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ORIGINAL REPORT

Randomized, Double-Blind, Placebo-Controlled Phase II Study of Single-Agent Oral Talactoferrin in Patients With Locally Advanced or Metastatic Non–Small-Cell Lung Cancer That Progressed After Chemotherapy

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ABSTRACT

Purpose
To investigate the activity and safety of oral talactoferrin (TLF) in patients with stages IIIB to IV non–small-cell lung cancer (NSCLC) for whom one or two prior lines of systemic anticancer therapy had failed.

Patients and Methods
Patients (n = 100) were randomly assigned to receive either oral TLF (1.5 g in 15 mL phosphate-based buffer) or placebo (15 mL phosphate-based buffer) twice per day in addition to supportive care. Oral TLF or placebo was administered for a maximum of three 14-week cycles with dosing for 12 consecutive weeks followed by 2 weeks off. The primary objective was overall survival (OS) in the intent-to-treat (ITT) patient population. Secondary objectives included progression-free survival (PFS), disease control rate (DCR), and safety.

Results
TLF was associated with improvement in OS in the ITT patient population, meeting the protocol-specified level of significance of a one-tailed $P = .05$. Compared with the placebo group, median OS increased by 65% in the TLF group (3.7 to 6.1 months; hazard ratio, 0.68; 90% CI, 0.47 to 0.98; $P = .04$ with one-tailed log-rank test). Supportive trends were also observed for PFS and DCR. TLF was well tolerated and, generally, there were fewer adverse events (AEs) and grade ≥ 3 AEs reported in the TLF arm. AEs were consistent with those expected in late-stage NSCLC.

Conclusion
TLF demonstrated an apparent improvement in OS in patients with stages IIIB to IV NSCLC for whom one or two prior lines of systemic anticancer therapy had failed and was well tolerated. These results should be confirmed in a global phase III trial.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide and accounts for 28% of cancer-related deaths in the United States.[1] Non–small-cell lung cancer (NSCLC) is the most prevalent form of lung cancer constituting 85% to 90% of lung cancers.[1]

Cisplatin- or carboplatin-based regimens have been associated with objective responses and improved survival and are a standard first-line therapy for patients with metastatic NSCLC. Besides chemotherapy, cytotoxic and targeted agents are used in second- and third-line settings.[2,3] Erlotinib is an epidermal growth factor receptor tyrosine kinase inhibitor and has been shown to significantly improve overall survival (OS) and progression-free survival (PFS) in patients with advanced NSCLC for whom prior platinum-based chemotherapy has failed.[4] Despite recent treatment advances, the overall outcome of patients with refractory NSCLC remains poor, and there continues to be an urgent need for the development and introduction of new therapies.

Lactoferrin is a member of the transferrin family of nonheme iron-binding proteins and is found in mammalian serum and exocrine secretions such as milk, seminal fluid, intestinal secretions, tears, sweat, saliva, and nasal secretions[5,6] and in secretory granules of neutrophils.[7] Talactoferrin alfa (TLF; also known as recombinant human lactoferrin) is a recombinant glycoprotein isolated from *Aspergillus*

niger var. *awamori*.[8] It is structurally similar to native human lactoferrin and is known to differ only in its glycosylation.[9]

TLF is an orally active immunomodulatory protein with a novel mechanism of action. Following oral administration, TLF interacts with the GI epithelium and gut-associated lymphoid tissue, recruiting circulating immature dendritic cells and inducing their maturation. In vitro studies demonstrate that dendritic cell maturation in the presence of tumor antigens and lymphoid effector cells induces strong innate and adaptive immune responses mediated by anticancer natural killer cells, CD8+ lymphocytes, and natural killer T cells. Such a mechanism may result in the activation of tumor-draining lymph nodes, cellular infiltration of distant tumors, and tumor cell death.[10-14] TLF is not systemically bioavailable.[15] It is plausible to speculate that TLF's initiation of the immune response in the gut-associated lymphoid tissue, which uses a physiologically important pathway that is anatomically distant from the primary tumor, may help minimize the effect of the cancer's local immunosuppressive defenses.

TLF has demonstrated antitumor activity in animal models.[12-14] In in vivo studies, oral TLF inhibited tumor growth in squamous cell and adenocarcinoma tumor models in immunocompetent mice. In phase I trials in healthy volunteers[15] and in patients with cancer,[16,17] oral TLF was well tolerated without any drug-related serious adverse events (SAEs) or grade 3 to 4 adverse events (AEs). Doses of 1.5 to 9 g/d were well tolerated without any dose-limiting toxicities or definition of a maximum-tolerated dose.[16] TLF also showed apparent anticancer activity in a phase IB cancer trial with 36 patients.[17] That trial included 12 patients with NSCLC whose disease had progressed following standard chemotherapy. The median PFS and median OS among those 12 patients were 4.3 months and 8.8 months, respectively.

On the basis of encouraging preclinical and clinical data, we conducted this randomized, double-blind, placebo-controlled, multicenter phase II trial of TLF or placebo in addition to best supportive care in patients with NSCLC whose disease had progressed following one or two prior lines of chemotherapy.

PATIENTS AND METHODS

Patient Population

The study population consisted of patients with histologically confirmed stages IIIB to IV NSCLC by American Joint Committee on Cancer (AJCC) Staging Manual (Sixth Edition) TNM staging[18] who had at least one target lesion measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) that had not been previously irradiated. For inclusion in the study, the patients had to have manifested disease progression following first-line platinum-based chemotherapy or second-line chemotherapy. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function were required.

Exclusion criteria included known uncontrolled CNS metastasis, active chemotherapy or radiotherapy, or use of steroids or an investigational agent within 4 weeks before initiating study treatment. All patients provided written informed consent in accordance with institutional and governmental regulations. Institutional review board approval was obtained at all 11 sites in India that were opened before enrolling patients.

Treatment Plan

The study was double-blind and placebo-controlled, and patients were centrally randomly assigned in a 1:1 ratio by using a permuted block method and were stratified by site. There were two treatment arms: arm 1, TLF 1.5 g in 15 mL phosphate-based buffer twice a day plus standard supportive care; arm 2, placebo 15 mL phosphate-based buffer twice a day plus standard supportive care.

A TLF dose of 3 g/d (1.5 g twice a day) was chosen as the optimum dose; it was higher than equivalent active doses in animal models, it was well tolerated in phase I studies, and higher doses did not result in any apparent increase

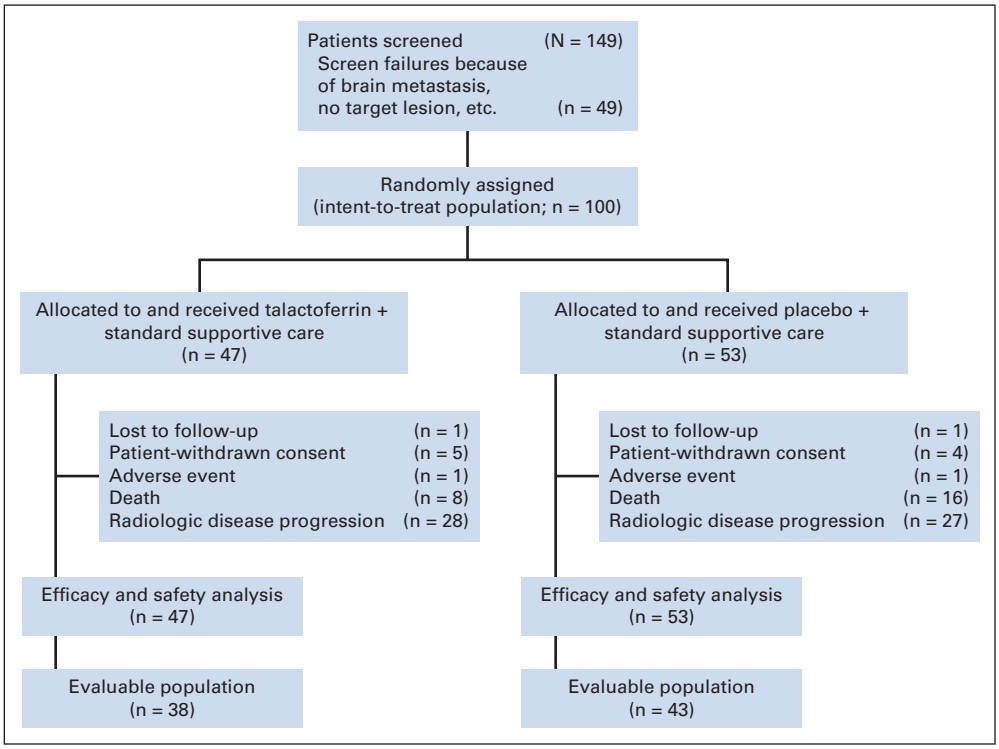

Fig 1. Trial flow.

in antitumor activity in prior clinical studies.[16,17] TLF or placebo was administered orally at the above doses for 12 consecutive weeks followed by 2 weeks off for a maximum of three cycles or until no clinical benefit was observed by the principal investigators. There were no dose reductions, and if a patient missed a dose, it was not replaced. Standard supportive care could not include any anticancer therapy.

Tumor assessment by computed tomography (CT) scan was performed approximately every 7 weeks during the first two cycles (weeks 7, 14, 21, and 28), and an additional CT scan was obtained on completion of the third cycle (week 42) if no disease progression had occurred. If a tumor response was noted, confirmation of the response was performed by a CT scan obtained a minimum of 4 weeks after it was first noted. Survival follow-up was performed for up to 18 months. Safety was assessed continuously during the study treatment period, and a safety follow-up was performed 30 days after the last dose of the study drug.

Outcome Analysis

Primary end point. The primary efficacy end point was OS in the intent-to-treat (ITT) patient population. In addition, the 6-month and 1-year OS rates were assessed. OS was defined as the duration of time from the date of random assignment to the date of death. Patients who dropped out or were lost to follow-up were censored at the last date they were known to be alive. Patients who were alive on the date of the final OS analysis were censored at that date.

Secondary efficacy end points. PFS was calculated from the date of random assignment until the date of radiologic progression or death. Disease control rate (DCR) was calculated as the sum of patients with a complete response (CR), a partial response (PR), or stable disease (SD) as assessed by CT scan according to RECIST version 1.0. Responses (PR or CR) required a confirmatory CT scan obtained at least 4 weeks after the scan first demonstrated a response. All CT assessments, including those by the site radiologist, were blinded to treatment group. The investigators, who were also blinded, provided input into determining the response status. The evaluable patient

Table 1. Summary of Baseline Patient Characteristics

Characteristic	Talactoferrin (n = 47) No.	%	Placebo (n = 53) No.	%	Overall (n = 100) No.	%
Age, years						
Mean	56.7		57.4		57.1	
SD for mean	10.4		10.7		10.5	
Median	57		59		58	
Range	32-78		27-76		27-78	
Ethnic origin						
Asian Indian	47	100	53	100	100	100
Sex						
Male	31	66	35	66	66	66
Female	16	34	18	34	34	34
NSCLC stage						
IIIB	13	28	12	23	25	25
IV	34	72	41	77	75	75
ECOG/Zubrod performance status						
0	11	23	12	23	23	23
1	36	77	41	77	77	77
Previous lines of therapy						
1	35	74	40	75	75	75
≥ 2	12	26	13	25	25	25
Prior systemic regimen						
Gemcitabine plus platinum	30	64	28	53	58	58
Taxane plus platinum	16	34	12	23	28	28
Pemetrexed plus cisplatin	4	8	8	15	12	12
Etoposide plus platinum	4	8	9	17	13	13
Other plus platinum	2	4	4	8	6	6
Prior anticancer drugs						
Platinum	47	100	53	100	100	100
Gemcitabine	30	64	28	53	58	58
Taxanes	16	34	12	23	28	28
Pemetrexed	4	8	8	15	12	12
Etoposide	4	8	9	17	13	13
Gefitinib	4	8	6	11	10	10

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer; SD, standard deviation.

Table 2. Patient Disposition, Study Drug Exposure, and Concomitant Medications for NSCLC

Variable	TLF (n = 47) No.	%	Placebo (n = 53) No.	%	Overall (n = 100) No.	%
Patient disposition						
Completed with final assessments	4	9	4	8	8	8
Discontinued from study prior to completion of three cycles	43	91	49	92	92	92
Reasons for study discontinuation						
Disease progression	28	65	27	55	55	60
Death	8	19	16	33	24	26
Patient withdrew consent	5	12	4	8	9	10
Adverse event	1	2	1	2	2	2
Lost to follow-up	1	2	1	2	2	2
Study drug exposure						
No. of cycles of study drug*						
< 1	29	62	40	75	69	69
1 to < 2	11	23	8	15	19	19
2 to < 3	4	9	1	2	5	5
3	3†	6	4	8	7	7
Weeks of administration‡						
Mean	12.7		10.2		11.4	
SD	12		10.1		11.1	
Median	7.1		6.6		6.9	
Talactoferrin or placebo compliance						
Mean		97		97		97
Median		99		99		99
Concomitant medications						
Analgesics	24	51	28	53	52	52
Antibiotics	15	32	11	21	26	26
Anti-inflammatory	13	28	19	36	32	32
Agents for cough and cold	14	30	16	30	30	30
Antiasthmatics	15	32	15	28	30	30
Antianemic agents	7	15	11	21	18	18
Corticosteroids	8	17	10	19	18	18
Antihistamines	9	19	8	15	17	17

Abbreviations: NSCLC, non–small-cell lung cancer; SD, standard deviation; TLF, talactoferrin.

*Cycles determined on the basis of whether a patient completed either required number of weeks or whether the required number of vials were returned.

†One patient in the TLF arm was recorded as having completed the final study assessments but was not counted in the summary of drug administration as having completed three cycles because of missing some doses of study drug.

‡Defined as the duration from the date of first dose to the date of the last dose.

population was prospectively defined as those patients who received at least one dose of TLF or placebo and had at least one CT scan after starting study drug (scheduled at 7 weeks after the start of study drug).

Safety end points. The safety population consisted of all patients who received at least one dose of study drug. The safety end points included treatment-emergent and study agent–related (TLF or placebo) AEs, SAEs, treatment discontinuations due to AEs, and grades 3 to 4 laboratory abnormalities according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0.

Statistical Methods

Assuming a one-sided significance level of 0.05, a sample size of 100 patients had 80% power to detect an increase in median OS from 4.5 months in the control arm to 8 months in the experimental arm. The primary analysis was conducted after 80 death events were observed. For time-to-event variables (OS and PFS), survival rates were estimated by using the Kaplan-Meier method and were compared between treatment arms by using the log-rank test. The survival rates at 6 months and 1 year were obtained by using Kaplan-Meier estimation, and the 90% CIs were estimated by using the log cumulative hazard transformation. The hazard ratios (HRs) and 90% CIs were calculated by using the Cox proportional hazard model. OS was also analyzed by prognostically important subgroups such as age (≤ 65 *v* > 65 years), sex (male *v* female), disease stage (IIIB *v* IV), ECOG performance status (0 *v* 1), prior line of systemic therapy (first *v* $\geq$ second), and histology (squamous *v* nonsquamous). Treatment interactions with each prognostic factor were also examined by using the Cox model. For categorical variables (DCR and AEs), the normal approximation method was used for point estimations. Data were compared by using the χ^2 test. As prospectively defined in the protocol, a one-tailed test and 90% CIs were used for the analyses of OS and PFS.

RESULTS

A total of 149 patients were screened, and 100 patients were randomly assigned with 47 patients in the TLF arm and 53 patients in the placebo arm. Eleven sites in India were opened, and patients were enrolled at 10 sites between October 2004 and December 2006. The primary reasons for exclusion (screening failure) included patients with brain metastases, the absence of target lesions, no prior platinum therapy, and consent withdrawal during the screening period. The trial flow is described in Figure 1. The two arms appeared to be well balanced for known prognostic factors at baseline. Prior systemic anticancer therapies also appeared to be balanced between the two arms. Demographic and baseline characteristics are summarized in Table 1.

All 100 randomly assigned patients were included in the ITT population. The prospectively defined evaluable population included 81 patients (43 in the placebo arm and 38 in the TLF arm) who received at least one dose of study drug and had at least one CT scan (scheduled at 7 weeks) after starting study drug. The reasons for being nonevaluable included death (nine in each arm) and study drug discontinuation (one in the placebo arm) before the first scheduled CT scan.

Eight patients (four in each arm) completed the study with final assessments (Table 2), and the remaining 92 patients discontinued study drug before completing three cycles of TLF or placebo. The primary reasons for study drug discontinuation were disease progression (55 patients) or death (24 patients). The study drug compliance rate was high with 97% mean and 99% median compliance in both arms (Table 2). Compliance was assessed by counting vials returned to the clinic by patients during each visit and by the patients' recording of number of vials taken in a diary.

Concomitant medications commonly used for palliative care of patients with NSCLC appeared to be balanced between the two arms (Table 2). A small number of patients received post–study drug systemic anticancer therapies (10 patients in the TLF arm and six patients in the placebo arm). Among them, five in each arm received chemotherapy, four in the TLF arm and one in the placebo arm received gefitinib, and two in the TLF arm and one in the placebo arm received other agents.

Table 3. Overall Survival (months) by Prognostic Group (ITT population)

Variable	Total		Death Events		Median		HR	90% CI
	TLF	Placebo	TLF	Placebo	TLF	Placebo		
ITT population	47	53	35	45	6.1	3.7	0.68	0.47 to 0.98
Age group, years								
≤ 65	36	39	27	32	6.1	3.3	0.70	0.45 to 1.08
> 65	11	14	8	13	5.8	4.7	0.54	0.25 to 1.18
Sex								
Male	31	35	22	30	6.1	3.3	0.62	0.39 to 0.99
Female	16	18	13	15	6.3	5.1	0.97	0.51 to 1.83
Disease stage								
IIIB	13	12	11	12	6.1	2.8	0.61	0.30 to 1.22
IV	34	41	24	33	6.1	4.0	0.68	0.44 to 1.06
ECOG performance status								
0	11	12	9	10	12.1	4.0	0.54	0.24 to 1.18
1	36	41	26	35	5.8	3.7	0.70	0.46 to 1.08
Line of therapy								
Second	35	40	26	34	6.3	3.5	0.71	0.46 to 1.10
≥ Third	12	13	9	11	5.8	4.0	0.58	0.26 to 1.28
Histology								
Squamous cell	6	15	6	14	7.9	4.2	0.43	0.16 to 1.13
Nonsquamous cell	41	38	29	31	5.8	3.5	0.70	0.45 to 1.07

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; TLF, talactoferrin.

OS

The median OS in the ITT population was 3.7 months (90% CI, 2.8 to 4.9 months) in the placebo arm and 6.1 months (90% CI, 4.7 to 8.4 months) in the TLF arm (HR, 0.68; 90% CI, 0.47 to 0.98; Table 3). The one-tailed $P = .04$ by log-rank test met the primary end point with the prospectively targeted level of statistical significance. The Kaplan-Meier curves for OS in the ITT population are shown in Figure 2A. Patients were followed for survival with a median follow-up time of 15.2 months (range, 0.2 to 24.6 months).

As shown in Figure 2D and Table 3, TLF also appeared to have an effect in prognostically important patient subsets in the ITT population (age, sex, ECOG performance status, disease stage, lines of therapy, and histology). No significant treatment interactions were observed with these prognostic factors. Adjusting for these prognostic factors in a multivariate Cox regression model showed that the treatment effect remained of the same magnitude (HR, 0.67; 90% CI, 0.46 to 0.99).

The 6-month OS rate in the ITT population was 30% (90% CI, 20% to 41%) in the placebo arm and 52% (90% CI, 39% to 63%) in the TLF arm. The 1-year OS rate in the ITT population was 16% (90% CI, 9% to 25%) in the placebo arm and 29% (90% CI, 18% to 41%) in the TLF arm.

Secondary Efficacy End Points

There were no patients with a CR. In the ITT population, a PR was observed in one patient (2%) in the placebo arm and two patients (4%) in the TLF arm, and SD was observed in 11 patients (21%) in the placebo arm and 15 patients (32%) in the TLF arm. In the ITT population, the DCR (CR + PR + SD) was 23% (90% CI, 13% to 32%) in the placebo arm and 36% (90% CI, 25% to 48%) in the TLF

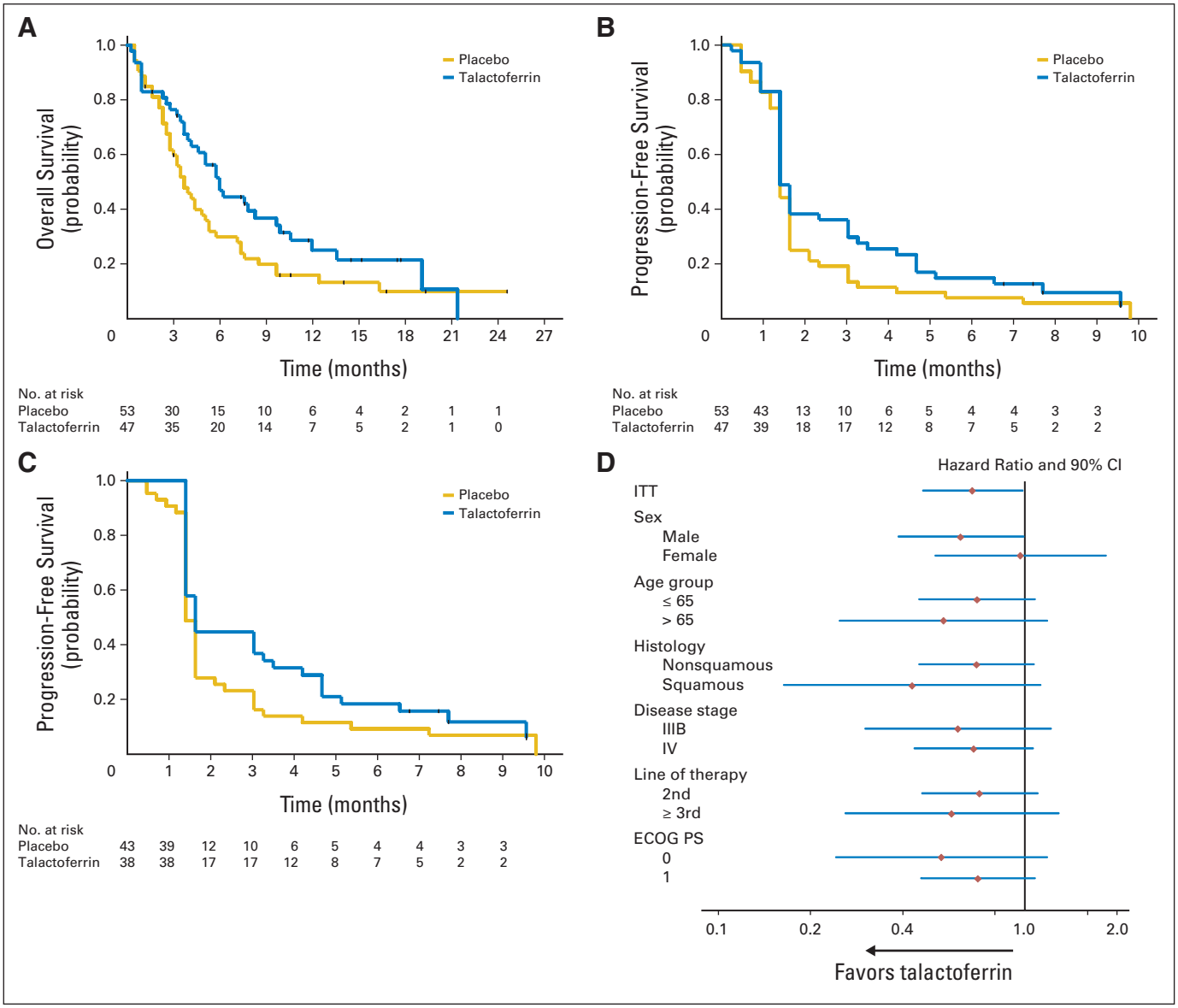

Fig 2. Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS) and forest plot for OS subgroups. (A) OS for intent-to-treat (ITT) population (n = 100). (B) PFS for ITT population (n = 100). (C) PFS for evaluable population (n = 81). (D) Forest plot for OS subgroups (n = 100). ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 4. Summary of Treatment-Emergent Adverse Events

Adverse Event	TLF (n = 47)				Placebo (n = 53)			
	Any Grade*		Grade ≥ 3†		Any Grade*		Grade ≥ 3†	
	No.	%	No.	%	No.	%	No.	%
Blood and lymphatic disorders	0	0	0	0	4	8	3	6
Anemia	0	0	0	0	3	6	2	4
Leukocytosis	0	0	0	0	1	2	1	2
Cardiac disorders	3	6	3	6	1	2	0	0
Cardiorespiratory arrest	1	2	1	2	0	0	0	0
Left ventricular failure	1	2	1	2	0	0	0	0
Supraventricular tachycardia	1	2	1	2	0	0	0	0
GI disorders	20	43	2	4	22	42	3	6
Abdominal pain	2	4	1	2	1	2	1	2
Constipation	8	17	0	0	9	17	1	2
Nausea	4	9	0	0	7	13	0	0
Vomiting	8	17	0	0	8	15	1	2
Dysphagia	2	4	1	2	0	0	0	0
General disorders and administration site conditions	21	45	2	4	31	58	6	11
Asthenia	5	11	0	0	13	25	4	9
Chest pain	7	15	1	2	7	13	0	0
Fatigue	4	9	0	0	4	8	1	2
Irritability	0	0	0	0	1	2	1	2
Pain	4	9	1	2	3	6	0	0
Peripheral edema	0	0	0	0	5	9	0	0
Pyrexia	5	11	0	0	5	9	1	2
Infections and infestations	3	6	0	0	1	2	0	0
Injury, poisoning, and procedural complications	1	2	0	0	1	2	1	2
Femoral neck fracture	0	0	0	0	1	2	1	2
Investigations	2	4	0	0	6	11	2	4
Blood ALP increased	0	0	0	0	1	2	1	2
Hemoglobin decreased	0	0	0	0	1	2	1	2
Metabolism and nutrition	13	28	2	4	16	30	4	8
Anorexia	5	11	0	0	10	19	2	4
Decreased appetite	6	13	1	2	4	8	1	2
Hypoglycemia	0	0	0	0	1	2	1	2
Hypokalemia	1	2	1	2	1	2	1	2
Hyponatremia	1	2	0	0	2	4	2	4
Musculoskeletal and connective tissue disorders	11	23	1	2	20	38	5	9
Arthralgia	1	2	0	0	4	8	2	4
Back pain	6	13	0	0	5	9	1	2
Bone pain	1	2	1	2	1	2	0	0
Muscular weakness	0	0	0	0	2	4	1	2
Pain in extremity	2	4	0	0	8	15	3	6
Shoulder pain	1	2	0	0	3	6	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1	2	1	2	0	0	0	0
Metastases to spine	1	2	1	2	0	0	0	0
Nervous system disorders	8	17	4	9	8	15	4	8
Cerebrovascular accident	1	2	1	2	0	0	0	0
Coordination abnormal	0	0	0	0	1	2	1	2
Depressed level of consciousness	1	2	1	2	0	0	0	0
Dizziness	0	0	0	0	1	2	1	2
Headache	4	8	0	0	4	8	2	4
Hemiparesis	1	2	1	2	0	0	0	0
Hemiplegia	1	2	1	2	0	0	0	0
Hypokinesia	1	2	1	2	0	0	0	0
Psychiatric disorders	1	2	1	2	3	6	1	2
Confusional state	0	0	0	0	1	2	1	2
Disorientation	1	2	1	2	1	2	1	2
Respiratory, thoracic and mediastinal disorders	27	57	10	21	28	53	17	32
Bronchospasm	0	0	0	0	1	2	1	2
Cough	15	32	2	4	9	17	2	4
Dyspnea	16	34	7	15	22	42	14	30
Dyspnea exertional	0	0	0	0	1	2	1	2
Hemoptysis	3	6	0	0	2	4	0	0
Hypercapnia	1	2	1	2	0	0	0	0
Hypoxia	1	2	1	2	0	0	0	0
Productive cough	4	9	0	0	1	2	0	0
Pleural effusion	1	2	1	2	2	4	2	4
Pneumothorax	1	2	1	2	0	0	0	0
Respiratory failure	0	0	0	0	1	2	1	2
Wheezing	0	0	0	0	1	2	1	2
Skin and subcutaneous tissue disorders	1	2	0	0	3	6	0	0
Vascular disorders	1	2	1	2	1	2	0	0
Hypertension	1	2	1	2	0	0	0	0

Abbreviation: TLF, talactoferrin.
*All adverse events of any grade reported by ≥ 5% of patients.
†Grade ≥ 3 adverse events reported by ≥ 2% of patients.

arm ($P = .14$, two-sided χ^2 test). In the evaluable population, the DCR was 28% (90% CI, 17% to 39%) in the placebo arm and 45% (90% CI, 31% to 58%) in the TLF arm ($P = .11$, two-sided χ^2 test).

The median PFS in the ITT population was 6 weeks in both arms (90% CI, 6 to 7 weeks; HR, 0.79; 90% CI, 0.56 to 1.12; $P = .10$, one-tailed log-rank test). In the evaluable population, the median PFS in the placebo arm was 6 weeks (90% CI, 6 to 7 weeks), and in the TLF arm, it was 7 weeks (90% CI, 6 to 13 weeks; HR, 0.73; 90% CI, 0.49 to 1.07; $P = .05$, one-tailed log-rank test). As shown in Figures 2B (ITT population) and 2C (evaluable population), the Kaplan-Meier curves for PFS separated after the median PFS was reached.

Safety Results

TLF was well-tolerated in the study. AEs were generally mild. No drug-related SAEs were reported. Relative to the patients who received placebo, patients who received TLF had a lower incidence of grade ≥ 3 AEs and SAEs. The most frequent AEs were consistent with those typically observed in patients with late-stage NSCLC.

Generally, there were fewer AEs and grade ≥ 3 AEs in the TLF arm. There were 165 AEs reported in the TLF arm and 230 in the placebo arm. For grade ≥ 3 AEs, there were 73 in the placebo arm and 36 in the TLF arm. Analysis for differences in the number of patients with AEs by body system showed a significantly lower proportion of patients in the TLF arm with AEs in musculoskeletal and connective tissues compared with patients in the placebo arm (two-tailed $P = .04$, χ^2 test). All AEs and grade ≥ 3 AEs reported by ≥ 5% and ≥ 2% of patients, respectively, are listed in Table 4.

DISCUSSION

Oral TLF is a novel agent with an immunomodulatory mechanism of action. TLF has demonstrated anticancer activity in animal models and in combination with chemotherapy.[12-14] More recently, apparent anticancer activity was observed with TLF in combination with carboplatin and paclixatel in a double-blind, placebo-controlled phase II trial in 110 chemotherapy-naive patients with stages IIIB to IV NSCLC.[19] Addition of oral TLF to standard first-line chemotherapy resulted in apparent improvements in response rate, PFS, and OS. Single-agent activity was also observed in a phase II trial[20] in patients with renal cell cancer for whom previous chemotherapy had failed.

On the basis of encouraging early data with oral TLF and its novel mechanism of action, we initiated a randomized, double-blind, placebo-controlled phase II trial in patients with NSCLC for whom one or two prior lines of chemotherapy had failed. This placebo-controlled trial enrolled patients at 10 of the leading cancer sites in India. The median age of patients enrolled in this trial (approximately age 58 years) is consistent with that reported in the literature for Indian patients with NSCLC[21] and is lower than the age of patients typically enrolled in clinical trials in Western populations.

In this report, we have shown that TLF improved survival compared with placebo with the protocol-specified level of significance. TLF also appeared to have an effect in prolonging survival in prognostically important patient subsets. TLF's anticancer activity appeared to be consistent across the prospectively defined secondary end points with improvement trends observed in PFS and DCR.

TLF was well tolerated in this trial. There were fewer total AEs and grade ≥ 3 AEs reported in the TLF arm compared with the placebo arm. The majority of the AE reductions were in constitutional symptoms including asthenia, anorexia, and musculoskeletal disorders that are attributable to end-stage cancer and are consistent with the known anti-inflammatory[22] and antinociceptive[23,24] activities of TLF. The reduction in AEs in the TLF arm is consistent with the findings seen in the trial of combined TLF and chemotherapy in first-line treatment of NSCLC.[19]

Since the phase II study was conducted in India, these results may not be generalizable to other populations. However, in a phase IB study conducted in the United States, there was some evidence of activity in a small number of patients with NSCLC,[17] which led to the conduct of this phase II study. The findings from this phase II study and the need for new therapies in NSCLC warrant the study of TLF in patients for whom prior therapies for NSCLC have failed. TLF is currently being evaluated in two phase III trials in NSCLC. The first study, conducted globally in patients for whom two or more previous treatments have failed, has a primary end point of survival and compares TLF to placebo in patients who are also receiving best supportive care. The second study is an NSCLC trial that compares the addition of TLF or placebo to carboplatin-paclitaxel in first-line treatment. Patients may receive up to six cycles of chemotherapy, and if the disease has not progressed following completion of chemotherapy, TLF or placebo will be continued until disease progression. The study coprimary end points are PFS and OS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Collection and assembly of data: All authors
Data analysis and interpretation: All authors
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