Talactoferrin alfa versus placebo in patients with refractory advanced non-small-cell lung cancer (FORTIS-M trial)


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Received 29 May 2013; revised 24 July 2013; accepted 25 July 2013

Background: Talactoferrin alfa is an oral dendritic cell (DC)-mediated immunotherapy (DCMI). We tested whether talactoferrin was superior to placebo in advanced non-small-cell lung cancer (NSCLC).

Patients and methods: An FORTIS-M trial was an international, multicenter, randomized, double-blind comparison of talactoferrin (1.5 g p.o. BID) versus placebo BID, in patients with stage IIIB/IV NSCLC whose disease had failed two or more prior regimens. Treatment was administered for a maximum of five 14-week cycles. The primary efficacy end point was overall survival (OS); secondary end points included 6- and 12-month survival, progression-free survival (PFS), and disease control rate (DCR).

Results: Seven hundred and forty-two patients were randomly assigned (2:1) to talactoferrin (497) or placebo (245). The median OS in the intent-to-treat (ITT) population was 7.66 months in the placebo arm and 7.49 months in the talactoferrin arm [hazard ratio (HR), 1.04; 95% CI, 0.873–1.24; P = 0.6602]. The 6-month survival rates were 59.9% (95% CI, 53.4% to 65.8%) and 55.7% (95% CI, 51.1% to 59.9%), respectively. The 12-month survival rates were 32.2% (95% CI, 26.3% to 38.2%) and 30.9% (95% CI, 28.6% to 35%), respectively. The median PFS rates were 1.64 months and 1.68 months, respectively [hazard ratio (HR), 1.09; 95% CI, 0.835–1.16; P = 0.6602]. The DCRs were 38.4 and 37.6%, respectively [stratified odds ratio (OR), 1.33; 95% CI, 0.873–1.99; P = 0.1633]. The safety profiles were comparable between arms.

Conclusions: There was no improvement in efficacy with talactoferrin alfa in patients with advanced NSCLC whose disease had failed two or more previous regimens.

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**Key words:** non-small-cell lung cancer, immunotherapy, phase III study, talactoferrin

**introduction**

Lung cancer is the most frequent cause of cancer-related deaths worldwide and non-small-cell lung cancer (NSCLC) accounts for the vast majority of all lung cancers [1,2]. While a number of different chemotherapeutic combinations and targeted treatments are approved for first- and/or second-line treatment of NSCLC [3–5], options for third-line treatment are limited. Docetaxel (Taxotere) (Sanofi Aventis, Bridgewater, NJ), pemetrexed, or erlotinib are recommended as second line treatment of NSCLC for patients with the performance status of 0–2 who have not received these agents previously [6]. At present, only erlotinib is approved for third-line treatment of NSCLC.

Immunotherapy is receiving increasing attention for the treatment of many malignancies [7,8] and it may be useful in patients with advanced NSCLC [9]. Talactoferrin alfa is an oral dendritic cell (DC)-mediated immunotherapy (DCMI). It is a recombinant form of human lactoferrin, an immunostimulatory protein that is thought to play an important role in establishing and maintaining the immune system [10–12]. Orally administered talactoferrin alfa is believed to bind to the gut epithelium and interact with DCs in the gut wall [11,13,14]. This binding produces an immunostimulatory cytokine cascade in the gut, which stimulates the migration and maturation of tumor antigen-presenting DCs. The matured DCs present tumor-associated antigens to T lymphocytes and activate them and the effector T lymphocytes make their way to distal tumors, where they infiltrate and inhibit tumor growth [11,14]. Talactoferrin alfa has demonstrated significant antitumor activity in multiple in vivo and in vitro models [11,15,16].

Monotherapy with talactoferrin alfa has been investigated in a randomized, double-blind, placebo-controlled trial in 100 patients with stage IIIIB/IV NSCLC for whom one or two prior lines of systemic anticancer therapy had failed [17]. Compared with placebo, talactoferrin alfa increased the median OS by 65% (3.7–6.1 months; one-tailed P = 0.04). The results from this phase II study prompted initiation of FORTIS-M.

**methods**

This was an international, phase III, randomized, double-blind, placebo-controlled trial of talactoferrin alfa in patients with histologically or cytologically confirmed stage IIIIB/IV NSCLC whose disease had failed two or more prior systemic anti-cancer regimens, including at least one platinum-containing regimen, for advanced or metastatic NSCLC. Patients were randomly assigned in a 2:1 ratio to receive oral talactoferrin alfa at a dose of 1.5 g twice daily (BID) or placebo BID. Randomization was carried out centrally using a permuted block method, and stratified according to (i) prior regimens for advanced or metastatic disease (2 versus ≥3); (ii) Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2); and (iii) geographic region [North America (NA) versus Europe versus rest of the world]. The proportions of patients enrolled with histologies other than squamous or adenocarcinoma or with stable brain metastases were each capped at 10%.

The study was conducted in compliance with the protocol, ICH Good Clinical Practice Guidelines, and the applicable local regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before study entry. An independent Data Safety Monitoring Board reviewed accumulating safety data from the ongoing study in an unblinded fashion.

**eligibility criteria**

Inclusion criteria included ≥18 years of age and one or more target lesions that was unirradiated and measurable by RECIST version 1.0, an ECOG performance status of 0–2 and life expectancy of >12 weeks.

Patients with brain metastases were excluded unless they had received brain irradiation. Patients with a history of other malignancies were excluded, except adequately treated basal or squamous cell carcinoma of the skin; curatively treated in situ carcinoma of the uterine cervix, prostate cancer, or superficial bladder cancer; or other curatively treated solid tumors with no evidence of disease for ≥5 years. Excluded were also patients with a history of allergic reactions to talactoferrin alfa or similar compounds, patients with any condition that interfered with the ability to take oral medications, those with uncontrolled ischemic heart disease or uncontrolled symptomatic congestive heart failure, those with serious active infections, patients who had received radiotherapy or any investigational agent within 4 weeks of randomization, women who were pregnant or lactating, and patients on oral corticosteroid therapy within 4 weeks before randomization, except replacement therapy for adrenal insufficiency.

**study setting and procedures**

The study was carried out at 163 medical centers in 23 countries in North America (NA), Europe, and the rest of the world. Within 14 days before randomization, medical history, physical examination, performance status, and baseline clinical signs and symptoms were assessed, an electrocardiogram, clinical laboratory tests, and baseline tumor assessment by computed tomography (CT) scan of the chest and abdomen to include the adrenal glands (and CT or magnetic resonance imaging to include all known or suspected sites of disease as appropriate) were done.

Treatment was administered within 24 h of randomization. Talactoferrin alfa 1.5 g BID, or an equivalent volume of placebo BID was administered in 14-week cycles. Each talactoferrin alfa or placebo cycle included 12 weeks on study drug and 2 weeks off. All patients also received best supportive care. Talactoferrin alfa or placebo were continued for up to a maximum of five 14-week cycles, until the occurrence of progressive disease (PD), start of a next-line therapy for NSCLC, unacceptable toxicity, withdrawal of consent, or withdrawal by investigator, whichever occurred first. Treatment could be continued beyond the occurrence of PD at the discretion of the investigator for up to a maximum of five 14-week cycles (70 weeks), provided that there appeared to be clinical benefit, and there were no appropriate additional therapies available. All patients were followed for survival for ≥12 months from the date of randomization or until the data cut-off for the principal analysis for survival occurred (16th April 2012), whichever was later. In addition, an extension protocol provided ongoing study drug to patients who previously completed all five cycles of study drug in the FORTIS-M study and had no other available alternative therapies. Patients entering this extension had no evidence of disease progression and sufficient medical condition.

**statistical analysis**

The primary end point was OS and secondary end points included 6- and 12-month survival rates, PFS, objective tumor response rate (ORR), disease control rate (DCR); safety and tolerability.
With 576 events (deaths) in an original sample size of 720 patients, this study was designed to have 85% power to detect a 30% improvement in median OS in intent-to-treat (ITT) patients from 4.6 months in the placebo arm to 6.0 months in the talactoferrin alfa arm with a two-sided P-value of 0.05. OS was estimated using the Kaplan–Meier method, and compared between treatment groups using the log-rank test, stratified by prior regimens for advanced or metastatic disease (2 versus ≥3), ECOG performance status (0 or 1 versus 2), and geographic region (NA versus Europe versus rest of the world). The HR between the treatment arms and its 95% CI were estimated from a stratified proportional hazard model (Cox model) including the stratification factors. PFS for the talactoferrin alfa and placebo groups was compared using a stratified log-rank test with the stratification factors noted for the randomization. A stratified Cox regression model was carried out to compare talactoferrin alfa and placebo and generate the HR and 95% CI. ORR and DCRs with 95% CIs were determined and the differences between groups were evaluated for statistical significance in a two-tailed test at the 0.05 level using a Cochran–Mantel–Haenszel test stratified for the factors used in the randomization.

results

patient characteristics

Between November 2008 and March 2011, a total of 1076 patients were screened and 742 were enrolled and randomly assigned to talactoferrin alfa (497) or placebo (245) (supplementary Figure S1, available at Annals of Oncology online). All patients enrolled were included in the efficacy and safety analyses. The groups were balanced with respect to baseline characteristics and important prognostic variables (Table 1). Most patients had stage IV NSCLC, and had received three or more prior treatment regimens.

efficacy

Patients were followed for survival for a median of 19.6 months in the talactoferrin alfa arm and 18.1 months in the placebo arm. At the time of analysis, 592 deaths had occurred (401 in the talactoferrin alfa group and 191 in the placebo group). The median OS in the ITT population was 7.66 months in the placebo arm and 17.5% in the placebo group. The median OS in the ITT population was 7.66 months in the placebo arm and 19.6 months in the talactoferrin alfa arm and 191 in the placebo group). The median OS in the ITT population was 7.66 months in the placebo arm and 7.66 months in the talactoferrin alfa arm (95% CI, 1.97; HR, 0.99; P = 0.8073) (Figure 1B).

Table 2 summarizes the tumor responses. The DCR was 38.4% (95% CI, 32.2–44.8%) for placebo and 37.6% (95% CI, 33.4–42.0%) for talactoferrin alfa (stratified OR, 0.96; 95% CI, 0.698–1.33; P = 0.8336). Overall, 17.4% of patients continued the study drug beyond disease progression (17.3% in the talactoferrin alfa group and 17.5% in the placebo group).

post-study treatment

A total of 215 patients treated with talactoferrin alfa (43.3%) and 116 of those who received placebo (47.3%) had additional anticancer treatments following the study (supplementary Table S1, available at Annals of Oncology online). Therapies
administered most often were chemotherapy (26.6% for talactoferrin alfa and 30.2% for placebo) and EGFR TKI (13.7% for talactoferrin alfa and 13.3% for placebo).

safety

Patients in the talactoferrin alfa arm took 97.6% of planned doses versus 97.8% for placebo. The median duration of treatment was 60 days for patients in each arm.

The safety profiles for placebo and talactoferrin alfa were comparable (Table 3). Treatment emergent adverse events (TEAEs, adverse events that occurred after initiation of treatment) were reported for 86.0% of patients who received placebo and 87.3% of those who received talactoferrin alfa. The respective values for grade ≥3 TEAEs were 46.7% and 48.5%, and those for serious TEAEs were 41.7% and 43.7% for the placebo and talactoferrin alfa arms. Treatment-related TEAEs were reported for 21.1% of patients who received placebo and 20.1% of those who received talactoferrin alfa. Dyspnea was the most common TEAE in each group (12.4% for placebo versus 9.1% for talactoferrin alfa).

discussion

This phase III trial demonstrated no benefit of oral talactoferrin alfa versus placebo, for improving OS, PFS, or DCR in patients with stage IIIIB/IV NSCLC whose disease had failed two or more prior treatment regimens. Safety results from this trial showed that the safety and tolerability of talactoferrin alfa were comparable to those for placebo. The lack of a significant effect of talactoferrin alfa monotherapy versus placebo in patients with advanced NSCLC was independent of known risk factors.
Patients with any TEAE leading to discontinuation of the study drug

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Talactoferrin alfa</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 TEAEs</td>
<td>258 (52.2)</td>
<td>143 (59.1)</td>
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The present results differ substantially from those obtained in a smaller phase II study of talactoferrin alfa in 100 patients with advanced NSCLC who had failed one or two prior treatment regimens [17]. In that trial, the median OS for talactoferrin alfa was 6.1 months versus 3.7 months for placebo (one-tailed P = 0.04). A few factors could potentially have impacted the different outcomes in the two trials. The phase II study was carried out in patients who had received one or two prior regimens and 75% had received only one prior line of treatment [17], whereas patients in FORTIS-M had received at least two prior regimens, and >50% had received three or more prior lines of treatment. In addition, the phase II trial was conducted in India, patients had an ECOG performance status of 0 or 1, and the median age of patients was 58 years, which is consistent with the previously reported younger age of Indian patients enrolled in NSCLC trials [18]. In contrast, 14% of patients in FORTIS-M had ECOG performance status of 2, only 17% of the patient population was Asian, and the median ages for patients in the talactoferrin alfa and placebo arms were 62 and 63 years, respectively. While these differences could potentially have impacted outcome, the subgroup analyses of results from FORTIS-M indicates that none of them were significant determinants of study results. There is a suggestion in the subgroup analysis that results favored talactoferrin alfa over placebo in Asian patients, but the confidence interval is very wide due to the fact that only 125 such patients were included in the study. It is worth noting that subset analyses of results from other recent studies of treatment of NSCLC have indicated a better efficacy in Asian patients versus entire study cohorts [19–21].

The major difference between the results of the phase II trial and FORTIS-M is that the median OS for patients who received placebo plus best supportive care in the present trial (7.66 months) was much longer than that in the phase II trial (3.7 months). The median OS for patients who received placebo in the present trial also appears to be substantially longer than that for patients receiving placebo in some older, but not more recent, studies of second- and third-line treatment for patients with advanced NSCLC. Results from the BR.21 study of erlotinib as second-line treatment in patients with NSCLC indicated an OS of 4.7 months for patients receiving placebo; [22] the median OS for patients receiving placebo in the ISEL study of gefitinib as second-line treatment of NSCLC was 5.1 months [23]. Results from some other more recent studies have suggested that OS with best supportive care has increased substantially. For example, LUX-Lung 1 randomized 585 patients with stage IIIB/IV adenocarcinoma and an ECOG performance score of 0–2 who had received one or two previous chemotherapy regimens and had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib to afatinib or placebo, each plus best supportive care. The median OS was 12.0 months in the placebo group [24]. Similarly, the ZEPHIR trial compared vandetanib with placebo in 914 patients with advanced NSCLC after prior treatment with an EGFR TKI and one or two chemotherapy regimens. The median OS was 7.8 months for placebo patients [25]. Overall, this represents a selection bias that appears to be intrinsic to studies conducted in the third-line setting and beyond, as the patients with more rapidly progressive disease do not survive to receive multiple lines of systemic therapy. The survival duration from our study will serve as benchmarks for future studies in this patient population. Another limitation of our study is the lack of mechanistic data on activation of DCs in patients treated with talactoferrin alfa. A reliable read-out in peripheral blood would have been useful in determining the correlation between biological activity and efficacy of this agent.

In conclusion, treatment options for advanced NSCLC beyond third-line setting continue to be an area of unmet need. Talactoferrin alfa was not active as monotherapy in this setting. As the development of agents that target the immune system is critical to their success, the phase II trial was conducted in India, patients had an ECOG performance status of 0 or 1, and the median age of patients was 58 years, which is consistent with the previously reported younger age of Indian patients enrolled in NSCLC trials [18]. In contrast, 14% of patients in FORTIS-M had ECOG performance status of 2, only 17% of the patient population was Asian, and the median ages for patients in the talactoferrin alfa and placebo arms were 62 and 63 years, respectively. While these differences could potentially have impacted outcome, the subgroup analyses of results from FORTIS-M indicates that none of them were significant determinants of study results. There is a suggestion in the subgroup analysis that results favored talactoferrin alfa over placebo in Asian patients, but the confidence interval is very wide due to the fact that only 125 such patients were included in the study. It is worth noting that subset analyses of results from other recent studies of treatment of NSCLC have indicated a better efficacy in Asian patients versus entire study cohorts [19–21].

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**Acknowledgements**

funding

This trial was funded by Agennix Inc.

disclosure

YW, PP, JZ, and RM are Agennix employees; all remaining authors have declared no conflicts of interest.

references