





A Randomized, Multi-Center, Open Label Study to Compare the Safety and Efficacy between Afatinib Monotherapy and Combination Therapy with HAD-BI for the Locally Advanced or Metastatic NSCLC Patients with EGFR Mutations

Eunbin Kwag, PhD^{1,2*}, Soo-Dam Kim, MD, PhD^{1,3*} , Seong-Hoon Shin, MD, PhD⁴ , Chulho Oak, MD, PhD⁵, So-Jung Park, KMD, PhD⁶, Jun-Yong Choi, KMD, PhD⁶, Seong Hoon Yoon, MD, PhD⁷, In-Cheol Kang, PhD⁸, Mi-Kyung Jeong, KMD, PhD³ , Hyun Woo Lee, MD, PhD⁹, Sun-Hwi Bang, KMD, PhD¹⁰, Ji Woong Son, MD, PhD¹¹, Sanghun Lee, PhD¹² , Seung Joon Kim, MD, PhD¹³, and Hwa-Seung Yoo, KMD, PhD¹ 

Abstract

Background: Lung cancer, especially non-small cell lung cancer (NSCLC), poses a significant health challenge globally due to its high mortality. Afatinib, a second-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), has shown superior efficacy over traditional chemotherapy in NSCLC treatment. However, issues like secondary resistance and adverse effects call for alternative therapies. HAD-BI, comprising 4 herbal medicines, has shown promise in lung cancer treatment in both preclinical and clinical settings. This study assesses the combination of HAD-BI and Afatinib in advanced NSCLC patients to potentially improve outcomes by addressing the limitations of current EGFR-TKI therapies. **Method:** A randomized, open-label trial evaluated the efficacy and safety of HAD-BI with Afatinib in 90 EGFR-mutation-positive NSCLC patients. Participants were divided into treatment and control groups, receiving Afatinib with or without HAD-BI. The study focused on the initial dose maintenance rate and disease control rate (DCR) of Afatinib, alongside secondary outcomes like survival rates and quality of life, under continuous safety monitoring. **Results:** Among the 90 participants, no significant difference was found in initial dose maintenance (60.98% in the treatment group vs 52.50% in the control, $P=.4414$) or DCR (80.49% vs 90.00%, $P=.2283$). Secondary outcomes like PFS, TTP, and OS showed no notable differences. However, physical functioning significantly improved in the treatment group ($P=.0475$, PPS group). The control group experienced higher rates of adverse events of special interest and adverse drug reactions ($P=.01$), suggesting HAD-BI with Afatinib might enhance physical function without increasing adverse effects. **Conclusion:** Combining HAD-BI with Afatinib potentially improves quality of life and reduces adverse events in advanced NSCLC patients. Further research is necessary to confirm the long-term benefits of this combination therapy, aiming to advance NSCLC treatment outcomes.

Trial registration: Clinical Research Information Service (CRIS) of the Republic of Korea, <https://cris.nih.go.kr/> (ID: KCT0005414).

Keywords

non-small cell lung cancer, EGFR-TKI, Afatinib, HAD-BI, randomized controlled trial

Submitted March 13, 2024; revised June 16, 2024; accepted July 1, 2024

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with 2.4 million new diagnoses and 1.8 million

deaths that occurred in 2022.¹ In South Korea, there were 33 413 new cases and 18 536 deaths in 2023,² highlighting a significant health burden due to its high incidence rates both worldwide and in South Korea. Non-small cell lung cancer



(NSCLC) is the predominant subtype, accounting for 85% of these cases.³ Among these, approximately 10%-15% of NSCLC patients harbor epidermal growth factor receptor (EGFR) mutations.⁴ In accordance with the current NCCN guidelines, the first-line treatment for patients with EGFR mutations is osimertinib.⁵ However, afatinib (GIOTRIF®; Boehringer Ingelheim, Ingelheim, Germany) remains an alternative option for these patients.^{6,7} Afatinib may be considered for patients who have exon 19 deletions or when there is a benefit in using afatinib as the first-line treatment and reserving osimertinib for second-line therapy.⁸ In a real-world clinical study, about 15% of patients with EGFR mutations received afatinib as their first-line treatment under these circumstances.⁹ However, its clinical utility is hindered by adverse events (AEs), predominantly gastrointestinal and dermatologic, impacting patient quality of life (QoL) and treatment adherence. Insights from phase 3 trials underscore efficacy of Afatinib, but its safety profile, akin to first-generation EGFR inhibitors, necessitates proactive management. Notably, recent animal studies have highlighted a dose-dependent relationship between afatinib and gastrointestinal epithelial damage, suggesting persistent effects even post-treatment discontinuation.¹⁰ Effective AE management strategies are crucial to optimizing afatinib therapy and improving patient outcomes.

Complementary and alternative medicine, particularly herbal medicine, has garnered interest as adjuvant therapy in cancer treatment, aiming to enhance therapeutic efficacy and manage side effects. In NSCLC treatment, many studies have looked at combining herbal medicine with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) to improve treatment outcomes. These studies found that this combination can prolong progression-free survival (PFS), reduce side effects, and

increase the 5-year survival rate.¹¹⁻¹⁴ HAD-B1, a Traditional Korean Medicine herbal formulation, has emerged as a promising adjuvant therapy for lung cancer patients in South Korea. Comprising *Panax Notoginseng Radix*, *Panax ginseng C. A. Meyer*, *Cordyceps militaris*, and *Boswellia carteri* Birdwood, HAD-B1 exhibits potential anticancer properties attributed to its constituent herbs. *Panax Notoginseng Radix* demonstrates anti-tumorigenic effects by modulating apoptotic markers, while *Panax ginseng* and *Cordyceps militaris* exert anticancer effects through various molecular pathways, including immune modulation and Hedgehog signaling inhibition.¹⁵⁻¹⁷ *Boswellia carteri* exhibits anti-inflammatory and anticancer effects via AKT inhibition and NF- κ B downregulation.¹⁸ HAD-B1 was additionally investigated as a formula, and it successfully suppressed the proliferation of A549-cisplatin-resistant cells in a dose-dependent manner.¹⁹ In a preclinical study that investigated the inhibitory effect of HAD-B1 in combination with afatinib on H1975 lung cancer cells (L858R/T790M double mutation) in mice, the treatment group demonstrated significant downregulation of pERK1/2 and upregulation of p16 in the cells, as well as tumor volume reduction.²⁰ Finally, a multi-center, randomized, double-blind, placebo-controlled exploratory trial that investigated the efficacy, safety, and dosage-finding of HAD-B1 discovered that HAD-B1 showed partial efficacy and that the combination of afatinib and HAD-B1 of 972mg/day was determined to be the most effective dose.²¹

Therefore, in this study, the authors aim to evaluate efficacy and safety of using HAD-B1 with afatinib for locally advanced or metastatic NSCLC patients. The results of this study may suggest HAD-B1 as a potential safe and effective adjuvant therapy for NSCLC patients who are receiving EGFR-TKIs, especially afatinib.

¹East West Cancer Center, Daejeon Korean Medicine Hospital, Daejeon University, Daejeon 35235, Republic of Korea

²Integrative Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

³Korea Institute of Oriental Medicine, Daejeon 34054, Republic of Korea

⁴Kosin University College of Medicine, Busan 49267, Republic of Korea

⁵Kosin University College of Medicine, Busan 49267, Republic of Korea

⁶School of Korean Medicine and Korean Medicine Hospital, Pusan National University, Yangsan 50612, Republic of Korea

⁷School of Medicine, Pusan National University Yangsan Hospital, Pusan National University, Yangsan 50612, Republic of Korea

⁸College of Life and Health Sciences and BioChip Research Center, Hoseo University, Asan-si, Chungcheongnam-do 336-795, Republic of Korea

⁹Ajou University School of Medicine, Suwon 16499, Republic of Korea

¹⁰Hwirim Korean Medicine Hospital, Busan 48942, Republic of Korea

¹¹Konyang University Hospital, Daejeon 35365, Republic of Korea

¹²Dankook University, Gyeonggi-do 16890, Republic of Korea

¹³Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

*E.K. and S.-D.K. are the first co-authors. They contributed to this article equally.

Corresponding Authors:

Seung Joon Kim, Division of Pulmonary Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea.

Email: cmcksj@catholic.ac.kr

Hwa-Seung Yoo, East West Cancer Center, Daejeon Korean Medicine Hospital of Daejeon University, 75 Daedeok-daero 176 beon-gil, Seo-gu, Daejeon 35235, Republic of Korea.

Email: altyhs@dju.ac.kr

Methods

Study Design

The clinical trial is a randomized, multi-center, open-label study to compare the safety and efficacy of HAD-B1 combined with afatinib therapy for patients with locally advanced or metastatic EGFR-mutation-positive NSCLC. The protocol was approved by Daejeon Korean Medicine Hospital IRB (IRB number: DJDSKH-20-DR-09) and was registered in the Clinical Research Information Service (CRIS) of Republic of Korea (ID: KCT0005414) on September 23, 2020. The clinical trial began on February 8, 2021 and completed on April 27, 2023. The last participant was enrolled on December 23, 2022. All participants were tracked for the entire planned 16-week duration of the treatment from their respective enrollment dates. Table 1 explains the procedures conducted at each visit (Figure 1 and Table 1).

Study Participants

We originally aimed to recruit 142 patients, for the following reasons: the starting dose maintenance rate for afatinib in the afatinib group is assumed to be 57.6% based on the previous research,²¹ while in the afatinib and HAD-B1 group, we hypothesized as 80.0%. Additionally, we hypothesized all patients to be recruited and observed for a minimum of 16 weeks. Therefore, the number of subjects in each group is 64. Considering a dropout rate of 10%, which would be 71 each group, this means a total of 142 participants. However, due to constraints imposed by the COVID-19 pandemic, as well as limitations in budget and time, the recruitment was restricted to 90 participants. The 90 patients with EGFR-mutation-positive locally advanced or metastatic NSCLC requiring afatinib therapy were enrolled from 6 centers, which are the Daejeon Korean Medicine University, Kosin University Gospel Hospital, Pusan National University, Yangsan Hospital, Konyang University Hospital, Catholic University of Korea Seoul St. Mary's Hospital, and Ajou University. All participants voluntarily agreed to participate in the clinical trial.

Participant selection was based on the following inclusion criteria:

1. Confirmed histopathological diagnosis of locally advanced or metastatic NSCLC (Stage IIIA-IV, per the eighth edition of the American Joint Commission on Cancer TNM staging system).
2. Presence of EGFR mutation requiring first-line afatinib therapy (determined by the researcher's judgment).
3. Measurable disease status according to Response Criteria for Clinical Trials of Cancer (RECIST) 1.1.
4. Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0-2.

5. Ability to orally administer the prescribed drug (as assessed by the researcher).
6. Age of 19 years or older.
7. Willingness to provide written consent for participation in the clinical trial.

Participant exclusion was based on the following exclusion criteria:

1. Presence of T790M mutation within the EGFR kinase domain (acquired mutation, requiring re-biopsy).
2. Active brain metastasis with stability of less than 4 weeks, accompanied by symptoms or leptomeningopathy, unless patients were on stable dexamethasone treatment for at least 4 weeks.
3. Severe or uncontrolled gastrointestinal disorder with significant diarrhea within 2 weeks of screening, such as CTC grade 2 or higher pathological diarrhea (per researcher's assessment).
4. Deemed unsuitable for the trial due to interstitial lung disease, as evaluated by the researcher.
5. Severe hepatopathy (Child Pugh C).
6. Severe nephropathy (eGFR <15 ml/minute) or requiring dialysis.
7. Clinically significant cardiovascular disease (NYHA class 3 congestive heart failure, unstable angina, uncontrolled arrhythmia, myocardial infarction, angina within 1 year prior to study participation, etc.).
8. Fertile women not using effective contraception prior to the trial.
9. Pregnant or breastfeeding women.
10. Suspected or diagnosed with severe mental illnesses, substance abuse, alcoholism, etc.
11. Hypersensitivity to afatinib or other EGFR-targeted medications.
12. Hypersensitivity to HAD-B1 or its components.
13. Participation in other clinical trials within the month preceding this study.
14. Deemed unsuitable for this clinical trial based on researcher's judgment, including severe infectious disease or organ failure.

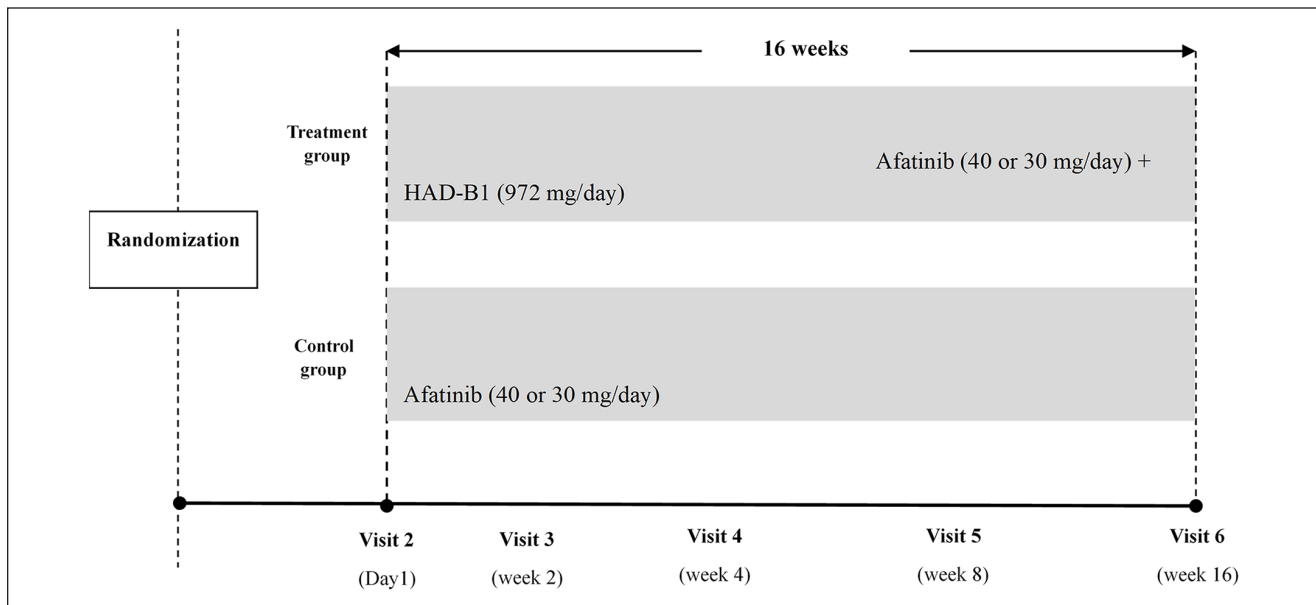
Randomization

In this clinical trial, subjects were assigned consecutive random assignment numbers, with allocation to the treatment or control group determined by a pre-generated random assignment table. Allocation was based on an advanced assignment code, with block sizes of 4 or 8 and a 1:1 ratio for group proportions. Random distribution was performed sequentially using either SAS system B or C.1. Manufacturing followed KGMP standards, with drug labeling preceding distribution.

Table I. Summary of Study Flow Chart.

Contents	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	(screening)	(randomization)				
	(approx.. -28 days)	(Day 0)	(Week 2 ± 7 days)	(Week 8 ± 7 days)	(Week 12 ± 7 days)	(Week 16 ± 7 days)
Informed consent	✓					
Eligibility screening	✓					
Demographics and medical history taking	✓					
Physical examination	✓	✓	✓			
Vital signs	✓	✓	✓	✓	✓	✓
Electrocardiogram	✓					
ECOG performance status	✓	✓	✓	✓	✓	✓
Laboratory test	✓			✓	✓	✓
EGFR mutation resistance testing	✓			✓	✓	
Pregnancy test (reproductive age women only)	✓					
Radiology examination	✓	✓			✓	✓
Tumor evaluation	✓				✓	✓
Tumor market testing	✓			✓		✓
HRQoL	✓					✓
Inclusion and exclusion criteria	✓	✓				
Prescription of investigational drug		✓				
Drug adherence monitoring			✓	✓	✓	✓
Concurrent drug monitoring			✓	✓	✓	✓
Adverse events monitoring		✓	✓	✓	✓	✓

Abbreviations: ECOG, eastern cooperative oncology group; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life.

**Figure 1.** Summary of study flow chart.

The random number list guided allocation, with selection criteria registered sequentially. To mitigate bias, testers received blind random assignment bags, opened only at the time of assignment disclosure to subjects. Participants were assigned in a 1:1 ratio to the treatment group or control group.

Intervention

Patients in the treatment group were given afatinib (30-40 mg/day orally) combined with HAD-B1 pills (972 mg/day, twice daily orally, 486 mg each). The control group received

only afatinib (30–40 mg/day orally). Any dosage modifications for afatinib was decided by the investigator's medical judgment; however, the patients were encouraged to begin with 40 mg in anticipation of future dose reduction. HAD-B1 administration ceased if afatinib was discontinued in the treatment group, while afatinib dosage variation had no effect on HAD-B1 dosage. HAD-B1 tablets were purchased from Hanpoong Pharmaceutical Co., Ltd. (Seoul, Korea).

Outcome Measures

The primary measurement is initial dose maintenance rate for afatinib and the disease control rate (DCR). Secondary outcomes encompassed control of the PFS assessed by RECIST 1.1, overall survival (OS), objective response rate (ORR), tumor size reduction, time to progression (TTP), health-related quality of life (HRQoL), and tumor markers (Carcinoembryonic antigen, CEA) between the 2 groups. The PFS, ORR, and TTP were evaluated based on RECIST 1.1 criteria.

Safety Assessments

Throughout the study, subjects underwent continuous monitoring for adverse events, including paronychia, loss of appetite, diarrhea, stomatitis, cheilitis, rash, acne dermatitis, interstitial lung disease, and severe hepatopathy. The comprehensive safety profile assessment involved tracking treatment-emergent adverse events (TEAEs), adverse events of special interest (AESI), adverse drug reactions (ADRs), severe adverse events (SAEs), serious adverse drug reactions (SADRs), and death-related ADRs. Parameters encompassed physical examination findings, abnormal vital signs, clinical laboratory results, and shifts in ECOG PS. Treatment discontinuation rates and reasons were documented. Abnormal cases were summarized by severity (NCI CTCAE grade), drug association, and categorized by treatment group according to System Organ Class and Preferred Term. A Data and Safety Monitoring Board convened every 6 months post-study commencement to oversee safety.

Result

Demographics

In this clinical trial, 90 subjects were enrolled. The demographic breakdown of participants is as follows: 41 (45.56%) were male and 49 (54.44%) were female. The mean age was 68.99 years with a standard deviation of 10.34 years, and a median of 69.50 years. Ages ranged from 49 to 92 years. Regarding ECOG PS scores, 42 participants in the treatment group and 39 in the control group had scores of 0–1, comprising 90.00% of the total. Scores of 2 were recorded for 5 participants in the treatment group and 4 in the control group, totaling 10.00%. There was no statistically significant difference

between the groups ($P=1.0000$). The mean time after NSCLC diagnosis was 1.19 ± 3.37 months in the treatment group and 0.37 ± 0.72 months in the control group, with an overall mean of 0.80 ± 2.52 months. There was no statistically significant difference between the 2 groups ($P=.1069$) (Table 2).

Three analysis groups were used to analyze the data. Out of 90 patients, 1 participant was excluded from the safety set (SS) due to not taking the treatment drug at least once. Out of the 89 patients in the SS group, 8 were excluded from full analysis set (FAS) group due to loss to follow up, and 14 participants were excluded from per protocol set (PPS) group due to violating the protocol, taking prohibited concomitant drugs, and randomization error (Figure 2). The majority were in advanced stages, with significant representation in Stage IV. Specifically, Stage IVA and IVB combined encompassed the majority of both groups, indicating a predominance of late-stage disease. TNM, cancer stage information, and information regarding EGFR mutations types are provided in Table 3.

Primary Outcome

In the FAS analysis group, 25 subjects (60.98%) in the treatment group and 21 (52.50%) in the control use group maintained the initial dose of afatinib, and there was no statistical significance difference ($P=.4414$). DCR was 80.49% in the treatment group and 90.00% in the control group. There was no statistical significance difference between the groups ($P=.2283$). In the PPS analysis group, 19 subjects (57.58%) maintained in the initial dose of afatinib in the treatment group and 21 (55.88%) in the control use group, and there was no statistical significance difference ($P=.8888$). DCR was 93.94% in the treatment group and 97.06% in the control group. There was no statistically significant difference ($P=.6135$) (Table 4).

Secondary Outcome

PFS. In the FAS group, the treatment group experienced 7 cases of disease progression (PD), 1 death, and 33 were censored. Meanwhile, the monotherapy group reported 4 PD cases, 2 deaths, and 34 censored cases. The Kaplan-Meier curve showed that the median PFS was 131 days for the treatment group, with the median for the monotherapy group not being calculable. There was no significant statistical difference between the 2 groups ($P=.4932$). In the PPS group, the treatment group had 2 PD cases, 1 death, and 30 were censored. The monotherapy group had 1 PD case, no deaths, and 33 censored cases. The Kaplan-Meier curve indicated that the median PFS for the treatment group was 131 days, with no calculable median for the monotherapy group. Similarly, no significant statistical difference was observed between the groups ($P=.3145$) (Supplemental Table 1 and Supplemental Figure 1).

Table 2. Baseline Demographics.

Variable	Treatment group (N=47), n (%)	Control group (N=43), n (%)	Sum (N=90), n (%)	P-value
Age				
Mean \pm SD	70.21 \pm 9.45	67.65 \pm 11.20	68.99 \pm 10.34	
Median	72.00	64.00	69.50	.24
Min, Max	49.00, 94.00	50.00, 97.00	49.00, 97.00	
Sex				
Male	19 (40.43)	22 (51.16)	41 (45.56)	.30
Female	28 (59.57)	21 (48.84)	49 (54.44)	
ECOG PS				
0-1	42 (89.36)	39 (90.70)	81 (90.00)	1.00
2	5 (10.64)	4 (9.30)	9 (10.00)	
NSCLC diagnosis (year)				
Mean \pm SD	1.19 \pm 3.37	0.37 \pm 0.72	0.80 \pm 2.52	
Median	0.05	0.05	0.05	.107
Min, Max	0.01, 22.00	0.01, 3.14	0.01, 22.00	
CEA				
Mean \pm SD	279.84 \pm 71.22	294.83 \pm 675.09	25944.81	
Median	19.2	19.35	19.35	.09
Min, Max.	1.1, 4015	1.1, 4015		

Abbreviations: N, Number of Subject; SD, standard deviation; ECOG, eastern cooperative oncology group; EGFR, epidermal growth factor receptor; PS, performance status; NSCLC, non-small cell lung cancer; CEA, Carcinoembryonic antigen.

TTP. In the FAS group, the treatment group experienced 7 events and 34 were censored, while the monotherapy group reported 4 events and 36 were censored. The Kaplan-Meier curve could not calculate the median TTP for either group. No significant statistical difference was found between the 2 groups ($P = .3226$). In the PPS group, the treatment group had 2 events and 31 were censored. The monotherapy group had 1 event and 33 were censored. The Kaplan-Meier curve again did not yield a median TTP time for either group. Similarly, no significant statistical difference was observed between the groups ($P = .5605$) (Supplemental Table 2).

OS. In the FAS group, there were 3 events and 38 censored cases in the treatment group, while the monotherapy group also had 3 events and 37 censored cases. The Kaplan-Meier estimated OS was 131.00 days for the treatment group, but it was not estimable for the monotherapy group. No statistical difference was observed between the 2 groups ($P = .8945$). In the PPS group, there was 1 event and 32 censored cases in the treatment group, compared to 0 events and 34 censored cases in the monotherapy group. The Kaplan-Meier estimated OS was not calculable. No statistical difference was found between the groups ($P = .3173$) (Supplemental Table 3 and Supplemental Figure 2).

EORTC QLQ-C30. In the FAS group, no statistically significant difference was observed in all categories. However, in the PPS group, the average increase in functional scales-physical functioning was 9.79 ± 19.08 in the treatment group

compared to 0.61 ± 15.03 in the control group. This difference was statistically significant ($P = .0475$), indicating higher improvement in the treatment group regarding physical function. No statistically significant difference was found in other categories in EORTC QLQ-C30 (Table 5).

EORTC QLQ-LC 13. In both the FAS group and the PPS group, symptom scales and items including dyspnea ($P = .53$), coughing ($P = .054$), hemoptysis (.27), sore mouth ($P = .95$), dysphagia ($P = .52$), peripheral neuropathy ($P = .22$), alopecia ($P = .19$), chest pain ($P = .34$), pain in arm or shoulder ($P = .44$), other pain ($P = .27$) showed no statistical difference between the 2 groups (Supplemental Table 4).

HRQoL. In the FAS group analysis, the treatment group showed a mean decrease of -0.05 ± 0.37 , while the control group demonstrated a change of 0.00 ± 0.22 . No statistically significant difference was observed between the 2 groups ($P = .6920$). In the PPS group analysis, the treatment group showed an average decrease of -0.06 ± 0.24 , whereas the control group showed an average increase of 0.03 ± 0.20 . Again, no statistically significant difference was found between the 2 groups ($P = .2214$) (Supplemental Table 5).

Tumor marker (CEA). In FAS group, the treatment group decreased by -292.89 ± 677.29 on average, and the control group decreased by -107.26 ± 230.65 on average. There was no statistical significance difference between the 2 groups ($P = .7146$). In PPS group, the treatment group

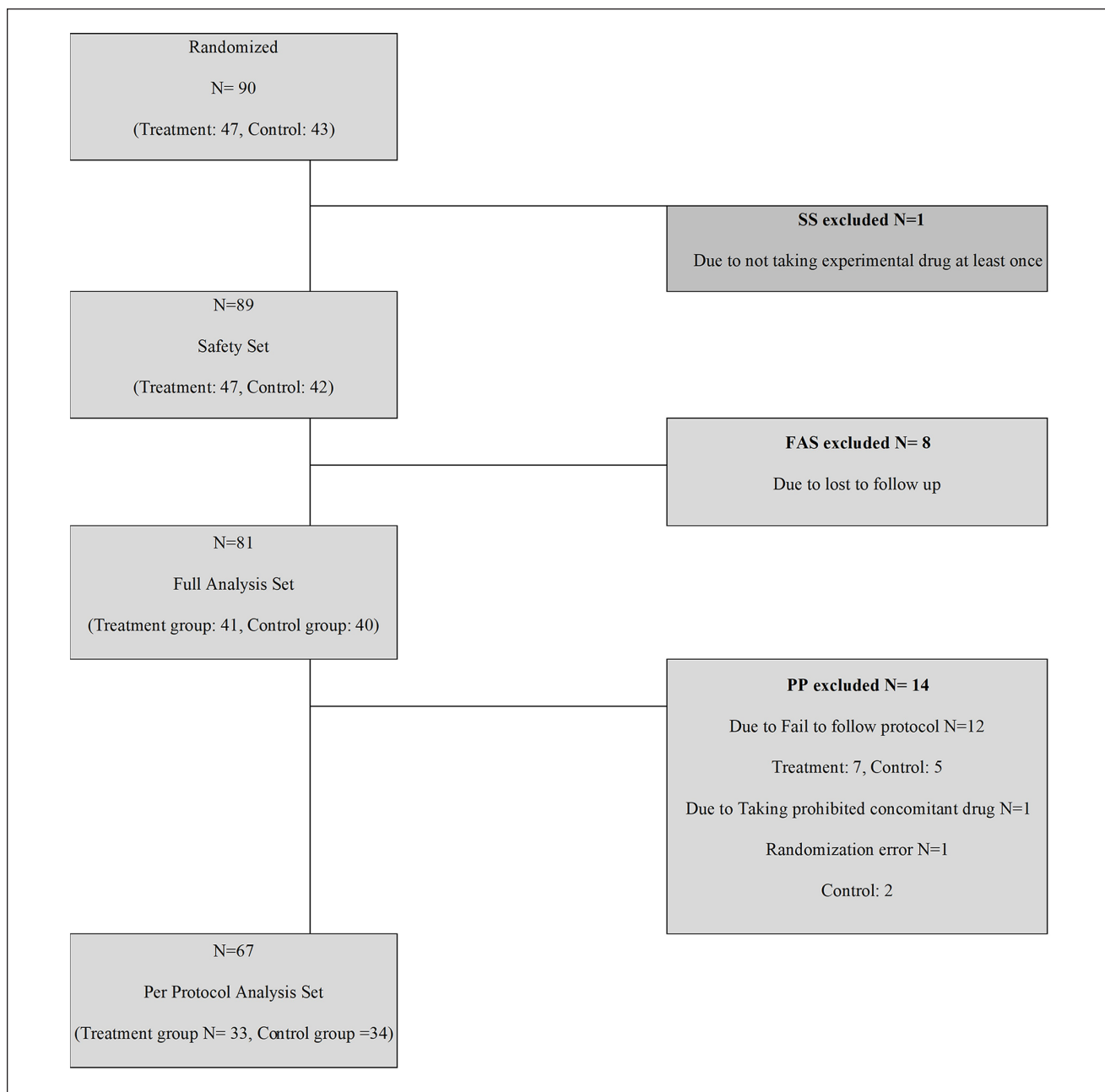


Figure 2. Number of participants and analysis groups.
Abbreviations: SS, Safety Set; FAS, Full Analysis Set; PP, Per Protocol.

decreased by -334.11 ± 744.34 on average, and the control group decreased by -106.82 ± 240.78 on average. Again, no statistically significant difference was found between the 2 groups ($P = .6350$) (Supplemental Table 6).

Safety Outcome

In this clinical trial, the treatment group, consisting of 47 participants, and the control group, with 42 participants,

experienced various adverse events. Treatment-emergent adverse events (TEAEs) were reported in 42 participants (89.36%) of the treatment group, totaling 159 cases, while in the control group, TEAEs were reported in all 42 participants (100%), totaling 189 cases, marking a significant difference in the incidence rate ($P = .05$) (Supplemental Table 7). Events of Special Interest (AESI) occurred in 40 participants (85.11%) with a total of 95 cases in the treatment group and in all 42 participants (100%) with a total of 101 cases in the

Table 3. TNM and EGFR Mutation of All Randomized Set.

Variable	Treatment group (N=47), n (%)	Control group (N=43), n (%)	Sum (N=90), n (%)	P-value
Classification				
Pathological	71 (14.89)	7 (16.28)		
Clinical	39 (82.98)	36 (83.72)		
Unknown or not evaluated	1 (2.13)	0 (0.00)		
T				
T1	10 (21.27)	9 (20.93)	19 (21.11)	
T2	20 (42.55)	11 (25.58)	31 (34.44)	
T3	5 (10.64)	6 (13.95)	11 (12.22)	
T4	12 (25.53)	17 (39.53)	29 (32.22)	
N				
N0	13 (27.66)	6 (11.63)	19 (21.11)	
N1	2 (4.26)	4 (9.30)	6 (6.67)	
N2	12 (23.40)	9 (18.60)	21 (23.33)	
N3	20 (42.55)	24 (55.81)	44 (73.33)	
M				
M0	3 (6.38)	2 (4.65)	5 (5.56)	
M1	44 (93.62)	41 (93.35)	85 (94.44)	
Staging				
IIIA	1 (2.13)	3 (6.98)	4 (4.44)	
IIIB	2 (4.26)	1 (2.33)	3 (3.33)	
IVA	23 (48.94)	13 (30.23)	36 (40.00)	
IVB	21 (44.68)	26 (60.47)	47 (52.22)	
Common EGFR mutation type				
N	44	43	87	
Exon 19 Deletion	23 (52.27)	19 (44.19)	42 (48.28)	
Exon 21 L858R	21 (47.73)	24 (55.81)	45 (51.72)	
Uncommon EGFR mutation type				
N	3	0	3	
Exon 18 G719X	1 (33.33)	0 (0.00)	1 (33.33)	
Exon 21 L861Q	1 (33.33)	0 (0.00)	1 (33.33)	
Exon 18 G719C	1 (33.33)	0 (0.00)	1 (33.33)	

Table 4. FAS and PPS Group Analysis of Dose Maintenance Rate and DCR.

FAS group	Treatment group (N=41), n (%)	Control group (N=40), n (%)	P-value
Afatinib starting dose maintenance rate	25 (60.98)	21 (52.50)	.44
DCR	33 (80.49)	36 (90.00)	.22
PPS group	Treatment group (N=33), n (%)	Control group (N=34), n (%)	P-value
Afatinib starting dose maintenance rate	19 (57.58)	19 (55.88)	.88
DCR	31 (93.94)	33 (97.06)	.61

Abbreviations: N, Number of Subject; FAS, full analysis set; DCR, disease control rate; PPS, per protocol set.

control group, demonstrating a statistically significant difference ($P=.01^*$), with a higher incidence in the control group (Supplemental Table 8). Adverse Drug Reactions (ADRs)

were noted in 40 participants (85.11%) with 125 cases in the treatment group and in all 42 participants (100%) with 125 cases in the control group, also showing a significant

Table 5. FAS Group and PPS Group Analysis of EORTC QLQ-C30.

EORTC QLQ-C30 scores FAS group	Mean changes from baseline (mean \pm SD)		P-value ^a
	Treatment group (N=41)	Control group (N=40)	
Global health status/QoL	9.38 \pm 28.00	6.94 \pm 26.24	.69
Physical functioning	2.83 \pm 24.24	-3.15 \pm 19.16	.19
Role functioning	-1.25 \pm 29.81	3.70 \pm 31.40	.45
Emotional functioning	6.25 \pm 23.55	2.78 \pm 20.31	.32
Cognitive functioning	-0.83 \pm 24.45	-0.93 \pm 20.29	.72
Social functioning	2.92 \pm 30.17	6.94 \pm 24.36	.60
Fatigue	-3.33 \pm 24.55	2.16 \pm 26.00	.34
Nausea and vomiting	-5.83 \pm 25.19	-5.09 \pm 17.28	.84
Pain	-10.00 \pm 36.94	-7.87 \pm 23.05	.37
Dyspnea	-10.00 \pm 33.93	-13.89 \pm 31.24	.46
Insomnia	-7.50 \pm 36.58	-12.04 \pm 28.90	.26
Appetite loss	-10.83 \pm 43.62	-8.33 \pm 36.84	.86
Constipation	-14.17 \pm 29.13	-8.33 \pm 25.67	.34
Diarrhea	22.50 \pm 34.08	30.56 \pm 30.21	.26
Financial difficulties	-9.17 \pm 29.22	-13.89 \pm 24.40	.54

EORTC QLQ-C30 scores PPS group	Mean changes from baseline (mean \pm SD)		P-value ^a
	Treatment group (N=33)	Control group (N=34)	
Global health status/QoL	15.63 \pm 25.64	6.57 \pm 27.06	.17
Physical functioning	9.79 \pm 19.08	0.61 \pm 15.03	.04*
Role functioning	6.77 \pm 23.89	5.05 \pm 32.41	1
Emotional functioning	11.46 \pm 20.16	3.79 \pm 20.63	.14
Cognitive functioning	5.21 \pm 20.93	-0.51 \pm 20.19	.17
Social functioning	6.77 \pm 30.49	7.07 \pm 25.36	.96
Fatigue	-9.72 \pm 21.82	-1.01 \pm 23.95	.13
Nausea and vomiting	-10.94 \pm 23.42	-5.56 \pm 15.96	.29
Pain	-18.75 \pm 28.63	-9.09 \pm 23.60	.07
Dyspnea	-16.67 \pm 23.95	-14.14 \pm 32.31	.93
Insomnia	-12.50 \pm 37.63	-11.11 \pm 29.66	.71
Appetite loss	-23.96 \pm 34.11	-9.09 \pm 37.52	.22
Constipation	-11.46 \pm 27.58	-6.06 \pm 24.23	.42
Diarrhea	16.67 \pm 28.08	31.31 \pm 31.11	.07
Financial difficulties	-9.38 \pm 30.80	-14.14 \pm 25.04	.72

Abbreviations: N, Number of Subject; SD, standard deviation; EORTC, European organisation for research and treatment of cancer; QLQ-C30, quality of life questionnaire core 30.

^aPaired t-test or Wilcoxon's signed rank test.

* $P < .05$.

difference ($P = .01^*$), indicating a higher occurrence in the control group (Supplemental Table 9). Severe Adverse Events (SAEs) were observed in 7 participants (14.89%) involving 10 cases in the treatment group and in 9 participants (21.43%) involving 13 cases in the control group, without a significant difference between the groups ($P = .42$) (Supplemental Table 10). Serious Adverse Drug Reactions (SADRs) occurred in 2 participants (4.26%) involving 2

cases in the treatment group and in 3 participants (7.14%) involving 3 cases in the control group, with no significant difference observed ($P = .66$) (Supplemental Table 11). Cases of adverse events leading to death were reported in 2 participants (4.26%) involving 5 cases in the treatment group and in 3 participants (7.14%) involving 4 cases in the control group, also without a significant difference between the groups ($P = .66$) (Supplemental Table 12 and Table 6).

Table 6. Safety Evaluation Summary.

Adverse event type	Treatment group (N=47)		Control group (N=42)		P-value ^a
	n (%)	[cases]	n (%)	[cases]	
Treatment-emergent adverse event	42 (89.36)	[159]	42 (100.00)	[189]	.05
Adverse events of special interest	40 (85.11)	[95]	42 (100.00)	[101]	.01*
Adverse drug reaction	40 (85.11)	[125]	42 (100.00)	[125]	.01*
Severe adverse event	7 (14.89)	[10]	9 (21.43)	[13]	.42
Serious adverse drug reaction	2 (4.26)	[2]	3 (7.14)	[3]	.66
Death related adverse drug reaction	2 (4.26)	[5]	3 (7.14)	[4]	.66

Abbreviation: N, Number of subject.

^aPaired *t*-test or Wilcoxon's signed rank test.

**P* < .05.

Discussion

The current treatment regimen for NSCLC often leads to drug resistance and various side effect.²² Complementary and alternative medicine, particularly herbal medicine, has emerged as a promising approach to address these challenges. Recent systematic reviews have suggested that combining herbal medicine with EGFR-TKI treatment can enhance both efficacy and tolerability.^{23,24} Studies have also indicated that the median PFS (mPFS) in patients receiving herbal medicine alongside EGFR-TKI was significantly longer than in those receiving monotherapy.^{25,26} Therefore, in this study, the authors aimed to evaluate the role of HAD-B1 as an adjuvant therapy in improving tumor control and the QOL of patients with advanced NSCLC.

In our primary outcome evaluation, no statistically significant differences were observed between the treatment group and the control group in terms of the initial dose maintenance rate for afatinib and the DCR. Similarly, secondary outcomes such as PFS, OS, TTP did not exhibit statistically significant differences between the treatment and control groups. On the other hand, the treatment group reported improved physical function in quality of life, which was statically significant (*P* = .04). Additionally, in drug safety evaluations, statistically significant differences were observed between the groups for ESI (*P* = .01) and ADR (*P* = .01). Overall, our finding suggests that while HAD-B1 did not demonstrate substantial benefits in terms of tumor reduction, it improved the physical functioning of NSCLC patients.

Although our original findings did not show a significantly positive effect of herbal medicine in enhancing afatinib's dose maintenance rate or DCR, additional studies of a similar nature may support the beneficial effect of herbal medicine as maintenance therapy. One RCT that investigated mPFS with 91 NSCLC patients with EGFR mutations using Chinese herbal medicine + EGFR-TKI group and EGFR-TKI group reported 8.9 months mPFS in treatment group compared to the 12.3 months mPFS in the control

group (*P* = .02). In addition, the mOS in the treatment group was 24.2 months compared to the 28.2 months in the control group (*P* = .02).²⁵ The constrained 16-week observation period in our study necessitates careful consideration of its potential implications. The abbreviated timeframe for data collection raises concerns regarding the comprehensive representation of the intricate dynamics inherent to the phenomenon under investigation. Specifically, the brevity of the observation period may have limited our ability to fully capture long-term trends relevant to the primary outcomes of our study. Moreover, it highlights the need for future research endeavors to employ extended observation durations, thereby fostering a more nuanced and holistic understanding of the subject matter.

Strengths of our study lie in its multi-center randomized clinical trial design, which enhances the generalizability of the findings. Additionally, HAD-B1 represents a quality-controlled herbal formula, ensuring safer use and potentially more effective treatment outcomes.²⁷ The study is subject to several limitations that warrant consideration. Firstly, the relatively short duration of the study period may have restricted the ability to capture longer-term treatment effects and outcomes adequately as well as restricted the maturation of the data. A longer follow-up duration would have provided a more comprehensive understanding of the sustained efficacy and safety profile of HAD-B1 in NSCLC management. Secondly, the open-label nature of the study design introduces the potential for bias, as both participants and investigators were aware of the treatment allocation. This lack of blinding could have influenced subjective endpoints and introduced confounding factors, thus affecting the robustness and reliability of the study results. Furthermore, the absence of blinding may have influenced treatment adherence and reporting of adverse events, potentially impacting the accuracy and completeness of safety assessments. Additionally, the study's generalizability may be limited by factors such as the specific patient population enrolled, the inclusion and exclusion criteria applied, and the geographic distribution of study sites. These factors

may restrict the extrapolation of findings to broader patient populations or clinical settings, thereby limiting the external validity of the study results.

In summary, the study provides valuable insights into the potential therapeutic role of HAD-B1 in NSCLC treatment. However, it is imperative to interpret the findings within the context of the inherent limitations outlined. Despite these constraints, the observed improvements in physical function and reduction in side effects associated with HAD-B1 administration underscore its potential clinical significance. Thus, addressing these limitations in future research endeavors will be pivotal for elucidating the broader therapeutic utility and clinical applicability of HAD-B1 in the comprehensive management of NSCLC.

Conclusion

In conclusion, our study provides valuable preliminary data regarding the potential role of HAD-B1 in non-small cell lung cancer, particularly in EGFR-positive patients. Significantly, our study demonstrates that HAD-B1, as an herbal medicine intervention, administered in locally advanced or metastatic NSCLC, can mitigate adverse events induced by EGFR-TKIs and enhance patients' physical functioning. Further research is warranted to substantiate the use of HAD-B1 in conjunction with EGFR-TKIs, as well as other herbal medicines, as a maintenance therapy for NSCLC patients.

Author Contributions

H.-S.Y. and S.J.K.: Conceptualization. S.-H.S., S.-J.P., and M.-K.J.: Methodology. S.-H.S., C.O., J.-Y.C., S.H.Y., I.-C.K., H.W.L., S.-H.B., J.W.S., S.L., and S.J.K.: Data curation. E.K., S.-D.K., and H.-S.Y.: Investigation. E.K. and S.-D.K.: Formal analysis and Writing—original draft. S.-H.S., C.O., S.-J.P., J.-Y.C., S.H.Y., I.-C.K., M.-K.J., H.W.L., S.-H.B., J.W.S., S.L., S.J.K., and H.-S.Y.: Writing—review & editing. H.-S.Y. and S.J.K.: Supervision. H.-S.Y. and E.K.: Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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.


Funding


The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development


Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C1046 and HI22C1936).


ORCID iDs

Soo-Dam Kim  <https://orcid.org/0000-0002-4872-2462>

Seong-Hoon Shin  <https://orcid.org/0000-0002-5745-560X>

Mi-Kyung Jeong  <https://orcid.org/0000-0002-0239-0159>

Sanghun Lee  <https://orcid.org/0000-0002-0573-9555>

Hwa-Seung Yoo  <https://orcid.org/0000-0003-3738-3239>

Supplemental Material

Supplemental material for this article is available online.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263.
2. Jung KW, Kang MJ, Park EH, et al. Prediction of cancer incidence and mortality in Korea, 2023. *Cancer Res Treat.* 2023;55(2):400-407.
3. Nieva J, Reckamp KL, Potter D, Taylor A, Sun P. Retrospective analysis of real-world management of EGFR-mutated advanced NSCLC, after first-line EGFR-TKI treatment: US treatment patterns, attrition, and survival data. *Drugs Real World Outcomes.* 2022;9(3):333-345.
4. Vanderpoel J, Emond B, Ghelerter I, et al. Healthcare resource utilization and costs in patients with EGFR-mutated advanced non-small cell lung cancer receiving first-line treatment in the United States: an insurance claims-based descriptive analysis. *Pharmacoecon Open.* 2023;7(4):617-626.
5. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung cancer, Version 4.2024. *J Natl Compr Canc Netw.* 2024;22(4):249-274.
6. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35(30):3484-3515.
7. Nan X, Xie C, Yu X, Liu J. EGFR TKI as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer. *Oncotarget.* 2017;8(43):75712-75726.
8. Lu S, Shih JY, Jang TW, Liam CK, Yu Y. Afatinib as first-line treatment in Asian patients with EGFR mutation-positive NSCLC: a narrative review of real-world evidence. *Adv Ther.* 2021;38(5):2038-2053.
9. Gilardone S, Thapa R, Laborde J, et al. Osimertinib vs. afatinib as first-line treatment for patients with metastatic non-small cell lung cancer with an EGFR exon 19 deletion or exon 21 L858R mutation. *J Thorac Dis.* 2023;15(11):6115-6125.
10. Zhang L, Hu A, Wang Y, et al. Medication adjustment of afatinib and combination therapy with sitagliptin for alleviating afatinib-induced diarrhea in rats. *Neoplasia.* 2023;43:100922.
11. Lee JH, Kim EY, Park CK, et al. Real-world study of osimertinib in Korean patients with epidermal growth factor receptor T790M mutation-positive non-small cell lung cancer. *Cancer Res Treat.* 2023;55(1):112-122.

12. Liu ZL, Zhu WR, Zhou WC, et al. Traditional Chinese medicinal herbs combined with epidermal growth factor receptor tyrosine kinase inhibitor for advanced non-small cell lung cancer: a systematic review and meta-analysis. *J Integr Med.* 2014;12(4):346-358.
13. Yang XB, Wu WY, Long SQ, Deng H, Pan ZQ. Effect of gefitinib plus Chinese herbal medicine (CHM) in patients with advanced non-small-cell lung cancer: a retrospective case-control study. *Complement Ther Med.* 2014;22(6):1010-1018.
14. Wang CY, Huang HS, Su YC, et al. Conventional treatment integrated with Chinese herbal medicine improves the survival rate of patients with advanced non-small cell lung cancer. *Complement Ther Med.* 2018;40:29-36.
15. Tan MM, Chen MH, Han F, Wang JW, Tu YX. Role of bioactive constituents of *Panax notoginseng* in the modulation of tumorigenesis: a potential review for the treatment of cancer. *Front Pharmacol.* 2021;12:738914.
16. Li QY, Hou CZ, Yang LP, et al. Study on the mechanism of Ginseng in the treatment of lung adenocarcinoma based on network pharmacology. *Evid Based Complement Alternat Med.* 2020;2020:2658795.
17. Jo E, Jang HJ, Shen L, et al. *Cordyceps militaris* exerts anti-cancer effect on non-small cell lung cancer by inhibiting hedgehog signaling via suppression of TCTN3. *Integr Cancer Ther.* 2020;19:1534735420923756.
18. Efferth T, Greten HJ. Anti-inflammatory and anti-cancer activity of boswellic acids from frankincense (*Boswellia serrata* Roxb. et Colebr, *B. carterii* Birdw.). *Onco Therapeutics.* 2011;2(4):303-313.
19. Kang HJ, Park JH, Yoo HS, et al. Effects of HAD-B1 on the proliferation of A549 cisplatin-resistant lung cancer cells. *Mol Med Rep.* 2018;17(5):6745-6751.
20. Kang HJ, Kim J, Cho SH, et al. Inhibitory effects of HangAmDan-B1 (HAD-B1) combined with afatinib on H1975 lung cancer cell-bearing mice. *Integr Cancer Ther.* 2019;18:1534735419830765.
21. Ko EJ, Kwag EB, Park JH, et al. Multi-center, randomized, double-blind, placebo-controlled, exploratory study to evaluate the efficacy and safety of HAD-B1 for dose-finding in EGFR mutation positive and locally advanced or metastatic NSCLC subjects who need afatinib therapy. *Integr Cancer Ther.* 2021;20:15347354211037917.
22. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol.* 2009;27(17):2874-2880.
23. Tanniou J, van der Tweel I, Teerenstra S, Roes KCB. Subgroup analyses in confirmatory clinical trials: time to be specific about their purposes. *BMC Med Res Methodol.* 2016;16(1):20.
24. Hung HY, Tseng YH, Liao CM, et al. The efficacy of traditional Chinese herbal medicine in the treatment of EGFR mutated stage IV pulmonary adenocarcinoma patients who received first-line EGFR-TKI treatment. *Integr Cancer Ther.* 2017;16(1):126-131.
25. Wang Y, Wu G, Li R, et al. Chinese medicine combined with EGFR-TKIs prolongs progression-free survival and overall survival of non-small cell lung cancer (NSCLC) patients harboring EGFR mutations, compared with the use of TKIs alone. *Front Public Health.* 2021;9:677862.
26. Song X, Cao L, Ni B, et al. Challenges of EGFR-TKIs in NSCLC and the potential role of herbs and active compounds: from mechanism to clinical practice. *Front Pharmacol.* 2023;14:1090500.
27. Balekundri A, Mannur V. Quality control of the traditional herbs and herbal products: a review. *Futur J Pharm Sci.* 2020;6:1-9.