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A Single-Arm Phase II Clinical Study of SBRT Combined with Tislelizumab and GM-CSF for Advanced Non-Small Cell Lung Cancer Progressing After Immunotherapy

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Research Article

Keywords: Stereotactic body radiotherapy, Immunotherapy resistance, Non-small cell lung cancer, Granulocyte-macrophage colony-stimulating factor, Abscopal effect.

Posted Date: October 27th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10591507/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Immune checkpoint inhibitors (ICIs) combined with chemotherapy have emerged as the first-line standard treatment for advanced driver gene-negative non-small cell lung cancer (NSCLC). However, options for effective therapy following resistance to immunotherapy are limited. Stereotactic body radiotherapy (SBRT) induces immunogenic cell death and can elicit the abscopal effect, while granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances antigen presentation. The combination of these modalities may mitigate immunotherapy resistance. This study aims to assess the efficacy and safety of SBRT in conjunction with tislelizumab and GM-CSF in patients with advanced NSCLC experiencing disease progression after immunotherapy.

Methods

A single-center, single-arm, phase II study (ChiCTR2100047048) was conducted. Ten patients with ICI-resistant advanced driver gene-negative NSCLC were prospectively enrolled. Patients initially underwent SBRT (24 Gy/3 fractions or 25 Gy/5 fractions), followed by GM-CSF (150 μg daily for 2 weeks) and tislelizumab (200 mg every 3 weeks, commencing the day after SBRT). Tislelizumab maintenance continued for up to 35 cycles (2 years) until disease progression or unacceptable toxicity occurred. The primary endpoint was the objective response rate (ORR), while secondary endpoints included out-of-field abscopal response rate (ASR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs).

Results

As of April 1, 2025, ten patients were enrolled, with a median follow-up of 12.97 months (IQR: 8.17–27.13 months). The ORR was 30%, disease control rate (DCR) was 70%, and ASR was 20%. Median PFS and OS were 6.48 months (95% CI: 4.06-NA) and 12.97 months (95% CI: 7.83-NA), respectively. In terms of safety, 60% of patients reported mild treatment-related adverse events, with one patient experiencing a grade 3 TRAE, and no grade 4–5 adverse events recorded. As of April 1, 2025, four patients had survived beyond 2 years, and two remained progression-free.

Conclusion

The combination of SBRT, tislelizumab, and GM-CSF demonstrates promising efficacy and manageable safety in patients with ICI-resistant advanced NSCLC, effectively activating the abscopal effect and offering a novel salvage therapy option. Further validation in larger cohorts is warranted.

Trial registration

ChiCTR2100047048 (Chinese Clinical Trial Register). Registration date 20210607.

Introduction

Immune checkpoint inhibitors (ICIs) combined with chemotherapy now represent the first-line standard of care for advanced non-small cell lung cancer (NSCLC). However, the emergence of immunotherapy resistance poses a significant clinical challenge, with most patients eventually develop acquired resistance after an initial response to ICIs., resulting in limited subsequent treatment options. Median progression-free survival (PFS) often falls below 4 months, and objective response rates (ORR) are typically under 15% [1, 2]. These patients urgently require innovative therapeutic strategies to overcome resistance and rejuvenate immune responses.

Recent studies indicate that stereotactic body radiotherapy (SBRT) and granulocyte-macrophage colony-stimulating factor (GM-CSF) can synergistically enhance the efficacy of immunotherapy. SBRT induces immunogenic cell death, releases tumor antigens, activates dendritic cells (DCs), remodels the tumor immune microenvironment, and triggers the abscopal effect [3, 4]. As an immune adjuvant, GM-CSF facilitates DC maturation and antigen presentation, thereby amplifying systemic anti-tumor immune responses. PD-1 inhibitors block T-cell exhaustion pathways, effectively restoring and sustaining T-cell cytotoxic function. These modalities may act synergistically through enhanced antigen release, improved antigen presentation, and restoration of T-cell function. The PEMBRO-RT trial demonstrated that the combination of SBRT and pembrolizumab was well tolerated in previously treated advanced NSCLC, achieving a 12-week ORR that was double that of pembrolizumab alone (36% vs. 18%), thereby providing feasibility evidence for combining radiotherapy with immunotherapy in pretreated populations [5]. The PRaG regimen (PD-1 inhibitor + radiotherapy + GM-CSF) reported a disease control rate (DCR) of 46.3% in metastatic solid tumors [6]. Additionally, the SWORD trial confirmed an ORR of 36.7% and an abscopal response rate (ASR) of 30.6% for the combination of sintilimab, SBRT, and GM-CSF in the second-line treatment of immunotherapy-pretreated advanced NSCLC, with acceptable toxicity [4]. In light of this background, a novel triple combination of SBRT, tislelizumab, and GM-CSF has been designed, utilizing the unique Fc-engineered properties of tislelizumab to enhance synergistic anti-tumor immunity and safety [7]. The present study (ChiCTR2100047048, registered on 7 June 2021) to our knowledge, represents the first prospective phase II study to evaluate this innovative combination in driver gene-negative advanced NSCLC with disease progression following immunotherapy, primarily focusing on ORR, PFS, ASR, and safety, with the goal of providing a new treatment option for immunotherapy-resistant NSCLC.

Methods

Study Design and Treatment Protocol

This investigator-initiated, single-arm, phase II clinical trial assessed the efficacy and safety of SBRT combined with tislelizumab and GM-CSF in patients with advanced NSCLC who experienced progression after immunotherapy. The study adhered to the Declaration of Helsinki (revised in 2013) and received approval from the Ethics Committee of Taizhou Cancer Hospital. Written informed consent was obtained from all patients prior to enrollment. The trial was registered at http://www.chictr.org.cn/index.aspx (ChiCTR2100047048).

Eligible patients underwent SBRT (24 Gy/3 fractions or 25 Gy/5 fractions) targeting a single suitable lesion. Beginning the day after SBRT completion (day 1 of treatment), patients received tislelizumab (200 mg intravenously every 3 weeks) and GM-CSF (150 μg subcutaneously daily for 2 weeks). Tislelizumab administration continued until disease progression, unacceptable toxicity, death, or withdrawal of consent, up to a maximum of 35 cycles (2 years). Other systemic anti-tumor therapies were not permitted during treatment. A schematic diagram of the treatment protocol is provided in Fig. 1.

Study Endpoints

The primary endpoint was the ORR, assessed according to RECIST version 1.1, defined as the proportion of patients achieving a complete response (CR) or partial response (PR). Secondary endpoints comprised ASR, DCR, PFS, and overall survival (OS). ASR was defined as the proportion of patients achieving a ≥ 30% reduction in the maximum diameter of unirradiated target lesions compared to baseline, while DCR represented the percentage of patients achieving CR, PR, or stable disease (SD). PFS was measured from enrollment until disease progression (RECIST 1.1) or death from any cause, with patients without progression at the last radiographic follow-up censored. OS was defined as the duration from enrollment until death from any cause, with surviving patients censored at the last follow-up. Safety was evaluated using the CTCAE v5.0 criteria, encompassing the nature, frequency, and severity of adverse events. Blood biomarkers were explored as exploratory endpoints. Follow-up data were collected through telephone interviews, outpatient records, and inpatient records, with a cutoff date of April 1, 2025.

Inclusion and Exclusion Criteria

Inclusion criteria included the following: age ≥ 18 years; pathologically confirmed advanced NSCLC; an ECOG performance status of 0–2; driver gene negativity (EGFR, ALK, ROS1 wild-type); disease progression following prior PD-1/PD-L1 inhibitor and chemotherapy; at least one lesion suitable for SBRT (diameter 1–5 cm) and at least one measurable non-irradiated lesion; and adequate organ function defined by an absolute neutrophil count of ≥ 1.5×10^9/L, creatinine ≤ 1.5 × ULN, AST/ALT ≤ 2.5 × ULN, and albumin ≥ 30 g/L. Patients with asymptomatic brain metastases (absence of neurological symptoms, corticosteroid requirement, or SD) were also eligible.

Exclusion criteria were as follows: active autoimmune diseases; symptomatic interstitial lung disease or active pneumonitis; active gastrointestinal diverticulitis, intra-abdominal abscess, or risk of intestinal perforation; severe cardiovascular or cerebrovascular diseases (myocardial infarction within 6 months, decompensated heart failure, or malignant arrhythmias); active infections (HBV/HCV/TB), HIV positivity, or a history of organ transplantation; other active malignancies except for basal cell carcinoma or cervical carcinoma in situ; histological components of small cell lung cancer; chronic systemic corticosteroid use (≥ 10 mg/day prednisone equivalent); pregnancy or breastfeeding; women of childbearing age not utilizing effective contraception; and other conditions deemed unsuitable for enrollment by the investigator.

Efficacy and Safety Assessments

Efficacy was evaluated every 9 weeks through chest and abdominal CT scans in accordance with RECIST v1.1, with assessments conducted by blinded independent radiologists. Adverse events were monitored from the time of informed consent until 90 days after the final dose and were graded according to CTCAE v5.0.

Statistical Analysis

In patients with advanced NSCLC who progressed after prior treatment with ICIs, the ORR for immune re-challenge or combination enhancement strategies ranges from 0% to 5.6% [8]. An increase of 20% in the ORR in this study would indicate superior efficacy. Using the PASS 15 software and employing the Z test with an alpha level of 0.05 (two-sided) and beta of 0.1, the sample size calculation aimed to detect a difference between an ORR of 5.6% and 25.6%, requiring a minimum of 25 evaluable subjects. Factoring in a 10% dropout rate, a total of at least 28 subjects were intended for enrollment.

Although the study was designed to recruit 28 patients, it was terminated early due to slow accrual, ultimately enrolling only 10 patients. Therefore, all efficacy and survival analyses should be interpreted as exploratory.Survival curves were constructed using the Kaplan-Meier method, with group comparisons performed via the log-rank test. Given the exploratory nature of this study and the limited sample size, Cox regression analyses were considered hypothesis-generating.Variables yielding $P < 0.10$ in univariate analysis, along with clinically relevant factors, were included in the multivariate model. Two-sided tests with $P < 0.05$ were considered statistically significant. Statistical analyses were conducted using R version 4.3.2 and GraphPad Prism 8.0.

Results

Patient Characteristics

Due to slow patient accrual, the study was terminated early. From December 2021 to March 2024, a total of 10 patients were enrolled and received at least one cycle of the treatment protocol. Baseline

demographic and clinical characteristics are summarized in Table 1. At baseline, three patients exhibited involvement of ≥ 3 metastatic organs, and three patients had ≥ 5 metastatic lesions. Four patients had an ECOG performance status of 1, while six had an ECOG status of 2. Disease progression occurred after first-line chemotimmunotherapy in three patients, after second-line treatment in four, and after three or more lines of treatment in three others. Prior immunotherapies included pembrolizumab (n = 3), camrelizumab (n = 2), sintilimab (n = 4), tislelizumab (n = 3), and atezolizumab (n = 1), Because three patients had received more than one prior ICI, the total number of prior ICI exposures exceeded the number of enrolled patients.. Pertaining to SBRT dosing, two patients received 24 Gy/3 fractions, and eight received 25 Gy/5 fractions. The irradiated sites comprised seven lung lesions and three regional lymph nodes. Eight patients underwent more than three cycles of tislelizumab following radiotherapy, with one patient completing 23 cycles.

Table 1
Demographics and Clinicopathologic Characteristics of Patients with Advanced Non-Small Cell Lung Cancer.

Demographic or Clinical Characteristic	**Number of patients**
	(n = 10)
Gender (%)	
Male	9 (90.0)
Female	1 (10.0)
Age (median [IQR]), years	72.00 [64.25, 77.75]
Smoking (%)	
No	5 (50.0)
Yes	5 (50.0)
ECOG performance status (%), points	
1	4 (40.0)
2	6 (60.0)
Histology (%)	
Squamous	3 (30.0)
Non-squamous	7 (70.0)
Number of metastatic organs (%)	
1	3 (30.0)
2	4 (40.0)
3	3 (30.0)
Number of metastatic lesions (%)	
2	1 (10.0)
3	4 (40.0)
4	2 (20.0)
≥5	3 (30.0)
Albumin (median [IQR]), g/L	40.35 [38.38, 42.38]

Abbreviations: IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; D-NLR, Derived Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

Demographic or Clinical Characteristic	Number of patients
	(n = 10)
Leukocyte count (median [IQR]) × 10^9/L	6.68 [5.22, 8.46]
Neutrophils count (median [IQR])× 10^9/L	3.91 [3.49, 5.48]
Lymphocyte count (median [IQR]), × 10^9/L	1.88 [1.20, 2.19]
Monocyte count (median [IQR]), × 10^9/L	0.55 [0.40, 0.70]
Platelet count (median [IQR])× 10^9/L	213.50 [178.50, 287.00]
NLR (median [IQR])	2.87 [2.28, 3.47]
PLR (median [IQR])	139.42 [107.64, 167.16]
MLR (median [IQR])	0.32 [0.29, 0.36]
D-NLR (median [IQR])	2.05 [1.53, 2.23]
SII (median [IQR])	697.79 [430.50, 737.26]
PNI (median [IQR])	49.25 [47.74, 52.64]
Abbreviations: IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; D-NLR, Derived Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.	

Clinical Efficacy

As of April 1, 2025, the median follow-up duration was 12.97 months (range: 8.17–27.13 months). Among the ten efficacy-evaluable patients, three achieved PR, four exhibited SD, and three had progressive disease (PD), resulting in an ORR of 30% and a DCR of 70% (Fig. 2). Two patients demonstrated significant shrinkage of non-irradiated lesions, yielding an ASR of 20% (Fig. 3). Median PFS was recorded at 6.48 months (95% CI: 4.06-NA), while median OS was 12.97 months (95% CI: 7.83-NA). Four patients achieved an overall survival duration exceeding 24 months,, with two remaining alive and progression-free as of April 1, 2025 (Fig. 4).

Safety

Details of treatment-related adverse events (TRAEs) are presented in Table 2. Six patients experienced any-grade TRAEs. Grade 1 TRAEs included fever (10.0%), fatigue (10.0%), bone pain (20.0%), pruritus (10.0%), hyperthyroidism (10.0%), and pneumonitis (10.0%). One patient encountered a grade 2 TRAE (chest pain, 10.0%). A grade 3 TRAE (rash) occurred in one patient, which resolved with prednisone

treatment and temporary discontinuation of tislelizumab. No grade 4–5 TRAEs were reported, indicating a favorable safety profile.

Table 2
Treatment-related adverse events.

Fever	Grade 1	Grade 2	Grade 3	Grade 4
	1 (10.0%)	**0**	**0**	**0**
Fatigue	1 (10.0%)	0	0	0
Ostealgia	2 (20.0%)	0	0	0
Skin rash	0	0	1 (10.0%)	0
Pruritus	1 (10.0%)	0	0	0
Chest pain	0	1 (10.0%)	0	0
Hyperthyroidism	1 (10.0%)	0	0	0
Pneumonia	1 (10.0%)	0	0	0

Univariate and Multivariate Cox Regression Analysis

Prognostic factor analysis (Table 3) revealed that the monocyte-to-lymphocyte ratio (MLR) change rate (MLR%) was significantly correlated with prognosis in univariate analysis (HR = 10.46, 95% CI: 1.451–75.4, P = 0.0199). Additionally, several other factors exhibited trends toward prognostic significance (P < 0.10), including histologic type (HR = 0.1055, 95% CI: 0.01052–1.059, P = 0.0559), SBRT site (HR = 9.476, 95% CI: 0.9445–95.08, P = 0.0559), pretreatment lymphocyte count (HR = 5.419, 95% CI: 0.8618–34.08, P = 0.0716), pretreatment MLR (HR < 0.0001, 95% CI: < 0.0001–1.878, P = 0.0601), and platelet-to-lymphocyte ratio (PLR) change rate (PLR%) (HR = 2.157, 95% CI: 0.8675–5.366, P = 0.0981). However, none of these variables achieved statistical significance in multivariate analysis (all P > 0.05, Table 3), likely attributed to the limited sample size and low number of events.

Table 3
Univariable and multivariable Cox regression analysis in patients with Advanced Non-Small Cell Lung Cancer.

Variables	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
Histology	0.1055 (0.01052-1.059)	0.0559	0.000 (0.000-Infinity)	0.826
Gender	0.000 (0.000-Inf)	0.999		
Age	1.008 (0.8918–1.139)	0.901		
Smoking	0.9143 (0.1981–4.219)	0.909		
ECOG PS	3.387 (0.6722–17.07)	0.139		
Number of metastatic organs	0.6241 (0.2416–1.612)	0.33		
Number of metastatic lesions	1.347 (0.6353–2.857)	0.437		
Site of SBRT	9.476 (0.9445–95.08)	0.0559	1.000 (0.000-Infinity)	1.000
Dose	0.8796 (0.1684–4.594)	0.879		
Pre-SBRT Albumin	0.978 (0.9084–1.053)	0.555		
Pre-SBRT Leukocyte	1.274 (0.8917–1.822)	0.183		
Pre-SBRT Neutrophil	1.226 (0.7723–1.945)	0.388		
Pre-SBRT Lymphocyte	5.419 (0.8618–34.08)	0.0716	Infinity (0.000-Infinity)	0.555
Pre-SBRT Monocyte	18.71 (0.1129-3101)	0.261		
Pre-SBRT Platelet	0.999 (0.9864–1.012)	0.875		

#: (POST-SBRT NLR - Pre-SBRT NLR) / Pre-SBRT NLR. Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; SBRT, Stereotactic Body Radiation Therapy; Dose, Radiation Dose; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; D-NLR, Derived Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Pre-SBRT NLR	0.5771 (0.2619–1.271)	0.173		
Pre-SBRT PLR	0.9869 (0.9709–1.003)	0.112		
Pre-SBRT MLR	< 0.0001 (< 0.0001–1.878)	0.0601	Infinity (0.000-Infinity)	0.708
Pre-SBRT D-NLR	0.4732 (0.1315–1.703)	0.252		
Pre-SBRT SII	0.9987 (0.9959–1.002)	0.386		
Pre-SBRT PNI	0.994 (0.9246–1.069)	0.871		
Best response of target lesions	0.2123 (0.02585-1.744)	0.149		
Best response of non-irradiated target lesions	0.486 (0.1467-1.61)	0.238		
Post-SBRT Albumin	0.924 (0.7103–1.202)	0.556		
Post-SBRT Leukocyte	1.045 (0.9433–1.157)	0.402		
Post-SBRT Neutrophil	1.072 (0.9395–1.224)	0.301		
POST-SBRT Lymphocyte	1.278 (0.483–3.383)	0.621		
POST-SBRT Monocyte	3.576 (0.3578–35.75)	0.278		
POST-SBRT Platelet	1 (0.992–1.008)	0.997		
POST-SBRT NLR	1.182 (0.8518–1.641)	0.317		
POST-SBRT PLR	0.9912 (0.9722–1.011)	0.373		

#: (POST-SBRT NLR - Pre-SBRT NLR) / Pre-SBRT NLR. Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; SBRT, Stereotactic Body Radiation Therapy; Dose, Radiation Dose; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; D-NLR, Derived Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
POST-SBRT MLR	3.961 (0.01553-1010)	0.626		
POST-SBRT D-NLR	1.28 (0.6837–2.395)	0.441		
POST-SBRT SII	1.001 (0.9993–1.002)	0.347		
POST-SBRT PNI	1.002 (0.8221-1.22)	0.988		
NLR%[#]	1.112 (0.8746–1.413)	0.387		
PLR%	2.157 (0.8675–5.366)	0.0981	0.000 (0.000-Infinity)	0.799
MLR%	10.46 (1.451–75.4)	0.0199	Infinity (0.000-Infinity)	0.598
D-NLR%	1.164 (0.8309–1.632)	0.377		
SII%	1.088 (0.8986–1.316)	0.389		
PNI%	0.9214 (0.01113-76.32)	0.971		

#: (POST-SBRT NLR - Pre-SBRT NLR) / Pre-SBRT NLR. Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; SBRT, Stereotactic Body Radiation Therapy; Dose, Radiation Dose; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; D-NLR, Derived Neutrophil-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; PNI, Prognostic Nutritional Index.

Discussion

This study represents the first evaluation of the SBRT, tislelizumab, and GM-CSF triple combination in immunotherapy-resistant advanced NSCLC. Results demonstrated an ORR of 30%, DCR of 70%, median PFS of 6.48 months, and median OS of 12.97 months (95% CI: 7.83-NA). Compared to historical data indicating an ORR of < 15%, median PFS of 3–4 months [9, 10], and DCR typically below 50% [11, 12] for docetaxel as second-line therapy in advanced pretreated lung cancer, these findings suggest encouraging anti-tumor activity compared with historical outcomes., a near-doubling of PFS, and numerically favorable DCR and OS outcomes. For ICI rechallenge strategies following progression on first-line immunotherapy, a retrospective study by Tian et al. [13] reported a median PFS of 5.0 months (95% CI: 4.5–5.5), median OS of 15.7 months (95% CI: 14.7–16.8), ORR of 9.3%, and DCR of 74.0%. The OS result of 12.97 months observed in this study is numerically superior to historical data for

conventional chemotherapy and aligns with the survival benefit trend noted in ICI rechallenge, suggesting that selected patients may still derive benefit from immunotherapy-based salvage strategies.

The synergistic anti-tumor mechanism of this triple combination can be summarized as follows: First, SBRT functions as an "in situ vaccine." The observed ASR of 20% suggests that radiotherapy may contribute to the induction of abscopal responses. [14], which parallels the 30.6% ASR reported in the SWORD study [4]. SBRT induces immunogenic cell death, liberates tumor neoantigens, upregulates MHC-I expression [15], and remodels the local immune microenvironment, characterized by decreased regulatory T cell (Treg) infiltration and heightened CD8 + T cell activation [6]. However, radiotherapy alone may lead to lymphodepletion, with immunomodulatory effects exhibiting bidirectionality and individual variability, necessitating the incorporation of immune adjuvants and PD-1 inhibitors [16]. Gkika et al. [17] prospectively demonstrated that SBRT in early-stage NSCLC increased the Ki-67 + CD8+ T cell proportion ($P = 0.006$) but also significantly reduced absolute CD8 + cytotoxic T lymphocyte counts, concurrently decreasing Tregs and MDSCs. This highlights the complexity and individual variability of SBRT's immunomodulatory effects, suggesting that the immunosuppressive pathways activated may partially diminish its synergistic effects, justifying the need for combination with GM-CSF and PD-1 inhibitors. Second, GM-CSF enhances the efficiency of antigen presentation. As a vital immune adjuvant, GM-CSF promotes the maturation and migration of DCs to lymphoid organs, thereby amplifying the "in situ vaccine" effect initiated by SBRT [6]. Clinical studies indicate that the combination of radiotherapy and GM-CSF yields an abscopal effect rate of 26.8% in metastatic solid tumors, with significantly extended OS for patients displaying abscopal responses [3]. Furthermore, GM-CSF enhances DC maturation, migration, and antigen presentation, amplifying the "in situ vaccine" effect and inducing the polarization of tumor-associated macrophages (TAMs) toward the M1 phenotype, potentially alleviating immunosuppressive mechanisms [18]. Lastly, tislelizumab blocks the PD-1/PD-L1 pathway, restoring the function of effector T-cells. Its unique Fc engineering prevents antibody-dependent cellular phagocytosis (ADCP), minimizes T-cell clearance, and enhances the durability of immune efficacy [7].

Regarding safety, the incidence of grade ≥ 3 TRAEs was only 10%, significantly lower than the rates reported for ICI rechallenge (6.3%–28.6%) and conventional immunotherapy combination regimens (13%–24%) [19]. The PRaG study noted a grade ≥ 3 adverse event rate of 12% for the combination of GM-CSF, radiotherapy, and a PD-1 inhibitor in solid tumors [6], supporting the findings of the current study and supporting the acceptable tolerability of this combination.. This good tolerability likely arises from three synergistic mechanisms: First, GM-CSF promotes M1 polarization of macrophages and enhances antigen presentation, contributing to an optimized immune microenvironment post-radiation while potentially mitigating radiotherapy-related inflammation. Second, the Fc modification of tislelizumab prevents binding to Fcγ receptors, inhibiting ADCP-mediated T cell clearance [7]. In combination with GM-CSF, this mechanism may hinder activated macrophages from clearing T cells, thus dampening pro-inflammatory signaling [18] and consequently lowering the risk of immune-related adverse events. Lastly, the short-course, precisely delivered SBRT minimizes damage to normal tissues. Collectively, these mechanisms may partly explain the encouraging efficacy and manageable toxicity observed in this study" associated with this triple combination.

The observed ASR in this study was 20%, slightly lower than the 30.6% reported in the SWORD study. However, the current cohort consisted of heavily pretreated patients exhibiting multi-line ICI resistance, with 70% of participants having ≥ 2 metastatic organs, reflecting a high-risk, refractory population. The presence of a noticeable abscopal effect in this challenging context suggests that the triple combination may induce systemic anti-tumor immune responses, indicating potential for clinical translation.

This study is the first to investigate prognostic factors associated with the SBRT, tislelizumab, and GM-CSF combination in patients with advanced NSCLC experiencing progression after immunotherapy. Univariate analysis identified MLR% as the only factor significantly linked to prognosis (HR = 10.46, P = 0.0199). This suggests that an increase in MLR before and after treatment correlates with a markedly heightened risk of disease progression or mortality, indicating that dynamic changes in MLR warrant further investigation as a potential biomarker. MLR is a critical indicator of the immune-inflammatory state, as monocytes can differentiate into TAMs within the tumor microenvironment, promoting immunosuppression and contributing to immunotherapy resistance [20]. In contrast, lymphocytes are key effector cells in anti-tumor immunity. An elevated MLR signifies a prevailing immunosuppressive environment and is associated with poor outcomes. This mechanistic rationale supports our findings, where an HR > 1 for MLR% suggests increased risk among patients with rising MLR. In a related study, Zheng et al. reported that a decrease in MLR among patients with advanced NSCLC receiving first-line PD-1 inhibitors with chemotherapy was linked to higher ORR and longer PFS, reinforcing the notion that dynamic MLR changes can predict response to immunochemotherapy [21]. Furthermore, a retrospective study of patients with lung cancer treated with SBRT found that peripheral blood inflammation-related metrics, such as lymphocyte and neutrophil counts, served as independent predictors for local control, with higher lymphocyte counts correlating with significantly improved local control rates [22]. This highlights the rationale for employing peripheral blood cell ratios like MLR as predictors of SBRT efficacy. Our findings indicate that dynamic MLR changes may reflect the immunomodulatory effects of SBRT combined with immunotherapy on the tumor microenvironment. Notably, MLR% did not maintain independent significance in multivariate analysis, likely due to the limited sample size and insufficient statistical power. Nonetheless, this exploratory analysis provides preliminary evidence supporting the use of SBRT plus immunotherapy in immunotherapy-pretreated populations, with MLR% emerging as a potential clinically valuable biomarker for treatment monitoring. Given the early termination of the study and the limited sample size, all efficacy, survival, and biomarker findings should be considered exploratory and require validation in larger prospective studies.

Despite these insights, the study has several limitations. First, unlike the larger PRaG (n = 54) and SWORD (n = 42) studies, our study enrolled only 10 patients due to slow accrual and early termination, resulting in inadequate statistical power for subgroup analyses. Second, as a single-arm, open-label, single-center study without a control group, observed efficacy may be influenced by selection bias. The median follow-up period of 12.97 months is relatively short, potentially missing durable responses and late-onset adverse events. Third, variability in prior immunotherapy regimens and durations among participants may have impacted the overall efficacy assessment, highlighting the need for further validation in larger, multicenter cohorts.

Conclusion

In conclusion, the triple combination of SBRT, tislelizumab, and GM-CSF exhibits encouraging anti-tumor activity and manageable safety in patients with ICI-resistant advanced NSCLC, suggesting the induction of abscopal responses showing encouraging efficacy relative to historical benchmarks. This regimen presents a novel salvage treatment option for patients with refractory disease. The underlying synergistic mechanisms are evident, and the favorable tolerability warrants further validation in multicenter, large-sample, randomized controlled trials.

Abbreviations

SBRT
stereotactic body radiation therapy
GM-CSF
granulocyte-macrophage colony-stimulating factor
NSCLC
non-small cell lung cancer
ICIs
immune checkpoint inhibitors
ASR
abscopal response rate
TRAEs
treatment-related adverse events
DCs
dendritic cells
TAMs
tumor-associated macrophages
ADCP
antibody-dependent cellular phagocytosis
MLR
monocyte-to-lymphocyte ratio
PLR
platelet-to-lymphocyte ratio.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Taizhou Cancer Hospital (Approval No. IRB-[2021]6). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for publication

The Department of Science and Education of Taizhou Cancer Hospital has reviewed and approved the publication of this manuscript. No individually identifiable personal data (e.g., names, photographs, or detailed imaging that could identify participants) are presented in this report; therefore, separate patient consent for publication is not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Science and Technology Bureau of Taizhou (Grant No. 21ywb112) and the Science and Technology Bureau of Wenling (Grant No. 2023S00037). The funders had no role in the study design, data collection, analysis, interpretation, or manuscript writing.

Authors' contributions

Conceptualization and design: L Zhu, G You; Administrative support: G You; Provision of study materials or patients: L Zhu, X Ying, X Zhu; Data collection and assembly: L Zhu, L Zheng; Data analysis and interpretation: L Zhu, L Zheng; Manuscript writing: All authors; Final approval of manuscript: All authors.

Acknowledgements

We thank all participating patients and their families. We also acknowledge the nursing staff, clinical research coordinators, and the Department of Radiology at Taizhou Cancer Hospital for their support and assistance.

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Figures

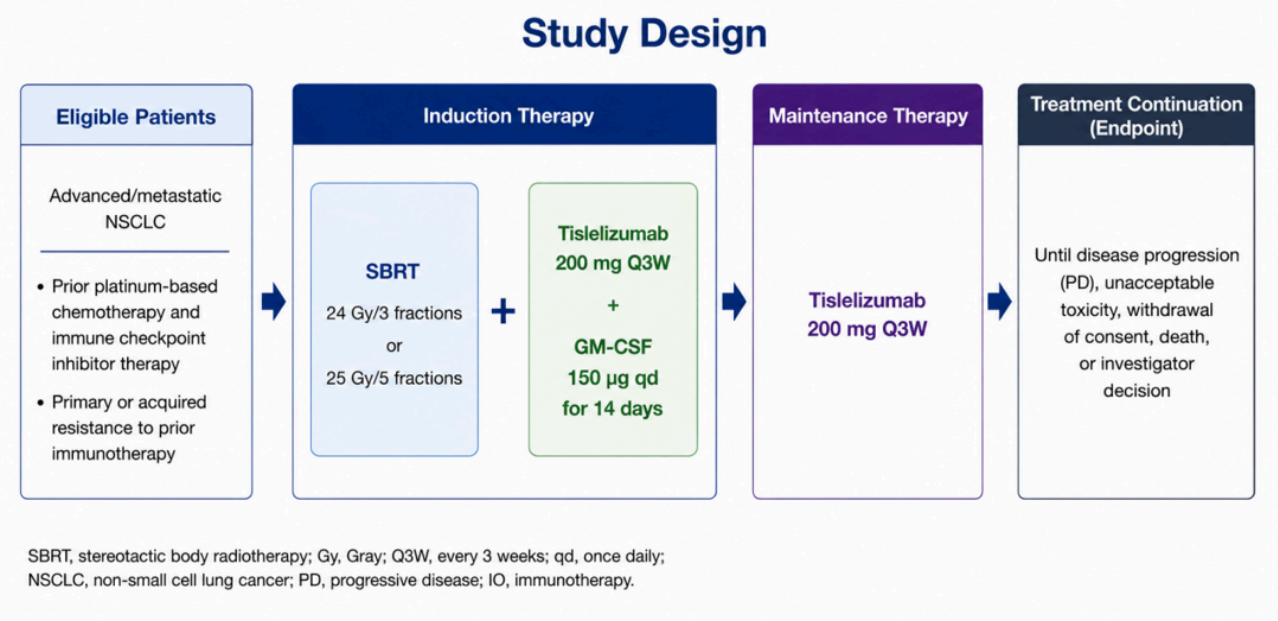


Figure 1

Treatment schedule of the study.

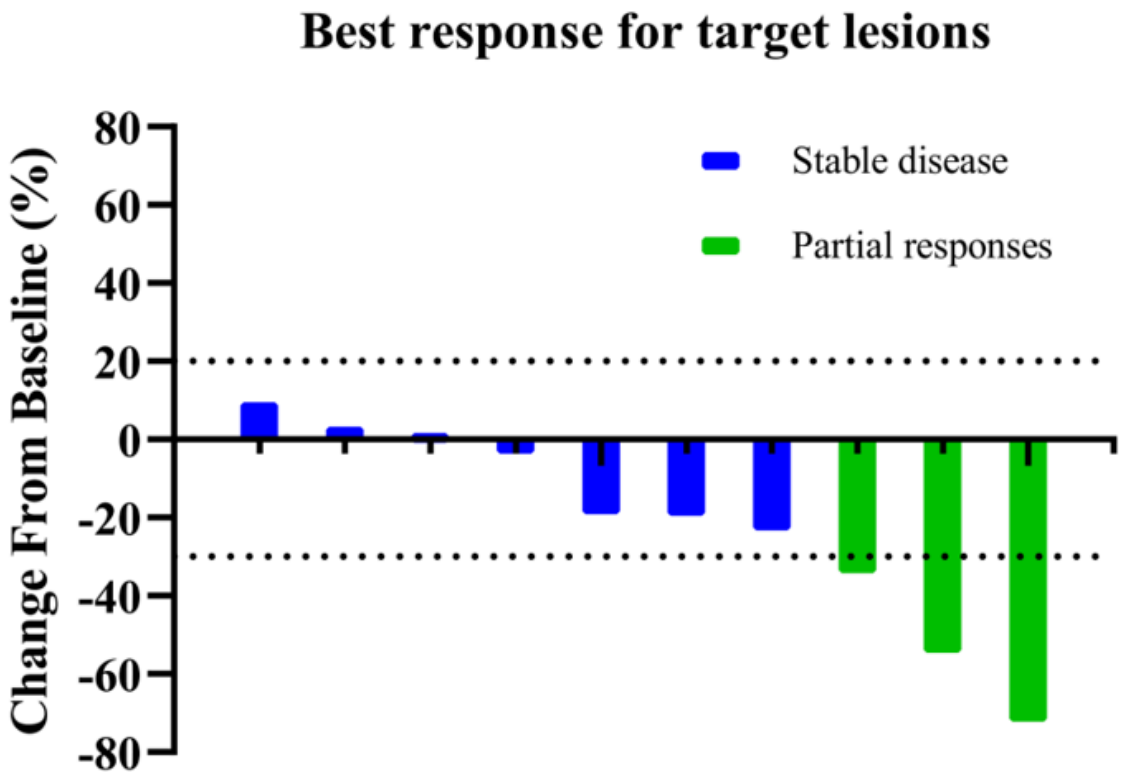


Figure 2

Waterfall plots of maximum percent change in irradiated RECIST target lesions. The ORR was 30% and the DCR was 70%.

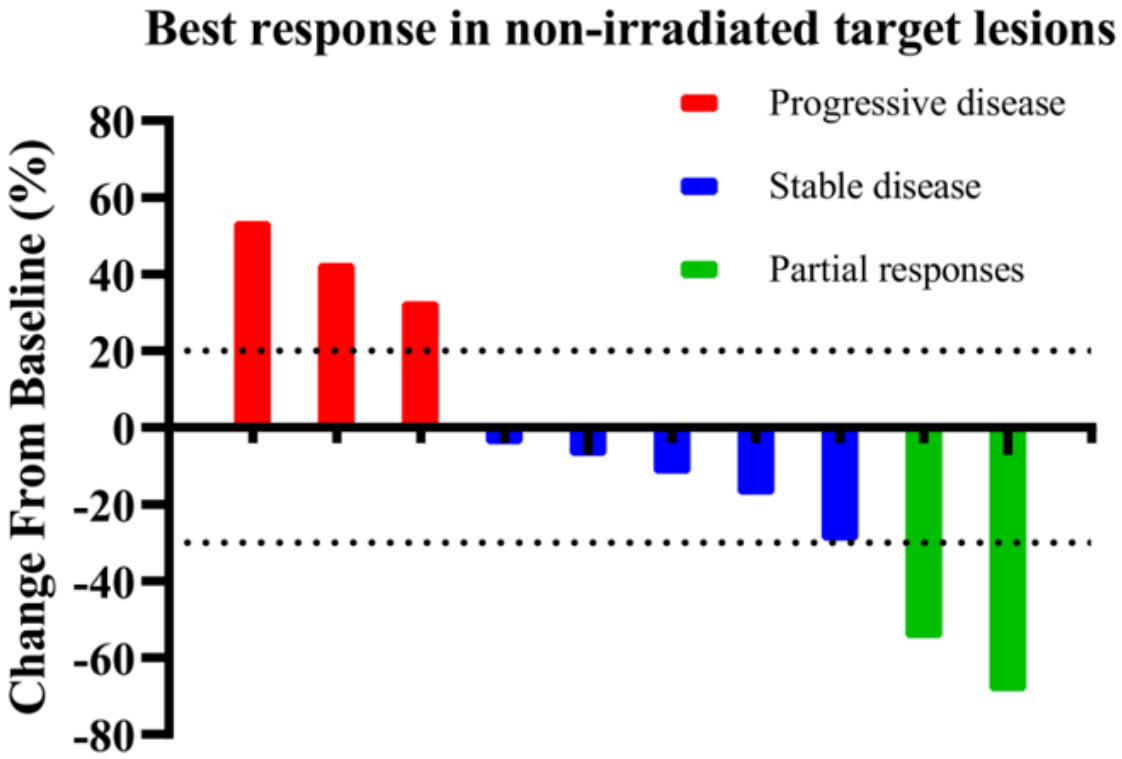


Figure 3

Waterfall plots of maximum percent change in non-irradiated RECIST target lesions. The abscopal response rate ASR was 20%.

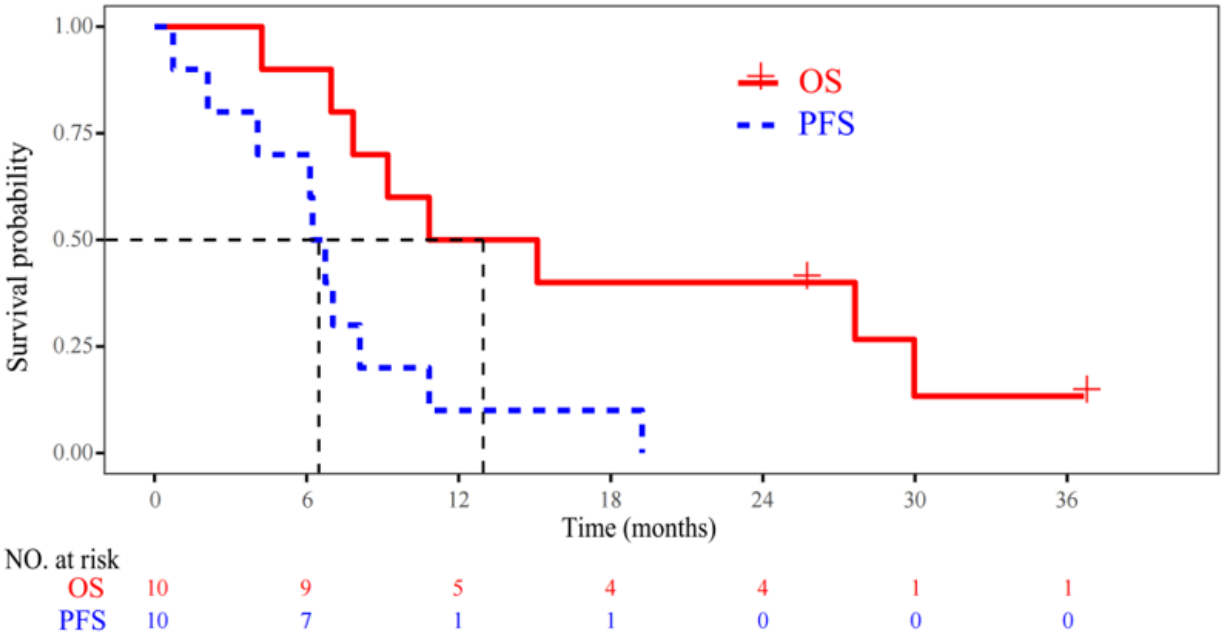


Figure 4

Kaplan–Meier curves of PFS and OS. The median PFS and OS were 6.48 months [95% CI: 4.06-NA] and 12.97 months [95% CI: 7.83-NA], respectively.