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Efficacy and Safety of Herbal Medicine Bojungikki-Tang in Combination with Pembrolizumab versus Pembrolizumab Monotherapy for Stage IV Non-Small Cell Lung Cancer: Study Protocol for a Randomized, Open-Label, Double-Arm, Multicenter Trial

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Abstract

Background: Non-small cell lung cancer (NSCLC) exhibits low survival rates. Although immune checkpoint inhibitors (ICIs) have become first-line treatment for NSCLC, their limited response to ICI monotherapy has led to exploration of combination treatments. However, the high incidence of treatment-related adverse events associated with conventional drug combinations has highlighted the need for alternative herbal therapy. Bojungikki-tang (BJIKT), a traditional herbal medicine, has been used to treat gastrointestinal disorders and enhance immune function. Our preclinical studies have demonstrated that BJIKT combined with anti-PD-1 or anti-PD-L1 antibodies exhibits significant efficacy in suppressing tumor growth by modulating the immunosuppressive tumor microenvironment. Building on these preclinical findings, this study aims to evaluate the efficacy and safety of BJIKT with pembrolizumab combination therapy compared to pembrolizumab monotherapy in advanced NSCLC patients. **Methods:** 70 individuals with stage IV NSCLC scheduled for first-line pembrolizumab monotherapy will be randomly assigned to intervention or control groups. The primary outcome will be progression-free survival, with secondary outcomes including disease control rate, overall survival, and quality of life assessment. Adverse events will be monitored for safety. This study will explore the synergistic mechanism of combinatorial therapy using immune profiling and multi-omics analysis, and the possibility for personalized integrative therapy based on cold-heat syndrome differentiation (SD) types in East Asian medicine. **Discussion:** This study will provide novel evidence regarding survival outcomes, quality of life, and safety profiles of combined ICI and BJIKT therapy for advanced NSCLC. The exploratory data will contribute to tailoring treatments to immune-based SD types in NSCLC patients.

Keywords

Bojungikki-tang, pembrolizumab, non-small cell lung cancer, randomized controlled trial, protocol

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Background

Lung cancer remains the leading type of cancer and associated mortality worldwide, with an estimated increase to reach 3.8 million cases by 2070.[1] Patients with non-small cell lung cancer (NSCLC) account for approximately 84% of lung cancer, and have a poor survival rate of 26.4%.[2,3] In recent years, immune checkpoint inhibitors (ICIs) have emerged as a new paradigm in first-line therapy for advanced NSCLC, enhancing antitumor immunity by activating immune responses against tumor cells. While ICIs, including CTLA-4, PD-1, and PD-L1 targeting antibodies,

have shown promising results compared to standard chemotherapy, their efficacy is limited by low response rates and the development of resistance in many patients.[4]

To address these limitations, various combination therapies have been investigated to enhance ICI efficacy.[5] For instance, the addition of atezolizumab to bevacizumab, carboplatin, and paclitaxel for non-squamous metastatic NSCLC has shown improved survival. However, this combination was associated with adverse events in 94.4% of patients, including grade 3 to 4 treatment-related adverse events in 55.7% of patients.[6] Moreover, the use of multiple ICIs increases the incidence of all grade immune-related adverse events (irAEs) compared to ICI monotherapy.[7] These results underscore the need for novel, safe, and effective combinatorial strategies to enhance ICI therapy.

In this context, integrative approaches combining Eastern and Western medicine have gained attention. Herbal medicines in East Asian medicine have been employed as adjunctive therapies to conventional cancer treatments, aiming to impede tumor progression and strengthen patients by modulating their immune systems.[8,9] For instance, Ginseng combined with chemotherapy has shown promise in prolonging survival and inhibiting tumor cells by targeting PD-L1 and NK cells.[8] Clinical studies have provided substantial evidence indicating the anticancer effects of herbal medicines, including prolonged survival, lower mortality hazard ratios, improved clinical symptoms, and enhanced quality of life.[9-11]

Bojungikki-tang (BJIKT), a popular herbal formula, has demonstrated particular potential in cancer care. BJIKT is known to enhance vitality and improve digestion.[10,12] When used in combination with conventional cancer treatments, including chemotherapy and targeted therapies, BJIKT has shown efficacy in reducing cancer-related fatigue,[13,14] alleviating cachexia,[15] and reversing chemotherapy resistance.[16] These effects directly contribute to improving patients' quality of life, a crucial aspect of cancer care that aligns with patient-centered outcomes.[17]

Our preclinical studies further suggest the potential of BJIKT in enhancing cancer immunotherapy. When combined with either anti-PD-1 or anti-PD-L1 antibodies, BJIKT effectively suppressed tumor growth by regulating the immunosuppressive tumor microenvironment. This was achieved through the activation of cytotoxic T lymphocytes and reduction of myeloid-derived suppressor cells.[18,19] These findings suggest a potential synergistic effect between BJIKT and ICIs, providing a supportive rationale for their combination in clinical settings.

Although initial findings are promising, the clinical efficacy and safety of combining BJIKT with ICIs are still not well established. We previously conducted a pilot placebo-controlled trial of BJIKT as an adjunct to anti-PD-L1 therapy in patients with advanced NSCLC, focusing on safety over a 9-week period.[20,21] Although this study will provide short-term safety data, further research is needed to evaluate the long-term benefits and safety of this combination therapy, particularly in terms of survival, and response rates compared to ICI monotherapy. Additionally, clinical trials that investigate the prolonged use of herbal medicine with ICIs, especially for over 6 months, remain limited.[22]

To address this research gap, we have designed a randomized controlled clinical trial lasting 45 weeks to examine the potential of BJIKT and pembrolizumab combinatorial therapy to extend survival, enhance quality of life, and ensure safety in patients diagnosed with stage IV NSCLC. The immune and multi-omics profiles derived from blood samples will provide critical insights into the underlying mechanisms of this combination therapy and enable a comprehensive analysis of its synergistic effects. This manuscript presents detailed methodologies and planned outcomes of the trial, aiming to contribute to the evidence for integrative therapeutic approaches in cancer immunotherapy.

Methods and Design

Study Design

This study has been designed as a multicenter, randomized, open-label, parallel-arm, exploratory clinical trial to evaluate the efficacy and safety of an ICI pembrolizumab, alone and in combination with BJIKT as first-line treatment in PD-L1 expression positive NSCLC patients without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations. The treatment and control groups will be administered pembrolizumab intravenously every

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3 weeks for 45 weeks, with the former additionally receiving BJIKT twice daily. This trial will conform to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement,[23] CONSORT for Chinese herbal medicine,[24] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[25]

A comprehensive explanation of the study encompassing the prospective advantages and hazards will be provided by researchers to all participants, and written informed consent for their involvement in the study and the collection of human resources will be obtained. The trial was registered on February 7, 2024 at ClinicalTrials.gov (NCT06249854), and is scheduled to be conducted between February 2024 and December 2025. The trial procedure is illustrated in Figure 1.

Study Setting

Seventy participants will be recruited from the outpatient departments and inpatients admitted to the respiratory (allergy) and medical oncology departments of Korea University Guro Hospital, The Catholic University of Korea, Seoul St. Mary's Hospital, Pusan National University Yangsan Hospital, Hallym University Medical Center, Hanyang University Seoul Hospital, Kyung Hee University Hospital, and Samsung Medical Center.

Inclusion Criteria

(1) Adult males and females aged ≥19 years.
(2) Patients with histologically or cytologically diagnosed advanced (stage IV) NSCLC as per the TNM eighth edition diagnostic criteria. In cases of recurrence, only extra-thoracic metastasis will be included.
(3) Patients scheduled for treatment with pembrolizumab monotherapy as first-line therapy, who exhibit ≥50% PD-L1 expression and do not harbor EGFR or ALK mutations.
(4) Patients with an expected survival time ≥3 months.
(5) Patients with ECOG (Eastern Cooperative Oncology Group) Performance Status score of 0 to 2.
(6) Patients with at least 1 measurable lesion as defined by response evaluation criteria in solid tumors (RECIST) V1.1.
(7) Patients with adequate bone marrow reserve or organ function with all the following:
- Hemoglobin ≥9.0 g/dl
- Absolute neutrophil count ≥1,500/μl
- Platelet ≥100×10^3/μl
- Serum creatinine ≤1.5 × upper limit of normal (ULN) or creatinine clearance ≥45 ml/min
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN*
- *in case of liver metastasis, AST and ALT ≤5 × ULN
- Total bilirubin ≤1.5 × ULN*
- *in case of liver metastasis or known Gilbert syndrome (Unconjugated hyperbilirubinemia), AST and ALT ≤5 × ULN

Exclusion Criteria

(1) Patients with active brain metastases with clinically meaningful neurologic symptoms or signs.
(2) Patients with other primary cancers diagnosed within the last 5 years that affect NSCLC*.
*Excludes effectively treated non-melanomatous skin cancer, uterine cervical intraepithelial carcinoma, ductal carcinoma in situ of the breast, thyroid cancer, or any other malignancy that has been effectively treated and has been in remission for more than 3 years and is consequently considered cured.
(3) Patients who received ICIs or anti-CTLA-4 therapy within the last 6 weeks or systemic immunosuppressive medications within the last 2 weeks*.
*Patients who have received low-dose corticosteroids of <10 mg/day prednisone or equivalent doses of corticosteroid medication within 7 consecutive days may be enrolled at the discretion of the investigator.
(4) Patients taking thiazide or loop diuretics
(5) Patients with hypokalemia with <3.0 mEq/l potassium
(6) Patients with active interstitial lung disease requiring oral or intravenous steroid therapy
(7) Patients with an autoimmune disease requiring systemic treatment at the time of enrollment
(8) Patients with poorly controlled diabetes at the time of enrollment with HbA1c ≥8.0%, not controlled with insulin and oral medications
(9) Patients with poorly controlled hypertension at time of enrollment with systolic pressure >150mmHg or diastolic pressure >100 mgHg even with blood pressure medication
(10) Patients with poorly controlled heart disease within the 6 months prior to enrollment, including severe heart failure, unstable angina pectoris, uncontrolled arrhythmias, or a history of life-threatening arrhythmias etc.
(11) Patients with genetic problems, such as, galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
(12) Patients with known active or uncontrolled HIV, tuberculosis, hepatitis B, or hepatitis C infection
(13) Pregnant or nursing women

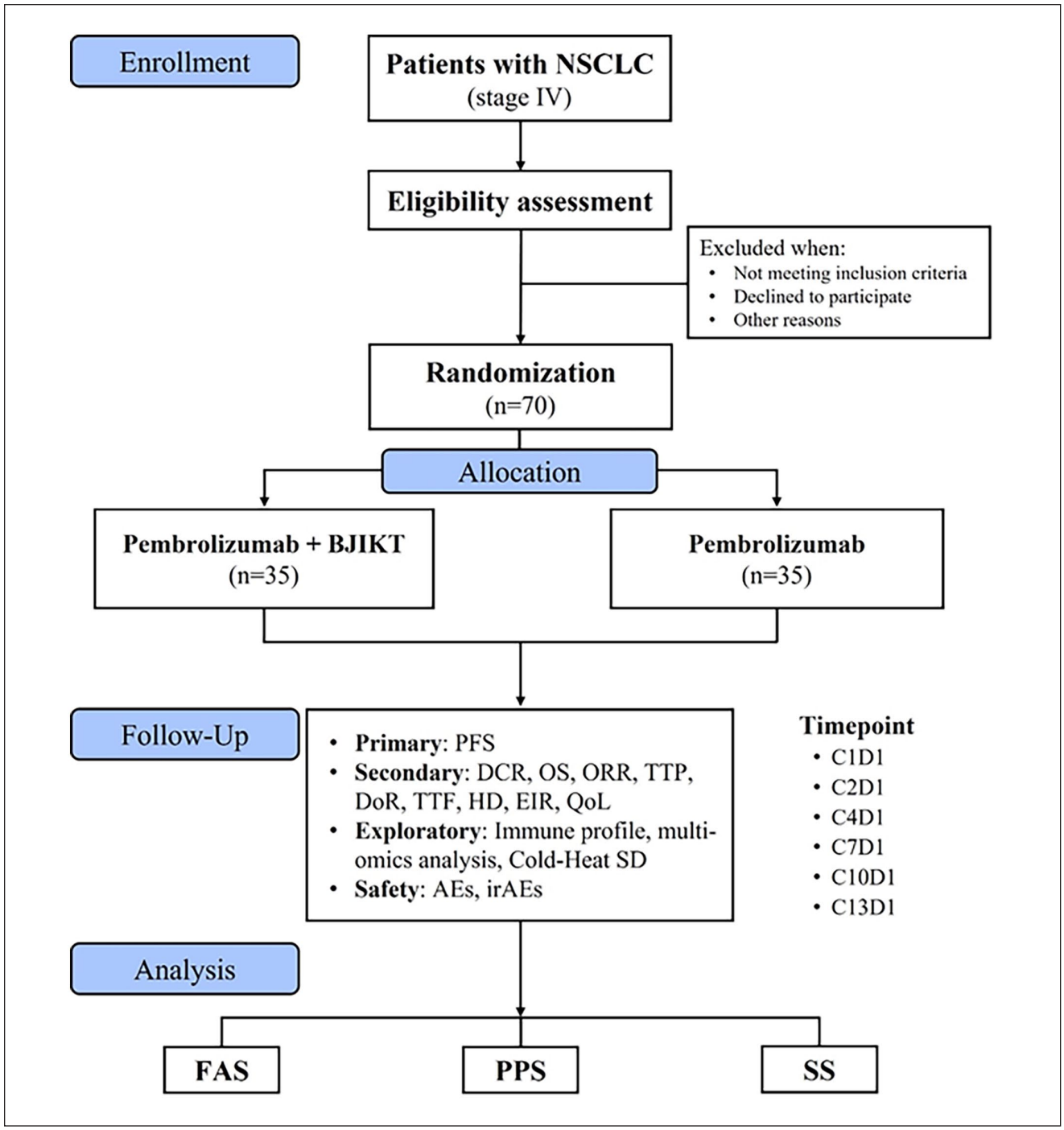

Figure 1. Study flow diagram.
NSCLC, non-small cell lung cancer; BJIKT, Bojungikki-tang; PFS, progression-free survival; DCR, disease control rate; OS, overall survival; ORR, objective response rate; TTP, time to progression; DoR, duration of response; TTF, time to treatment failure; HD, hyperprogressive disease; EIR, early interruption rate; QoL, quality of life; AEs, adverse events; irAEs, immune-related adverse events; SD, syndrome differentiation; FAS, full analysis set; PPS, per-protocol set; SS, safety set.

(14) Patients who refuse to use effective contraception during the study treatment and for at least 5 months post completion of the study treatment

(15) Patients who ingested herbal medicines within the 4 weeks prior to the first BJIKT administration, such that it may affect the study or the patients' safety, as per the judgment of the investigator

Table 1. Composition and Pharmacological Effects of the Herbs in Bojungikki-Tang Extract.

Herbal name[a]	Pharmacological effects	Proportion (%)
Ginseng radix	Activates immune response,[26] reduces antioxidative stress, inhibits inflammation, regulates various cytokines[27]	16.7
Atractylodis Rhizoma Alba	Inhibitory effect on solid tumors, antitumor effect via increasing reactive oxygen species content,[28] immunomodulatory activity, and intestinal immune system modulating activity[29]	16.7
Astragali Radix	Direct anti-proliferation or pro-apoptosis effect on tumor cells,[30] immune-enhancement via regulating innate and acquired immunity[31]	16.7
Angelicae Gigantis Radix	Anti-cancer activity via regulating cell differentiation, growth, and boosting the immune system,[32] Anti-cancer activity of natural killer and natural killer T cells[33]	12.5
Zizyphi Fructus	Anti-inflammatory effect, immune stimulation via anti-complement activity[34]	8.3
Bupleuri Radix	Inhibits inflammation, antiproliferative activity against tumor cells[35]	8.3
Citri Unshius Pericarpium	Hinders lipid accumulation,[36] inhibits vascular inflammatory reaction and stabilizes plaque, reduces ALT and AST[37]	8.3
Glycyrrhizae Radix et Rhizoma	Antioxidative activity, anticancer activity, immunomodulatory effect[38]	6.3
Cimicifugae Rhizoma	Anti-inflammatory, antipyreptic, antiosteoporosis, analgesic, anti-ulcer effect[39]	4.2
Zingiberis Rhizoma	Anti-emetic effect,[40] Reduces viability of gastric cancer cells induced by tumor necrosis factor-related apoptosis-inducing ligand[41]	2.1

AST, aspartate aminotransferase; ALT, alanine aminotransferase. [a]Each herbal medicine was extracted, mixed in proportions, and packaged in bags for daily use.

(16) Patients who have received any other investigational drug within the 30 days prior to the first BJIKT administration
(17) Severe hypersensitivity, including rashes, redness, urticaria, eczema, dermatitis, and pruritus to BJIKT and its components
(18) Patients who are not suited for this study, for instance, those suffering from serious infectious disease or organ insufficiency, as per the judgment of the investigator.

Randomization

Patients who meet all screening procedures and inclusion criteria will be openly randomized to either the intervention or control arm at a 1:1 ratio via the electronic data capture system and assigned a randomization code. Patients who do not fulfill all eligibility criteria will not be randomized under any circumstance. If a patient is found to not fulfill the eligibility criteria post randomization, treatment will not be initiated.

Interventions

BJIKT, Bojungikgitang extract fine granule, will be manufactured by Kracie, Ltd. (Tokyo, Japan), which adheres to the Good Manufacturing Practice requirements. Throughout the study, multiple batches of the extract will be accessed as needed. Each batch will undergo standardized quality control testing including heavy metal testing, microbial limit testing, and quantitative analysis of the major compounds. A 1-day dose of BJIKT (7.5 g) contains a hot water extract of 6.4 g derived from 10 medicinal herbs and an excipient. Table 1 shows the composition, and pharmacological properties of each herbal medicine component in BJIKT. BJIKT will be administered to the intervention group only. These patients will receive a single dose of BJIKT extract (3.75 g) twice a day, either before or between meals.

Both the intervention and control groups will be administered 200 mg of pembrolizumab intravenously every 3 weeks, for a total of 45 weeks, unless there is evidence of disease progression (PD) or unacceptable toxicity, following standard procedures. The dosage of pembrolizumab can be adjusted according to the guidelines provided in its license. After completion of the 45-week study period, pembrolizumab may be continued up to 2 years after the first dose. If PD is not confirmed at the study end-of-treatment visit (EOT) or if treatment is not discontinued because of unacceptable toxicity, patients will be followed up as often as possible every 9 weeks unless PD is confirmed.

Withdrawal and discontinuation criteria. Withdrawal refers to a stoppage of study participation for any reason before the end of the planned treatment and study procedures. In accordance with the Declaration of Helsinki, subjects may withdraw their consent at any time during the trial without fair reason. Reasons for a subject to withdraw from the

study or be removed by the investigator will include withdrawal of consent, loss of contact and failure to follow-up, unacceptable adverse events that make continuation impossible, serious non-compliance with the protocol as per the judgement of the investigator, or other reasons the investigator may deem sufficient cause to discontinue participation in the study.

BJIKT should be discontinued along with pembrolizumab withdrawal or discontinuation. In case BJIKT is discontinued alone early owing to safety issues, pembrolizumab may be continued at the discretion of the investigator. The investigator may temporarily halt BJIKT administration for a maximum period of 12 weeks in case of adverse events or at his/her discretion. In cases where BJIKT is suspended for durations exceeding 12 weeks, the decision to re-initiate BJIKT administration must be deliberated by the investigator and study coordinator. The recommendations for BJIKT associated adverse event management have been defined (Supplemental table 1). Further, since the daily BJIKT dose contains more than 1 g of liquorice, it will be discontinued on detection of serum potassium level abnormalities during monitoring.

Drug combination. All drug treatments administered to the subjects during the trial will be recorded in a case report form. Supportive care or combinatorial treatments to relieve NSCLC associated symptoms will be limited to drugs, surgery, and radiation therapy. The investigator will document medications employed for the treatment and prevention of underlying and comorbid illnesses, as well as all treatments that may impact tumor assessment in the case report forms. Usage of anticancer drugs other than pembrolizumab, and herbal medications other than BJIKT, as well as herbal-based dietary supplements (such as red ginseng) are not permitted during the study treatment period. The concomitant use of BJIKT with potassium-containing preparations, liquorice-containing preparations, preparations containing glycyrrhizinic acid, loop diuretics, and thiazide diuretics should be undertaken with caution owing to the risk of hyperaldosteronism or hypokalemia-induced myopathy.

Study Procedure

The study will extend over 2 years, including enrollment and a minimum 45-week follow-up period. Tumor response will be assessed every 9 weeks, that is, for a total of 3 cycles, as per RECIST version 1.1. Blood collection for immune/omics analysis will be conducted at baseline and day 1 of cycles 2, 4, 7, 10, and 13, and at the end of treatment at 45 weeks. Adverse events will be recorded at each post treatment visit, and for 4 weeks after administration of the final dose (Table 2). The enrolled patients will be followed up at specific time points until the end of the study or death, post obtaining informed consent.

Outcomes

Primary outcome. Progression-free survival (PFS) will be measured in days from the date of randomization to the first recorded instance of disease progression as assessed by the investigator, as per RECIST Version 1.1, or death.

Secondary outcomes. The disease control rate (DCR) will be measured as the proportion of subjects with a complete response, partial response, or stable disease from the date of randomization. The objective response rate (ORR) is defined as the proportion of subjects with measurable lesions at baseline during screening assessment with complete or partial response in 2 consecutive cycles over a period of at least 4 weeks. Overall survival (OS) refers to the number of days from randomization to death. Time to progression will be assessed as the number of days from the date of randomization to the first recorded instance of disease progression as determined by RECIST V1.1. Quality of life will be measured using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, the EORTC QLQ for Lung Cancer Module (EORTC QLQ-LC13), and the Functional Assessment of Anorexia/Cachexia Therapy Anorexia/Cachexia Subscale (FAACT A/CS).

Safety outcomes. Safety analysis will detail the number of adverse events (AEs), number of affected patients, and the rate of AEs, including irAEs and non-irAEs, for each arm. Additionally, the incidence of AEs with the common terminology criteria for adverse events (CTCAE) grade ≥ 3 will be calculated for both irAEs and non-irAEs.

Exploratory outcomes. Immunoactivities and changes in immune cells and cytokines, including lymphocytes (T/B/NK cells), monocytes, Th1, Th2, Th17, Treg cells, naïve/memory/senescence markers, NK cells, myeloid-derived suppressor cells, and cytokines related to the Th1/Th2 phenotype, will be analyzed. Approximately 11 ml of blood will be drawn at visits 1, 3, 7, and at the end of the treatment for the immunity index. Plasma and peripheral blood mononuclear cells will be isolated and used for immune analysis. Further, we plan to conduct a multi-omics analysis of blood samples to perform in-depth immune profiling and determine the underlying mechanism of herbal intervention. Multi-omics analyses, including transcriptome, proteome, and metabolome analyses will subsequently be performed.

We will additionally explore whether treatment response and prognosis differ with the results of syndrome differentiation (SD), a unique diagnostic method in East Asian medicine. Tongue and pulse analyses are critical objective criteria for SD diagnosis. Consequently, quantitative data from a pulse analyzer (DMP-Lifeplus, Daeyo Medi, Republic of Korea) and digital TD equipment for tongue

Table 2. Schedule of Clinical Study.

Period	Screening	Treatment (45 wk)						EOT	FU	
	Baseline	Visit1	Visit2	Visit3	Visit4	Visit5	Visit6	EOT	Safety FU	Long-term FU
Time point	~4 wk	Week 1 C1D1	Week 4 ±3 d C2D1	Week 10 ±7 d C4D1	Week 19 ±7 d C7D1	Week 28 ±7 d C10D1	Week 37 ±7 d C13D1	Week 46	28 d after last dose	Every 9 wk
Enrollment										
Informed consent	×									
Demographic characteristics	×									
Medical history	×									
NSCLC details[a]	×									
PD-L1 expression, EGFR/ALK mutation test	×									
Physical examination[b]	×	×		×	×	×	×	×	×	
ECOG PS	×	×		×	×	×	×	×	×	
Eligibility screen		×								
Registration and random allocation		×								
Intervention										
Arm 1: BJIKT + pembrolizumab		×	×	×	×	×	×	×		
Arm 2: Pembrolizumab		×	×	×	×	×	×	×		
Assessments										
Tumor response evaluation	×			×	×	×	×	×		
EORTC-QLQ-C30	×			×				×		
EORTC-QLQ-LC13	×			×				×		
FAACT-A/CS	×			×				×		
Lab tests[c]	×			×	×	×	×	×		
Blood collection for immune/omics analysis	×		×	×	×	×	×	×		
Electrocardiogram	×			×	×	×	×	×		
X-ray	×			×	×	×	×	×		
Cold-Heat syndrome[d]	×			×				×		
Treatment compliance				×	×	×	×	×		
Adverse events		×	×	×	×	×	×	×	×	
Investigating antecedents and concomitant medications	×	×	×	×	×	×	×	×	×	
Investigating concurrent therapies		×	×	×	×	×	×	×	×	×
Disease progression and survival										×

C, cycle; D, day; EOT, end of treatment; FU, follow-up; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire and Lung Cancer Module; FAACT-A/CS, Functional Assessment of Anorexia/Cachexia Therapy Anorexia/Cachexia Subscale.

[a]Date of NSCLC diagnosis, histochemical diagnosis, and TNM stage (American Joint Committee on Cancer, eighth edition). [b]Height (first measurement only), weight, and vital signs. [c]Hematological, blood biochemical, C-reactive protein, thyroid function, urine, and pregnancy tests. [d]Tongue analysis, pulse analysis, and Cold-Heat questionnaire. We aim to focus on the classification of SD types at baseline prior to treatment and changes in quantitative data post treatment.

diagnosis (computerized tongue image analysis system, TAS-4000; Korea Institute of Oriental Medicine, Republic of Korea) will be acquired and analyzed. A questionnaire on cold heat SD[42] will be administered to all patients, and a comprehensive SD diagnosis will be performed by at least 3 doctors of Korean Medicine, utilizing all data to determine the Cold or Heat, Cold or Non-cold, and Heat or Non-heat SD categories at the end of the trial.

Sample Size

As this is an exploratory study without previous clinical data on the combination of BJIKT and pembrolizumab, the sample size was not formally calculated based on statistical power analysis. Considering the average monthly number of new patients across the 7 participating centers, a sample size of 35 patients per group was determined to be the maximum number that could be recruited within the study timeframe. This size was determined to be appropriate to assess feasibility, gather preliminary efficacy data, and estimate effect sizes that will inform sample size calculations for future larger-scale randomized controlled trials.

Statistical Analysis

The data obtained from the subjects in this study will be analyzed using 3 datasets, namely, the full analysis set (FAS), per-protocol set (PPS), and safety set (SS). FAS is defined as patients receiving pembrolizumab and/or BJIKT who will undergo at least 1 measurement of the primary endpoint. All subjects will be randomized for treatment with pembrolizumab and/or BJIKT, except for those that can be justifiably excluded, such as, patients who did not receive at least 1 dose of pembrolizumab and/or BJIKT and patients with no data available since randomization. PPS is defined as the inclusion of subjects in the FAS who successfully completed the study in accordance with the protocol. Subjects who did not meet the inclusion criteria, those who violated the protocol by concomitantly using prohibited drugs during the study period, and those with $<50\%$ compliance during the entire study period are excluded from the PPS statistical analysis. SS refers to subjects who received at least 1 dose of pembrolizumab and/or the BJIKT. The primary analysis will be performed using the FAS, with the PPS serving as secondary confirmation, as required, based on data from the study subjects.

PFS will be analyzed using the Kaplan-Meier method using median and 95% confidence intervals. Differences between groups will be analyzed using the log-rank test. The first questionnaire score will be used as the baseline for screening quality of life and will subsequently be compared with the scores at each assessment time point. If necessary, the difference between the follow-up and baseline scores will be calculated and compared between groups using Student's independent t-test or Wilcoxon rank sum test. Response rates, such as the DCR and ORR, will be calculated using the frequency of subjects relative to the number of eligible patients, and 95% confidence intervals will be obtained using the Clopper-Pearson method. Comparisons between groups will be performed using the Cochran-Mantel-Haenszel test. Survival or time-related variables, such as overall survival (OS), will be identified by plotting survival curves using the Kaplan-Meier method, and comparisons between groups will be performed using the log-rank test. If necessary, hazard ratios and 95% confidence intervals will be calculated using the Cox proportional hazards model. For safety outcomes, the number of AEs will be calculated based on AE characteristics, including severity, action, and outcome. Differences between the treatment and control groups will be analyzed using the chi-square test or Fisher's exact test. SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA) will be used for statistical analysis.

Discussion

Multiple therapy combinations are currently being tested with the aim of enhancing survival, quality of life, and patients' safety. In particular, studies on integrative cancer therapies have explored the use of herbal medicine in conjunction with conventional cancer treatments for enhanced efficacy and minimal adverse reactions.[15,43-45] In this new era of cancer immunotherapy, the relevance of herbal medicine is expected to grow significantly in view of the benefits of tumor microenvironment regulation and immune response improvement.[22,46,47] Based on our previous reports[18,19,48] and a pilot clinical study,[20] we have designed this clinical trial to evaluate the efficacy of BJIKT and pembrolizumab combination therapy compared to pembrolizumab monotherapy, with progression-free survival as the primary endpoint.

Studies have shown the benefits of traditional herbal medicine enhancing the effects of ICIs by modulating the tumor microenvironment and regulating the gut microbiota. Herbal medicines are also used with ICIs to strengthen the immune system and treat immune-related adverse events.[22,49] Owing to multiple targets and pathways of herbal medicines, their interactions with ICIs need to be carefully evaluated.[22] Our preclinical drug-drug interaction study of BJIKT and anti-PD-L1 demonstrated no significant pharmacokinetic interactions or interference with antitumor effects in a CMT-167 lung cancer mouse model.[48] BJIKT has shown promising immunomodulatory effects on anti-cancer by impacting lymphocyte modulation, regulating immune suppression and activation, and influencing tumor microenvironment.[50] In our preclinical study, BJIKT effectively suppressed tumor growth by enhancing the response to anti-PD-1 antibody treatment.[18] Combination of BJIKT and anti-PD-L1 significantly suppressed tumor

growth and the population of myeloid-derived suppressor cells, indicating the potential to regulate the T-cell immunological function by improving the tumor microenvironment.[19] While our preclinical findings focused on the tumor microenvironment, recent evidence emphasizes that cancer immunotherapy requires effective systemic immune responses beyond the local tumor site.[51,52] Therefore, this clinical trial will evaluate systemic immunological effects of BJIKT and pembrolizumab combination therapy through the immune profiling of peripheral blood.

Regarding safety, serious adverse events were not reported in previous clinical studies when BJIKT was administered for long-term use exceeding 6 months. Patients with advanced gastric cancer (stages II or III) were treated with BJIKT alongside S-1 adjuvant therapy for 1 year, showing no significant differences in the frequency or severity of adverse events compared to the control group.[53] All adverse events were moderate in severity when BJIKT was administered for 24 weeks to patients with atopic dermatitis.[54] Based on previous safety evidence of long-term BJIKT administration, this clinical trial will evaluate the safety and therapeutic efficacy of BJIKT in combination with anti-PD-1 in patients with NSCLC.

In this trial, we will collect comprehensive data on the duration of survival, response rates, patient quality of life, SD, immune profiling, and multi-omics. The mechanisms underlying improved efficacy of integrative therapy will be profoundly analyzed with immune/omics data obtained from blood samples. Additionally, the integrated analysis of our data will provide novel insights into personalized integrative strategies. With the recent innovative developments in machine learning, multimodal data fusion has been applied in the diagnosis and prognosis of precision health, most commonly in the field of oncology.[55]

SD is a unique diagnosis based on a combination of the patient's subjective complaints and objective assessments by practitioners of traditional medicine that provides evidence-based treatment in East Asia.[56] It represents a traditionally personalized approach, as the treatment is tailored to each patient's condition and SD, even for patients with the same disease. The present trial is unique in that it will collect various SD-related data, including validated questionnaires, quantitative data from tongue and pulse analyzers, and comprehensive evaluations by 3 doctors of Korean Medicine. The feasibility of data collection methods for these parameters in large-scale clinical studies was demonstrated in our previous study.[57] In the current trial, the correlation between Cold-Heat SD and survival, treatment response, and immune data will be investigated. Our pilot study demonstrated longer PFS in the non-cold-type compared to cold-type lung adenocarcinoma patients.[58] This study with higher subject enrollment than that in the previous study, will uncover specific immunological characteristics or immune subtypes using immuno-omics data and evaluate the efficacy of combination therapy and ICI monotherapy treatment, based on Cold-Heat SD types. Therefore, the results of this study will make valuable contribution toward tailoring treatments to the immune-based SD-type of patients with NSCLC.

Despite the notable benefits of this study, certain limitations must be acknowledged. First, the study duration is 2 years, which is relatively short for survival analysis. Furthermore, the study has a small number of 35 participants per group. In general, while the use of herbal medicine therapy for over 6 months is considered high exposure,[59] safety data on long-term BJIKT use are limited. Notably, previous clinical studies on BJIKT administration for 6 months or more did not report any severe adverse events. The open-label design may introduce potential bias in the assessment of subjective outcomes, particularly patient-reported outcomes (PRO); however, certain studies have shown that trial design does not affect baseline PRO scores.[60] Potential bias can be minimized as objective outcomes such as progression-free survival based on radiologic assessment will be used as primary outcome, and all imaging evaluations will be conducted according to standardized RECIST criteria. Considering the potential for adverse events of BJIKT, including hypokalemia caused by glycyrrhizic acid,[61] we have reviewed available literature[44,53,54,62-69] and formulated recommendations for potential BJIKT-associated adverse events. Patients with hypokalemia are excluded from this trial and potassium or liquorice-containing medications are declared as concomitant precautions. The present trial will closely monitor adverse reactions, including hyperaldosteronism,[70] resulting from the long-term use of liquorice. The AEs identified in this trial may provide further evidence in support of the long-term use of BJIKT or otherwise.

This is the first trial to investigate patient survival using a combinatorial therapy of BJIKT and an ICI. The results of this trial will provide a rationale for integrative anticancer therapy, thereby increasing its feasibility in real-world practice.

Abbreviations

NSCLC: Non-small cell lung cancer; ICI: Immune checkpoint inhibitor; BJIKT: Bojungikki-tang; irAEs: Immune-related adverse events; CONSORT: Consolidated Standards of Reporting Trials; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; RECIST: Response evaluation criteria in solid tumors; ULN: Upper limit of normal; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PD: Disease progression; EOT: End-of-treatment; PFS: Progress-free survival; DCR: Disease control rate; ORR: Objective response rate; OS: Overall survival; EORTC QLQ: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13: EORTC QLQ

for Lung Cancer Module; FAACT A/CS: Functional Assessment of Anorexia/Cachexia Therapy Anorexia/Cachexia Subscale; AE: Adverse event; CTCAE: Common terminology criteria for adverse events; SD: Syndrome differentiation; FAS: Full analysis set; PPS: Per protocol set; SS: Safety set.

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Authors' Contributions

MKJ and SYL: conceptualization and design. MKJ: Administrative Support. SYL, SHY, SHL, SHJ, DWP, SJK, SWU, JMY, JC, and HJ provided study materials and patients. EC and MKJ: Statistical Design. EC and MKJ wrote the manuscript All authors revised and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics and Dissemination

This clinical trial was approved by the institutional review board of Korea University Guro Hospital (2023GR0478), The Catholic University of Korea-Seoul St. Mary's Hospital (KIRB-NEW20240419-019), Pusan National University Yangsan Hospital (13-2023-002), Hallym University Medical Center (HALLYM 2023-09-022-001), Hanyang University Seoul Hospital (HYUH 2023-09-049-002), Kyung Hee University Hospital (KHUH 2023-10-049-004), and Samsung Medical Center (SMC 2024-02-015-001). All modifications to the research protocol were submitted and approved.

Consent for Publication

Informed consent was obtained from all patients, including a statement that the results of the study will be published while keeping their identities confidential.

Role of Study Funders

The funding source had no input regarding the design, execution, analysis, or interpretation of the data, or the decision to submit the results.

Trial Status

The protocol version is 1.5 and was issued in 10 May 2024. The trial began on 8 February 2024. Patient recruitment for the trial is ongoing at the time of manuscript submission, with seventy patients to be enrolled in the intervention and control groups.

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Supplemental Material

Supplemental material for this article is available online.

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