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ORIGINAL RESEARCH ARTICLE

Efficacy and safety of the combination of PEG–rhG-CSF with camrelizumab and chemotherapy in advanced squamous nonsmall cell lung cancer: A randomized controlled trial

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Abstract

Introduction: Optimizing first-line chemoimmunotherapy for advanced squamous non–small cell lung cancer (sqNSCLC) remains challenging, particularly in balancing efficacy with treatment-related hematologic toxicity.

Objective: This study aims to evaluate whether adding polyethylene glycol–recombinant human granulocyte colony-stimulating factor (PEG–rhG-CSF) to first-line camrelizumab and platinum-based chemotherapy improves outcomes in patients with advanced sqNSCLC.

Methods: In this single-center, randomized controlled trial, 212 patients with treatment–naïve stage IV sqNSCLC were enrolled between 2020 and 2021. Among them, 23 were lost to follow-up, leaving 189 patients included in the study. They were randomly assigned (1:1) to receive either camrelizumab, paclitaxel, and carboplatin (control group, n = 94) or the same regimen plus prophylactic PEG–rhG-CSF (experimental group, n = 95). The primary endpoint was progression-free survival (PFS), and the secondary endpoints were objective response rate (ORR), overall survival (OS), and safety.

Results: Among the evaluable patients, the ORR was significantly higher in the experimental group (58.95% vs. 43.62%; p = 0.0355). The disease control rate was comparable between groups (85.26% vs. 76.60%; p = 0.2431). The experimental group demonstrated significantly longer median PFS (10.5 vs. 8.4 months; hazard ratio [HR] = 0.72, 95% confidence interval [CI] 0.52–0.99; p = 0.0423) and a strong trend toward improved median OS (not reached vs. 22.3 months; HR = 0.67, 95% CI 0.45–0.99; p = 0.0432). Survival benefit was consistent across all predefined subgroups. The incidence of neutropenia was significantly lower in the experimental group ($p < 0.0001$), while fever was more common ($p = 0.0256$). Other adverse events were similar between groups.

Conclusion: The addition of PEG–rhG-CSF to first-line camrelizumab-based chemoimmunotherapy in advanced sqNSCLC significantly improved tumor response and PFS, showed a promising OS benefit, reduced chemotherapy–induced neutropenia, and maintained a manageable safety profile. These findings suggest a potential synergistic role for PEG–rhG–CSF beyond supportive care in this setting.

Keywords: Polyethylene glycol–recombinant human granulocyte colony–stimulating factor, Camrelizumab, Advanced squamous non–small cell lung cancer, Immunotherapy, Chemotherapy

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1. Introduction

The Camel-Sq study established a foundational basis for the use of camrelizumab in combination with paclitaxel and platinum-based chemotherapeutic agents as a first-line treatment for locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).[1] The objective response rate (ORR) in their experimental cohort was 64.8%, indicating that nearly one-third of patients exhibited suboptimal therapeutic efficacy. Enhancing the effectiveness of immunotherapy remains a pivotal concern. Primary and secondary resistance to immunotherapy constitute the principal challenges impeding patient outcomes.[2] The mechanisms underlying immunotherapy resistance are multifaceted, involving not only intrinsic tumor factors (e.g., low tumor mutational burden and impaired antigen presentation) but also an immunosuppressive tumor microenvironment (TME) characterized by myeloid-derived suppressor cells, regulatory T cells, and altered cytokine profiles that hinder effective T-cell infiltration and function.[3,4] Therefore, strategies aimed at reprogramming the immunosuppressive TME are crucial to overcome resistance and improve clinical outcomes.

Studies have explored the potential of augmenting immunotherapy efficacy through the combined use of immune checkpoint inhibitors and chemotherapy with low-dose radiation, epigenetic therapy, targeted therapy, or oncolytic virus therapy. However, these investigations have not yielded satisfactory outcomes, primarily due to suboptimal efficacy or the occurrence of excessive adverse reactions.[5,6] Furthermore, research has demonstrated that polyethylene glycol–modified recombinant human granulocyte–colony-stimulating factor (PEG–rhG-CSF) can influence the distribution of peripheral blood lymphocytes, the diversity and clonality of T-cell receptors (TCRs), and cytokines associated with CD4+ T cells. This results in an increased ratio of peripheral blood CD3+ T cells and CD4+ T cells, thereby modulating the immune status of cancer patients.[7]

Beyond its well-established role in myelopoiesis, G-CSF and its PEGylated form have been shown to exert immunomodulatory effects, including promoting dendritic cell maturation and potentially mitigating chemotherapy-induced lymphodepletion, which is critical for maintaining an anti-tumor immune response during chemoimmunotherapy.[8,9] Recent preclinical and translational studies further suggest that G-CSF signaling can influence the polarization and function of tumor-associated macrophages and modulate systemic cytokine networks, presenting a plausible mechanism for reshaping the TME.[10,11] PEG–rhG-CSF is extensively utilized in the prevention and treatment of chemotherapy-induced neutropenia, with numerous studies focusing on its effects on neutrophils.[12,13] However, emerging evidence suggests its role extends beyond myelopoiesis to immunomodulation. While a prior study has established the safety and feasibility of prophylactic PEG–rhG-CSF in maintaining chemotherapy dose intensity during immunochemotherapy for NSCLC[14], its potential to actively enhance anti-tumor immune responses and thereby improve clinical efficacy remains underexplored. There is a lack of international research on the effects of PEG–rhG-CSF in the context of immunotherapy for NSCLC.

Consequently, this study prospectively examines patients with late-stage squamous NSCLC treated at our institution, focusing on the efficacy and safety of a combined regimen of PEG–rhG-CSF, camrelizumab, paclitaxel, and platinum-based therapy. Specifically, the novelty of this study lies in being the first randomized controlled trial to shift the investigative focus from the supportive role (safety and treatment continuity) of PEG–rhG-CSF to its potential as an active efficacy-enhancing agent within a chemoimmunotherapy regimen for advanced squamous NSCLC. We hypothesized that by leveraging its immunomodulatory properties, PEG–rhG-CSF may synergize with camrelizumab and chemotherapy to remodel the TME and overcome therapeutic resistance. Therefore, the primary objective of this study is to investigate whether the addition of PEG–rhG-CSF not only ensures treatment continuity but also significantly augments the clinical efficacy (assessed by ORR, progressionfree survival [PFS], and overall survival [OS]) of first-line camrelizumab-based chemoimmunotherapy in this patient population.

2. Materials and methods

2.1. Sample size estimation

The Camel-Sq study targeted an experimental group that used the same treatment as the control group, aiming to achieve a two-year OS rate exceeding 50%.[1] Assuming a two-year OS rate of 50% in the control arm and 72.5% in the experimental arm, we calculated the required cohort size for comparing survival curves via the log-rank test, employing the Freeman methodology. To detect a statistically significant divergence in survival outcomes between the experimental and control cohorts, an a priori power analysis was conducted. Assuming a two-tailed significance threshold (α) of 0.05, a statistical power ($1-\beta$) of 0.80, and an equal allocation ratio (N1:N2 = 1:1), the calculation indicated that a total sample size of at least 168 subjects is necessary. This requirement translates to 84 participants per arm for both the intervention and control

groups. Accounting for an anticipated attrition rate of approximately 10% during follow-up, the adjusted sample size necessitates 92 participants per group.

2.2. Patients' enrollment and randomization

The study enrollment process involved the selection of 212 patients diagnosed with stage IV squamous cell lung cancer, all of whom received therapeutic management within the Oncology Division at Jinan Eighth People's Hospital from January 2020 thro December 2021. Among them, 23 were lost to follow-up, leaving 189 patients included in the study. The randomization sequence was generated by a computer using a block randomization method with a block size of 4. Allocation concealment was maintained using sequentially numbered, sealed, opaque envelopes, and the assignment was carried out by an independent research coordinator who was not involved in patient enrollment or outcome assessment. Participants, investigators, and outcome assessors were blinded to group assignment until after database lock. Utilizing a random number table for allocation, the study cohort was stratified into two distinct arms: an experimental group (n = 95) administered PEG–rhG-CSF alongside camrelizumab, paclitaxel, and a platinum agent (carboplatin or cisplatin), versus a control group (n = 94) treated with camrelizumab, paclitaxel, and the same platinum options, but without PEG–rhG-CSF.

2.3. Inclusion criteria

Patients must have a histologically or cytologically verified diagnosis of stage IV squamous cell lung carcinoma; age ≥ 18 years; with an anticipated survival exceeding 3 months; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–1; the presence of evaluable lesions as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; completion of programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) assessment; and absence of previous systemic antineoplastic treatment for advanced-stage disease (including both chemotherapy and immunotherapy for metastatic disease; prior adjuvant/neoadjuvant therapy completed > 6 months before enrollment was allowed). Furthermore, participants were required to demonstrate good compliance and cooperation with follow-up procedures. Every individual enrolled in this investigation participated voluntarily and furnished written informed consent.

2.4. Exclusion criteria

Patients exhibiting substantial impairment of major organ systems, such as cardiac or cerebral impairments; individuals diagnosed with psychiatric disorders or cognitive impairments; those with a documented history of drug allergies pertinent to this study; and individuals who declined to participate in the research (Figure 1).

2.5. Treatment protocols

Patients in both groups received treatment in 21-day cycles. During the induction phase (4-6 cycles), the treatment is as follows:

- Camrelizumab: 200 mg intravenously over 30–60 min on Day 1.
- Paclitaxel: 175 mg/m^2 intravenously on Day 1.
- Platinum agent: Either cisplatin (area under the curve [AUC] = 5) or carboplatin (AUC = 6) intravenously on Day 1, selected according to the investigator's judgment and the patient's renal function.
- PEG–rhG-CSF/placebo: A single subcutaneous injection of 6 mg PEG–rhG-CSF (experimental group) or placebo (control group) was administered 24–48 h after completion of chemotherapy (usually on Day 2 or 3).

Dose modifications and treatment delays were implemented according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, a standardized framework developed by the United States (US) National Cancer Institute[15], for managing specific adverse events.

During the maintenance phase (up to 24 months or until progression/unacceptable toxicity), patients received subcutaneous injections of either 6 mg PEG–rhG-CSF or a placebo every 3 weeks, administered 24–48 h after the camrelizumab infusion. Additionally, 200 mg camrelizumab was administered intravenously every 3 weeks. Patients remained on the prescribed medication regimen until the occurrence of disease progression, death, or the emergence of intolerable adverse reactions.

2.6. Endpoints

The study's primary endpoint was PFS, defined as the time from randomization to the earliest occurrence of disease progression or death from any cause. Secondary endpoints included OS, measured as the time from randomization to death from any cause; ORR, representing the fraction of patients attaining a verified complete or partial response; disease control rate (DCR), denoting the proportion of individuals achieving a confirmed complete response (CR), partial response (PR), or stable disease (SD); and safety outcomes.

A statistical analysis of adverse events associated with two distinct drug regimens was conducted. Adverse events were systematically classified and stratified according to the CTCAE version 5.0.

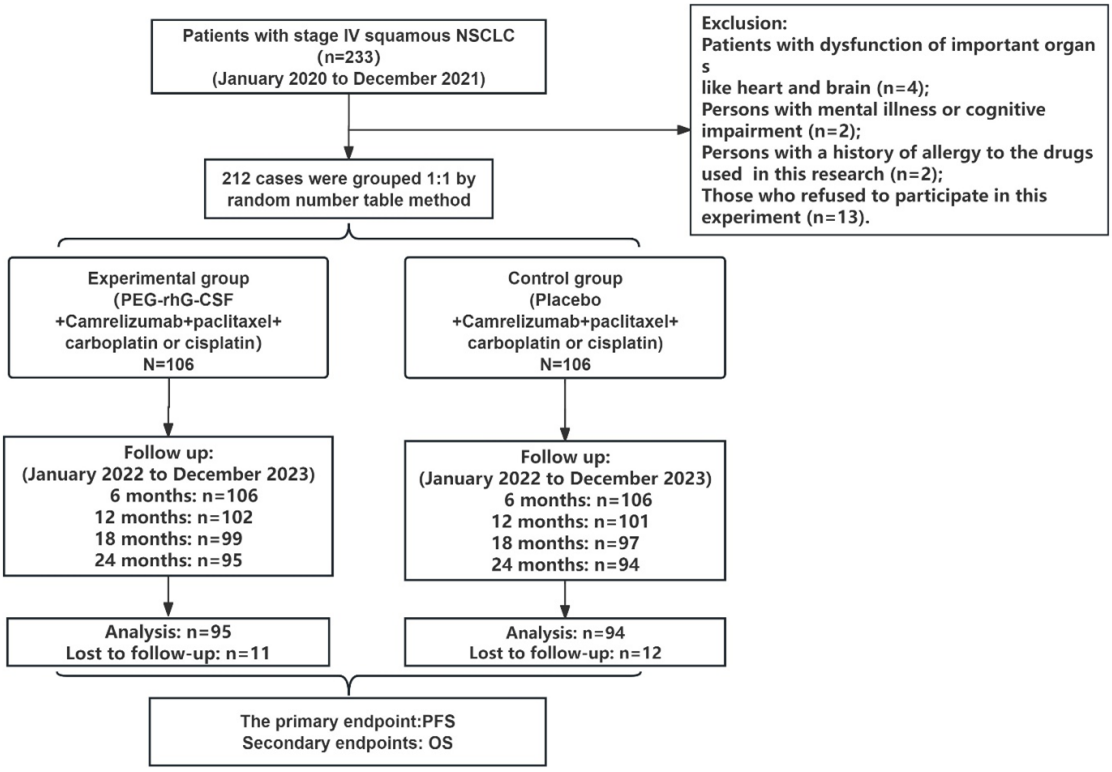

Figure 1. Flowchart of patient selection
Abbreviations: DCR: Disease control rate; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

2.7. Statistical analysis

All statistical analyses were performed using SPSS Statistics (version 22.0, IBM, US) and MedCalc Statistical software (version 23.0.2, MedCalc Software Ltd, Belgium). Categorical variables are presented as counts and percentages, with inter-group comparisons assessed through the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student's *t*-test or the Mann–Whitney *U* test. We constructed survival plots utilizing the Kaplan–Meier approach and applied the Log-rank test to assess significant differences in survival outcomes across cohorts. Findings are expressed as hazard ratios (HRs) accompanied by 95% confidence intervals (CIs). To identify independent prognostic factors, variables with *p*-values below 0.05 from univariate screening were entered into a multivariate Cox proportional hazards model, which adjusted for treatment group, age, sex, ECOG PS, and metastasis site. A p-value < 0.05 was defined as statistical significance for all observed differences. The primary analysis was conducted on the intention-to-treat population.

3. Results

3.1. Patient characteristics

The final analysis comprised 189 individuals with advanced squamous NSCLC, stratified into an experimental arm (n = 95) and a control arm (n = 94). Comprehensive baseline demographics are summarized in Table 1. The study population consisted of 141 male and 48 female participants, with ages spanning from 46 to 81 years. A history of smoking was reported in 109 cases, representing 57.67% of the cohort. The PD-L1 TPS was ≥1% in 123 cases (65.08%) and <1% in 66 cases (34.92%). Carboplatin was administered in 115 cases (60.85%), while cisplatin was utilized in 74 cases (39.15%). Among the study cohort, 40 participants (22.16%) presented with an ECOG PS of 0, whereas the remaining 149 individuals (78.84%) were classified as status 1. Comparative analysis of baseline demographics revealed no statistically significant disparities between the two groups, with all corresponding *p*-values exceeding the 0.05 threshold.

3.2. Efficacy

In the experimental cohort, the ORR reached 58.95%, demonstrating a statistically significant superiority over the 43.62% observed in the control arm (χ^2 = 4.421, p = 0.0355). Regarding DCR, figures stood at 85.26% and 76.60% for the experimental and control groups, respectively; however, this disparity did not attain statistical significance (χ^2 = 1.362, p = 0.2431), as detailed in Table 2. Furthermore, the experimental group exhibited a more profound depth of response compared to controls, with mean values of −29.2367 (95% CI: −36.7645 to −21.6987) versus −18.0106 (95% CI: −25.5121 to −10.5092). This difference was statistically significant (χ^2 = 2.096, p = 0.0374), as visualized in Figure 2.

The experimental group had a deeper response than the control group, with values of −29.2367 (95% CI: −36.7645 to −21.6987) and −18.0106 (95% CI: −25.5121 to −10.5092), respectively (χ^2= 2.096, p = 0.0374).

At the 2-year follow-up, 23 patients were lost to follow-up (11 in the experimental group, 12 in the control group), resulting in an overall follow-up rate of 89.15% (189 out of 212). The median PFS in the experimental group was significantly superior to that in the control group (10.5 months [95% CI: 9.8–11.9] vs. 8.4 months [95% CI: 7.0–10.5]; HR = 0.72 [95% CI: 0.53–0.98], χ^2 = 4.1227, p = 0.0423; Figure 3).

The experimental group reported 51 survivors and 44 deaths, whereas the control group had 34 survivors and 60 deaths. In the experimental cohort, the median OS was not reached, whereas the control group recorded a median OS of 22.3 months (95% CI: 17.9–23.4), corresponding to an HR of 0.67 (95% CI: 0.46–0.99). Statistical analysis revealed a significant survival advantage for the experimental arm relative to controls (χ^2 = 4.0867; p = 0.0432), as illustrated in Figure 4.

In each predetermined subgroup, both PFS and OS HR were less than 1.0 when comparing the experimental group to the control group. Statistically significant trends in PFS and OS benefits (all $p < 0.05$) were noted across subgroups stratified by various factors such as age (<65 years), male, smoking history (yes vs. no), PD-L1 TPS (≥1), type of platinum-based drugs (cisplatin or carboplatin), and ECOG PS score (0 or 1) (Figures 5 and 6).

3.3. Safety

The incidence of any-grade neutropenia was significantly lower in the experimental group compared to the control group (5.26% vs. 43.62%; χ^2 = 37.543, $p < 0.0001$). The incidence of grade ≥ 3 neutropenia was 0% in the experimental group and 12.77% in the control group. Conversely, the incidence of fever was significantly higher in the experimental group compared to the control group (24.21% vs. 11.70%; χ^2 = 4.984, p = 0.0256). Only 1 case of grade ≥ 3 fever occurred in the experimental group.

No statistically significant differences were observed between the two groups in the incidence rates of nausea, anemia, reactive cutaneous capillary endothelial proliferation (RCCEP), fatigue, constipation, diarrhea, decreased appetite, vomiting, cough, dyspnea, peripheral edema, muscle pain, thrombocytopenia, hypothyroidism, and immune-mediated pneumonitis (Table 3).

4. Discussion

At present, immune checkpoint inhibitors targeting programmed death-1 (PD-1) constitute the category IA first-line therapeutic standard for managing advanced NSCLC.[16] Nevertheless, the aggregate efficacy of immunotherapeutic regimens remains inadequate, with 60–80% of patients exhibiting no response.[17] Resistance mechanisms to immunotherapy targeting the PD-1/PD-L1 pathway can be categorized into four primary types: immune suppression, alterations in the microbiome, epigenetic modifications, and metabolic abnormalities.[18] Immune suppression is characterized by compromised interferon signaling and defective antigen presentation, reduced T cell numbers, upregulation of immune-inhibitory molecule expression, and alterations in PD-L1 levels.[19] Prolonged exposure to tumor antigens can progressively attenuate the intrinsic capacity of T cells to recognize antigens, initiate proliferation, and secrete interleukin (IL)-2, ultimately leading to functional loss due to regulatory T cell suppression and culminating in T cell exhaustion.[20,21] Recent single-cell transcriptomic studies have further delineated T cell exhaustion as a differentiation state with distinct epigenetic and metabolic landscapes, which poses a significant barrier to reinvigoration by PD-1 blockade alone.[22] Anti-PD-1/PD-L1 therapy loses efficacy in the absence of substantial T cell infiltration within the TME. For these therapies to be effective, activated T cells must migrate to and infiltrate the tumor site to exert their cytotoxic functions.[23]

In the context of squamous NSCLC, the Camel-Sq study established camrelizumab plus paclitaxel and carboplatin as a standard first-line regimen, reporting an ORR of 64.8% and a median PFS of 8.5 months.[1] As the first registered Phase 3 study of camrelizumab combined with chemotherapy in squamous NSCLC, the CamelSq study provided the benchmark regimen for clinical practice and subsequent research. In our study, the control arm (receiving the same chemoimmunotherapy backbone) demonstrated an ORR

Table 1. Baseline demographic and disease characteristics of patients

Parameters	Experimental group (n = 95)	Control group (n = 94)	χ^2	*p*-value
Sex				
Male	75 (78.95)	66 (70.21)	1.892	0.1689
Female	20 (21.05)	28 (29.79)		
Age				
≥65 years	64 (67.37)	61 (64.89)	0.129	0.0260
<65 years	31 (32.63)	33 (35.11)		
Smoking history				
Yes	58 (61.05)	51 (54.26)	0.890	0.3456
No	37 (38.95)	43 (45.74)		
PD-L1 TPS				
<1%	32 (33.68)	34 (36.17)	0.128	0.7207
≥1%	63 (66.32)	60 (63.83)		
Platinum choice				
Cisplatin	39 (41.05)	35 (37.23)	0.288	0.5917
Carboplatin	56 (58.95)	59 (62.77)		
ECOG PS score				
0	18 (18.95)	22 (23.40)	0.560	0.4544
1	77 (81.05)	72 (76.60)		

Note: Data are presented as *n* (%).
Abbreviations: ECOG: Eastern Cooperative Oncology Group; PD-L1: programmed death-ligand 1; PS: Performance status; TPS: Tumor proportion score.

Table 2. Comparison of short-term efficacy between the two groups

Parameter	CR	PR	SD	PD	ORR	DCR
Experimental group (n = 95)	3 (3.16)	53 (55.79)	25 (26.32)	14 (14.73)	56 (58.95)	81 (85.26)
Control group (n = 94)	2 (2.13)	39 (41.49)	31 (32.98)	22 (23.40)	41 (43.62)	72 (76.60)
χ^2	-	-	-	-	4.421	1.362
p-value	-	-	-	-	0.0355	0.2431

Note: Data are presented as *n* (%).
Abbreviations: CR: Complete response; DCR: Disease control rate; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease.

of 43.62% and a median PFS of 8.4 months, consistent with the expected efficacy range. Notably, the experimental arm, which added PEG–rhG-CSF, achieved a significantly higher ORR of 58.95% and a prolonged median PFS of 10.5 months. More importantly, a clear trend toward improved OS was observed (HR = 0.67). This comparative analysis suggests that the adjunctive use of PEG–rhG-CSF may provide an incremental clinical benefit over the established chemoimmunotherapy regimen alone.

The superior efficacy observed in our study is consistent with the emerging concept that supportive care agents with immunomodulatory activity can enhance the effect of PD–1 inhibitors plus chemotherapy. Compared with other camrelizumab-containing combinations reported

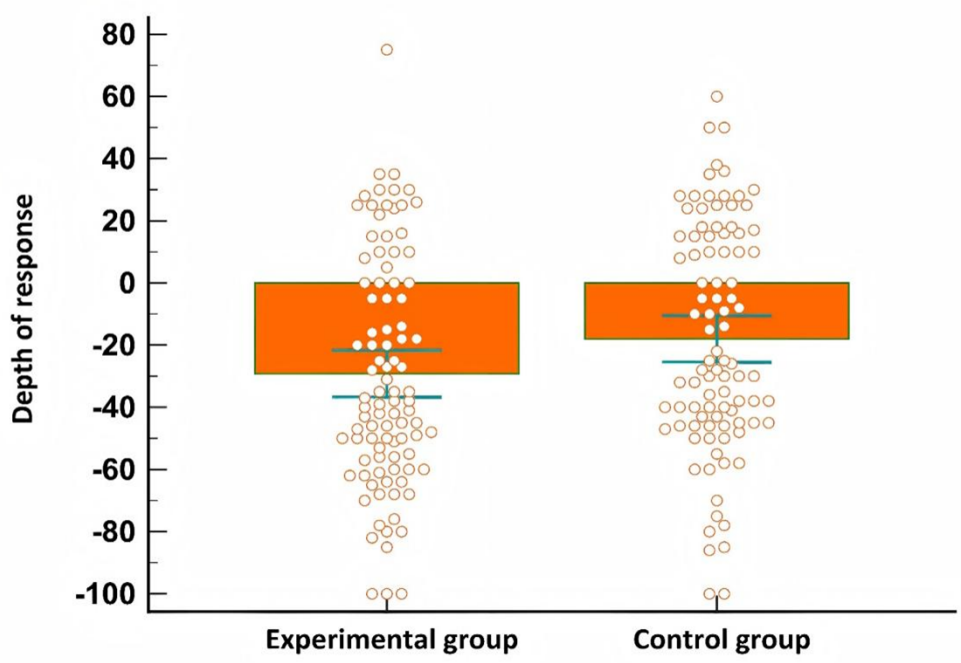

Figure 2. Response depth of the experimental and control groups

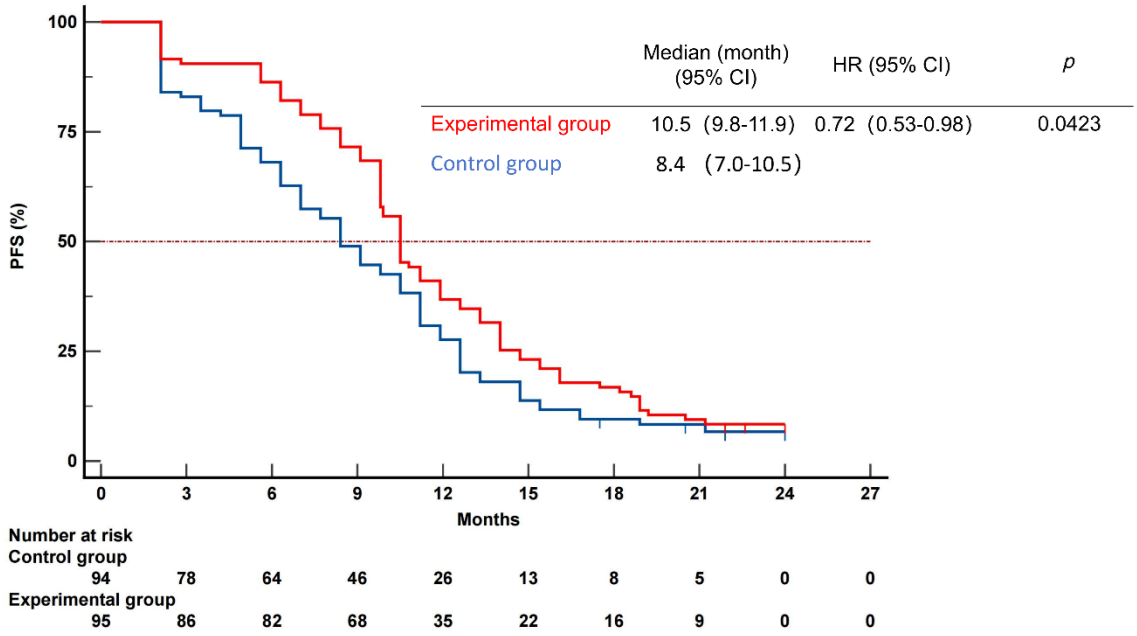

Figure 3. Kaplan–Meier curves for PFS. The number at risk at the final time point is 0, as the last event/censoring occurred prior to this prespecified landmark.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival.

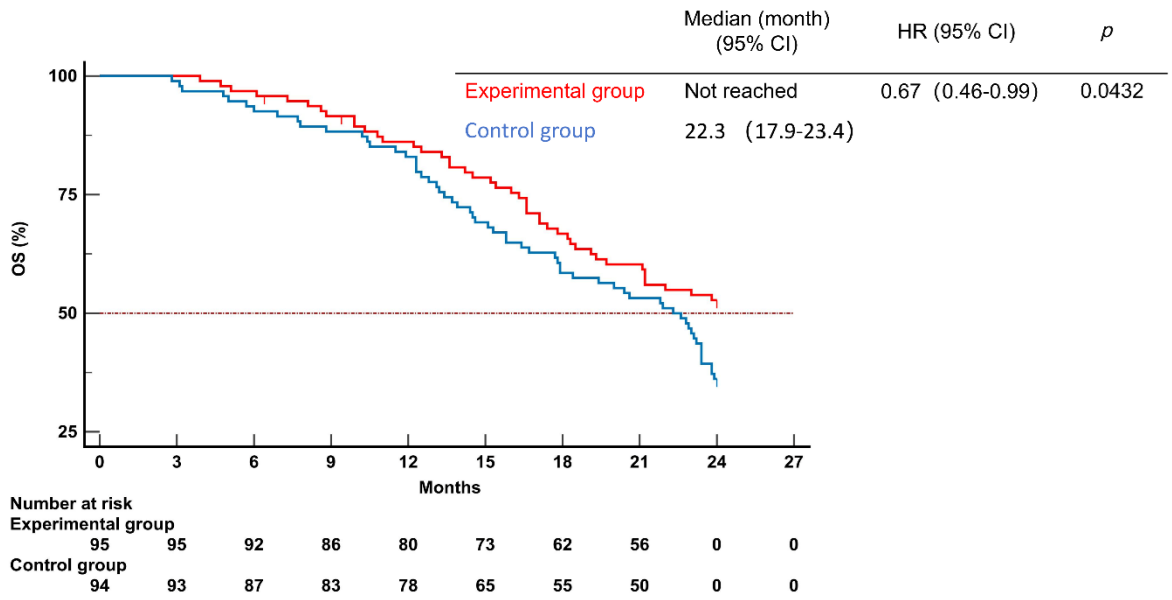

Figure 4. Kaplan–Meier curves for OS. The number at risk at the final time point is 0, as the last event/censoring occurred prior to this prespecified landmark.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; OS: Overall survival.

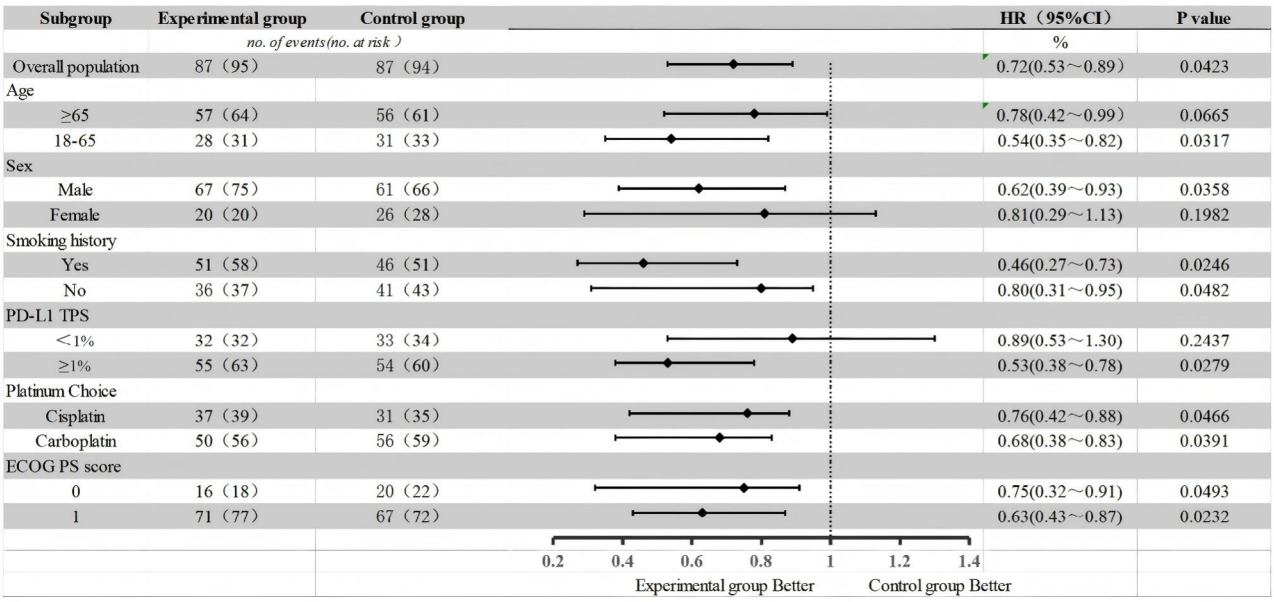

Figure 5. Subgroup analysis of PFS benefit according to baseline characteristics
Abbreviations: CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; PS: Performance status; TPS: Tumor proportion score.

in squamous NSCLC, our regimen achieved comparable or improved survival outcomes with a more favorable safety profile due to reduced neutropenia. The observed extension in PFS and the trend toward improved OS may be mechanistically linked to the immunomodulatory effects of PEG–rhG-CSF beyond its neutrophil-supporting effects. Preclinical evidence suggests that G-CSF can enhance dendritic cell maturation and modulate lymphocyte subsets, potentially fostering a more favorable immune milieu.[7-9] By mitigating chemotherapy-induced

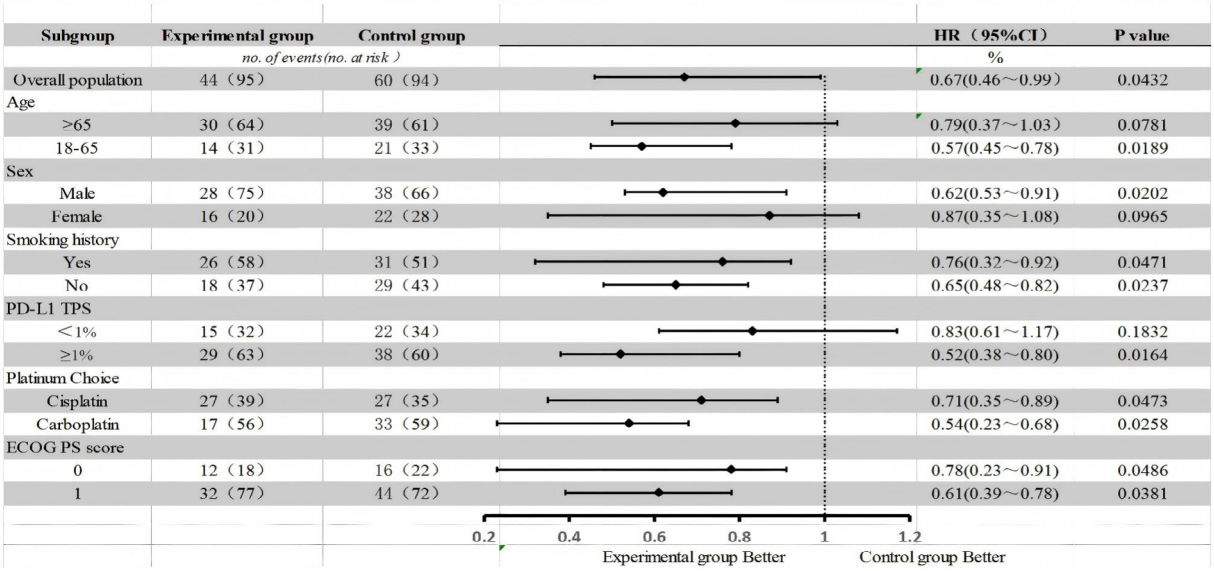

Figure 6. Subgroup analysis of OS benefit according to baseline characteristics
Abbreviations: CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; PD-L1: Programmed death-ligand 1; OS: Overall survival; PS: Performance status; TPS: Tumor proportion score.

Table 3. Comparison of treatment-related adverse events between the two groups

Events	Experimental group (n = 95)		Control group (n = 94)		χ^2	p-value
	All grade	Grade ≥ 3	All grade	Grade ≥ 3		
Nausea	50 (52.63)	5 (5.26)	46 (48.94)	3 (3.19)	0.132	0.7181
Anemia	41 (43.16)	13 (13.86)	48 (51.06)	15 (15.96)	0.632	0.4267
Fatigue	39 (41.05)	5 (5.26)	36 (38.29)	4 (4.26)	0.149	0.6995
Constipation	33 (34.74)	3 (3.16)	29 (30.85)	2 (2.13)	0.021	0.8860
Diarrhea	26 (27.37)	2 (2.11)	26 (27.66)	3 (3.19)	1.827	0.1765
Decreased appetite	32 (33.68)	4 (4.21)	30 (31.91)	3 (3.19)	0.067	0.7961
Neutropenia	5 (5.26)	0 (0)	29 (43.62)	12 (12.77)	37.543	<0.0001
Vomiting	24 (25.26)	4 (4.21)	25 (26.60)	3 (3.19)	0.043	0.8349
Cough	28 (29.37)	2 (2.11)	26 (27.66)	2 (2.13)	0.076	0.7831
Dyspnea	19 (20.00)	3 (3.16)	21 (22.34)	2 (2.13)	0.154	0.6945
Peripheral edema	13 (13.86)	0 (0)	11 (11.70)	0 (0)	0.167	0.6832
Muscle soreness	22 (23.16)	2 (2.11)	14 (14.89)	2 (2.13)	2.082	0.1491
Fever	23 (24.21)	1 (1.05)	11 (11.70)	0 (0)	4.984	0.0256
RCCEP	67 (70.53)	3 (3.16)	65 (69.15)	2 (2.13)	0.042	0.8370
Thrombocytopenia	16 (16.84)	2 (2.11)	17 (18.09)	2 (2.13)	0.050	0.8224
Hypothyroidism	8 (8.42)	0 (0)	7 (6.98)	0 (0)	0.061	0.8048
Immune-mediated pneumonitis	8 (8.42)	1 (1.05)	6 (6.38)	1 (1.06)	0.285	0.5937
Immune-mediated enteritis	1 (1.05)	0 (0)	2 (2.13)	0 (0)	0.348	0.5554

Note: Data are presented as n (%).
Abbreviation: RCCEP: Reactive cutaneous capillary endothelial proliferation.

lymphodepletion and potentially attenuating certain immunosuppressive elements within the TME, PEG–rhG-CSF might synergize with PD-1 blockade to improve T-cell functionality and tumor infiltration. This provides a plausible biological rationale for the delayed disease progression observed in our experimental group. Our research is centered on augmenting lymphocyte counts, reversing lymphocyte exhaustion, and modifying the immune microenvironment to enhance the efficacy of immunotherapy. This approach aligns with the emerging concept of "immuno-modulatory support" in cancer therapy, where agents traditionally used for supportive care are re-evaluated for their potential to directly enhance anti-tumor immunity.[24]

The underlying mechanism can be summarized as follows: PEG–rhG–CSF increases peripheral lymphocyte counts, promotes CD8+ T cell and natural killer (NK) cell activation, enriches TCR diversity, reduces T cell exhaustion, and reshapes the tumor immune microenvironment to enhance sensitivity to camrelizumab. Empirical evidence indicates that a more diverse TCR repertoire in the peripheral blood is associated with an increased capacity of TCR clones to specifically recognize tumor antigens. Multiple studies in oncology have demonstrated that the TCR repertoire can serve as a biomarker of immunotherapy efficacy.[25-27] Research by Sun Jing *et al.*[7] has revealed that PEG–rhG-CSF can regulate the distribution of peripheral blood lymphocyte subsets in patients with small cell lung cancer. Additionally, it impacts TCR repertoire characteristics and cytokine levels, thereby modulating the immune status of cancer patients. Previous research conducted by our team has demonstrated that PEG–rhG-CSF can elevate lymphocyte counts in cancer patients.[28] In the experimental group in the current study, the baseline lymphocyte count was $1.1409 \pm 0.2346 \times 10^9$/L, increasing to $1.3185 \pm 0.3175 \times 10^9$/L after two treatment cycles with PEG–rhG-CSF, camrelizumab, and platinum-based chemotherapy. With a t-statistic of 3.516 and a corresponding p-value of 0.0007, the analysis revealed a statistically significant disparity between the groups under investigation. In the control group, baseline and post-treatment lymphocyte counts after two cycles of camrelizumab with platinum chemotherapy were $1.2423 \pm 0.2388 \times 10^9$/L and $1.3384 \pm 0.3524 \times 10^9$/L, respectively. Given a t-statistic of 1.784 and an associated p-value of 0.0779, the observed variation failed to reach statistical significance; nonetheless, this supports the idea that PEG–rhG-CSF can boost lymphocyte counts in advanced lung cancer patients. Critically, the increase in lymphocyte count may not merely represent a quantitative change. G-CSF has been shown to influence the differentiation and functional polarization of T cells, potentially favoring the generation or maintenance of stem-like memory T cells or precursor exhausted T cells, which possess superior self-renewal capacity and are the primary responders to checkpoint blockade.[29] Concurrent administration of PD-1 blockade agents has demonstrated considerable promise in overcoming therapeutic resistance and improving clinical outcomes in patients with NSCLC. Robust evidence from Phase 3 trials validates diverse combinatorial regimens, ranging from immunotherapy paired with cytotoxic chemotherapy to triple-modality approaches integrating anti-angiogenic agents. Furthermore, these studies substantiate the efficacy of dual-immunotherapy strategies combined with chemotherapy, as well as protocols employing simultaneous blockade of two distinct immune checkpoints.[30,31] The current prospective clinical investigation is structured to rigorously assess the therapeutic efficacy and safety profile of a quadruple regimen comprising PEG–rhG-CSF, camrelizumab, paclitaxel, and platinum-based agents in patients with advanced squamous NSCLC. Participants assigned to the control arm underwent a standard first-line protocol identical to that validated in the landmark Camel-Sq trial. Meanwhile, the experimental cohort received an augmented strategy, incorporating PEG–rhG-CSF alongside the foundational therapy administered to the control group.

Recent efficacy data indicate that the ORR in the experimental cohort of the current study was 58.95%, surpassing that of the control cohort (43.62%). The observed disparity reached statistical significance (p = 0.0355). Although the experimental cohort exhibited a slightly elevated DCR relative to the control arm, this variation failed to achieve statistical significance. The following four reasons were considered:

(i) The experimental group demonstrated higher rates of CR and PR compared to the control group, with CR rates of 3 (3.16%) vs. 2 (2.13%) and PR rates of 53 (55.79%) vs. 39 (41.49%), respectively. The tumors in the experimental group exhibited significant shrinkage. The ORR and DCR serve as key indicators for assessing the short-term efficacy of treatment. Disease stabilization may represent the natural progression of the disease, whereas tumor shrinkage serves as a direct indicator of therapeutic efficacy. Consequently, the ORR might hold greater significance than the DCR. Moreover, patients assigned to the control arm were administered the standard first-line therapeutic protocol for locally advanced or metastatic NSCLC, achieving a DCR of 76.60% and demonstrating notable efficacy. Although the experimental group exhibited an improved DCR of 85.26%, the difference was not statistically significant.

(ii) It is postulated that the observed phenomenon may be attributable to the therapeutic application of PEG–rhG-CSF within the intervention group, resulting in an elevated lymphocyte count, thereby influencing immune function and the efficacy of the PD-1 inhibitor. Notably, in patients demonstrating a substantial therapeutic response (PR and CR), the observed lymphocytic expansion was primarily driven by CD8+ T cells and NK cells, populations that are critically implicated in enhancing immune surveillance and facilitating pathogen clearance. Among the various lymphocyte subsets, aside from those that augment the efficacy of immunotherapy, as previously discussed, there exist subsets such as inducible regulatory T-cells that may attenuate the effectiveness of immunotherapeutic interventions.[32] In patients with elevated levels of these lymphocyte subsets, the PD-1 inhibitor was less effective than in the control group, leading to progressive disease (PD). This heterogeneity in immune response underscores the complexity of biomarker discovery and the need for dynamic, multi-parameter immune monitoring rather than static, single-parameter assessments.[33] At present, significant efforts are underway to identify biomarkers beyond PD-L1 expression levels to more accurately delineate the population that derives benefit from immunotherapy. Subsequently, rigorous follow-up studies are warranted to elucidate the specific impact of PEG–rhG-CSF on lymphocyte subpopulations and overall immune competence in patients with advanced NSCLC. These studies aim to identify potential biomarkers to facilitate the selection of suitable candidates for the combined PEG–rhG-CSF and immunotherapy treatment modality.

(iii) The limited sample size of this study, coupled with the extended follow-up and evaluation intervals, as well as the immature OS data at the study's conclusion, may contribute to the lack of a statistically significant difference in DCR between the two groups.

(iv) RECIST 1.1 is the leading method for assessing solid tumor responses in cancer research, but its qualitative criteria (CR, PR, SD, and PD) have limitations, such as high variability and broad tumor size change intervals. Additionally, it fails to capture the unique response patterns of PD-1/PD-L1 inhibitors accurately. These atypical responses encompass an initial increase in tumor burden, followed by a decrease (commonly referred to as tumor flare or pseudoprogression), or an initial reduction in tumor volume accompanied by the emergence of new lesions, which eventually regress. To accurately assess the efficacy and response of tumor immunotherapy, recent studies have suggested evaluating solid tumors based on the depth of response.[34,35] The metric is defined as the percentage change in the size of target lesions in tumors relative to baseline measurements, offering a more individualized and nuanced assessment. In the current study, the depth of response in the experimental group was −29.2367 (95% CI: −36.7645 to −21.6987), while the control group exhibited a depth of response of −18.0106 (95% CI: −25.5121 to −10.5092). The observed difference between the two groups was statistically significant. The significantly greater depth of response in the experimental group provides a more granular and compelling measure of anti-tumor activity, reinforcing the ORR findings and suggesting a more profound cytoreductive effect.[36]

Our data suggest that integrating PEG–rhG-CSF into a regimen of camrelizumab, paclitaxel, and platinum-based chemotherapy could augment short-term therapeutic outcomes in individuals with advanced squamous NSCLC. Notably, the experimental cohort exhibited a more profound level of transient remission, which may translate into superior quality-of-life benefits for these patients. Regarding long-term therapeutic outcomes, the experimental cohort demonstrated superior median PFS and OS compared to the control arm. Specifically, the control group exhibited a median OS of 22.3 months; this figure falls short of the results from the Camel-Sq trial, wherein the median OS remained unreached yet surpassed the 24-month threshold. This divergence may stem from variations in patient inclusion criteria across these investigations. The Camel-Sq investigation recruited individuals diagnosed with stage IIIB and IV squamous cell carcinoma of the lung, whereas the present study exclusively included patients with stage IV squamous NSCLC, who typically present with more advanced disease, thereby resulting in a slightly lower median OS. Remarkably, the median OS in our experimental cohort remains unreached and demonstrates a statistically significant advantage over the control arm. The calculated HR of 0.67 signifies a 33% decrement in mortality risk, yielding a p-value of 0.0432. This suggests that the combination of PEG–rhG-CSF with camrelizumab, alongside paclitaxel and platinum-based therapy, holds significant promise for enhancing long-term clinical prognosis in individuals afflicted with advanced squamous cell lung carcinoma. The extension of OS, beyond PFS, is a critical endpoint in immuno-oncology, as it may reflect the successful induction of a durable, memory-based anti-tumor immune response—a hallmark of effective immunotherapy that our PEG–rhG-CSF-augmented regimen appears to foster.[37]

In all prespecified subgroup analyses, the HRs for both PFS and OS remained below 1.0 when the experimental cohort was evaluated against the control arm. This indicates that the combination of PEG–rhG-CSF with camrelizumab and platinum-based chemotherapy significantly prolonged PFS and OS in patient cohorts exhibiting diverse disease characteristics. Statistically significant trends in PFS and OS benefits (all $p < 0.05$) were observed across subgroups stratified by age (<65 years), gender, smoking history (yes vs. no), PD-L1 TPS of 1% or higher, administration of platinum-based chemotherapy agents (specifically cisplatin or carboplatin), and an ECOG PS ranging from 0 to 1. This consistent directional benefit across most subgroups underscores the robustness of the PEG–rhG-CSF add-on effect. Additionally, PD-L1 TPS expression serves as a critical biomarker for predicting the efficacy of immunotherapy.[25] Within the Camel-Sq cohort, patients exhibiting high PD-L1 TPSs demonstrated significantly prolonged progression-free and OS relative to those with low PD-L1 TPSs. In our current investigation, stratification by PD-L1 TPS revealed distinct therapeutic outcomes. Among patients exhibiting TPS < 1%, the HR for PFS was 0.89 (95% CI: 0.53–1.30; $p = 0.2437$), while the HR for OS stood at 0.83 (95% CI: 0.61–1.17; $p = 0.1832$); notably, neither endpoint reached statistical significance. In stark contrast, the subgroup with TPS ≥ 1% demonstrated a robust PFS advantage, characterized by an HR of 0.53 (95% CI: 0.38–0.78; $p = 0.0279$), and for OS benefit was 0.52 (95% CI: 0.38-0.80, $p = 0.0164$), indicating statistically significant improvements. The pronounced benefit in the PD-L1 positive subgroup aligns with the known mechanism of PD-1 inhibitors, while the trend toward benefit in PD-L1 negative patients (HR < 1) invites further investigation. It is plausible that PEG–rhG-CSF, by enhancing overall immune competence and potentially facilitating alternative anti-tumor mechanisms (e.g., NK cell activity), may provide a complementary pathway to efficacy that is less dependent on PD-L1/PD-1 axis blockade. In the female cohort, HRs for PFS and OS were 0.81 (95% CI: 0.29–1.13; $p = 0.1982$) and 0.87 (95% CI: 0.35–1.08; $p = 0.0965$), respectively, revealing no statistically significant treatment effects. Likewise, among patients aged 65 years or older, the corresponding HRs for PFS and OS were 0.78 (95% CI: 0.42–0.99; $p = 0.0665$) and 0.79 (95% CI: 0.37–1.03; $p = 0.0781$), respectively, also failing to reach statistical significance. The lack of statistical significance in these smaller subgroups (female and ≥65 years) is likely attributed to limited sample size, a common challenge in subgroup analyses. Future studies with larger cohorts are needed to definitively assess the efficacy in these populations. It is hypothesized that male patients, those aged <65 years, and individuals with positive or high PD-L1 TPS expression may derive greater benefit from the combination of PEG–rhG-CSF, camrelizumab, and platinum-based chemotherapy.

Chemotherapy-naive patients exhibited neutropenia in 25–40% of cases, leading to delays and dose reductions in chemotherapy for over 60% of these individuals. Consequently, G-CSFs are extensively utilized in routine clinical management.[38] As a long-acting therapeutic formulation, PEG–rhG-CSF requires only one subcutaneous injection per chemotherapy cycle, typically delivered 24 h after completion of cytotoxic treatment. This regimen has demonstrated efficacy comparable to or exceeding that of short-acting human G-CSF in alleviating chemotherapy-associated myelosuppression and febrile neutropenia (FN).[39] Research by Wang *et al.*[40] on breast cancer patients indicates that PEG-rhG-CSF exhibits a more pronounced immunomodulatory effect compared to rhG-CSF. The high-risk FN regimen in this study comprised trastuzumab, paclitaxel, and a platinum agent, with carboplatin inducing greater neutropenia and FN than cisplatin. For patients undergoing high-risk chemotherapy for FN with one or more patient-specific risk factors, primary prophylaxis with rhG-CSF or PEG–rhG-CSF is already recommended.[41] The usage rates of carboplatin in the experimental and control groups were 56 out of 95 (58.95%) and 59 out of 94 (62.77%), respectively, with both groups demonstrating higher usage rates of carboplatin compared to cisplatin. In the control group of the current study, the incidence of neutropenia was 71.60%, which is comparable to the 78% reported in the Camel-Sq study.[1] In contrast, the experimental group receiving PEG–rhG-CSF demonstrated a significantly lower incidence of neutropenia compared to the control group ($p < 0.0001$). Additionally, a more pronounced divergence was observed in the early PFS curves between the two groups, particularly within the 3- to 9-month period. This trend may be attributed to the higher incidence of early neutropenia or FN in the control group, potentially resulting in reduced tolerance to chemotherapy or immunotherapy, ultimately leading to treatment discontinuation or disease progression. The experimental group demonstrated enhanced tolerance and safety of the treatment regimen following the administration of PEG–rhG-CSF. This highlights a crucial, often underappreciated aspect of combination therapy: maintaining dose intensity and treatment continuity through effective supportive care can itself be a key determinant of long-term oncologic outcomes.[42]

Adverse reactions to PEG–rhG-CSF predominantly included fever (2.92%) and musculoskeletal pain (1.17%).[43] Notably, the experimental group in this study exhibited

a significantly higher incidence of fever compared to the control group (p = 0.0256). However, neither cohort exhibited severe or prolonged episodes of high fever; the majority of cases resolved spontaneously or with antipyretic medications, such as ibuprofen, without necessitating treatment discontinuation or resulting in mortality. While fever is a known side effect of G-CSF, its occurrence in the context of combined immunotherapy may also be interpreted as a biomarker of systemic immune activation. The release of endogenous pyrogens, such as IL-1, IL-6, and tumor necrosis factor-alpha (TNF-α) during immune cell activation could underpin this symptom, potentially linking it to the enhanced anti-tumor activity observed.[44]

Additionally, no statistically significant difference in musculoskeletal pain incidence was observed between the two cohorts (p = 0.1491). Furthermore, a comparable spectrum of additional adverse events emerged across both treatment arms, encompassing RCCEP, nausea, anemia, fatigue, constipation, diarrhea, anorexia, emesis, cough, dyspnea, peripheral edema, cutaneous rash, thrombocytopenia, hypothyroidism, immune-mediated pneumonitis, and enteritis. Crucially, statistical analysis revealed no meaningful differences in the frequency of these reactions between the groups (all $p > 0.05$). Importantly, the incidence of serious immune-related adverse events, such as pneumonitis and enteritis, was not increased with the addition of PEG–rhG-CSF. This safety profile is reassuring and suggests that the immunomodulatory effects of PEG–rhG-CSF in this setting are synergistic rather than indiscriminately hyper-activating, which is a key consideration for clinical adoption.[45] In patients with advanced squamous NSCLC, concurrent administration of camrelizumab, a platinum-based doublet chemotherapy, and PEG–rhG-CSF demonstrates a manageable safety profile.

We have commenced enrollment for research studies focusing on esophageal and liver cancers. The forthcoming phase of our research aims to systematically expand the clinical utility of PEG–rhG-CSF-based combinatorial immunotherapy, integrated with either cytotoxic chemotherapy or molecularly targeted agents, for managing advanced-stage malignancies, including esophageal and hepatic carcinomas, alongside other neoplastic entities. The primary objective of these studies is to rigorously assess both the clinical viability and therapeutic effectiveness of this integrated treatment strategy. The rationale for this expansion is strengthened by the growing understanding that mechanisms of immunosuppression and chemotherapy-induced lymphodepletion are common across many malignancies. Therefore, a strategy that mitigates these barriers while potentiating immunotherapy could have broad translational relevance.[46]

This study has several limitations. First, this was a single–center study, which may limit the generalizability of the conclusions to other clinical settings. Second, the sample size was relatively small, which may have reduced statistical power and compromised the stability of some subgroup analyses. Third, the follow-up duration was still relatively short, and the OS data in the experimental group were not yet mature. Additionally, the generalizability of our efficacy findings is also limited to the specific population studied—patients with advanced squamous NSCLC—and should not be directly extrapolated to all NSCLC histological subtypes. The potential synergy between PEG–rhG-CSF and chemoimmunotherapy for efficacy enhancement remains to be validated in broader populations. Furthermore, as a study primarily designed to assess clinical endpoints, it did not include systematic biospecimen collection for deep immune profiling (e.g., cytokines and immune cell subsets). Consequently, the immunological interactions underlying the treatment regimen could not be elucidated here and warrant dedicated investigation. While beyond the scope of this clinical efficacy and safety study, the relatively high cost of PEG–rhG-CSF is a practical consideration for real-world application. Future multicenter, large-sample, long-term follow-up clinical trials are warranted to verify and confirm the findings of the present study.

5. Conclusion

Incorporating PEG–rhG-CSF into a regimen comprising camrelizumab, paclitaxel, and platinum agents seems to enhance both immediate therapeutic responses and long-term survival prospects for individuals with advanced squamous NSCLC, while simultaneously reducing the incidence of neutropenia. This therapeutic approach is deemed safe and reliable. Notably, male patients younger than 65 years, who exhibit positive or high expression of PD-L1 TPS, may experience enhanced benefits from the combination of PEG–rhG-CSF with camrelizumab and platinum-based chemotherapy regimens.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Author contributions

Conceptualization: Weike Zhang
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Funding acquisition: Weike Zhang
Investigation: Tong Zhao
Methodology: Tong Zhao
Writing–original draft: Tong Zhao, Lei Chen, Weike Zhang
Writing–review & editing: Tong Zhao, Tingting Zhu, Weike Zhang

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Jinan Eighth People's Hospital (Approval No. 2022024). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Informed consent for publication was obtained from all subjects involved in the study.

Availability of data

The datasets generated and/or analyzed during the present study can be obtained from the corresponding author upon reasonable request.

Further disclosure

This clinical investigation has been formally recorded in the Medical Clinical Research Filing System under identifier MR-37-23-007805, and concurrently registered with the Chinese Clinical Trial Registry bearing the unique code ChiCTR2400094635.

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