Predictive value analysis of CEA, CA125 and CYFRA21-1 levels in evaluating the efficacy of tislelizumab combined with gemcitabine-cisplatin chemotherapy in patients with advanced non-small cell lung cancer

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Abstract. While chemoimmunotherapy is the standard for advanced non-small cell lung cancer (NSCLC), effective and accessible tools for monitoring early treatment response are needed. The present study evaluated the clinical efficacy and safety of tislelizumab + gemcitabine-cisplatin (GP) chemotherapy vs. GP alone in NSCLC, and assessed serum CEA, CA125 and cytokeratin 19 fragment (CYFRA21-1) levels for treatment monitoring. In total, 90 patients with advanced NSCLC (from January 2021 to December 2024) were randomized in a 1:1 manner to receive tislelizumab + GP (n=45) or GP chemotherapy alone (n=45). Outcomes included short-term response [objective response rate (ORR) and disease control rate (DCR)], long-term progression-free survival (PFS) and overall survival (OS) (data cut-off, May 31, 2025; median follow-up, 23.5 months), 3-month biomarker changes and adverse events (AEs). The tislelizumab + GP group demonstrated numerically higher ORR/DCR (P>0.05), significantly longer median PFS (20.8 vs. 10.0 months, P=0.03) and a trend toward improved OS (not reached vs. 16.0 months; P=0.095). Post-treatment biomarker levels were significantly decreased in the study group (P<0.05) with comparable AEs. Receiver operating characteristic curves analyzed the diagnostic value of the combined biomarker panel compared with each biomarker individually for the prediction of short-term efficacy, which demonstrated significantly enhanced performance for the combination (P<0.05). In conclusion, combined CEA, CA125 and CYFRA21-1 effectively evaluated short-term efficacy. Furthermore, tislelizumab + GP demonstrated favorable safety and improved survival outcomes (particularly PFS) within follow-up.

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Introduction

Lung cancer remains a global health crisis, which ranks as the second most common malignancy worldwide by incidence and the leading cause of cancer-related mortality (1,2). In China, lung cancer holds the highest incidence and mortality rates among all cancer types (1,2). Non-small cell lung cancer (NSCLC), which accounts for ~85% of lung cancer cases, is characterized by its insidious onset and lack of early symptoms, which results in >70% of patients being diagnosed at advanced stages when surgical resection is no longer feasible (3). For these patients, multimodal therapies, including chemotherapy, radiotherapy, targeted therapy, immunotherapy and anti-angiogenic agents form the cornerstone of treatment (4).

The gemcitabine-cisplatin (GP) regimen is a first-line chemotherapy option for advanced NSCLC. However, the long-term application of GP is limited by cumulative toxicity and variable efficacy, which underscores the need for safer and more effective therapeutic strategies (4). Tislelizumab, a humanized monoclonal antibody targeting programmed cell death protein-1 (PD-1), has emerged as a potential immunotherapeutic agent. PD-1, expressed on activated T cells, binds to its ligands programmed death ligand (PD-L)1 and PD-L2, which are often upregulated on tumor cells and other cells within the tumor microenvironment, such as antigen-presenting cells including macrophages and dendritic cells (5). This interaction delivers an inhibitory signal that dampens T-cell effector functions, such as cytokine production and cytotoxicity, which allows cancer cells to evade immune destruction (5,6). By blocking PD-1-mediated immunosuppression, tislelizumab prevents this inhibitory signaling,

thereby unleashing antitumor T-cell activity and potentiating tumor cell apoptosis. Initially approved for relapsed Hodgkin's lymphoma, tislelizumab has demonstrated efficacy in gastrointestinal cancer types, esophageal carcinoma and NSCLC, which offers potential survival benefits (7). Ongoing research continues to explore the efficacy of tislelizumab in diverse cancer types and combination strategies, which aim to further optimize its clinical application and patient outcomes (8).

Serum biomarkers such as CEA, CA125 and cytokeratin 19 fragment (CYFRA21-1) serve key roles in cancer monitoring (9). CEA, a glycoprotein associated with epithelial malignancies, is elevated in 30-60% of NSCLC cases, and has been associated with tumor burden and progression (10). CA125, traditionally associated with ovarian cancer, is also aberrantly expressed in NSCLC, which reflects pleural involvement or metastatic spread (11). CYFRA21-1, a structural component of epithelial cell cytokeratins, facilitates tumor cell detachment and metastasis by disrupting intercellular adhesion (12). These biomarkers collectively provide a non-invasive tool for the assessment of therapeutic response and prognosis.

Therefore, the primary aim of the present study was to compare the efficacy, long-term survival and safety of tislelizumab + GP chemotherapy against GP chemotherapy alone in patients with advanced NSCLC. As a secondary objective, the present study sought to address the gap in monitoring tools by analyzing the predictive value of a combined panel of serum CEA, CA125 and CYFRA21-1 to evaluate the short-term efficacy of the tislelizumab-based regimen.

Patients and methods

Study design. The present study protocol was approved by the Ethics Committee of Fourth Affiliated Hospital of Harbin Medical University (approval no. HRB-2020-23; Harbin, China) and was performed in accordance with The Declaration of Helsinki. Written informed consent was obtained from all study subjects before enrollment. Sample size was estimated based on an anticipated 20% improvement in objective response rate (ORR) with the addition of tislelizumab (from 25 to 45%), which required ≤42 patients per group to achieve 80% power at a two-sided α level of 0.05. To account for potential dropouts, 45 patients per group were enrolled in the present study.

A total of 90 patients diagnosed with advanced NSCLC between January 2021 and December 2024 were enrolled in the present study. Participants were randomly assigned in a 1:1 ratio to either the study group (n=45) or the control group (n=45) using a computer-generated randomization sequence. Allocation concealment was ensured by the Investigational Drug Service pharmacy of the Fourth Affiliated Hospital of Harbin Medical University, which dispensed the study drugs according to the computer-generated randomization sequence. Inclusion criteria required patients to meet the diagnostic standards for NSCLC outlined in the Chinese Clinical Guidelines for Radiotherapy of Non-Small Cell Lung Cancer (2020 Edition) (13), confirmed through lung biopsy and imaging studies. Eligible patients had TNM stage (14) IIIa-IIIc disease without surgical indications, an Eastern Cooperative Oncology Group performance status (15) of 0 or 1 and were candidates for chemotherapy, and exhibited no contraindications to tislelizumab, gemcitabine or cisplatin. Additional criteria included an expected survival period of >3 months and provision of written informed consent. Exclusion criteria encompassed severe infections, concurrent primary malignancies, notable organ dysfunction (for example, heart, liver or kidney failure), cognitive impairments affecting treatment compliance, prior chemotherapy exposure, treatment interruptions during the present study, loss to follow-up, hematopoietic or systemic dysfunction, and pregnancy or lactation.

Interventions. The control group received the GP chemotherapy regimen. Gemcitabine hydrochloride (0.2 g/vial; Harbin Yulian Pharmaceutical Co., Ltd.) was administered intravenously at 1.2 g/m^2 diluted in 100 ml 0.9% sodium chloride on days 1 and 8 of a 21-day cycle. Cisplatin (10 ml/10 mg; Guangdong Lingnan Pharmaceutical Co., Ltd.) was administered intravenously at 75 mg/m^2 diluted in 500 ml 0.9% sodium chloride on day 1 of each cycle. Treatment continued for 4-6 cycles (3-4.5 months, with biomarker assessment after 3 months as planned).

The study group received tislelizumab combined with the same GP regimen. Tislelizumab (10 ml/100 mg; Boehringer Ingelheim Biopharmaceuticals) was administered at 200 mg per dose, diluted in 100 ml 0.9% sodium chloride, via intravenous infusion every 3 weeks. The treatment duration and chemotherapy protocol matched those of the control group.

Outcome measures. Short-term efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (16), referenced alongside the Chinese Expert Consensus on PD-L1 Immunohistochemical Testing in NSCLC (17). Complete response (CR) was defined as the disappearance of all target lesions maintained for ≤4 weeks, while partial response (PR) referred to a ≥30% reduction in the sum of diameters of target lesions. Stable disease (SD) indicated neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, and progressive disease (PD) was characterized by ≥20% increase in the sum of diameters of target lesions or the appearance of novel metastases. ORR (%) and disease control rate [DCR (%)] were calculated as (CR + PR)/total cases x100 and (CR + PR + SD)/total cases x100, respectively.

Long-term efficacy outcomes included progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause, and overall survival (OS), defined as the time from randomization to death from any cause. Patients were followed up every 3 months. The data cut-off date for the present analysis was May 31, 2025.

Serum levels of CEA, CA125 and CYFRA21-1 were measured pre-treatment and 3 months post-treatment. Fasting venous blood (4 ml) was centrifuged at 1,500 x g for 10 min at room temperature and serum was analyzed via electrochemiluminescence using the Cobas e601 immunoassay analyzer and corresponding kits (Elecsys CEA Immunoassay, cat. no. YDLC-15737; Elecsys CA125 II Immunoassay, cat. no. YDLC-15799; Elecsys CYFRA 21-1 Immunoassay, cat. no. YDLC-9257; all from Shanghai Yuduo Biotechnology Co., Ltd.). Each biomarker was evaluated in triplicate, with means recorded. Positive thresholds were defined as >5 ng/ml for CEA, >35 U/ml for CA125 and >3.3 ng/ml for CYFRA21-1.

Adverse events (AEs) were classified using the Common Terminology Criteria for Adverse Events by the National Cancer Institute (version 5.0) (18). Receiver operating

Table I. Comparison of general patient characteristics between the two groups.

Characteristic	Control group (n=45)	Study group (n=45)	t/χ^2	P-value
Age, years	53.23±8.03	53.09±8.76	-0.079	0.937
Male/female sex, n	31/14	33/12	0.216	0.642
Smoking, n	12	14	0.216	0.642
Alcohol consumption, n	9	13	0.963	0.326
Clinical stage (I), n			0.048	0.827
Stage III	17	16		
Stage IV	28	29		
Pathological type, n			0.200	0.655
Squamous carcinoma	16	14		
Adenocarcinoma	29	31		
Primary site, n			0.563	0.905
Upper lobe	5	6		
Middle lobe	24	26		
Lower lobe	7	5		
Overlap	9	8		
Tumor location, n			-	0.745[a]
Left lung	19	17		
Right lung	24	27		
Bilateral	2	1		

Data are presented as the mean ± standard deviation or n. P-values were determined using an independent Student's t-test for continuous data and χ^2 test for categorical data, except where indicated. [a]P-value was determined using Fisher's exact test due to low expected cell counts.

characteristic (ROC) curve analysis evaluated the predictive value of biomarkers for short-term therapeutic efficacy.

Statistical analysis. SPSS (version 26.0; IBM Corp.) was employed for data analysis. Normally distributed continuous variables were expressed as the mean ± SD and compared using unpaired Student's t-test, while non-normally distributed variables were reported as the median (interquartile range) and analyzed using Mann-Whitney U test. Categorical data were described as frequencies (%) and assessed via χ^2 or Fisher's exact tests as appropriate. PFS and OS were estimated using the Kaplan-Meier method and differences between groups were assessed using the log-rank test. Hazard ratios (HRs) and their 95% CIs were calculated using Cox proportional hazards models. ROC curves determined sensitivity, specificity and area under the curve (AUC) for biomarkers. The DeLong test was used to assess the statistical significance of the differences between the AUC of the combined biomarker panel and those of the individual markers. P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of the two groups. No statistically significant differences were observed between the study and control groups in terms of age, sex, smoking history, alcohol consumption, clinical stage or histological subtypes (P>0.05), as detailed in Table I. The mean age was 53.23±8.03 years in the control group vs. 53.09±8.76 years in the study group (t=-0.079; P=0.937). Male/female ratios were comparable (31/14 vs. 33/12; χ^2=0.216; P=0.642), as were smoking (12 vs. 14) and alcohol consumption (9 vs. 13) rates. Both groups exhibited similar distributions of advanced-stage disease (Stage III, 17 vs. 16; Stage IV, 28 vs. 29) and histological classifications (squamous carcinoma, 16 vs. 14; adenocarcinoma, 29 vs. 31). Tumor localization and laterality (left lung, 19 vs. 17; right lung, 24 vs. 27; bilateral, 2 vs. 1) also demonstrated no significant differences (P>0.05 for all comparisons).

Short-term efficacy outcomes. The study group demonstrated numerically higher ORR (33.33 vs. 22.22%) and DCR (77.78 vs. 60.00%) compared with the control group; however, these differences did not reach statistical significance (P=0.239 and P=0.069, respectively) (Table II). In the study group, 5 patients achieved CR and 10 demonstrated PR, whereas the control group had 3 CR and 7 PR cases. SD was observed in 20 patients in the study group vs. 17 in the control group, and PD occurred in 10 patients in the study group vs. 19 in the control group, which favored the tislelizumab combination regimen.

Predictive value of serum biomarkers for short-term therapeutic efficacy. ROC curve analysis demonstrated that the combination of CEA, CA125 and CYFRA21-1 levels provided notable predictive performance for evaluating the short-term efficacy of tislelizumab + GP chemotherapy in patients with advanced NSCLC, compared with individual biomarkers (Table III; Fig. 1). The combined model achieved the highest AUC (0.705; 95% CI, 0.411-0.999), sensitivity (87.16%) and specificity (88.35%), which significantly outperformed individual markers (χ^2=9.021;

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

Outcome measure	Control group (n=45)	Study group (n=45)	t/χ^2	P-value
CR, n	3	5		
PR, n	7	10		
SD, n	17	20		
PD, n	19	10		
ORR, n (%)	10 (22.22)	15 (33.33)	1.385	0.239
DCR, n (%)	27 (60.00)	35 (77.78)	3.318	0.069

P-values were determined using the χ^2 test. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table III. Evaluation of the efficacy of CEA, CA125, CYFRA21-1 levels and combined detection for the short-term treatment of non-small cell lung cancer with tislelizumab combined with gemcitabine-cisplatin chemotherapy.

Factor	AUC (95% CI)	Key value	Sensitivity, %	Specificity, %
CEA, pg/ml	0.530 (0.269-0.791)	89.15	73.23	68.79
CA125, U/ml	0.594 (0.297-0.891)	31.4	76.56	70.67
CYFRA21-1, ng/ml	0.583 (0.312-0.855)	19.05	74.64	69.67
Combined detection	0.705 (0.411-0.999)	-	87.16	88.35

The significance of the outperformance of the combined model over individual markers (χ^2=9.021; P<0.05) was determined by comparing the AUCs using the DeLong test. CYFRA21-1, cytokeratin 19 fragment; AUC, area under the curve.

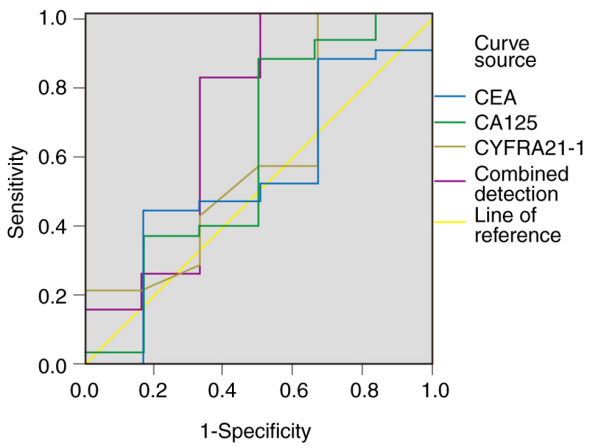

Figure 1. Receiver operating characteristic curve analysis of serum biomarkers for the prediction of short-term therapeutic efficacy of tislelizumab + gemcitabine-cisplatin chemotherapy in patients with advanced non-small cell lung cancer. CYFRA 21-1, cytokeratin 19 fragment.

P<0.05). By contrast, no significant differences were observed among the individual biomarkers: i) CEA demonstrated an AUC of 0.530 (95% CI, 0.269-0.791), sensitivity of 73.23%, specificity of 68.79% at a cut-off of 89.15 pg/ml; ii) CA125 demonstrated an AUC of 0.594 (95% CI, 0.297-0.891), sensitivity of 76.56%, specificity of 70.67% at 31.4 U/ml; iii) CYFRA21-1 demonstrated an AUC of 0.583 (95% CI, 0.312-0.855), sensitivity of 74.64%, specificity of 69.67% at 19.05 ng/ml.

Long-term efficacy outcomes. The median follow-up duration for the entire cohort was 23.5 months (range, 5.0-52.0 months). Long-term follow-up data revealed notable survival outcomes in the study group compared with those in the control group. As shown in the Kaplan-Meier analysis for PFS (Fig. 2), the median PFS (the time at which 50% of patients were progression-free) was significantly longer in the study group (20.8 months; 95% CI, 13.6-25.4) compared with in the control group (10.0 months; 95% CI, 7.1-12.9) (HR, 0.66; 95% CI, 0.43-0.98; log-rank P=0.038). Regarding OS (Fig. 3), the study group demonstrated a trend towards improvement, with a median OS (the time at which 50% of patients remained alive) that was not reached (95% CI, 19.8-not reached) compared with 16.0 months (95% CI, 13.5-18.5) in the control group (HR, 0.71; 95% CI, 0.47-1.07; log-rank P=0.095).

Serum biomarker levels. Pretreatment levels of CEA, CA125 and CYFRA21-1 were comparable between groups (P>0.05) (Table IV). At 3 months post-treatment, the study group exhibited significantly lower biomarker levels compared with the control group for CEA [4.02±0.82 ng/ml vs. 4.61±0.89 ng/ml (t=-3.270; P=0.002)], CA125 [42.18±5.82 U/ml vs. 49.76±5.66 U/ml (t=-6.263; P<0.001)] and CYFRA21-1 [3.42±0.43 ng/ml vs. 4.39±0.56 ng/ml (t=9.216; P<0.001)].

Comparison of AEs. The incidence of AEs in the study group was numerically lower compared with that in the control group, although no statistically significant differences were observed (P>0.05 for all comparisons) (Table V). Grade I anemia occurred

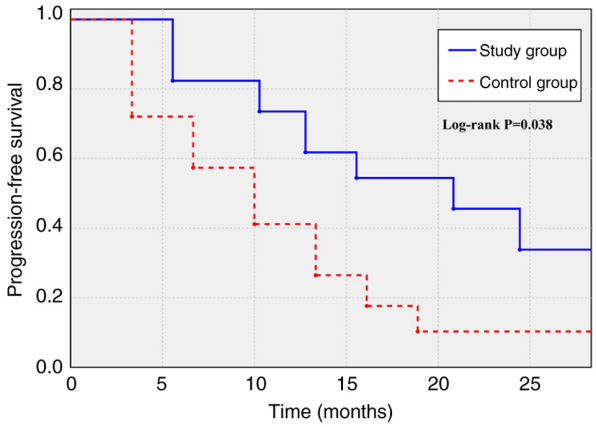

Figure 2. Kaplan-Meier curve for PFS. The present analysis compared PFS between the study group (tislelizumab + GP chemotherapy; n=45) and the control group (GP chemotherapy alone; n=45). The study group exhibited a statistically significant improvement in median PFS (20.8 vs. 10.0 months; hazard ratio, 0.66; 95% CI, 0.43-0.98; log-rank P=0.038). PFS, progression-free survival; GP, gemcitabine-cisplatin.

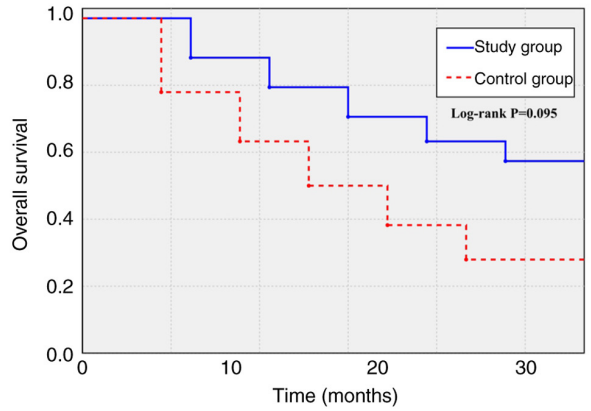

Figure 3. Kaplan-Meier curve for OS. The analysis compared OS between the study group (tislelizumab + GP chemotherapy; n=45) and the control group (GP chemotherapy alone; n=45). The study group exhibited a trend towards improved median OS, although the difference was not statistically significant (not reached vs. 16.0 months; hazard ratio, 0.71; 95% CI, 0.47-1.07; log-rank P=0.095). OS, overall survival; GP, gemcitabine-cisplatin.

in 4 patients in the control group vs. 2 patients in the study group (χ^2=0.714; P=0.398), whereas Grade II anemia was reported in 2 vs. 1 cases (χ^2=0.322; P=0.570). Neutropenia rates were similarly comparable: Grade I (3 vs. 2; χ^2=0.212; P=0.645) and Grade II (2 vs. 1; χ^2=0.345; P=0.557). Elevated alkaline phosphatase levels also indicated no significant intergroup differences, with similar numbers of Grade I (3 vs. 2) and Grade II (2 vs. 1) events. Cutaneous reactions such as Grade I maculopapular rash (1 vs. 0; χ^2=1.011; P=0.315) and gastrointestinal toxicities, including Grade I nausea (12 vs. 8; χ^2=1.029; P=0.310), Grade II nausea (8 vs. 11; χ^2=0.600; P=0.439) and Grade I vomiting (9 vs. 5; χ^2=1.353; P=0.245), were marginally reduced in the study group but did not reach statistical significance.

Discussion

NSCLC is a highly aggressive malignancy characterized by insidious onset, rapid progression and a lack of effective early diagnostic methods. Most patients are diagnosed at advanced stages (III or IV) with local or distant metastases, resulting in a poor prognosis, with the 5-year survival rate for distant-stage disease being ~7% (19). Currently, the GP chemotherapy regimen remains a common first-line treatment for advanced NSCLC. While it improves local control rates, survival rates and reduces distant metastases to some extent, its efficacy is limited by factors such as tumor sensitivity, drug resistance, dose-limiting toxicity and compromised patient performance status (20). Furthermore, chemotherapy-induced toxicities, such as damage to germ, gastrointestinal epithelial and immune cells (for example, lymphocytes and hematopoietic cells) exacerbate immune dysfunction, impair antitumor responses and accelerate disease progression (21).

Recent advances in immunotherapy, particularly immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1, have revolutionized NSCLC management (22-24). Tumor cells evade immune surveillance by expressing PD-L1, which binds to PD-1 on T cells, suppressing their activity. ICIs block this interaction, which restores T-cell-mediated antitumor immunity and inhibits cancer progression (25). Tislelizumab, a novel PD-1 monoclonal antibody developed in China, exhibits enhanced antitumor activity compared with traditional PD-1 inhibitors, such as pembrolizumab and nivolumab, due to structural modifications in its crystallizable fragment (Fc) region, which minimizes binding to Fcγ receptors on macrophages, thereby reducing antibody-dependent phagocytosis of T cells (26). It demonstrates lower IC_{50} values, higher binding affinity and improved safety profiles, particularly reduced incidences of capillary hyperplasia, compared with other agents such as camrelizumab. Additionally, the cost-effectiveness of tislelizumab compared with imported PD-1 inhibitors (for example, pembrolizumab and atezolizumab) enhances patient accessibility (25,27).

The combination of immunotherapy with chemotherapy is founded on several potential synergistic mechanisms. Chemotherapy can induce immunogenic cell death, which releases tumor antigens (such as CALR and HMGB1) and damage-associated molecular patterns (including ATP and Hsp70/90) that can prime and enhance antitumor T-cell responses (28). Furthermore, chemotherapy may modulate the tumor microenvironment by reducing the numbers of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells and by upregulating PD-L1 expression on tumor cells, potentially sensitizing them to PD-1 blockade (29). Tislelizumab, by invigorating the T-cell response, can then more effectively target and eliminate tumor cells rendered vulnerable by chemotherapy. Although chemotherapy alone can induce some level of immunogenic cell death, its clinical success is limited because this effect is often transient and insufficient to overcome the highly immunosuppressive tumor microenvironment. Tumors employ multiple escape mechanisms, of which the chief mechanism is the upregulation of checkpoint proteins such as PD-L1, which actively inhibit T-cell function and lead to T-cell exhaustion. Therefore, even if chemotherapy enhances antigen presentation, the responding T cells remain suppressed. This limitation highlights the rationale for combination therapy: Chemotherapy acts to increase tumor immunogenicity, while tislelizumab simultaneously blocks the PD-1/PD-L1 inhibitory axis, thereby unleashing a potent and durable antitumor T-cell response that neither agent could achieve alone (30).

Table IV. Comparison of CEA, CA125 and CYFRA21-1 levels between the two groups.

A, CEA, ng/ml

Time	Control group (n=45)	Study group (n=45)	t	P-value
Before treatment (1 day)	6.23±0.94	6.19±0.97	-0.199	0.843
3 months after treatment	4.61±0.89	4.02±0.82	-3.270	0.002

B, CA125, U/ml

Time	Control group (n=45)	Study group (n=45)	t	P-value
Before treatment (1 day)	63.98±5.32	64.23±5.86	0.212	0.833
3 months after treatment	49.76±5.66	42.18±5.82	-6.263	<0.001

C, CYFRA21-1, ng/ml

Time	Control group (n=45)	Study group (n=45)	t	P-value
Before treatment (1 day)	6.34±0.76	6.29±0.81	-0.302	0.763
3 months after treatment	4.39±0.56	3.42±0.43	-9.216	<0.001

Data are presented as the mean ± SD. P-values were calculated using unpaired Student's t-test. CYFRA 21-1, cytokeratin 19 fragment.

Table V. Comparison of adverse reactions between the control (n=45) and study (n=45) groups.

Adverse event	Control group (n=45)	Study group (n=45)	P-value
Anemia			
Grade I	4	2	0.438[a]
Grade II	2	1	0.616[a]
Neutropenia			
Grade I	3	2	0.695[a]
Grade II	2	1	0.616[a]
Alkaline phosphatase elevation			
Grade I	3	2	0.695[a]
Grade II	2	1	0.616[a]
Grade I rash	1	0	0.494[a]
Nausea			
Grade I	12	8	0.294[b]
Grade II	8	11	0.439[b]
Grade I vomiting	9	5	0.245[b]

Data are presented as n. [a]P-value determined using Fisher's exact test. [b]P-value determined using the χ^2 test.

The present study findings regarding short-term efficacy (ORR and DCR) exhibited numerically higher rates in the tislelizumab-GP group; however, these differences were not statistically significant. This lack of statistical significance might be attributed to the relatively small sample size. However, the observed trend, coupled with the significant improvement in median PFS (11.8 vs. 8.7 months; P=0.038) and the positive trend in OS (median 23.5 vs. 18.2 months; P=0.095) at a median follow-up of 23.5 months, suggested a clinically meaningful benefit from the addition of tislelizumab to GP chemotherapy. This aligns with findings from several large-scale trials but also highlights the ongoing debate, as outcomes can vary based on study design, patient populations and treatment regimens. For example, Santoro *et al* (31) evaluated spartalizumab and various chemotherapy backbones in a PD-L1-unselected metastatic NSCLC population, and provided a relevant comparison. Their gemcitabine/cisplatin group (Group A) reported a higher ORR (57.6%) compared with the present study (33.33%); however, the median PFS (7.5 months) was shorter compared with 11.8 months from the present study results, which suggests potential differences in drug-specific activity or patient characteristics. By contrast, a meta-analysis by Zhou *et al* (32) offers a different perspective, which focused on the neoadjuvant setting for resectable NSCLC. It concluded that the addition of adjuvant immunotherapy to a neoadjuvant chemoimmunotherapy regimen did not improve PFS or OS; however, this previous study had a different clinical question and setting compared with the focus of the present study on first-line treatment for advanced, unresectable disease. Furthermore, Mathew *et al* (33) outlined the preclinical rationale for these combinations in a review article, but did not provide comparative clinical trial data. A notable comparison is the EMPOWER-Lung 3 trial by Makharadze *et al* (34), which evaluated cemiplimab + chemotherapy in first-line, advanced NSCLC irrespective of PD-L1 status. This previous study reported an ORR of 43.6% and a median PFS of 8.2 months

(HR, 0.55), with a median OS of 21.1 months. Although the ORR in this previous study was higher, the present study exhibited a more favorable median PFS (11.8 months), a difference that might be attributed to the specific GP regimen, regional population differences or other unmeasured patient factors. Finally, Zhu *et al* (35) also evaluated a distinct setting: Neoadjuvant toripalimab + chemotherapy in resectable stage II-III NSCLC. Its primary endpoints were the major pathological response rate (55.6%) and R0 resection rate (100%), which are not applicable to the palliative-intent treatment of the advanced-stage cohort in the present study. This highlights the key importance of treatment setting when comparing efficacy outcomes.

Serum biomarkers such as CEA, CA125 and CYFRA21-1 are key for monitoring therapeutic efficacy. The present study corroborated findings from Strum *et al* (36) and Clevers *et al* (37), which reported markedly reduced post-treatment levels of all three biomarkers in the tislelizumab-GP group ($P<0.05$). These reductions are considered clinically relevant as they may reflect a decrease in tumor burden. The ROC analysis in the present study further revealed that the multi-biomarker panel outperformed individual markers in the prediction of short-term therapeutic outcomes, which underscores their clinical utility for early response assessment.

Safety is a key consideration. In the present study cohort, AEs were manageable and comparable between groups, which supports the tolerability of the combination regimen. This practical implication, that the addition of tislelizumab does not markedly exacerbate toxicity, makes it a viable option for patients who can tolerate standard chemotherapy. Despite these potential synergies, the widespread adoption of tislelizumab and other ICIs faces challenges. A primary concern is the occurrence of immune-related AEs (irAEs), which can affect any organ system and include pneumonitis, colitis, hepatitis and endocrinopathies. Although often manageable, these irAEs can be severe or even life-threatening, which requires vigilant monitoring and specialized management, with fatal outcomes reported particularly for pneumonitis, hepatitis, colitis and myocarditis (38). Furthermore, a notable portion of patients exhibit primary or acquired resistance to ICI therapy, which limits its long-term benefit, with resistance rates varying markedly between monotherapies (for example, ~30% for PD-1 inhibitors) and combination therapies (for example, 60-70% for CTLA-4 inhibitors or combinations) (39). The modest predictive power of biomarkers such as PD-L1 expression indicates that patient selection remains suboptimal due to the lack of reliable biomarkers (39,40). These factors, combined with the high cost of immunotherapy, contribute to the complexities of its integration into routine clinical practice (39).

The present study had several limitations. Firstly, the sample size was relatively small, which may have limited the statistical power to detect significant differences in some secondary outcomes, such as ORR, DCR and 2-year survival rates, and may have affected the generalizability of the findings. Secondly, it was a single-center study, which potentially introduced selection bias. Thirdly, while the present study incorporated long-term follow-up for PFS and OS, further follow-up would have been beneficial to ascertain the durability of the observed survival benefits. Finally, PD-L1 expression status was not uniformly assessed or associated with outcomes. Future multicenter studies with larger sample sizes and comprehensive biomarker analyses are warranted.

In conclusion, the addition of tislelizumab to GP chemotherapy markedly improved PFS and exhibited a favorable trend towards improved OS in advanced NSCLC, with a manageable safety profile. The combined assessment of serum CEA, CA125 and CYFRA21-1 provides robust predictive value for short-term therapeutic monitoring. These findings advocate for the consideration of tislelizumab-based combinations in NSCLC, which offers a more effective therapeutic option, while the biomarker panel can potentially aid in early clinical decision-making in the future.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LW conceptualized the study, designed the methodology and prepared the original draft of the manuscript. TG performed data acquisition and analysis, and contributed to the preparation of the original draft. YC performed data analysis and data visualization. ML provided supervision and performed the statistical analyses using the appropriate software. YW contributed to the development of the methodology, and also reviewed and edited the manuscript. LW and TG confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study protocol was approved by the relevant Ethics Committee of Fourth Affiliated Hospital of Harbin Medical University (approval no. HRB-2020-23; Harbin, China). The study was performed in accordance with The Declaration of Helsinki and written informed consent was obtained from all of the present study subjects before enrollment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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