



OPEN

Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial

Miranda Gogishvili¹✉, Tamar Melkadze², Tamta Makharadze³, Davit Giorgadze⁴, Mikhail Dvorkin⁵, Konstantin Penkov⁶, Konstantin Laktionov⁷, Gia Nemsadze⁸, Marina Nechaeva⁹, Irina Rozhkova¹⁰, Ewa Kalinka¹¹, Christian Gessner^{12,13}, Brizio Moreno-Jaime¹⁴, Rodolfo Passalacqua¹⁵, Siyu Li¹⁶, Kristina McGuire¹⁶, Manika Kaul¹⁶, Anne Paccaly¹⁶, Ruben G. W. Quek¹⁶, Bo Gao¹⁶, Frank Seebach¹⁶, David M. Weinreich¹⁶, George D. Yancopoulos¹⁶, Israel Lowy¹⁶, Giuseppe Gullo¹⁶ and Petra Rietschel¹⁶

First-line cemiplimab (anti-programmed cell death-1 (PD-1)) monotherapy has previously shown significant improvement in overall survival (OS) and progression-free survival (PFS) versus chemotherapy in patients with advanced non-small cell lung cancer (aNSCLC) and PD-ligand 1 (PD-L1) expression $\geq 50\%$. EMPOWER-Lung 3 (NCT03409614), a double-blind, placebo-controlled, phase 3 study, examined cemiplimab plus platinum-doublet chemotherapy as first-line treatment for aNSCLC, irrespective of PD-L1 expression or histology. In this study, 466 patients with stage III/IV aNSCLC without *EGFR*, *ALK* or *ROS1* genomic tumor aberrations were randomized (2:1) to receive cemiplimab 350 mg ($n = 312$) or placebo ($n = 154$) every 3 weeks for up to 108 weeks in combination with four cycles of platinum-doublet chemotherapy (followed by pemetrexed maintenance as indicated). In total, 57.1% (266/466 patients) had non-squamous NSCLC, and 85.2% (397/466 patients) had stage IV disease. The primary endpoint was OS. The trial was stopped early per recommendation of the independent data monitoring committee, based on meeting preset OS efficacy criteria: median OS was 21.9 months (95% confidence interval (CI), 15.5–not evaluable) with cemiplimab plus chemotherapy versus 13.0 months (95% CI, 11.9–16.1) with placebo plus chemotherapy (hazard ratio (HR) = 0.71; 95% CI, 0.53–0.93; $P = 0.014$). Grade ≥ 3 adverse events occurred with cemiplimab plus chemotherapy (43.6%, 136/312 patients) and placebo plus chemotherapy (31.4%, 48/153 patients). Cemiplimab is only the second anti-PD-1/PD-L1 agent to show efficacy in aNSCLC as both monotherapy and in combination with chemotherapy for both squamous and non-squamous histologies.

PD-1 and PD-L1 inhibitors are the mainstay of systemic treatment for aNSCLC in patients without therapeutically actionable tumor genomic aberrations, such as epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) translocations or ROS proto-oncogene 1 (*ROS1*) fusions^{1–3}. Pembrolizumab and atezolizumab (anti-PD-L1) are both approved as first-line therapies in combination with platinum-based chemotherapy and other therapies for certain patient populations with metastatic NSCLC, although atezolizumab approval with platinum-doublet chemotherapy is limited to non-squamous histology^{2,4,5}. Combinations of checkpoint inhibitors—ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4) plus nivolumab (anti-PD-1) with or without chemotherapy—are also approved for patients with aNSCLC irrespective of histology, but the clinical

utility of these agents compared to single-agent checkpoint treatments alone or in combination with chemotherapy is unclear^{6,7}.

After demonstration of superior survival benefit for cemiplimab as monotherapy versus chemotherapy in EMPOWER-Lung 1 (ref. ⁸), cemiplimab was approved in the United States and the European Union as first-line treatment for patients with aNSCLC and PD-L1 $\geq 50\%$ and with no *EGFR*, anaplastic *ALK* or *ROS1* genomic aberrations, and is a preferred treatment for these patients by National Comprehensive Cancer Network (NCCN) guidelines^{1,8–11}.

In EMPOWER-Lung 3, we examined first-line cemiplimab in combination with investigator's choice of platinum-doublet chemotherapy in patients with aNSCLC (metastatic or unresectable locally advanced disease not suitable for definitive chemoradiation), with either squamous or non-squamous histology and any level of PD-L1 expression.

¹High Technology Medical Centre, University Clinic Ltd., Tbilisi, Georgia. ²Acad. F. Todua Medical Center, Tbilisi, Georgia. ³LTD High Technology Hospital Med Center, Batumi, Georgia. ⁴David Tvildiani Medical University, Tbilisi, Georgia. ⁵State Budgetary Healthcare Institution of Omsk Region, Omsk, Russia. ⁶Private Medical Institution Euromedservice, Saint Petersburg, Russia. ⁷Federal State Budgetary Institution 'N.N. Blokhin National Medical Research Center of Oncology' of the Ministry of Health of the Russian Federation, Moscow, Russia. ⁸The Institute of Clinical Oncology, Tbilisi, Georgia. ⁹Chelyabinsk Regional Clinical Oncology Center, Chelyabinsk, Chelyabinsk, Russia. ¹⁰Kaluga Regional Clinical Oncology Dispensary, Kaluga, Russia. ¹¹Polish Mother's Memorial Hospital Research Institute, Łódź, Poland. ¹²POIS Leipzig GbR, Leipzig, Germany. ¹³Institute of Clinical Immunology, University of Leipzig, Leipzig, Germany. ¹⁴Hospital Regional ISSSTE, León, Mexico. ¹⁵Istituti Ospitalieri Di Cremona, Cremona, Italy. ¹⁶Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA. ✉e-mail: mirandagogishvili@yahoo.com

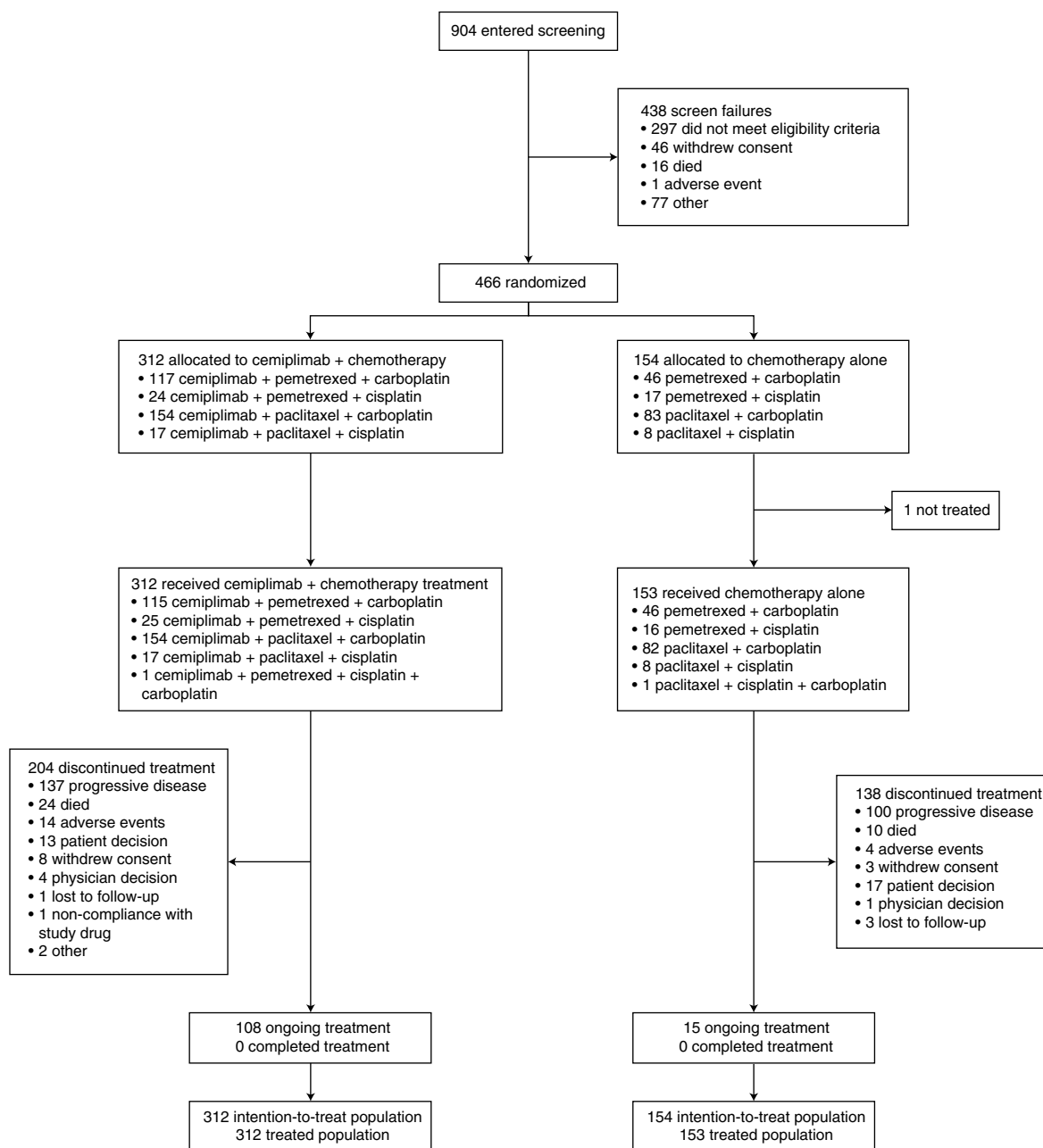


Fig. 1 | CONSORT diagram of EMPOWER-Lung 3 part two. All randomized patients were included in the efficacy analyses, and all patients who received treatment were included in the safety analyses.

Results

Patient characteristics. In total, 904 patients were screened for enrollment at 74 sites in ten countries (Supplementary Table 1). Between 17 June 2019 and 30 September 2020, 466 patients were enrolled and randomly assigned 2:1 to cemiplimab plus chemotherapy ($n=312$) and placebo plus chemotherapy ($n=154$) treatment arms (Fig. 1). All patients who received cemiplimab plus chemotherapy and 153 patients (99.4%) in the placebo plus chemotherapy arm received at least one dose of study treatment. Baseline characteristics were generally well balanced between both arms; 42.9% ($n=200$) of patients had squamous histology, 84.3% ($n=393$) of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, and 14.8% ($n=69$) of patients had locally advanced disease (Table 1).

The trial was stopped early per recommendation of the independent data monitoring committee (IDMC), based on meeting preset criteria for OS efficacy (Methods). At the time of data cutoff (14 June 2021), 108 patients in the cemiplimab plus chemotherapy arm and 15 patients in the placebo plus chemotherapy arm remained on treatment. In the cemiplimab plus chemotherapy arm, 204 (65.4%) patients discontinued treatment, primarily due to progressive disease. In the placebo plus chemotherapy arm, 138 (89.6%) patients discontinued treatment, primarily due to progressive disease. The median duration of follow-up was 16.3 months (interquartile range (IQR), 13.9–19.1) in the cemiplimab plus chemotherapy arm and 16.7 months (IQR, 14.2–19.0) in the placebo plus chemotherapy arm. Treatment exposures are summarized in Supplementary Table 2.

Table 1 | Baseline characteristics of the intention-to-treat patient population

Characteristic	Cemiplimab + chemotherapy (n = 312)	Placebo + chemotherapy (n = 154)	Total (n = 466)
Age, years			
Median (IQR)	63.0 (57–68)	63.0 (57–68)	63.0 (57–68)
≥65, n (%)	128 (41.0)	60 (39.0)	188 (40.3)
Sex, n (%)			
Women	44 (14.1)	31 (20.1)	75 (16.1)
Men	268 (85.9)	123 (79.9)	391 (83.9)
Geographic region, n (%)			
Europe	270 (86.5)	138 (89.6)	408 (87.6)
Asia	42 (13.5)	16 (10.4)	58 (12.4)
Histology, n (%)			
Non-squamous	179 (57.4)	87 (56.5)	266 (57.1)
Squamous	133 (42.6)	67 (43.5)	200 (42.9)
PD-L1 expression, n (%)			
<1%	95 (30.4)	44 (28.6)	139 (29.8)
1–49%	114 (36.5)	61 (39.6)	175 (37.6)
≥50%	103 (33.0)	49 (31.8)	152 (32.6)
ECOG PS, n (%)			
0	51 (16.3)	18 (11.7)	69 (14.8)
1	259 (83.0)	134 (87.0)	393 (84.3)
Brain metastasis, n (%)	24 (7.7)	7 (4.5)	31 (6.7)
Cancer stage at screening, n (%)			
Metastatic	267 (85.6)	130 (84.4)	397 (85.2)
Locally advanced	45 (14.4)	24 (15.6)	69 (14.8)
Smoking history, n (%)			
Current smoker	173 (55.4)	75 (48.7)	248 (53.2)
Past smoker	96 (30.8)	55 (35.7)	151 (32.4)
Never smoker	43 (13.8)	24 (15.6)	67 (14.4)
Previous cancer-related therapy, n (%)			
Systemic adjuvant therapy	5 (1.6)	1 (0.6)	6 (1.3)
Systemic other	1 (0.3)	0	1 (0.2)
Radiotherapy	40 (12.8)	11 (7.1)	51 (10.9)

The intention-to-treat population includes all randomized patients.

OS. With 214 deaths, the primary endpoint, median OS with cemiplimab plus chemotherapy, was 21.9 months (95% CI, 15.5–not evaluable (NE)) versus 13.0 months (95% CI, 11.9–16.1) with placebo plus chemotherapy (HR=0.71; 95% CI, 0.53–0.93; $P=0.014$; Fig. 2a). In the cemiplimab plus chemotherapy arm, the secondary endpoint of estimated proportion of patients who were alive at 12 months was 65.7% (95% CI, 59.9–70.9) versus 56.1% (95% CI, 47.5–63.8) in the placebo plus chemotherapy arm.

Although the study was not powered to examine efficacy within predefined subgroups, numeric improvements in OS were seen in both the squamous and non-squamous histology subgroups. In the squamous histology subgroup, median OS was 21.9 months (95% CI, 15.6–NE) with cemiplimab plus chemotherapy versus 13.8 months (95% CI, 9.3–18.0) in the placebo arm (HR=0.56; 95% CI, 0.37–0.84). In the non-squamous histology subgroup, median OS was 15.8 months (95% CI, 13.7–NE) with cemiplimab arm versus 13.0 months (95% CI, 10.0–NE) with placebo plus chemotherapy (HR=0.79; 95% CI, 0.54–1.14). Of note, due to the capping applied to the enrollment of patients with squamous histology, follow-up was shorter in the non-squamous subset (14.7 months;

IQR, 12.5–17.9) versus the squamous subset (18.2 months; IQR, 15.9–20.2).

In other predefined subgroups, OS estimates consistently favored cemiplimab plus chemotherapy except in women, never-smokers and patients with PD-L1 <1% (Fig. 2b). Of note, there was overlap among these three subgroups, which were generally small, and the discrepancies noted in OS were not observed in the other efficacy endpoints of PFS and objective response rate (ORR), which reflect an earlier treatment effect.

PFS. With 326 events of progressive disease or death, the key secondary endpoint of median PFS with cemiplimab plus chemotherapy was 8.2 months (95% CI, 6.4–9.3) versus 5.0 months (95% CI, 4.3–6.2) for the placebo plus chemotherapy arm (HR=0.56; 95% CI, 0.44–0.70; $P<0.0001$). The estimated proportion of patients receiving cemiplimab plus chemotherapy who were alive and had no disease progression at 12 months was 38.1% (95% CI, 32.4–43.8) versus 16.4% (95% CI, 10.5–23.4) for the placebo plus chemotherapy arm (Fig. 2c). PFS benefits also consistently favored cemiplimab plus chemotherapy in all predefined subgroups (Fig. 2d).

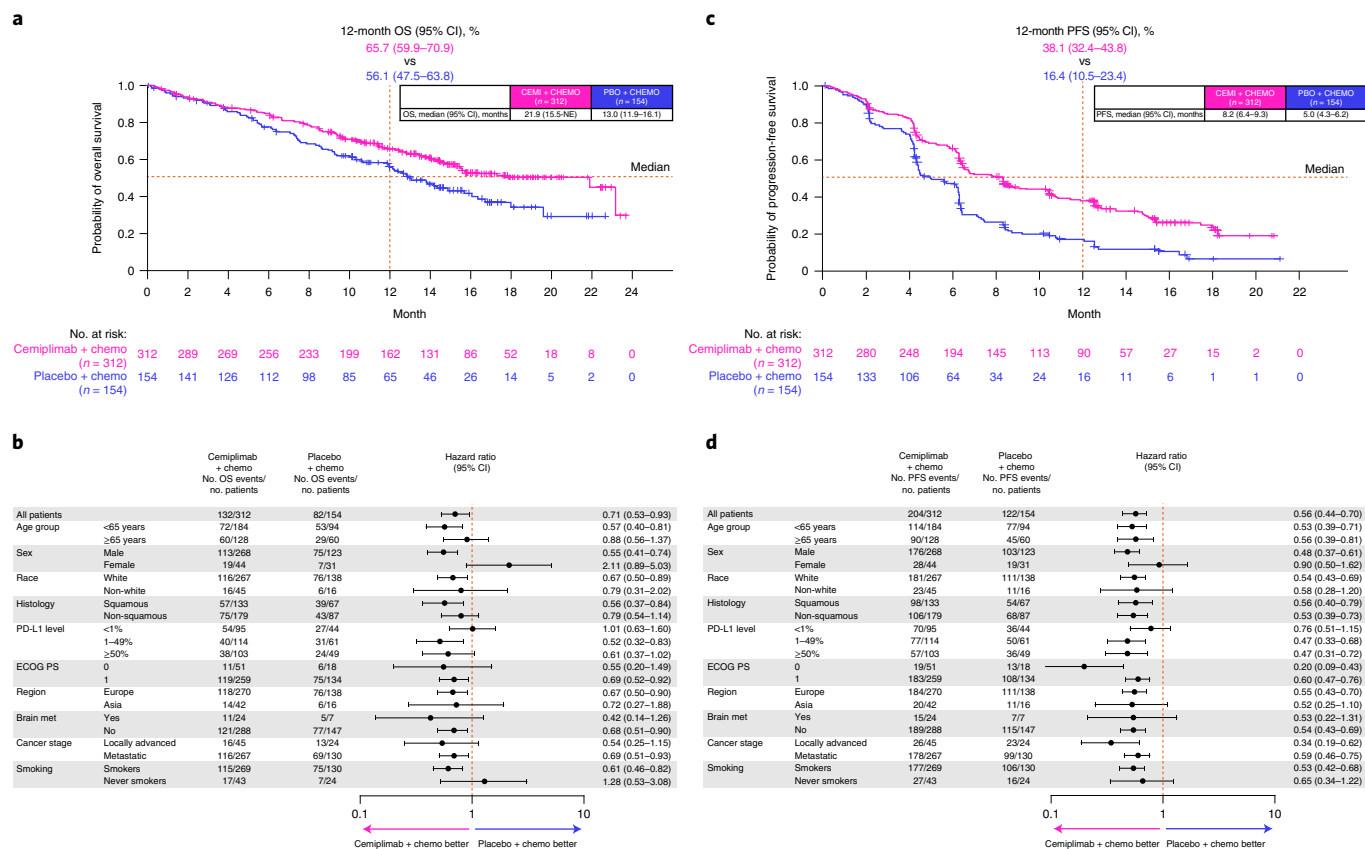


Fig. 2 | Survival data for the cemiplimab plus chemotherapy and placebo plus chemotherapy arms. a, Kaplan–Meier OS curves of all patients. **b**, Forest plots of OS by subgroups. **c**, Kaplan–Meier PFS curves of all patients. **d**, Forest plots of PFS by subgroups. Median OS and PFS and corresponding two-sided 95% CIs were estimated by the Kaplan–Meier method. HRs and corresponding two-sided 95% CIs for OS and PFS were calculated using a stratified Cox proportional hazard model with Efron’s method of tie handling. Cemi, cemiplimab; chemo, chemotherapy; met, metastasis; PBO, placebo.

Table 2 | Summary of tumor response per RECIST 1.1 by independent review committee in the intention-to-treat patient population

Response	Cemiplimab + chemotherapy (n = 312)	Placebo + chemotherapy (n = 154)
Objective response		
Patients, n	135	35
% (95% CI)	43.3 (37.7–49.0)	22.7 (16.4–30.2)
Odds ratio (95% CI)	2.68 (1.72–4.19); <i>P</i> < 0.0001	
Best overall response, n (%)		
Complete response	8 (2.6)	0
Partial response	127 (40.7)	35 (22.7)
Stable disease	121 (38.8)	74 (48.1)
Progressive disease	22 (7.1)	24 (15.6)
NE	30 (9.6)	20 (13.0)
Kaplan–Meier estimated DOR, median (95% CI), months	15.6 (12.4–NE)	7.3 (4.3–12.6)
Observed time to response, median (IQR), months	2.1 (2.0–2.3)	2.1 (2.1–3.9)

Objective response and the corresponding two-sided 95% CI were calculated using the Clopper–Pearson method. The odds ratio and corresponding two-sided 95% CI of the objective response were calculated by the Cochran–Mantel–Haenszel method. The median DOR and corresponding two-sided 95% CI were estimated by the Kaplan–Meier method. Observed time to response and the corresponding IQR were summarized descriptively.

Tumor response. The key secondary endpoint of ORR per independent central review was 43.3% (95% CI, 37.7–49.0) with cemiplimab plus chemotherapy treatment, with complete response (CR) observed in 2.6% of patients (8/312) and partial response (PR) observed in 40.7% of patients (127/312) (Table 2 and Extended

Data Fig. 1a). With placebo plus chemotherapy treatment, the ORR was 22.7% (95% CI, 16.4–30.2), and all responses were PR (Table 2 and Extended Data Fig. 1b). The median duration of response (DOR) with cemiplimab plus chemotherapy was 15.6 months (95% CI, 12.4–NE) versus 7.3 months (95% CI, 4.3–12.6) for the placebo

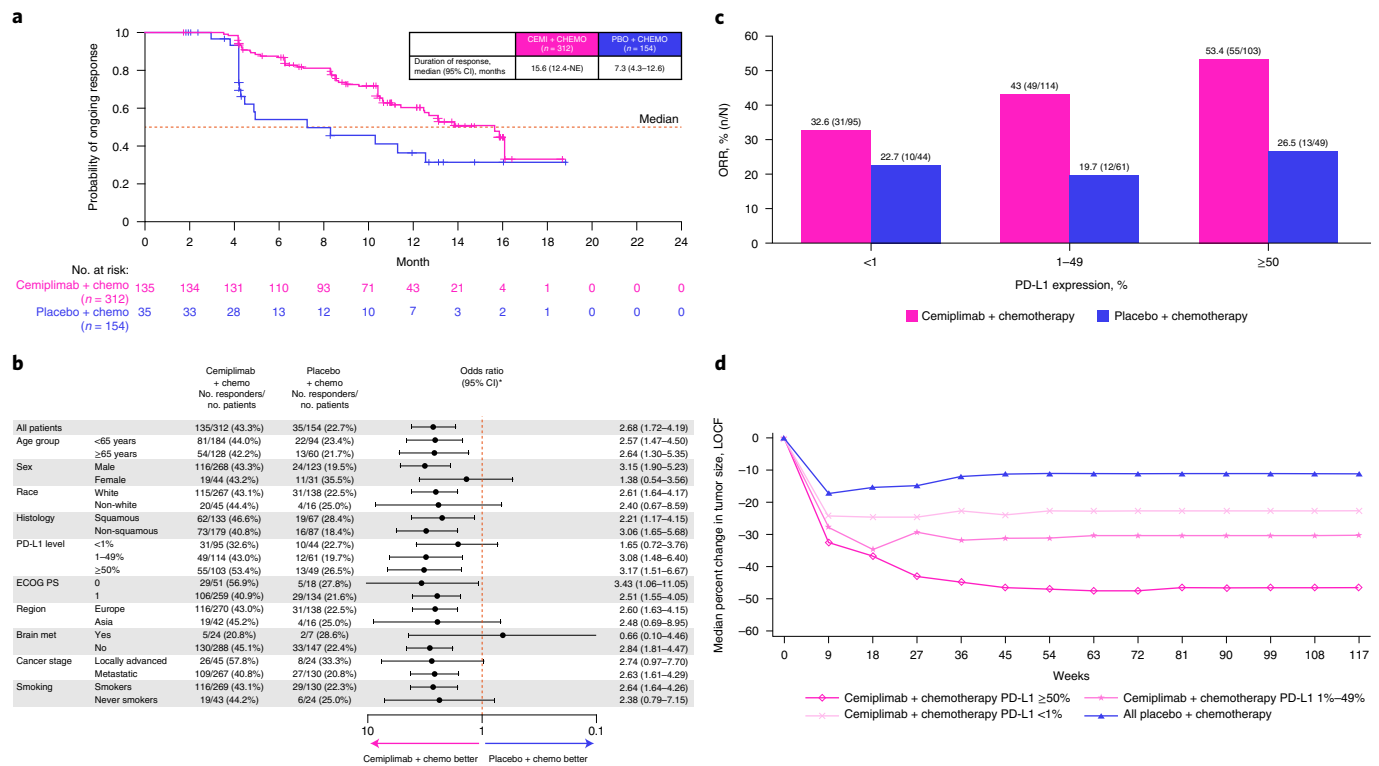


Fig. 3 | Tumor response data for the cemiplimab plus chemotherapy and placebo plus chemotherapy arms. a, Kaplan-Meier curves of DOR in all patients. The median DOR and corresponding two-sided 95% CI were estimated by the Kaplan-Meier method. **b**, Forest plots of objective response in pre-specified subgroups. Odds ratios and corresponding two-sided 95% CIs were calculated using the Cochran-Mantel-Haenszel method. **c**, ORR in correlation with baseline PD-L1 levels. ORR and the corresponding two-sided 95% CI were calculated using the Clopper-Pearson method. **d**, Tumor response in correlation with baseline PD-L1 levels. Median percent change in tumor size over time was calculated descriptively (LOCF). Cemi, cemiplimab; chemo, chemotherapy; LOCF, last observation carried forward; met, metastasis; PBO, placebo.

plus chemotherapy arm (Fig. 3a). ORR results consistently favored cemiplimab plus chemotherapy in predefined subgroups (Fig. 3b). In the cemiplimab plus chemotherapy group, there was a consistent relationship between ORR and baseline PD-L1 expression (Fig. 3c), with benefits versus placebo plus chemotherapy seen across all levels of baseline PD-L1 expression; there was also a clear association between continuous measure of changes in tumor size over time and baseline PD-L1 expression (Fig. 3d).

Patient-reported outcomes. A significant improvement in the secondary endpoints of overall change from baseline in global health status (GHS)/quality of life (QoL) on the European Organization for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30) questionnaire was observed in the cemiplimab plus chemotherapy arm (least squares mean change: 1.69; 95% CI, 0.20-3.19) compared to a non-significant overall change in the placebo plus chemotherapy arm (1.08; 95% CI, -1.34 to 3.51). The overall difference between treatment groups was not significant (0.61; 95% CI, -2.23 to 3.45; $P=0.673$). Compared to placebo plus chemotherapy, cemiplimab plus chemotherapy treatment resulted in a trend toward a delay in the onset of definitive clinically meaningful deterioration according to the GHS/QoL scale (HR=0.78; 95% CI, 0.51-1.19; $P=0.248$) (Extended Data Fig. 2a).

There was also a significant overall improvement from baseline in pain symptoms (EORTC QLQ-C30) with cemiplimab plus chemotherapy (-4.52; 95% CI, -6.32 to -2.73) compared to a non-significant overall change with placebo plus chemotherapy (0.46; 95% CI, -2.42 to 3.34). Significant overall difference between treatment groups favored the cemiplimab plus chemotherapy arm (-4.98; 95% CI, -8.36 to -1.60; $P=0.004$). Compared to placebo plus

chemotherapy, cemiplimab plus chemotherapy treatment resulted in a significant delay in the onset of definitive clinically meaningful deterioration according to pain symptoms scale (HR=0.39; 95% CI, 0.26-0.60; $P<0.0001$) (Extended Data Fig. 2b).

Pharmacokinetics and immunogenicity. Cemiplimab concentrations in serum in patients from the cemiplimab plus chemotherapy arm were similar, irrespective of tumor histology type and baseline PD-L1 expression level, and in agreement with those reported for cemiplimab monotherapy. At steady state (week 24; $n=177$), mean C_{max} (s.d.) was 129 (46.9) mg/L, and mean C_{trough} (s.d.) was 48.6 (25.0) mg/L.

Immunogenicity was low, with treatment-emergent anti-drug antibodies (ADAs) in 3.5% (7/200) of patients who received cemiplimab plus chemotherapy, at low titer (<1,000) and negative in the neutralizing ADA assay; this did not affect cemiplimab concentrations in serum.

Safety. The median duration of treatment exposure was 38.5 weeks (IQR, 20.7-63.9) for cemiplimab plus chemotherapy and 21.3 weeks (IQR, 12.0-38.4) for placebo plus chemotherapy (Supplementary Table 2).

Treatment-emergent adverse events (TEAEs) occurred in 95.8% of patients receiving cemiplimab plus chemotherapy; 43.6% of patients experienced grade ≥ 3 TEAEs, with the most common grade ≥ 3 TEAEs being anemia (9.9%) and neutropenia (5.8%) (Table 3 and full list in Supplementary Table 3). TEAEs of any grade occurred in 94.1% of patients receiving placebo plus chemotherapy. Grade ≥ 3 TEAEs occurred in 31.4% of patients, with the most common being anemia (6.5%) and neutropenia

Table 3 | TEAEs regardless of attribution

Event, n (%)	Cemiplimab + chemotherapy (n = 312)		Placebo + chemotherapy (n = 153)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any	299 (95.8)	136 (43.6)	144 (94.1)	48 (31.4)
Led to discontinuation	16 (5.1)	13 (4.2)	4 (2.6)	4 (2.6)
Led to death	19 (6.1)	19 (6.1)	12 (7.8)	12 (7.8)
Events that occurred in $\geq 10\%$ of patients in either group ^a				
Anemia	136 (43.6)	31 (9.9)	61 (39.9)	10 (6.5)
Alopecia	115 (36.9)	0	66 (43.1)	0
Nausea	78 (25.0)	0	25 (16.3)	0
Hyperglycemia	55 (17.6)	6 (1.9)	18 (11.8)	0
Decreased appetite	53 (17.0)	3 (1.0)	18 (11.8)	0
Alanine aminotransferase increased	51 (16.3)	7 (2.2)	22 (14.4)	3 (2.0)
Arthralgia	48 (15.4)	2 (0.6)	20 (13.1)	0
Neutropenia	48 (15.4)	18 (5.8)	19 (12.4)	9 (5.9)
Aspartate aminotransferase increased	46 (14.7)	1 (0.3)	18 (11.8)	3 (2.0)
Constipation	43 (13.8)	1 (0.3)	17 (11.1)	0
Thrombocytopenia	41 (13.1)	8 (2.6)	19 (12.4)	2 (1.3)
Dyspnea	39 (12.5)	7 (2.2)	10 (6.5)	1 (0.7)
Asthenia	38 (12.2)	6 (1.9)	18 (11.8)	2 (1.3)
Fatigue	38 (12.2)	7 (2.2)	11 (7.2)	1 (0.7)
Vomiting	38 (12.2)	0	15 (9.8)	0
Weight decreased	35 (11.2)	4 (1.3)	13 (8.5)	0
Insomnia	34 (10.9)	0	11 (7.2)	0
Diarrhea	33 (10.6)	4 (1.3)	10 (6.5)	0
Hypoalbuminemia	32 (10.3)	2 (0.6)	9 (5.9)	0

The safety population includes all randomized patients who received at least one dose of any study drug. The events are listed in descending order of frequency in the cemiplimab plus chemotherapy arm. Events were coded according to the Preferred Terms of the Medical Dictionary for Regulatory Activities version 22.1. Severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. ^aThe events are listed in descending order of frequency in the cemiplimab + chemotherapy group.

(5.9%) (Table 3 and full list in Supplementary Table 3). TEAEs that led to treatment discontinuation occurred in 16 (5.1%) patients in the cemiplimab plus chemotherapy arm and four patients (2.6%) in the placebo plus chemotherapy arm (Table 3). TEAEs of any grade that led to death occurred in 19 patients (6.1%) treated with cemiplimab plus chemotherapy and in 12 patients (7.8%) treated with placebo plus chemotherapy (Table 3).

Treatment-related adverse events (TRAEs) occurred in 88.1% of patients treated with cemiplimab plus chemotherapy and in 84.3% of patients treated with placebo plus chemotherapy. TRAEs are summarized in Supplementary Table 4.

Sponsor-identified immune-related adverse events (irAEs) occurred in 18.9% of patients treated with cemiplimab plus chemotherapy, with grade ≥ 3 irAEs occurring in 2.9% of patients (Supplementary Table 5). Three patients (1.0%) discontinued cemiplimab plus chemotherapy due to an irAE, and one patient (0.3%) died due to immune-mediated pneumonitis (Supplementary Table 5).

Discussion

EMPOWER-Lung 3 part two was stopped early per recommendation of the IDMC, based on meeting preset OS efficacy criteria, resulting in a primary analysis in which cemiplimab plus chemotherapy showed superior efficacy versus placebo plus chemotherapy in first-line treatment of aNSCLC as measured by OS (primary endpoint) and PFS and ORR (key secondary endpoints). A median OS of 21.9 months was achieved after cemiplimab plus chemotherapy, with a reduced the risk of death by 29% versus placebo plus

chemotherapy. Cemiplimab plus chemotherapy was also associated with higher median PFS (8.2 months versus 5.0 months), ORR (43.3% versus 22.7%) and DOR (15.6 months versus 7.3 months) versus placebo plus chemotherapy. Overall change from baseline and time to definitive clinically meaningful deterioration in patient-reported pain symptoms were superior with cemiplimab plus chemotherapy. Cemiplimab is only the second anti-PD-1/PD-L1 agent to show efficacy in advanced NSCLC as both monotherapy and in combination with chemotherapy for both squamous and non-squamous histologies^{6,12}.

EMPOWER-Lung 3 part two was designed to efficiently evaluate the efficacy of cemiplimab in combination with chemotherapy in a single phase 3 study of patients with both squamous and non-squamous NSCLC. This obviated the need to conduct separate clinical trials for these two main tumor histology categories, avoiding a distinction that is not rooted in clinical practice. Using this practical design, the study was powered to detect statistically robust results in the overall population irrespective of histology and PD-L1 expression levels. In addition, the patient eligibility criteria of this study were designed to closely resemble the real-world patient population undergoing first-line treatment for advanced NSCLC, including patients with unresectable locally advanced disease not suitable for definitive chemoradiation; patients with previously treated and controlled brain metastases (symptoms were controlled without immunosuppressive doses of steroids, as is most often done in clinical practice, without mandatory radiological evidence of response to treatment); patients with known controlled

viral infections (for example, hepatitis B virus, hepatitis C virus or HIV); and patients who were never smokers. Consistent with these broad inclusion criteria, most patients enrolled in this study had an ECOG PS of 1 (84.3%), which was higher than those enrolled in trials in similar settings^{2,3}.

In this study, most patients were enrolled in Central and Eastern Europe, where smoking is more common than in the United States, especially among men. Consequently, the number of men enrolled was higher than women, consistent with the men-to-women ratio (2:1) of lung cancer incidence in Eastern Europe¹³. The absence of enrollment in the United States and in Western Europe was due to the availability of an approved anti-PD-1 therapy in combination with platinum-doublet chemotherapy for patients with aNSCLC, irrespective of PD-L1 expression, at the time of the present study^{4,14}. Despite differing geographic areas of enrollment, patient characteristics were similar and results were generalizable. Median PFS and OS in the control arm and the safety profile observed in this study were consistent with those observed in studies conducted across various geographies, including those conducted predominantly in Western Europe and the United States^{3,15}.

Median OS was greater with cemiplimab plus chemotherapy than with placebo plus chemotherapy in the overall population and across most subgroups, except for patients with PD-L1 < 1%, never smokers and women. These three subgroups were relatively small, overlapping and underpowered for OS assessment; additionally, in these subgroups, HR point estimates for earlier endpoints such as PFS and ORR were all less than 1, and ORR was consistently superior to chemotherapy alone. Given that cemiplimab plus chemotherapy showed consistently superior PFS and ORR in all subgroups, longer-term follow-up data are awaited to further inform OS results.

Cemiplimab plus chemotherapy demonstrated a favorable benefit-risk profile. The incidence of TEAEs was similar between treatment arms, although incidence of grade ≥ 3 TEAEs was higher with cemiplimab plus chemotherapy (43.6%, 136/312 patients) versus placebo plus chemotherapy (31.4%, 48/153 patients). Low rates of adverse events leading to discontinuation were seen in both treatment arms, and the safety profile was generally consistent with what has been reported for cemiplimab as monotherapy and for platinum-based chemotherapy⁸. Maintenance in GHS and QoL as well as improvements in pain symptoms indicated that cemiplimab plus chemotherapy demonstrated a good benefit-risk profile that does not impose toxicities that interfere with QoL in patients with aNSCLC.

EMPOWER-Lung 3 addresses an unmet clinical need for patients with locally advanced disease who are not candidates for surgical resection or definitive chemoradiation. NCCN guidelines recommend that patients with unresectable stage IIIA and IIIB NSCLC receive definitive concurrent chemoradiation followed by consolidation with durvalumab (anti-PD-L1)¹. However, for patients who are not candidates for concurrent chemoradiation, platinum-based chemotherapy remains the only standard of care available. EMPOWER-Lung 3 included patients with locally advanced disease who are not candidates for definitive chemoradiation (14.8% of the total patient population), thus providing prospective data to guide treatment for these patients rather than extrapolating from stage IV disease, as is often done in practice^{2,6}. Therefore, this study fills a gap in the available evidence that is important for clinical practice and establishes a potential new standard-of-care treatment option for these patients.

The results of EMPOWER-Lung 3 demonstrate that cemiplimab in combination with platinum-doublet chemotherapy is a potential first-line treatment option for patients with advanced squamous and non-squamous NSCLC, regardless of PD-L1 expression level and without *EGFR*, *ALK* or *ROS1* aberrations.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-022-01977-y>.

Received: 23 May 2022; Accepted: 27 July 2022;

Published online: 25 August 2022

References

- National Comprehensive Cancer Network. Clinical practice guidelines in oncology: non-small cell lung cancer. Version 6.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (2021).
- Paz-Ares, L. et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N. Engl. J. Med.* **379**, 2040–2051 (2018).
- Gandhi, L. et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N. Engl. J. Med.* **378**, 2078–2092 (2018).
- Merck Sharp & Dohme Corp. KEYTRUDA (pembrolizumab) injection, for intravenous use (US prescribing information). https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf (2021).
- Genentech, Inc. TECENTRIQ (atezolizumab) injection, for intravenous use (US prescribing information). https://www.gene.com/download/pdf/tecentriq_prescribing.pdf (2021).
- Paz-Ares, L. et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol.* **22**, 198–211 (2021).
- Bristol Myers Squibb. YERVOY (ipilimumab) injection, for intravenous use (US prescribing information). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s110lbl.pdf (2020).
- Sezer, A. et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet* **397**, 592–604 (2021).
- Migden, M. R. et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N. Engl. J. Med.* **379**, 341–351 (2018).
- Burova, E. et al. Characterization of the anti-PD-1 antibody REGN2810 and its antitumor activity in human PD-1 knock-in mice. *Mol. Cancer Ther.* **16**, 861–870 (2017).
- Regeneron Pharmaceuticals, Inc. LIBTAYO (cemiplimab-rwlc) injection, for intravenous use (US prescribing information). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf (2021).
- Gettinger, S. et al. Nivolumab monotherapy for first-line treatment of advanced non-small-cell lung cancer. *J. Clin. Oncol.* **34**, 2980–2987 (2016).
- Sung, H. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**, 209–249 (2021).
- Merck & Co., Inc. European Commission approves KEYTRUDA (pembrolizumab) for first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression with no EGFR or ALK positive tumor mutations. https://s2.q4cdn.com/584635680/files/doc_news/European-Commission-Approves-KEYTRUDA-pembrolizumab-for-First-Line-Treatment-of-Patients-with-Metastatic-Non-Small-Cell-Lung-Cancer-N-8VF0U.pdf (2017).
- Herbst, R. S. et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N. Engl. J. Med.* **383**, 1328–1339 (2020).

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022

Methods

Patients. Adult patients with squamous or non-squamous NSCLC and any PD-L1 expression level were enrolled. The number of patients with squamous histology was capped per protocol at 50%. PD-L1 subgroups were also capped to ensure a homogenous representation of all PD-L1 levels. PD-L1 levels were capped as follows: at least 30% but no more than 40% of patients enrolled must have tumors that express PD-L1 in $\geq 50\%$ of tumor cells; enrollment of patients whose tumors express PD-L1 in $< 1\%$ of tumor cells will be capped at 30%; and enrollment of patients with tumors that express PD-L1 in $< 50\%$ of tumor cells will be capped at 70%.

Inclusion criteria included men and women ≥ 18 years of age (≥ 20 years of age for Japanese patients); availability of an archival or on-study-obtained formalin-fixed, paraffin-embedded tumor tissue sample; at least one radiographically measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); histologically or cytologically confirmed squamous or non-squamous stage III/IV NSCLC (if deemed not candidates for treatment with definitive chemoradiation) or stage IV NSCLC; ECOG PS ≤ 1 ; anticipated life expectancy of at least 3 months; adequate organ and bone marrow function; willingness and ability to comply with clinic visits and study-related procedures; provided signed informed consent; and ability to understand and complete study-related questionnaires.

Exclusion criteria included active or untreated brain metastases or spinal cord compression (patients with adequately treated and clinically stable brain metastases were eligible); tumors positive for *EGFR* mutations, *ALK* translocations or *ROS1* fusions; encephalitis, meningitis or uncontrolled seizures in the year before enrollment; history of interstitial lung disease or of active, non-infectious pneumonitis that required immunosuppressive doses of glucocorticoids to assist with management or of pneumonitis within the last 5 years; ongoing or recent evidence of substantial autoimmune disease that required treatment with systemic immunosuppressive treatments; active or suspected autoimmune disease that required systemic treatment; corticosteroid therapy within 14 days of randomization; another malignancy that is progressing or requires treatment (exception of non-melanoma skin cancer that has undergone potentially curative therapy or any other localized tumor that has been treated, and the patient was deemed to be in complete remission for at least 2 years before enrollment); active hepatitis B or C; prior anti-PD-1/PD-L1 therapy; treatment-related immune-mediated adverse events from immune-modulatory agents; receipt of an investigational drug or device within 30 days of enrollment; receipt of a live vaccine within 30 days of planned start of study drug; major surgery or substantial traumatic injury within 4 weeks before the first dose; documented allergic or acute hypersensitivity reaction attributed to antibody treatments; known psychiatric or substance abuse disorder; pregnant or breastfeeding women; and sexually active adults of childbearing potential who were unwilling to practice highly effective contraception before the start of treatment. Of note, never smokers, defined as individuals who had smoked fewer than 100 cigarettes in their lifetime, were allowed in the study.

Study design and treatment. EMPOWER-Lung 3 (NCT03409614) is a two-part, randomized, phase 3 study (see Supplementary Information for full study protocol). This manuscript reports results from EMPOWER-Lung 3 part two, which compared cemiplimab plus chemotherapy versus placebo plus chemotherapy in patients with aNSCLC and any PD-L1 expression level. The time point for primary analysis has been reached for part two, and the results are reported here. Part one is considered a separate study evaluating cemiplimab plus abbreviated chemotherapy and ipilimumab or cemiplimab plus chemotherapy compared to platinum-doublet chemotherapy alone in patients with aNSCLC whose tumors express PD-L1 in $< 50\%$ of tumor cells (part one is ongoing, and results will be reported separately).

Patients were randomly assigned 2:1 via an interactive web response system and stratified by histology and PD-L1 expression ($< 1\%$, 1–49% and $\geq 50\%$ as measured using a PD-L1 immunohistochemistry assay) to receive either cemiplimab 350 mg once every 3 weeks or placebo every 3 weeks in combination with four cycles of chemotherapy. Investigators' choice of histology-specific chemotherapy options included paclitaxel plus carboplatin, paclitaxel plus cisplatin, pemetrexed plus carboplatin and pemetrexed plus cisplatin (Supplementary Table 6). Patients were treated for a maximum of 108 weeks, or until disease progression or unacceptable toxicity. Maintenance pemetrexed was mandatory for patients with non-squamous histology assigned to a pemetrexed-containing regimen.

Patients reserved the right to withdraw from the study at any time for any reason. Criteria for discontinuation of treatment included toxicity that did not resolve within 84 days of last treatment infusion; any severe or life-threatening event; pregnancy; and a grade ≥ 3 infusion reaction during or directly after treatment infusions.

Major protocol amendments that occurred during the study (EMPOWER-Lung 3 part two) included updating PFS to be a key secondary endpoint instead of being a primary endpoint; adding an interim analysis at 50% OS events in addition to the planned interim analysis at 70% OS events; and adding a clarification that the superiority or futility of cemiplimab treatment will be decided at the interim analysis if the statistical boundary is crossed, because a two-sided test is used.

Endpoints. The primary endpoint, OS, was defined as the time from randomization to the date of patient death. Key secondary endpoints included PFS, defined as the time from randomization to the date of the first documented tumor progression (as determined by the blinded independent review committee) or death, whichever is earlier, and ORR, defined as the proportion of patients with a best overall response of confirmed CR or PR, per blinded independent review committee. Patient-reported outcomes (PROs) were measured as predefined secondary endpoints using multiple instruments, including the EORTC QLQ-C30. Secondary endpoints also included pharmacokinetics (PK), as measured by concentrations of cemiplimab in serum over time, and immunogenicity, as measured by ADAs.

All efficacy endpoints were assessed in the intention-to-treat population. Safety was assessed in all randomized patients who received at least one dose of the assigned treatment.

Clinical data were captured in the clinical database using the Medidata Rave Electronic Capture Data system (version 2021.2.0).

Trial oversight. The protocol and all amendments were approved by the appropriate institutional review board or independent ethics committee at each participating study site (Supplementary Table 7). The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

All patients provided written informed consent before enrollment. The study was sponsored by Regeneron Pharmaceuticals and Sanofi and was designed by employees of Regeneron Pharmaceuticals in collaboration with the investigators.

Treatment for part two of the study was double-blinded except for an unblinded pharmacist at each site. Patients, the principal investigators and study site personnel (apart from the unblinded investigative site pharmacist) remained blinded to all randomization assignments throughout the study.

A blinded independent review committee, independent of the sponsor and the study investigators, reviewed all tumor assessments to determine tumor response per RECIST 1.1. An IDMC reviewed unblinded safety and efficacy data, including all available tumor assessments, for efficacy analyses.

The data were collected by investigators, analyzed by statisticians employed by the sponsors, and interpreted by the authors, including employees of the sponsors. Authors had full access to the data and were responsible for all content and editorial decisions.

Assessments. Baseline assessments included collection of tumor tissue samples for evaluation of PD-L1 expression. Formalin-fixed, paraffin-embedded tumor samples were assessed at a central laboratory using the SP263 assay¹⁶. Tumor tissue samples were also tested for *EGFR*, *ALK* and *ROS1* genomic tumor aberrations by a central laboratory.

Radiographic tumor assessments were performed every 9 weeks for the first year, beginning at week 9, and then every 12 weeks beginning at week 55 (during the second year) until disease progression, withdrawal of consent, death or initiation of another anti-cancer treatment. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The full assessment schedule is available in the study protocol. Responses were assessed by RECIST 1.1 criteria.

PROs were measured with multiple instruments including the EORTC QLQ-C30 questionnaire at baseline, at the beginning of each treatment cycle for the first six doses and then at the start of every three cycles and at the end of treatment. EORTC QLQ-C30 is a 30-item questionnaire composed of five multiple-item functional subscales, three multiple-item symptom scales, a GHS/QoL subscale and six single-item symptom scales assessing other cancer-related symptoms. Responses to all items are converted to a 0–100 scale with a standard scoring algorithm. For GHS/QoL, higher scores indicate better QoL. For the pain symptoms scale, higher scores indicate greater severity of symptoms. Hence, a negative change from baseline in pain symptoms score reflects an improvement, and a positive change reflects a deterioration. Conversely, a negative change from baseline in GHS/QoL score reflects a deterioration, and a positive change reflects an improvement.

Cemiplimab concentrations (PK), immunogenicity (ADAs), and neutralizing anti-cemiplimab antibodies (NAbs) were measured in serum from blood samples collected pre-dose and at various times throughout the treatment and follow-up periods. A validated ELISA with a lower limit of quantitation (LLOQ) of 0.078 mg/L was used to measure cemiplimab concentrations in serum. Immunogenicity was assessed using a validated electrochemiluminescence bridging immunoassay for ADAs and a validated competitive ligand-binding assay for NAbs measured in ADA-positive serum samples only.

Statistical analysis. We estimated that a sample size of 450 randomized patients would yield approximately 93% power to detect a statistically significant difference in OS at a two-sided type 1 error level of 0.05 between the two treatment arms. Timing of the second interim analysis was pre-specified to occur when approximately 204 deaths (70% of total OS events) were observed. An IDMC reviewed the results of this second interim analysis based on a Lan–DeMets approach to the O'Brien–Fleming alpha-spending function and concluded that statistical significance was

demonstrated for OS. The IDMC recommended that the study be unblinded, and the sponsor accepted the recommendation, concluding the study at this second interim analysis and designating these data as the primary analysis. All statistical analyses were performed using SAS software version 9.4 or above.

OS was analyzed by stratified log-rank test using histology and PD-L1 expression level as stratification factors. HRs and 95% CIs were estimated by a stratified Cox regression model using the treatment as covariate and adjusted by the same stratification factors.

PFS was analyzed using the same statistical method as in the OS analysis. ORR was analyzed using the Cochran–Mantel–Haenszel test stratified by histology and PD-L1 expression. DOR was analyzed using the Kaplan–Meier method for each treatment arm.

The primary endpoint of OS and secondary endpoints PFS and ORR were tested hierarchically, in the order of OS, PFS and ORR.

Pre-specified PRO analyses included overall change from baseline, estimated by a mixed-effects model for repeated measures, and the time to definitive clinically meaningful deterioration, analyzed by a stratified log-rank test and summarized by Kaplan–Meier estimation. Time to definitive clinically meaningful deterioration for the GHS/QoL scale was defined as the time from randomization to the first observation with a ≥ 10 -point decrease and no subsequent observations with a decrease of < 10 points from baseline¹⁷ or if patient dropout resulted in missing data. Time to definitive clinically meaningful deterioration for the pain symptoms scale was defined as the time from randomization to the first observation with a ≥ 10 -point increase from baseline and no subsequent observations with an increase of < 10 points from baseline¹⁷ or if patient dropout resulted in missing data.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (for example, the US Food & Drug Administration, the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org/>.

References

16. Tsao, M. S. et al. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint Phase 2 Project. *J. Thorac. Oncol.* **13**, 1302–1311 (2018).
17. Osoba, D. et al. Interpreting the significance of changes in health-related quality-of-life scores. *J. Clin. Oncol.* **16**, 139–144 (1998).

Acknowledgements

The authors thank the patients, their families, all other investigators and all investigational site members involved in this study. This study was funded by Regeneron Pharmaceuticals and Sanofi. Medical writing support under the direction of the authors was provided by J. Lee of Prime (Knutsford, United Kingdom) and funded by Regeneron Pharmaceuticals, according to Good Publication Practice guidelines (<https://doi.org/10.7326/M15-0288>). The sponsor was involved in the study design and in the collection, analysis and interpretation of data as well as data checking of information provided in the manuscript. The authors had unrestricted access to study data, were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

Author contributions

S.L., K.M., B.G., F.S., C.G., B.M.-J., R.P., D.M.W., G.D.Y., I.L., G.G. and P.R. conceived and designed the study. M.G., T. Melkadze, T. Makharadze, D.G., M.D., K.P., K.L., G.N., M.N., I.R. and E.K. recruited patients and collected the data. B.G., S.L. and A.P. conducted the data analysis. All authors had full access to the data and contributed to the data analysis and interpretation as well as critical review, revision and approval of the report.

Competing interests

M.G., T. Melkadze, T. Makharadze, D.G., M.D., K.L., G.N., M.N., I.R. and B.M.-J. report no conflicts of interest. K.P. reports honoraria from AstraZeneca, Merck Sharp & Dohme, Nektar, Pfizer, Regeneron Pharmaceuticals and Roche and a consulting or advisory role with Nektar. E.K. reports honoraria from Merck Sharp & Dohme, Bristol Myers Squibb, Nektar, Pfizer, Roche, AstraZeneca, Amgen and Regeneron Pharmaceuticals. C.G. reports advisory board fees or honoraria from GlaxoSmithKline, Pfizer, AstraZeneca, Roche, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Berlin-Chemie, Chiesi, Boehringer Ingelheim and Sanofi. R.P. reports advisory board or speaker roles for Astellas, Bristol Myers Squibb, Ipsen, Janssen, Merck Sharp & Dohme, Roche and Sanofi-Aventis and institutional funding for research projects from Amgen, AstraZeneca, Novartis and Pierre-Fabre. S.L., K.M., A.P., R.G.W.Q., B.G., F.S., D.M.W., G.D.Y., I.L., G.G. and P.R. are employees and shareholders of Regeneron Pharmaceuticals.

Additional information

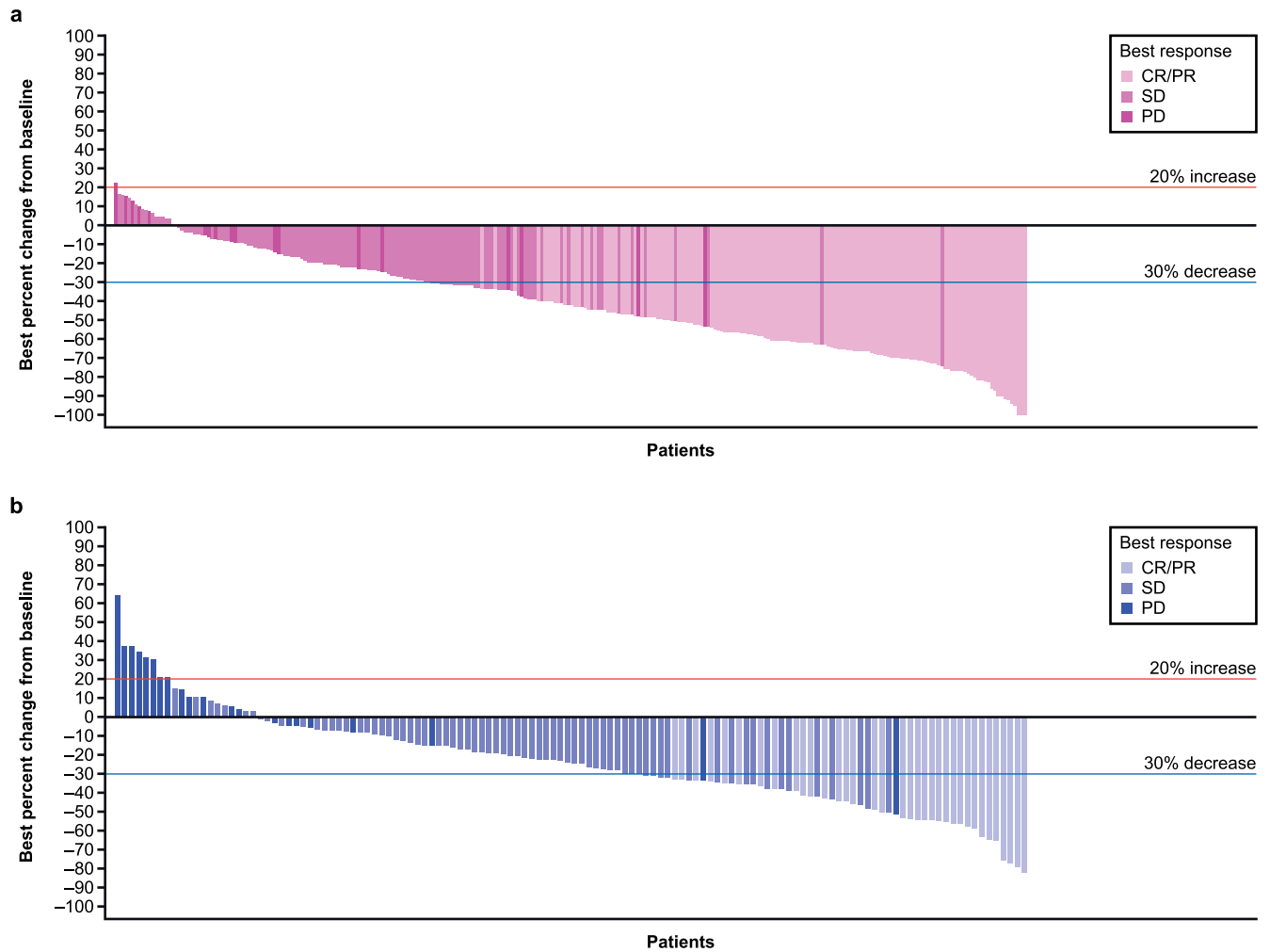
Extended data is available for this paper at <https://doi.org/10.1038/s41591-022-01977-y>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-022-01977-y>.

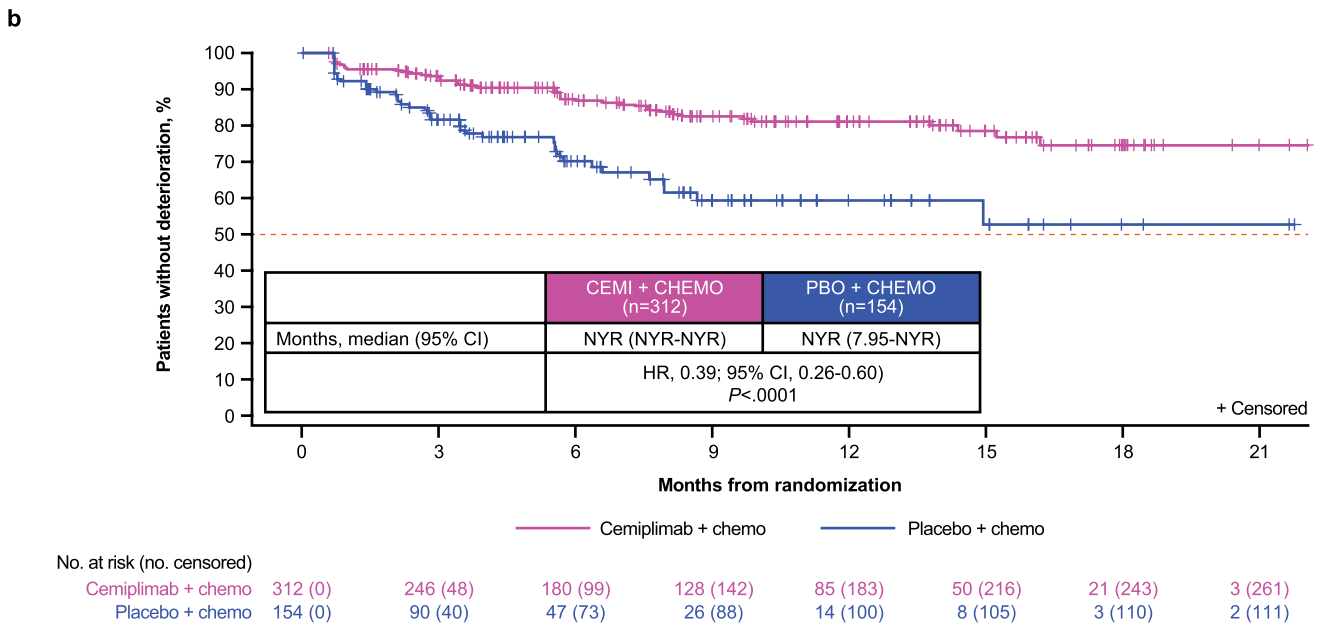
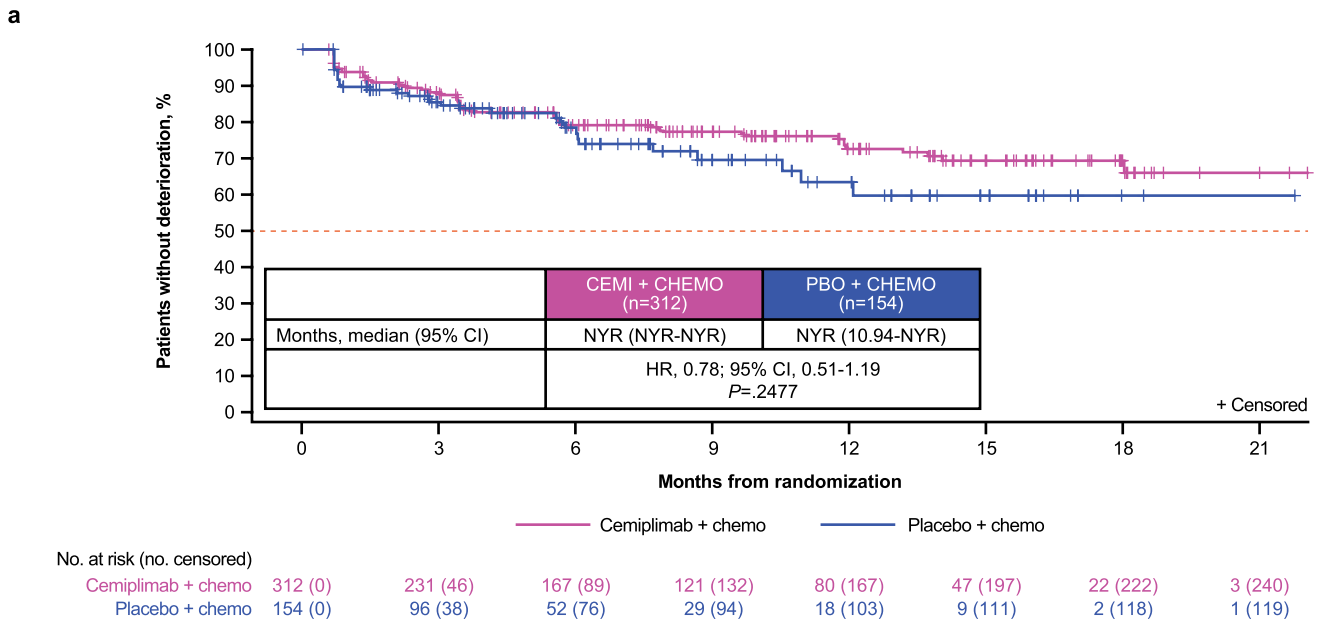
Correspondence and requests for materials should be addressed to Miranda Gogishvili.

Peer review information *Nature Medicine* thanks Bright Offorha, Leena Gandhi and Giuseppe Giaccone for their contribution to the peer review of this work. Primary handling editor: Jennifer Sargent, in collaboration with the *Nature Medicine* team.

Reprints and permissions information is available at www.nature.com/reprints.



Extended Data Fig. 1 | Clinical activity of tumor response in patients with evaluable post-baseline tumor assessment per RECIST 1.1 by independent review committee. a, Waterfall plot of tumor response in patients who received cemiplimab plus chemotherapy (n = 312). **b,** Waterfall plot of tumor response in patients who received placebo plus chemotherapy (n = 154). PD, progressive disease; SD, stable disease.



Extended Data Fig. 2 | Time to definitive clinically meaningful deterioration in a, GHS/QoL and b, pain symptoms. Median time to clinically meaningful deterioration in GHS/QoL and pain symptoms, and corresponding two-sided 95% CIs for each, were estimated using the Kaplan-Meier method. Hazard ratios and corresponding two-sided 95% CIs for time to definitive clinically meaningful deterioration were calculated using a stratified Cox proportional hazard model with Efron's method of tie handling. Cemi, cemiplimab; chemo, chemotherapy; NYR, not yet reached; PBO, placebo.

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided
Only common tests should be described solely by name; describe more complex techniques in the Methods section.
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection

Data analysis

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc.), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org/>.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We estimated that a sample size of 450 randomized patients would yield approximately 93% power to detect a statistically significant difference in overall survival at a two-sided type 1 error level of 0.05 between the two treatment arms.
Data exclusions	There were no data exclusions
Replication	Not applicable for clinical data, as we are reporting pre-specified analysis of a phase III clinical trial.
Randomization	Randomization (2:1) was performed according to a central randomization scheme provided by an interactive web response system manual. Randomization was stratified by histology (non-squamous versus squamous) and levels of programmed cell death-ligand 1 (PD-L1) expression.
Blinding	Open label cemiplimab was blinded by an unblinded pharmacist at each site; patients, principal investigators, and other study site personnel remained blinded to all randomization.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input type="checkbox"/>	<input checked="" type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used	Cemiplimab; Regeneron Pharmaceuticals, Inc.
Validation	<p>Cemiplimab-rwlc is a human programmed death receptor-1 (PD-1) blocking antibody. Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Cemiplimab-rwlc is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. Cemiplimab-rwlc has an approximate molecular weight of 146 kDa.</p> <p>For further information, please see the prescribing information, which may be found here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf</p>

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	Adult patients (both male and female) with stage III or IV non-small cell lung cancer and no actionable tumor mutations (eg, epidermal growth factor receptor, anaplastic lymphoma kinase, or ROS proto-oncogene 1 mutations). Sex and/or gender was not considered in the study design. Sex and/or gender of participants was determined based on self reporting to the treating physician and the study Sponsor was not involved in the process nor gave specific indications to the Investigators regarding the methodology used.
----------------------------	--

Recruitment

Patients were recruited at 74 study sites across 10 countries (primarily in Central and Eastern Europe). There was no selection bias in recruitment of patients in the trial.

Ethics oversight

Ethics Committee of Shanghai Pulmonary Hospital, No.507 Zhengmin Road, Yangpu District, Shanghai, 200433, China; Life Ethics Committee of Beijing Friendship Hospital, Capital Medical University, No.95 YongAn Road, Xicheng District, Beijing, 100050, China; Ethics Committee of Jinan Central Hospital, No.105 Jiefang Road, Jinan, Shandong, 250013, China; Ethics Committee of Affiliated Hospital of Hebei University, No. 648 Dongfeng east road, Lianchi Qu, Baoding Shi, Hebei Sheng, State Zip Code 071105, China; The Ethics Committee of Cancer Hospital of Xinjiang Medical University, No.789, Suzhou East Street, New urban area, Urumqi, Xinjiang, 830000, China; Ethics Committee of Clinical Trials of the First Affiliated Hospital, College of Medicine, Zhejiang University, No.79 Qingchun Road, Hangzhou, Zhejiang, 310003, China; Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine, No.88 Jiefang Road, Shangcheng District, Hangzhou, Zhejiang, 310009, China; Institutional Review Board of Huadong Hospital, No.168 Yan'an Road West, Jing'an District, Shanghai, 200040, China; Clinical Trial Ethics Committee of the Henan Provincial Peoples Hospital, No.7, Weiwu Road, Zhengzhou, Henan, 450003, China; Ethics Committee of The Second Affiliated Hospital of Nanjing Medical University, No.121 Jiangjiayuan Road, Gulou district, Nanjing, Jiangsu, 210011, China; The First Affiliated Hospital of Guangzhou Medical University, No. 151, Yanjiang West Road, Yuexiu District, Guangzhou City, Guangdong Province, China, 510030; Ethics Committee of Xiangyang Central Hospital, No.136 Jinzhou Street, Xiangcheng, Xiangyang City, Hubei, 441021, China; Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University, No. 19 Nonglinxia road, Yuexiu District, Guangzhou, Guangdong, 510000, China; Ethics Committee of Henan Cancer Hospital, No.127 Dongming Road, Zhengzhou, Henan, 450008, China; Good Clinical Practice Office of Hangzhou First Peoples Hospital, Hangzhou Cancer Hospital No.34, Yanguan Xiang, Shangcheng district, Hangzhou City, Zhejiang Province, China, 310002; Anhui Provincial Cancer Hospital Clinical Trial Ethics Committee, No.107, Huanhu East Road, Shushan District, Hefei, Anhui, 230031, China; Ethics Committee of Fuzhou Pulmonary Hospital of Fujian, No.2 Hubian, Cangshan District, Fuzhou, Fujian, 350008, China; Medical Ethics Committee of Liaoning Cancer Hospital and Institute, No. 44, XiaoHeYan Road, Dadong District, Shenyang, Liaoning, 110042, China; Ethics Committee of Hunan Cancer Hospital, No.283, Tongzipo Road, Yuelu District, Changsha, Hunan, 410013, China; Ethics Committee of Linyi Cancer Hospital, Linyi Cancer Hospital, Intersection between Zhongsheng street and Zhicheng Road, Hedong District, Linyi City, Shangdong Province, 276000, China; Ethics Review Committee of Zhejiang Hospital, No.12 Lingyin Road, Xihu District, Hangzhou, Zhejiang Province, 310013, China; Local Ethics Committee of High Technology Medical Center University Clinic, 9 Tsinandali Street, 0144 Tbilisi, Georgia; Local Ethics Committee of Adjara Autonomic Republic, 118 Pushkin Street, 6000 Batumi, Georgia; Local Ethics Committee of JSC "Neo Medi", 12 Kristine Sharashidze Street, 0159 Tbilisi, Georgia; Local Ethics Committee of Institute of Clinical Oncology, 5 Lubliana Street, 0156 Tbilisi, Georgia; Local Ethics Committee of Research Institute of Clinical Medicine, 13 Tevdore Mgvdeli Street, 0112 Tbilisi, Georgia; LEC of "Multi-Profile Clinic Consilium Medulla", 6g Politkovskaia Steet, 0186 Tbilisi, Georgia; Hellenic Republic Ministry of Health National Ethic Committee (NEC) 284 Mesogion Avenue, 155 62 Cholargos, Greece; Medical Research & Ethics Committee, C/o Kompleks Institut Kesehatan Negara Blok A, No 1, Jalan Setia Murni U13/52, Seksyen U13, Bandar Setia Alam, 40170 Shah Alam, Selangor, Malaysia; Clinical Investigation Centre, 5th Floor, East Tower, University Malaya Medical Centre, 59100, Lembah Pantai, Kuala Lumpur, Malaysia; Research Ethics Committee, The National University of Malaysia, 1st Floor, Clinical Block, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia; Komisja Bioetyczna przy Okręgowej Izbie Lekarskiej w Lublinie Ul, Chmielna 4, 20-079 Lublin, Poland; Romania Academy of Medical Sciences, National Bioethics Committee for Medicines and Medical Devices, Sos. Stefan cel Mare nr. 19-21, Sector 2, Bucharest, Romania; Ethics Committee of State Budgetary Healthcare Institution of Sverdlovsk Region "Sverdlovsk Regional Oncology Dispensary", 29, Soboleva Street, Yekaterinburg, 620036, Russian Federation; Ethics Council at the Ministry of Healthcare of the Russian Federation 127994, Moscow, Rakhmanovskiy pereulok, 3; Ethics Committee at the Regional Budget Healthcare Institutio "Kursk Regional Scientific Clinical Centra n.a. G. E. Ostroverkhov" Ul, Eliseeva, 1 Kisilino, 305524 Kursk Region, Kursk District, Russian Federation; Ethics Committee at City Clinical Oncologic Dispensary of St. Petersburg, 3/5, 2-ya Berezovaya alleya, Saint Petersburg, Russian Federation / 56, Prospekt Veteranov, Saint Petersburg, 197022 Russian Federation; Ethics Committee of Arkhangelsk Clinical Oncology Dispensary Bld.1, 145, Obvodniy Kanal Prospekt, Arkhangelsk, 163045 Russian Federation; Federal State Budgetary Institution "National Medical Research Centre of Oncology named after N.N. Petrov" of the Ministry of Healthcare of the Russian Federation 68, Leningradskaya Street., pos. Pesochny, Saint Petersburg, 197758, Russian Federation; Federal State Budgetary Educational Institution of Higher Education "National Research Ogarev Mordovia State University", Medical Institute, 26a, Ulyanov Street, 430032 Saransk, Republic of Mordovia, Russian Federation; Independent Ethics Committee of "Arte Med Assistance" LLC, Office 44, Lit. Ts, 27 prospekt Engelsa, 194156 St. Petersburg, Russian Federation; Federal State Budgetary Educational Institution of Higher Education "Siberian State Medical University" of Ministry of Healthcare of Russia, 15, Kotovskogo Street, 634034 Tomsk, Russian Federation; Ethics Committee at the State Budgetary Healthcare Institution of Kaluga Region "Kaluga Regional Clinical Oncology Dispensary", 2, Vishnevskogo Street., Kaluga, Kaluga Region, 248007, Russian Federation; Committee for Biomedical Ethics at the Research Institute of Oncology of Tomsk National Research Medical Centre ul. Savinykh, 12/1, 634028 Tomsk Region, Tomsk, Russian Federation; Ethics Committee of State Budgetary Healthcare Institution of Kemerovo Region "Regional Clinical Oncology Dispensary", 35, Volgogradskaya Street., Kemerovo, Kemerovo Region, 650036, Russian Federation; Ethics Committee at the Private Institution Educational Organisation of Higher Education Reaviz Medical University ul. Chkalova, d. 100, 443030 Samara, Russian Federation; Ethics Committee of Federal State Budgetary Institution "N. N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, 24, Kashirskoe shosse, Moscow, 115478, Russian Federation; Local Ethics Committee of "EVIMED" LLC Offices 10, 22, 9-v, Blyukhera Street., Chelyabinsk, 454048, Russian Federation; Ethics Committee of "Komanda" LLC, Room 37-N, Lit. A, Bld. 2, 19 Frunze Street., Saint-Petersburg, 196135, Russian Federation; Federal State Budgetary Educational Institution of Higher Education Bashkir State Medical University of the Ministry of Healthcare of the Russian Federation ul. Lenina 3, 450008 Ufa, Republic of Bashkortostan; Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies, 51, Leningradskiy Avenue, 125468 Moscow, Russian Federation; Ethics Committee at the State Budgetary Healthcare Institution "Leningrad Regional Clinical Oncology Dispensary", Liteyny prospect 37-39, 191014 St. Petersburg, Russian Federation; State Autonomous Healthcare Institution Republican Clinical Oncology Center of the Ministry of Healthcare of the Republic of Tatarstan, Sibirskiy trakt, 29, 420029 Kazan, Russian Federation; State Budgetary Healthcare Institution of Stavropol Region "Pyatigorsk Interdistrict Oncology Dispensary", 31, Kalinina Prospect, Pyatigorsk, Stavropol Territory, 357502, Russian Federation; Committee on Ethics Expertise of Clinical Studies of Regional Budgetary Healthcare Institution "Belgorod Oncology Dispensary", 1, Kuybysheva Street, 308010, Belgorod, Russian Federation; Ethics Committee of Budgetary Healthcare Institution of Omsk Region "Clinical Oncology Dispensary", Bld. 1, 9, Zavertyayeva Street, Omsk, 644013, Russian

Federation; Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies, 51, Leningradskiy Avenue, 125468 Moscow, Russian Federation; Ethics Committee in Human Research, Udonthani Cancer Hospital, 36 Moo 1, Udonthan Kean Road, Muang, Udonthani 41330, Thailand; Central Research Ethics Committee, 5th Floor, Building 2, The National Research Council of Thailand, Paholyothin Road, Lad Yao Sub-district, Chatuchak District, Bangkok 10900, Thailand; Naresuan University Institutional Review Board, 99 Moo 9 Tha Pho, Muang, Phitsanulok 65000, Thailand; Lopburi Cancer Hospital Ethics Committee for Human Research, 11/1 Paholyothin Road, Thalee Chup Son, Mueang, Lopburi 15000, Thailand; Institution Review Board, Royal Thai Army Medical Department, 5th floor Phramongkutklao wejvitya Building, Phramongkutklao College of Medicine, 317/5 Rajavithi Road, Rajathevee, Bangkok 10400, Thailand; The Ethics Committee of Lampang Cancer Hospital, 199 Moo12, Pichai, Muang, Lampang 52000, Thailand; Central Research Ethics Committee, 3rd Floor, Building 3, The National Research Council of Thailand, 196 Moo 5, Paholyothin Road, Ladyao, Chatuchak, Bangkok 10900, Thailand; Human Research Ethics Committee Faculty of Medicine, Prince of Songkla University, 15 Karnjanavanit Road, Hat Yai, Songkhla 90110, Thailand; The Ethical Committee for Research in Human Subject, Chiangrai Prachanukroh Hospital, 1039 Sathanpayaban Road, Muang, Chiang Rai 57000, Thailand; Khon Kaen Hospital Institute Review Board in Human Research, 54, 56 Sri Chan Road, Naimaung sub-district, Muang district, Khon Kaen 40000, Thailand; Ankara University Faculty of Medicine Clinical Trials Ethics Committee, Ankara Üniversitesi Tıp Fakültesi Morfoloji Binası, 6100 Sıhhiye/Ankara, Turkey; Local ethics committee of MI "City Dnipropetrovsk Multi-field Clinical Hospital #4 of DRC", 31, Blizhniaya Street, Dnipro, 49102, Ukraine; Ethics committee of Medical and Diagnostic Center of Private Enterprise of Private Production Company "Acinus", 65, Velyka Perspektyvna Street, Kropyvnytskyi, 25006, Ukraine; Ethics committee of Municipal non-profit enterprise "Regional oncology center", 4, Lisoparkivska Street, Kharkiv, 61070, Ukraine; Ethics committee of Podilsky Regional Center of Oncology, 84, Khmelnytske Highway, Vinnytsia, 21029, Ukraine; Ethics committee of National Cancer Institute, 33/43, Lomonosova Street, Kyiv, 03022, Ukraine; Ethics Committee at Municipal Non-profit Enterprise "Transcarpathian Antitumor Center" of the Transcarpathian Regional Council, 2, Brodlakovych Street, Uzhorod, 88014, Ukraine.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	NCT03409614
Study protocol	The trial protocol will be made available as part of the supplementary material.
Data collection	Data was collected between June 2019 and September 2020 at 74 sites in 10 countries, primarily in Central and Eastern Europe.
Outcomes	<p>The primary endpoint was overall survival, defined as the time from randomization to the date of death.</p> <p>Secondary endpoints included:</p> <ul style="list-style-type: none"> - Progression-free survival, defined as the time from randomization to the date of the first documented tumor progression as determined by the blinded independent review committee or death, whichever is earlier. - Objective response rate, defined as the proportion of patients with a best overall response of confirmed complete response or partial response, per blinded independent review committee. - Patient-reported outcomes (PROs) were measured as predefined secondary endpoints using multiple instruments, including the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) questionnaire. - To evaluate the safety and tolerability of cemiplimab plus chemotherapy versus placebo plus chemotherapy. <p>All efficacy endpoints were assessed in the intention-to-treat population. Safety was assessed in all randomized patients who received at least one dose of the assigned treatment.</p> <p>Assessments:</p> <ul style="list-style-type: none"> - Baseline assessments included collection of tumor tissue samples for evaluation of PD-L1 expression; formalin-fixed, paraffin-embedded tumor samples were assessed at a central laboratory using the SP263 assay. Tumor tissue samples were also tested centrally for EGFR, ALK, and ROS1 mutations. - Radiographic tumor assessments were obtained every 9 weeks for the first year and every 12 weeks thereafter until disease progression, withdrawal, death, or initiation of another anticancer treatment; responses were assessed by RECIST 1.1 criteria. - PROs were measured using the EORTC QLQ-C30 questionnaire at baseline, the beginning of each treatment cycle for the first six doses, then at the start of every three cycles, and at the end of treatment. - Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.