Camrelizumab Plus Carboplatin and Pemetrexed as First-line Treatment for Advanced Non-squamous NSCLC: Extended Follow-up of CameL Phase 3 Trial

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Title page

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Declaration of interests

Caicun Zhou has received payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Amoy Diagnostics, Boehringer Ingelheim, C-Stone, Hengrui, Innovent Biologics, Lilly China, LUYE Pharma, Merck Sharp & Dohme, Qilu, Roche, Sanofi, and TopAlliance Biosciences Inc.; and is on data safety monitoring boards or advisory boards for Hengrui, Innovent Biologics, Qilu, and TopAlliance Biosciences Inc. Yanfei Tai, Xinjing Ma, and Wei Shi are employees of Hengrui. The remaining authors declare no conflict of interest.

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Abstract

Introduction: In CameL phase 3 study (ClinicalTrials.gov, NCT03134872), addition of camrelizumab to first-line chemotherapy significantly improved the progression-free survival in patients with stage IIIB-IV non-squamous NSCLC. Here, we present outcomes after a minimum follow-up of 43.9 months since last patient randomization.

Methods: Eligible patients were randomized 1:1 to 4–6 cycles of camrelizumab plus carboplatin and pemetrexed or chemotherapy alone every 3 weeks, followed by maintenance camrelizumab plus pemetrexed or pemetrexed only (n=205 and 207, respectively). Total camrelizumab exposure was up to 2 years.

Results: As of January 31, 2022, camrelizumab plus chemotherapy exhibited substantially improved overall survival over chemotherapy alone (median, 27.1 versus 19.8 mo; hazard ratio, 0.72 [95% CI, 0.57–0.92]). In the chemotherapy alone group, 95 (45.9%) patients crossed over to camrelizumab monotherapy. After adjustment for crossover, the survival benefit with camrelizumab plus chemotherapy was more pronounced (adjusted hazard ratio, 0.55 [95% CI, 0.42–0.71]). In camrelizumab plus chemotherapy group, 33 patients completed 2 years of camrelizumab. Objective response rate was 97.0%, with ongoing responses in 17 of the 32 responses (53.1%); and 93.9% (31/33) of patients were alive at data cutoff. Safety profiles were consistent with the previous report, and no obvious evidence of cumulative toxicity was found with long exposure to camrelizumab.

Conclusions: Camrelizumab plus carboplatin and pemetrexed provides long-term survival benefit over chemotherapy, with manageable toxicity, as well as remarkable and durable response in patients receiving 2 years of camrelizumab, further supporting camrelizumab combination as first-line treatment for advanced non-squamous NSCLC.

Keywords: Immunotherapy; PD-1; Camrelizumab; Chemotherapy; non-squamous non–small-cell lung cancer

Introduction

Advent of immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) has changed the treatment paradigm of various cancers, including non-squamous NSCLC with no *EGFR*/*ALK* genomic tumor aberrations. Several immune-strategies have been approved worldwide including ICI monotherapy or dual immunotherapy for population harboring PD-L1 positive tumors.[1-4] Combination with platinum-based chemotherapeutics could enhance the sensitivity of tumor cells to PD-1/PD-L1 inhibitors,[5-7] providing a compelling rationale for PD-L1 unselected patients. Nowadays, ICI monotherapy or dual immunotherapies plus platinum-containing doublet chemotherapy is the main first-line treatment strategy for population regardless PD-L1 expression.[8-15]

Camrelizumab is a humanized high-affinity IgG4 monoclonal antibody against PD-1 that can efficiently block the interaction between PD-1 on T cells and PD-L1 on tumor cells and consequently inhibit the immune escape of tumor cells.[16] We conducted a randomized, open-label, multicenter, phase 3 study (CameL) to compare camrelizumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced non-squamous NSCLC without *EGFR/ALK* alterations.[13] This was the first phase 3 study showing the superiority of an ICI plus chemotherapy in Chinese population. In the prespecified interim analysis with a median follow-up of 11.9 months, camrelizumab plus carboplatin and pemetrexed significantly improved the progression-free survival (PFS per blinded independent central review [BICR]; median, 11.3 versus 8.3 mo; hazard ratio [HR], 0.60 [95% CI, 0.45–0.79]; one-sided p = 0.0001) and objective response rate (ORR per BICR; 60.5% versus 38.6%; treatment difference, 21.8% [95% CI, 12.2%–30.9%]; one-sided p <0.0001) compared with carboplatin and pemetrexed. A clear trend toward improvement in overall survival (OS) was observed

with camrelizumab plus chemotherapy over chemotherapy alone; however, the data were immature at the interim analysis.

In this updated analysis of CameL study with 22 additional calendar months of follow-up from the interim analysis, we evaluated the long-term efficacy and safety in overall study population and in those who completed 2 years of camrelizumab.

Materials and Methods

Study Design and Patients

CameL was a randomized, open-label, multicenter, phase 3 study of camrelizumab plus chemotherapy versus chemotherapy alone as first-line therapy in patients with advanced non-squamous NSCLC done at 52 sites in People's Republic of China (ClinicalTrials.gov, number NCT03134872). A full description of the eligibility criteria was published previously.[13] Briefly, eligible patients were 18–70 years of age, had previously untreated histologically/cytologically confirmed stage IIIB-IV non-squamous NSCLC without *EGFR*/*ALK* alterations, had at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had a life expectancy of at least 3 months. Patients with untreated central nervous system metastases or corticosteroid use within 2 weeks before study treatment were excluded.

This study was approved by independent ethics committees/institutional review boards of the participating institutions and conducted in accordance with the Declaration of Helsinki, Guidelines for Good Clinical Practice, and local laws and regulations of People's Republic of China. All patients provided written informed consent.

Treatment

Patients were randomly assigned in a 1:1 ratio to camrelizumab plus chemotherapy or chemotherapy alone, with randomization stratified by sex (male versus female) and smoking history (≥20 pack-years versus <20 pack-years or never). Patients and investigators were not masked to treatment assignments; however, the sponsor was masked to treatment allocation until interim analysis completion.

In the camrelizumab plus chemotherapy group, patients were given 4 to 6 cycles of camrelizumab (200 mg) plus carboplatin (area under curve, 5 mg/ml per min) and pemetrexed (500 mg/m^2), followed by maintenance therapy with camrelizumab plus pemetrexed; in the chemotherapy alone group, patients were given 4 to 6 cycles of carboplatin and pemetrexed, followed by pemetrexed maintenance therapy. Medication was administered intravenously on day 1 of each 3-week treatment cycle. Treatment continued until disease progression, unacceptable toxicity, death, consent withdrawal, investigator decision, or study completion. Patients who assigned to chemotherapy alone and had radiographic progression according to RECIST version 1.1 could cross over to receive camrelizumab monotherapy at the investigator's discretion, if the patient had not received any systemic anticancer therapies other than the allocated chemotherapeutic agents and still met all eligibility criteria except treatment naive. The total camrelizumab exposure was up to 2 years. Camrelizumab could be withheld for up to 12 weeks, but dose modifications were not allowed. Treatment interruptions and dose adjustments of chemotherapeutic agents were permitted as prespecified in the protocol.

Outcomes and Assessments

The two primary endpoints of this study were PFS in all patients (overall study population) and in PD-L1–positive population, as assessed by BICR. The secondary

efficacy endpoints included OS, PFS per investigator, as well as ORR, disease control rate (DCR), and duration of response (DoR) per BICR and investigator.

Tumor imaging was scheduled every 6 weeks for the first 54 weeks and every 12 weeks thereafter. Before interim analysis completion, the tumor responses were assessed by both BICR and investigator per RECIST version 1.1; whereas after treatment allocation was unblinded to sponsor following interim analysis, only investigator assessments were performed. Thus, in the current analysis, tumor response outcomes reported were assessed by investigators. Survival was followed up every 3 months after discontinuation of study treatment. Adverse events (AEs) were monitored until 90 days after the last dose and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03.

Statistical analysis

Details of the statistical analyses have been reported previously.[13] Overall, 412 patients were to be randomised. Efficacy was assessed in the full-analysis set which included all randomly assigned patients who received at least one dose of the study treatment. Safety was assessed in the as-treated population. The outcomes were also analyzed in patients in the camrelizumab plus chemotherapy group who completed 2 years of camrelizumab.

OS, PFS, and DoR were estimated with the Kaplan-Meier method. The stratified log-rank test was used to compare these time-to-event endpoints between the two treatment groups, with HRs and 95% CIs determined using the stratified Cox proportional hazards model. Additional analysis of OS was done using the rank-preserving structural failure time model to adjust for crossover. The same stratification factors used in randomization were used for all stratified analyses. ORR between the two treatment groups were compared with the Chi-square test. For these updated analyses, no alpha

was allocated, and nominal one-sided *p* values were shown. Statistical analyses were performed with SAS version 9.4.

Results

Patients and Treatments

Between May 12, 2017, and June 6, 2018, 412 patients were enrolled and received the assigned treatment (camrelizumab plus chemotherapy, n = 205; chemotherapy alone, n=207). The two treatment groups had similar baseline characteristics, except a slightly higher proportion of patients with PD-L1 tumour proportion score (TPS) ≥1% in the camrelizumab plus chemotherapy group (67.3% versus 56.8%; Supplementary Table 1).

As of the data cutoff for this analysis (January 31, 2022), the median follow-up duration (ie, time from randomization to death or last known date alive) was 24.2 months (range, 0.2–54.0) in the camrelizumab plus chemotherapy group and 17.8 months (range, 0.5–54.0) in the chemotherapy alone group. Overall, 21 (10.2%) patients in the camrelizumab plus chemotherapy group and 4 (1.9%) in the chemotherapy alone group remained on the initially assigned treatment (Fig. 1). After the end of the allocated treatment, at least one subsequent therapy was received by 111 (54.1%) patients in the camrelizumab plus chemotherapy group and 144 (69.6%) patients in the chemotherapy alone group.

Updated Efficacy in Overall Study Population

At data cutoff with a minimum follow-up (ie, time from randomization of the last patient to data cutoff date) of 43.9 months, there were 123 (60.0%) deaths in the camrelizumab plus chemotherapy group and 146 (70.5%) in the chemotherapy alone

group, representing an additional 126 deaths across both groups since the previous prespecified interim analysis.[13] A clinically meaningful improvement in OS was observed with camrelizumab plus chemotherapy over chemotherapy alone. The median OS was 27.1 months (95% CI, 21.9–31.5) in the camrelizumab plus chemotherapy group and 19.8 months (95% CI, 15.9–23.7) in the chemotherapy alone group (HR, 0.72 [95% CI, 0.57–0.92]; $p = 0.0038$; Fig. 2A). The estimated OS rates at 12, 24, 36, and 48 months were 74.9% (95% CI, 68.3%–80.3%) versus 67.4% (95% CI, 60.4%–73.4%), 54.0% (95% CI, 46.8%–60.6%) versus 43.1% (95% CI, 36.1%–49.9%), 39.3% (95% CI, 32.5%–46.1%) versus 30.4% (95% CI, 24.1%–37.0%), and 37.2% (95% CI, 30.3%–44.1%) versus 25.6% (95% CI, 19.5%–32.0%) in the camrelizumab plus chemotherapy versus chemotherapy alone group, respectively. OS benefit was consistently greater with camrelizumab plus chemotherapy compared with chemotherapy alone across all subgroups with a HR less than 1, including age, sex, history of smoking, ECOG performance status, brain metastases status, and PD-L1 expression (Fig. 2B and Supplementary Table 2).

In the chemotherapy alone group, 95 (45.9%) patients crossed over to camrelizumab monotherapy upon radiological progression. The crossover-adjusted median OS was 16.5 months (95% CI, 12.8–18.5) for chemotherapy alone, and the survival benefit favored camrelizumab plus chemotherapy with a HR of 0.55 (95% CI, 0.42–0.71; $p < 0.0001$; Fig. 2A).

Totally, 151 (73.7%) patients in the camrelizumab plus chemotherapy group and 176 (85.0%) in the chemotherapy alone group had disease progression or died. With extended follow-up, camrelizumab plus chemotherapy continued to exhibit a clinically meaningful improvement over chemotherapy alone in PFS. The median PFS was 11.0 months (95% CI, 8.5–12.5) with camrelizumab plus chemotherapy and 6.5 months (95%

CI, 5.5–7.2) with chemotherapy alone (HR, 0.55 [95% CI, 0.44–0.69]; p <0.0001; Fig. 3A). The estimated PFS rates at 12, 24, and 36 months were 45.8% (95% CI, 38.5%–52.7%) versus 25.1% (95% CI, 19.1%–31.6%), 27.1% (95% CI, 20.8%–33.8%) versus 10.5% (95% CI, 6.5%–15.7%), and 20.4% (95% CI, 14.7%–26.8%) versus 5.3% (95% CI, 2.5%–9.5%) in the camrelizumab plus chemotherapy versus chemotherapy alone group, respectively. The 48-month PFS rate was 15.6% (95% CI, 10.3%–21.8%) with camrelizumab plus chemotherapy and not available with chemotherapy alone because patients in this group developed disease progression, died, or were censored within 48 months after randomization. Prolonged PFS with camrelizumab plus chemotherapy was consistently observed across all tested subgroups (Fig. 3B).

Compared with chemotherapy alone, camrelizumab plus chemotherapy showed greater anti-tumor activity (ORR, 55.1% [95% CI, 48.0%–62.1%] versus 32.9% [95% CI, 26.5%–39.7%], with a difference of 22.3% [95% CI, 12.7%–31.3%; p <0.0001]) and more durable response (median DoR, 15.5 months [95% CI, 9.9–25.4] versus 10.3 months [95% CI, 6.8–14.0]; HR, 0.60 [95% CI, 0.43–0.86]; p = 0.0022; Table 1 and Supplementary Fig. 1).

Updated Safety in Overall Study Population

The median number of treatment cycles in the camrelizumab plus chemotherapy group was 10 (range, 1–35) for camrelizumab, 5 (range, 1–7) for carboplatin, and 11 (range, 1–72) for pemetrexed. In the chemotherapy group, the median number of treatment cycles was 4 (range, 1–6) for carboplatin and 7 (range, 1–53) for pemetrexed.

Treatment-related AEs (TRAEs) were reported in 204 (99.5%) patients in the camrelizumab plus chemotherapy group and 199 (96.1%) in the chemotherapy alone group. Grade ≥3 TRAEs occurred in 145 (70.7%) and 101 (48.8%) patients, respectively, with the most common being hematological toxicities including decreased

neutrophil count (81 [39.5%]) and 64 [30.9%]), decreased white blood cell (WBC) count (41 [20.0%]) and 30 [4.5%]), anemia (41 [20.0%]) and 23 [11.1%]), and decreased platelet count (34 [16.6%]) and 24 [11.6%]; Table 2). A total of 76 (37.1%) patients treated with camrelizumab plus chemotherapy and 27 (13.0%) treated with chemotherapy alone had serious TRAEs, and the most frequently reported ones were decreased platelet count, myelosuppression, and hepatic function abnormal (Supplementary Table 3). Six (2.9%) and 3 (1.4%) deaths in the camrelizumab plus chemotherapy and chemotherapy alone groups were considered to be attributed to TRAEs (Supplementary Table 4).

Immune-mediated AEs of all grades were reported in 182 (88.8%) patients with camrelizumab plus chemotherapy, and those of grade 3 or worse were reported in 32 (15.6%) patients. The most common immune-mediated AEs occurring in 10% of the patients included reactive cutaneous capillary endothelial proliferation (RCCEP; 158 [77.1%]), increased alanine aminotransferase (ALT; 30 [14.6%]), increased aspartate aminotransferase (AST; 30 [14.6%]), hypothyroidism (22 [10.7%]), and rash (21 [10.2%]; Supplementary Table 5). Grade 1 or 2 RCCEP occurred in 154 (75.1%) patients; only 4 (2.0%) patients had grade 3 RCCEP.

Outcomes in Patients Who Completed 2 Years of Camrelizumab

In the camrelizumab plus chemotherapy group, 33 (16.1%) patients completed 2 years of camrelizumab, with a median follow-up duration of 46.1 months (range, 27.9–54.0). Among them, no patient had brain metastasis, and the majority of patients had PD-L1 TPS ≥1% (90.9%; with those with PD-L1 TPS ≥50% accounting for 27.3%). Other baseline characteristics were generally similar with the overall study population in the camrelizumab plus chemotherapy group (Supplementary Table 1).

At data cutoff, 2 (6.1%) deaths occurred, and the median OS was not reached yet.

The OS rate was 97.0% (95% CI, 80.4%–99.6%) at 36 months and 92.1% (95% CI, 71.0%–98.1%) at 48 months. Thirteen (39.4%) patients had disease progression or died, and the median PFS was not reached (95% CI, 34.8 months–not reached). The PFS rates at 12, 24, 36, and 48 months were 97.0% (95% CI, 80.4%–99.6%), 87.9% (95% CI, 70.9%–95.3%), 67.5% (95% CI, 47.9%–81.1%), and 55.7% (95% CI, 35.8%–71.7%), respectively. The ORR was 97.0% (95% CI, 84.2%–99.9%), with ongoing response in 17 of the 32 responders (53.1%). The median DoR was not reached (95% CI, 31.3 mo–not reached), and rates at 12, 24, and 36 months were as high as 93.6% (95% CI, 76.9%–98.4%), 87.2% (95% CI, 69.4%–95.0%), and 54.2% (95% CI, 34.3%–70.5%), respectively (Table 1).

TRAEs were reported in all patients who completed 2 years of camrelizumab. Twenty (60.6%) patients experienced grade ≥3 TRAEs. Immune-mediated AEs occurred in all patients, and 3 (9.1%) patients experienced grade ≥3 immune-mediated AEs including RCCEP, rash, and increased blood bilirubin (3.0% for each; Supplementary Table 6).

Discussion

This updated analysis of CameL study with longer follow-up confirmed and extended findings from the interim analysis.[13] A median OS of 27.1 months was achieved in the camrelizumab plus chemotherapy group, representing an improvement of 7.3 months and reduction in risk of death (HR, 0.72) compared with chemotherapy, despite 45.9% of patients in the chemotherapy alone group crossed over to camrelizumab monotherapy. After adjustment for crossover, the survival benefit was more pronounced (adjusted HR, 0.55). The OS improvement was well maintained, with around 10% survival gain at 24, 36, and 48 months (54.0% versus 43.1%, 39.3% versus 30.4%, and 37.2% versus 25.6%,

respectively). The OS benefit achieved with camrelizumab plus chemotherapy over chemotherapy was maintained across all subgroups with a HR less than 1. Notably, camrelizumab plus chemotherapy in patients with low PD-L1 expression (1%–49%) and those with high PD-L1 expression (≥50%) achieved a numerically similar HR over chemotherapy (0.76 and 0.68, respectively). Besides, camrelizumab plus chemotherapy was also associated with improved PFS (11.0 versus 6.5 mo), ORR (55.1% versus 32.9%), and DoR (15.5 versus 10.3 mo) versus chemotherapy alone in overall study population.

In addition to camrelizumab, combination of other PD-1/PD-L1 inhibitors with platinum-based doublet chemotherapy have been approved for this indication (Supplementary Table 7). The 5-year follow-up of Keynote-189 study further confirmed the long-term benefit, with a median OS of 22.0 months with pembrolizumab plus chemotherapy versus 10.6 months with chemotherapy (HR, 0.60).[17] However, Keynote-189 study of pembrolizumab combination and IMpower-130 study of atezolizumab combination were conducted predominantly in non-Asian populations; thus cross-trial comparisons of our study with these two studies are quite challenging. The patient characteristics in this study were similar with those in studies conducted in China, including ORIENT-11 study of sintilimab combination, RATIONALE 304 study of tislelizumab combination, and GEMSTONE-302 study of sugemalimab.[11, 12, 14, 18, 19] The PFS benefit with camrelizumab combination versus chemotherapy (HR, 0.55) was in concordance with combinations with other PD-1/PD-L1 inhibitors in Chinese population (HR, 0.482–0.645), with numerically longest median PFS with camrelizumab combination (11.1 compared with 8.9–9.7 mo). In addition, camrelizumab combination showed similar favorable OS benefit compared with combinations with other PD-1/PD-L1 inhibitors (HR, 0.65–0.72) in Chinese population,

despite the highest crossover rate in this study (45.9% compared with less than 30% in other studies). To our knowledge, this is the first report of >3 years outcomes of immunotherapy combined with chemotherapy in the Chinese population.

The safety profile of camrelizumab plus chemotherapy remained consistent with the interim analysis of this study[13] and previous reports for this combination.[20-22] The addition of camrelizumab did not seem to increase the frequency of AEs that were commonly associated with chemotherapy, such as decreased neutrophil count, decreased WBC count, anemia, increased AST, increased ALT, nausea, asthenia, and decreased appetite. Despite longer follow-up with 22 additional calendar months, no new toxicity signals emerged in this updated analysis. The TRAEs of grade ≥3, serious TRAEs, and deaths due to TRAEs in both groups occurred at similar frequencies with the previous report.[13] Three additional deaths owing to AEs occurred; among them, one death from unknown cause was cautiously considered to be attributed to camrelizumab plus chemotherapy.

In the camrelizumab plus chemotherapy group, the majority of patients who completed 2 years of camrelizumab had PD-L1 TPS ≥1%, which was similar with Keynote-189 study.[23] Responses with camrelizumab combination were durable, with 53.1% of patients having an ongoing response at a median follow-up of 46.1 months and with 93.9% of patients alive at data cutoff. Overall, 21.7% (30/138) of the patients with positive PD-L1 at baseline completed 2 years of camrelizumab. The proportion was 19.4% (21/108) in those with PD-L1 TPS 1%–49% and 30.0% (9/30) in those with PD-L1 TPS ≥50%, indicating that patients harboring low or high PD-L1 expression had a similar chance of completing 2 years of camrelizumab exposure and thus attaining robust and sustained anti-tumor activity and long-term survival benefit.

No obvious evidence of cumulative toxicity was found with 2 years of exposure to

camrelizumab. The incidence of grade ≥3 TRAEs in those patients (60.6%) was similar to the overall population in the camrelizumab plus chemotherapy group (70.7%). Although immune-mediated AEs were reported in all patients who completed 2 years of camrelizumab, most were mild in severity and there were no new concerns or emergencies. Grade ≥3 immune-mediated AEs occurred in only 9.1% of patients with 2 years of camrelizumab exposure, generally in line with 15.6% of overall population in the camrelizumab plus chemotherapy group. Our findings supported the 2-year treatment duration for camrelizumab plus carboplatin and pemetrexed and long-term benefit with acceptable toxicity.

In summary, in this updated analysis of CameL phase 3 trial, camrelizumab plus carboplatin and pemetrexed continued to exhibit substantial improvement in survival and anti-tumor activity compared with carboplatin and pemetrexed. Camrelizumab combination provided durable responses, with 93.9% of patients who completed 2 years of camrelizumab alive at data cutoff. Together with manageable safety, the current analysis further supported the use of camrelizumab plus carboplatin and pemetrexed in first-line treatment of advanced NSCLC without *EGFR/ALK* alterations.

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Tables

Table 1. Tumor responses per investigator in overall population and in those who completed 2 years of camrelizumab

	Overall study population		Completed 2 years of camrelizumab (n=33)
	Camrelizumab plus chemotherapy (n = 205)	Chemotherapy alone (n = 207)	
Best overall response, n (%)			
CR	1 (0.5%)	2 (1.0%)	1 (3.0%)
PR	112 (54.6%)	66 (31.9%)	31 (93.9%)
Non-CR/Non-PD	0	1 (0.5%)	0
SD	67 (32.7%)	85 (41.1%)	1 (3.0%)
PD	19 (9.3%)	38 (18.4%)	0
NE	6 (2.9%)	15 (7.2%)	0
ORR, % (95% CI)	55.1% (48.0%–62.1%)	32.9% (26.5%–39.7%)	97.0% (84.2%–99.9%)
Increase in ORR, % (95% CI); *p*	22.3% (12.7%–31.3%); *p* <0.0001		N/A
DCR, % (95% CI)	87.8% (82.5%–92.0%)	74.4% (67.9%–80.2%)	100% (89.4%–100%)
Increase in DCR, % (95% CI); *p*	13.4% (5.9%–20.8%); *p* = 0.0003		N/A
DoR			
Ongoing responses, n/N (%)	29/113 (25.7%)	10/68 (14.7%)	17/32 (53.1%)
Median (95% CI), mo	15.5 (9.9–25.4)	10.3 (6.8–14.0)	NR (31.3–NR)

HR (95% CI); *p*	0.60 (0.43–0.86); p = 0.0022		N/A
12-mo rate, % (95% CI)	55.0% (45.2%–63.8%)	42.1% (30.1%–53.6%)	93.6% (76.9%–98.4%)
24-mo rate, % (95% CI)	41.5% (32.1%–50.7%)	15.7% (7.9%–25.9%)	87.2% (69.4%–95.0%)
36-mo rate, % (95% CI)	26.9% (18.5%–36.0%)	9.0% (3.2%–18.6%)	54.2% (34.3%–70.5%)
48-mo rate, % (95% CI)	23.6% (15.3%–32.9%)	Not available	54.2% (34.3%–70.5%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; NR, not reached; N/A, not applicable.

Table 2. Treatment-related adverse events occurring in at least 10% of patients in either group.

	Camrelizumab plus chemotherapy (n = 205)		Chemotherapy alone (n = 207)	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
Hematological toxicities				
Neutrophil count decreased	148 (72.2%)	81 (39.5%)	133 (64.3%)	64 (30.9%)
White blood cell count decreased	146 (71.2%)	41 (20.0%)	133 (64.3%)	30 (14.5%)
Anemia	139 (67.8%)	41 (20.0%)	125 (60.4%)	23 (11.1%)
Platelet count decreased	97 (47.3%)	34 (16.6%)	79 (38.2%)	24 (11.6%)
Lymphocyte count decreased	23 (11.2%)	9 (4.4%)	21 (10.1%)	5 (2.4%)
Hemoglobin decreased	20 (9.8%)	3 (1.5%)	22 (10.6%)	2 (1.0%)
Non-hematological toxicities				
Reactive cutaneous capillary endothelial proliferation	158 (77.1%)	4 (2.0%)	2 (1.0%)	0
Aspartate aminotransferase increased	96 (46.8%)	4 (2.0%)	68 (32.9%)	2 (1.0%)
Alanine aminotransferase increased	90 (43.9%)	10 (4.9%)	79 (38.2%)	6 (2.9%)
Nausea	75 (36.6%)	2 (1.0%)	61 (29.5%)	2 (1.0%)
Asthenia	68 (33.2%)	7 (3.4%)	60 (29.0%)	3 (1.4%)
Decreased appetite	66 (32.2%)	5 (2.4%)	56 (27.1%)	5 (2.4%)
Constipation	45 (22.0%)	0	35 (16.9%)	1 (0.5%)

Vomiting	44 (21.5%)	2 (1.0%)	35 (16.9%)	4 (1.9%)
Hepatic function abnormal	43 (21.0%)	4 (2.0%)	32 (15.5%)	1 (0.5%)
Gamma-glutamyltransferase increased	38 (18.5%)	6 (2.9%)	18 (8.7%)	1 (0.5%)
Blood creatinine increased	31 (15.1%)	1 (0.5%)	14 (6.8%)	1 (0.5%)
Rash	29 (14.1%)	4 (2.0%)	11 (5.3%)	0
Pruritus	25 (12.2%)	1 (0.5%)	3 (1.4%)	0
Myelosuppression	24 (11.7%)	14 (6.8%)	10 (4.8%)	4 (1.9%)
Blood bilirubin increased	23 (11.2%)	2 (1.0%)	14 (6.8%)	0
Oedema peripheral	23 (11.2%)	0	17 (8.2%)	0
Hypothyroidism	23 (11.2%)	1 (0.5%)	0	0

Data are n (%). Safety data for the chemotherapy alone group did not include data from the crossover phase.

Figure Legends

Figure 1. Trial profile

Figure 2. Kaplan-Meier estimates for OS

A: OS in overall study population and crossover-adjusted OS in the chemotherapy alone group. The HR was estimated from the stratified Cox proportional hazards model with treatment as the fixed effect. Comparisons between groups were analyzed using the stratified one-sided log-rank test. Stratified factors included sex (male versus female) and smoking history (≥20 pack-years versus <20 pack-years or never.

B: Subgroup analysis of OS. For sex and smoking history, the HR was estimated from an unstratified Cox proportional hazards model with treatment as the fixed effect. For other variables, the HR was estimated from a Cox proportional hazards model stratified by sex (male versus female) and smoking history (≥20 pack-years versus <20 pack-years or never, with treatment as the fixed effect.

OS, overall survival; Chemo, chemotherapy; Camre+chemo, camrelizumab plus chemotherapy; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; HR, hazard ratio; CI, confidence interval.

Figure 3. **Kaplan-Meier estimates for PFS per investigator**

A: PFS in overall study population. The HR was estimated from a stratified Cox proportional hazards model. Comparisons between groups were analyzed using stratified one-sided log-rank test. Stratified factors included sex (male versus female) and smoking history (≥20 pack year versus <20 pack year or never).

B: Subgroup analysis of PFS.

For sex and smoking history, the HR was estimated from an unstratified Cox proportional hazards model with treatment as the fixed effect. For other variables, the

HR was estimated from a Cox proportional hazards model stratified by sex (male versus female) and smoking history (≥20 pack-years versus <20 pack-years or never, with treatment as the fixed effect.

PFS, progression-free survival; Chemo, chemotherapy; Camre+chemo, camrelizumab plus chemotherapy; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; HR, hazard ratio; CI, confidence interval.

Supplementary material. docx

Supplementary Figure 1. Tumor response

Supplementary Table 1. Baseline characteristics in overall population and in those who completed 2 years of camrelizumab

Supplementary Table 2. Efficacy by PD-L1 tumor proportion score

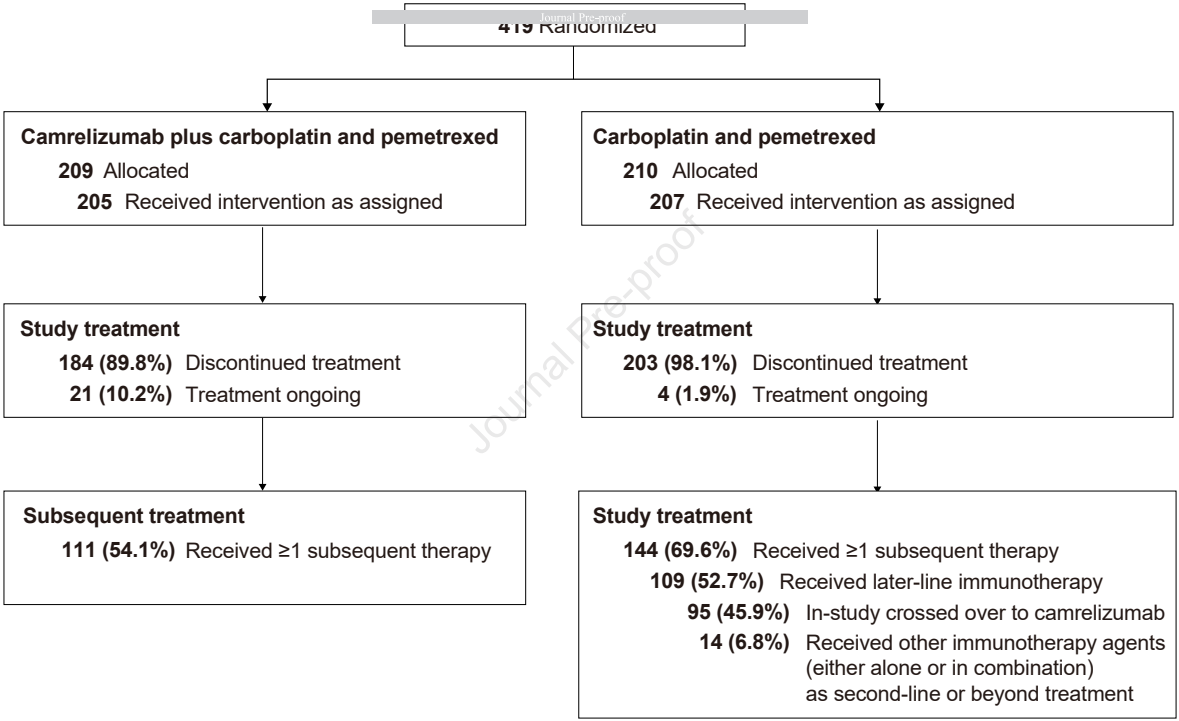
Supplementary Table 3. Serious TRAEs occurring in at least 2% of patients in either group (overall study population)

Supplementary Table 4. AEs leading to death (overall study population)

Supplementary Table 5. Immune-mediated adverse events occurring in at least 2% of patients who received camrelizumab plus chemotherapy

Supplementary Table 6. Immune-mediated adverse events in patients who completed 2 years of camrelizumab

Supplementary Table 7. Summary of phase 3 trials with anti–PD-1/PD-L1 antibody plus chemotherapy in first-line non-squamous NSCLC Setting



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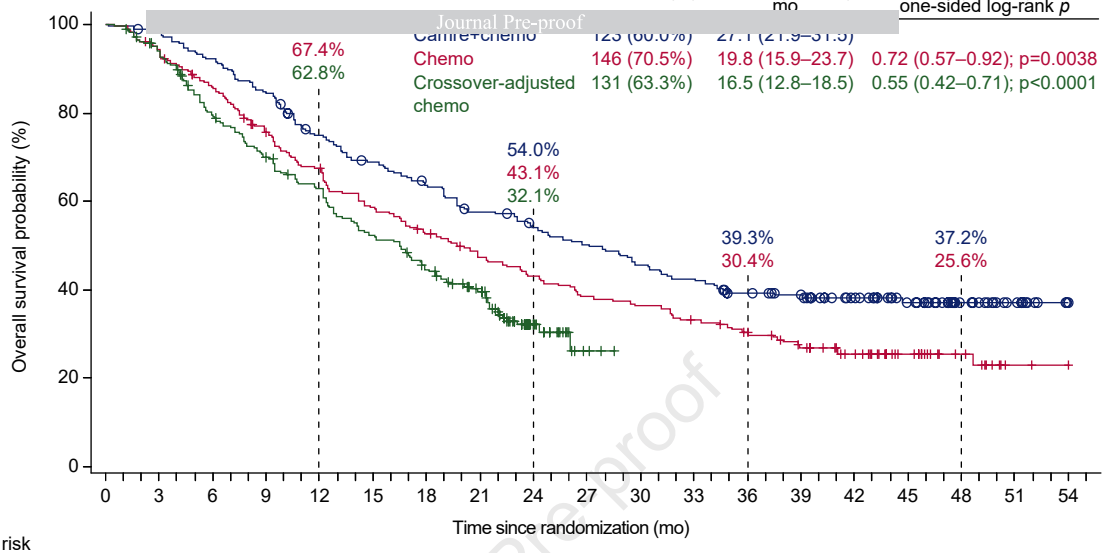
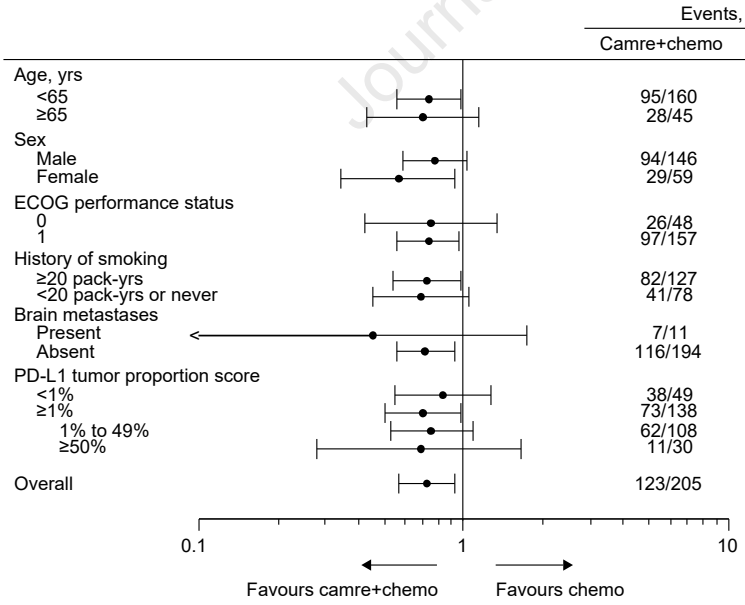


No. at risk

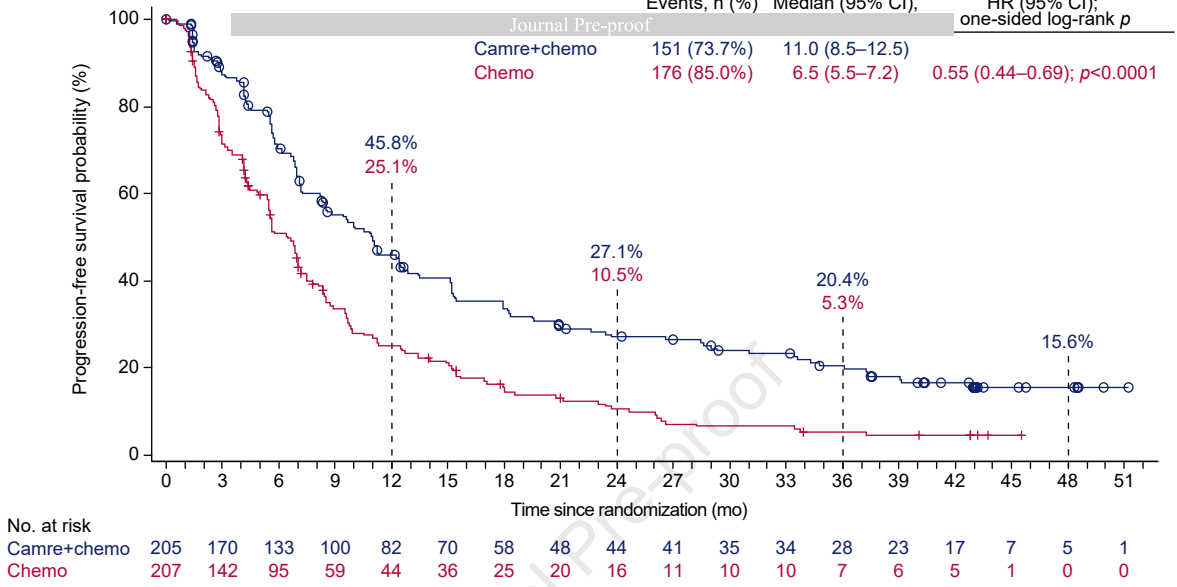
Camre+chemo	205	201	188	173	149	136	125	112	103	96	87	81	71	66	52	39	21	11	1
Chemo	207	194	174	150	133	115	102	90	82	73	69	62	55	45	35	22	11	2	0
Adjusted chemo	207	191	158	137	121	101	84	66	23	3	0								

B



	Events, (n/N)		HR (95% CI)
	Camre+chemo	Chemo	
Age, yrs			
<65	95/160	105/154	0.74 (0.56–0.98)
≥65	28/45	41/53	0.71 (0.43–1.15)
Sex			
Male	94/146	108/149	0.78 (0.59–1.03)
Female	29/59	38/58	0.57 (0.35–0.92)
ECOG performance status			
0	26/48	23/36	0.75 (0.43–1.32)
1	97/157	123/171	0.73 (0.56–0.96)
History of smoking			
≥20 pack-yrs	82/127	96/130	0.73 (0.54–0.98)
<20 pack-yrs or never	41/78	50/77	0.69 (0.45–1.04)
Brain metastases			
Present	7/11	6/6	0.45 (0.10–1.73)
Absent	116/194	140/201	0.72 (0.56–0.92)
PD-L1 tumor proportion score			
<1%	38/49	54/69	0.84 (0.55–1.27)
≥1%	73/138	77/117	0.70 (0.51–0.97)
1% to 49%	62/108	64/97	0.76 (0.53–1.08)
≥50%	11/30	13/20	0.68 (0.28–1.63)
Overall	123/205	146/207	0.72 (0.57–0.92)

A



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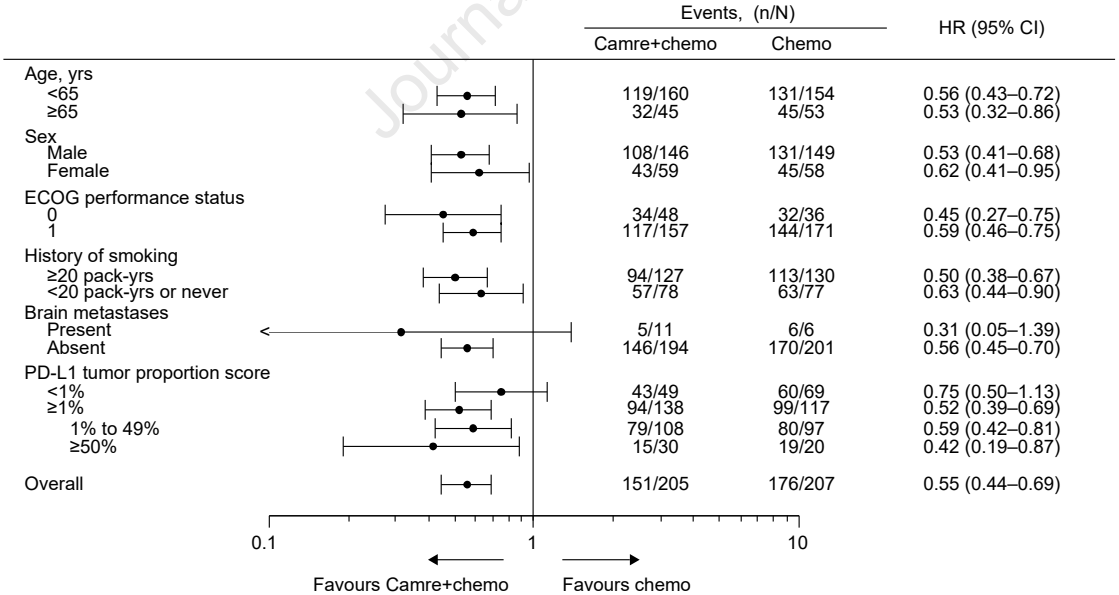

CRediT Statement

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