or patients: Gilberto de Castro Jr, Yi-Long Wu, Li Zhang, Vichien Srimuninnimit, Igor Bondarenko, Kaoru Kubota, Tony S.K. Mok

Collection and assembly of data: Gilberto de Castro Jr, Iveta Kudaba, Gilberto Lopes, Dariusz M. Kowalski, Hande Z. Turna, Li Zhang, Boguslawa Karaszewska, Konstantin K. Laktionov, Vichien Srimuninnimit, Kaoru Kubota, Rinee Mukherjee, Fabricio Souza, Tony S.K. Mok, Byoung Chul Cho

Data analysis and interpretation: Gilberto de Castro Jr, Yi-Long Wu, Gilberto Lopes, Dariusz M. Kowalski, Christian Caglevic, Konstantin K. Laktionov, Igor Bondarenko, Kaoru Kubota, Rinee Mukherjee, Jianxin Lin, Fabricio Souza, Tony S.K. Mok, Byoung Chul Cho

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non–Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study

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Gilberto de Castro Jr
Honoraria: AstraZeneca, Pfizer, Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Roche, Amgen, Janssen, Merck Serono, Bayer
Consulting or Advisory Role: Boehringer Ingelheim, Pfizer, Bayer, Roche, Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, Yuhan, Merck Serono, Janssen, Libbs, Sanofi, Novartis, Lilly, Amgen
Speakers' Bureau: AstraZeneca, Bayer, Novartis, Roche, Merck Serono, Bristol Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim, Pfizer, Janssen, Amgen
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Novartis, Pfizer, Roche, AstraZeneca, Boehringer Ingelheim, Bayer, Bristol Myers Squibb, Merck Serono, Amgen

Yi-Long Wu
Honoraria: AstraZeneca, Lilly, Roche, Pfizer, Boehringer Ingelheim, MSD Oncology, Bristol Myers Squibb/China, Hengrui Pharmaceutical
Consulting or Advisory Role: AstraZeneca, Roche, Boehringer Ingelheim, Takeda
Research Funding: Boehringer Ingelheim (Inst), Roche (Inst), Pfizer (Inst), BMS (Inst)

Gilberto Lopes
Stock and Other Ownership Interests: Lucence Diagnostics, Xilis
Honoraria: Boehringer Ingelheim, Blueprint Medicines, AstraZeneca, Merck
Consulting or Advisory Role: Pfizer, AstraZeneca
Research Funding: Merck Sharp & Dohme (Inst), EMD Serono (Inst), AstraZeneca (Inst), AstraZeneca, Blueprint Medicines (Inst), Tesaro (Inst), Bavarian Nordic (Inst), Novartis (Inst), G1 Therapeutics (Inst), Adaptimmune (Inst), BMS (Inst), GlaxoSmithKline (Inst), AbbVie (Inst), Rgenix (Inst), Pfizer (Inst), Roche (Inst), Genentech (Inst), Lilly (Inst), Janssen (Inst), Lucence, Xilis, E.R. Squibb Sons, LLC
Travel, Accommodations, Expenses: Boehringer Ingelheim, Pfizer, E.R. Squibb Sons, LLC, Janssen, Seattle Genetics, Celgene, Ipsen, Pharmacyclics, Merck, AstraZeneca
Other Relationship: Mirati Therapeutics

Dariusz M. Kowalski
Consulting or Advisory Role: Bristol Myers Squibb, Boehringer Ingelheim, Merck Serono, Roche/Genentech, AstraZeneca, MSD, Pfizer, Amgen, Johnson & Johnson/Janssen, Takeda

Christian Caglevic
Consulting or Advisory Role: MSD, Roche
Speakers' Bureau: MSD, Roche
Research Funding: Merck Sharp & Dohme, Medivation, AstraZeneca, Roche, Astellas Pharma, Bristol Myers Squibb, GlaxoSmithKline, Athenex

Kaoru Kubota
Honoraria: Bristol Myers Squibb Japan, Taiho Pharmaceutical, Lilly Japan, MSD Oncology, Chugai Pharma, AstraZeneca, Nihonkayaku, Takeda, Pfizer, Ono Pharmaceutical, Kyowa Kirin, Novartis, Sawai Pharmaceutical Co
Research Funding: Daiichi Sankyo (Inst), Boehringer Ingelheim (Inst), Taiho Pharmaceutical (Inst), Ono Pharmaceutical (Inst)

Jianxin Lin
Employment: Merck
Stock and Other Ownership Interests: Merck

Fabricio Souza
Employment: Merck
Stock and Other Ownership Interests: Merck
Travel, Accommodations, Expenses: Merck

Tony S.K. Mok
Employment: The Chinese University of Hong Kong
Leadership: AstraZeneca, Aurora Tele-Oncology Platform, Lunit, ACT Genomics-Sanomics Group, HUTCHMED
Stock and Other Ownership Interests: Aurora Tele-Oncology Platform, HUTCHMED, ACT Genomics-Sanomics Group
Honoraria: AstraZeneca, Alpha Biopharma, ACEA Pharmaceutical Research, Amgen, Amoy Diagnostics, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Fishawack Facilitate, InMed, Lilly, Merck Sharp & Dohme, Novartis, Origimed, Pfizer, Prime Oncology, Roche, Sanofi Aventis GmbH, Taiho Pharmaceutical, Takeda, Lucence, Medscape, Permanyer Publications, PeerVoice, Physicans' Education Resource, Research to Practice, Shanghai BeBirds Translation & Consulting, Liangyihui Network Technology Co, Ltd, AbbVie, Berry Oncology, Blueprint Medicines, C4 Therapeutics, CStone Pharmaceuticals, Curio Science, D3, Eisai, Gilead Sciences, Gritstone Bio, Guardant Health, touchIME
Consulting or Advisory Role: AbbVie, ACEA Pharmaceutical Research, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca, BeiGene, Berry Oncology, Boehringer Ingelheim, Blueprint Medicines, Bristol Myers Squibb, CStone Pharmaceuticals, Curio Science, Daiichi Sankyo/UCB Japan, Eisai, Fishawack Facilitate, Gritstone Bio, Guardant Health, Hengrui Therapeutics, Ignyta, Incyte, Inivata, IQvia, Lilly, Loxo, Lunit, Merck Serono, Merck Sharp & Dohme, Mirati Therapeutics, Novartis, Pfizer, Puma Biotechnology, Roche, SFJ Pharmaceuticals Group, Takeda, Vertex, Yuhan, Qiming Development (HK) Ltd, D3, C4 Therapeutics, G1 Therapeutics, Gilead Sciences, Janssen, geneDecode
Research Funding: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), Novartis (Inst), SFJ Pharmaceuticals Group (Inst), Roche (Inst), Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Xcovery (Inst), G1 Therapeutics (Inst), Merck Serono (Inst), Takeda (Inst)

Byoung Chul Cho
Leadership: Interpark Bio Convergence Corp., J INTS BIO
Stock and Other Ownership Interests: TheraCanVac Inc, Gencurix Inc, Bridgebio therapeutics, KANAPH Therapeutic Inc, Cyrus therapeutics, Interpark Bio Convergence Corp, J INTS BIO
Consulting or Advisory Role: KANAPH Therapeutic Inc, Bridgebio therapeutics, Guardant Health, Oscotec Inc, Abion, BeiGene, Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, CJ, CureLogen, Cyrus therapeutics, Ono, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI-Cell, Guardant, HK Inno-N, Imnewrun Biosciences Inc, Janssen, Takeda, MSD, Janssen, Medpacto, Blueprint medicines, RandBio, Hanmi
Research Funding: MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, GIInnovation, GI-Cell, Abion, Abbvie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Onoclogy, CJ bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, Bridgebio therapeutics, Yuhan, ImmuneOncia, Illumina, Kanaph Therapeutics, Therapex, JINTSbio, Hanmi
Patents, Royalties, Other Intellectual Property: Champions Oncology
Other Relationship: DAAN Biotherapeutics
Uncompensated Relationships: ASCO, AstraZeneca, Guardant, Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Onoclogy, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Society, Pfizer

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