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Phase I/II study of tecemotide as immunotherapy in Japanese patients with unresectable stage III non-small cell lung cancer

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ABSTRACT

Objectives: Unresectable stage III NSCLC (non–small cell lung cancer) confers a poor prognosis and interest is growing in the use of immunotherapy to improve outcomes for patients with this disease. We investigated the safety and efficacy of maintenance tecemotide, a mucin 1 (MUC1)-specific agent that induces T-cell responses to MUC1, versus placebo in Japanese patients with stage III unresectable NSCLC and no disease progression after primary chemoradiotherapy.

Materials and methods: Patients aged ≥20 years with unresectable stage III NSCLC, stable disease or clinical response after primary chemoradiotherapy and performance status ≤1, were recruited across 25 centers in Japan. Patients were randomized 2:1 to tecemotide (930 μg as lipopeptide) or placebo subcutaneously once weekly for 8 weeks, then every 6 weeks until disease progression or treatment withdrawal. Cyclophosphamide 300 mg/m^2 (maximum dose 600 mg) was given intravenously 3 days before the first dose of tecemotide. The primary endpoint was overall survival (OS). Secondary endpoints were progression–free survival, time to progression, time to treatment failure and safety.

Results: The intent–to–treat population comprised 172 patients; 114 received tecemotide and 58 placebo. Baseline characteristics were comparable between treatment arms. Most patients (94%) received primary concurrent chemoradiotherapy. There was no apparent trend toward increased OS time with tecemotide over placebo (median 32.4 versus 32.2 months, hazard ratio 0.95, 95% confidence interval 0.61–1.48; $P = 0.83$). No improvements in secondary efficacy endpoints were observed. The frequency of treatment–related adverse events was similar, and serious adverse event rates were the same in both arms. There were no new safety signals.

Abbreviations;: AJCC, American Joint Committee on Cancer; ANA, antinuclear antibody; CI, confidence intervals; EGFR, epidermal growth factor; HR, hazard ratio; ISR, injection site reactions; ITT, intent-to-treat; mITT, modified intent-to-treat; MUC1, mucin 1; NSCLC, non-small cell lung cancer; OS, overall survival; PD, disease progression; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; sMUC1, soluble mucin 1; START, stimulating targeted antigenic response to NSCLC; TEAE, treatment-emergent adverse events; TTF, time to treatment failure; TTP, time to progression; UICC, Union Internationale Contre le Cancer.

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Conclusions: These results do not support those from a randomized phase III study (START) of improved OS with tecemotide in the subgroup of patients treated with primary concurrent chemoradiotherapy.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for 80–85% of cases [1], and around 30% of patients present with stage III (locally advanced) disease [2].

Standard treatment of patients with locally advanced NSCLC who have good performance status is based on platinum doublet chemotherapy plus thoracic radiotherapy, and is given with curative intent [1]. However, results are frequently suboptimal, and 5-year overall survival (OS) for patients with locally advanced NSCLC remains disappointing at only 15% with concurrent chemoradiotherapy [3]. Addition of consolidation chemotherapy after concurrent chemoradiotherapy does not appear to yield further benefit [4].

Interest is growing in the use of immunotherapy in lung cancer [5], and therapeutic cancer vaccines in development include tecemotide (L-BLP25; Merck KGaA, Darmstadt, Germany), a mucin 1 (MUC1)-specific agent that induces T-cell responses to MUC1 [6,7], MUC1 is overexpressed and abnormally glycosylated in NSCLC [8,9], which leads to inappropriate activation of signaling pathways and the subsequent growth, proliferation and survival of cancer cells [10].

The international phase III START (Stimulating Targeted Antigenic Response To NSCLC) trial of tecemotide versus placebo as maintenance therapy in patients with stage III NSCLC who had received chemoradiotherapy indicated potential OS improvement over placebo in the subgroup of patients who had received primary concurrent rather than sequential chemoradiotherapy [11,12]. The present phase I/II trial (NCT00960115) was designed to investigate the safety and efficacy of maintenance tecemotide versus placebo in Japanese patients with stage III unresectable NSCLC and no disease progression (PD) after primary chemoradiotherapy. The results of the phase I safety run-in part confirmed the tolerability and safety of tecemotide for the phase II part and have been reported previously [13].

The phase II results are reported here. The primary objective was to compare OS time with tecemotide and placebo; secondary objectives were to compare progression-free survival (PFS), time to progression (TTP), time to treatment failure (TTF) and safety.

2. Materials and methods

2.1. Patients

Patients aged ≥20 years with unresectable histologically or cytologically documented stage III NSCLC, with stable disease or clinical response (Response Evaluation Criteria In Solid Tumors; RECIST version 1.0) after primary chemoradiotherapy (≥2 cycles of platinum-based chemotherapy plus ≥50 Gy concurrent or sequential thoracic radiotherapy), white blood cell count ≥2500/mm^3 [2.5 × 10^9/L], hemoglobin ≥9.0 g/dL [90 g/L], and platelet count ≥140,000/mm^3 [140 × 10^9/L], and Eastern Cooperative Oncology Group performance status ≤1 were recruited. Randomization was within 4–12 weeks of primary treatment completion.

Patients were excluded if they had received NSCLC-specific therapy other than primary chemoradiotherapy (e.g. surgery), or if they had metastatic disease, malignant pleural effusion, autoimmune disease or conditions requiring long-term corticosteroid or immunosuppressive treatment (except therapy for radiation pneumonitis). Patients with immunodeficiency, splenectomy, significant infection or hepatitis B or C infection were also excluded, as were those with safety concerns such as pregnancy or significant organ dysfunction.

2.2. Study design

This was a multicenter (25 centers), randomized, double-blind and placebo-controlled trial, conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice. The protocol was approved by all relevant authorities and institutional review boards, and fully informed consent was obtained from all participants.

Central randomization and treatment allocation in the phase II part was performed. Patients were randomized 2:1 to receive tecemotide (930 μg as lipopeptide) or placebo subcutaneously once a week for 8 weeks (initial treatment), then every 6 weeks (maintenance) until PD or withdrawal. Patients were stratified by disease stage at first diagnosis (IIIA versus IIIB; American Joint Committee on Cancer [AJCC]/Union Internationale Contre le Cancer [UICC] 6th edition), histology (adenocarcinoma versus non-adenocarcinoma), and concurrent versus sequential primary chemoradiotherapy. Best supportive care was provided to all patients according to institutional standards and the investigator's judgment.

A clinical hold was placed on tecemotide trials in March 2010 to allow re-evaluation of the risks and benefits of the drug, but was subsequently lifted in June 2010 [11].

2.3. Cyclophosphamide

A single dose of cyclophosphamide 300 mg/m^2 (maximum dose 600 mg) was given intravenously 3 days before the first tecemotide dose to overcome immune suppression due to malignant disease that might have interfered with responses to tecemotide (patients randomized to placebo received intravenous saline).

Cyclophosphamide is known to have a dose-dependent effect on the immune system. High doses can induce immunosuppression by reducing T cell proliferation and inducing apoptosis [14]. Low doses (metronomic cyclophosphamide) have been shown to reduce the levels of T_{regs} and dampen their T cell suppressive ability, thus boosting the immunological benefit of vaccines. Furthermore, cyclophosphamide has been shown to restore effector T cell and natural killer (NK) cell function, deplete B cells, and augment the activation and function of dendritic cells (DC) [15]. Combining low-dose cyclophosphamide with new generation anticancer vaccines has paved the way for new treatment strategies in the field of cancer immunotherapy [16]. In the present study, low-dose intravenous cyclophosphamide was incorporated into the tecemotide schedule. The rationale for this incorporation was based on a trial by MacLean and colleagues that showed a superior immune response to the STn-KLH (Theratope) vaccine in patients with breast cancer who received intravenous cyclophosphamide compared with those who received oral cyclophosphamide [17].

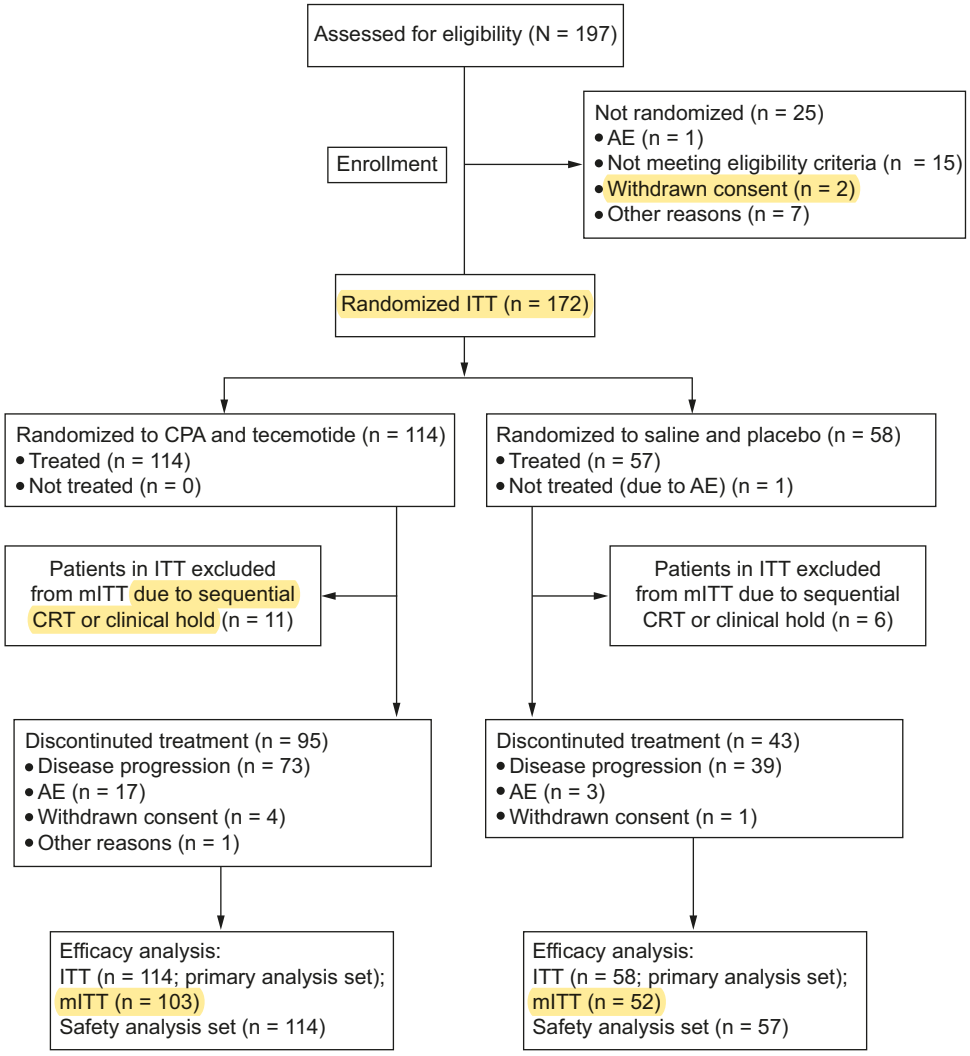

Fig. 1. Patient disposition throughout the phase II study. CRT, chemoradiotherapy; AE, adverse event; TEAE, treatment-emergent AE; CPA, cyclophosphamide; ITT, intention-to-treat; mITT, modified ITT.

2.4. Assessments

OS time was defined as the time between date of randomization and death. PD was determined according to RECIST version 1.0 criteria, confirmed radiologically where possible, and was determined by the investigator according to institutional standards.

Safety was assessed in terms of rate, intensity and relationship to trial drug of individual treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation and serious TEAEs. Events of special interest included injection site reactions (ISRs), potentially immune-related events and flu-like symptoms.

All data were collected and managed using electronic case report forms.

2.5. Analysis

Analysis was based on the intent-to-treat (ITT) patient population randomized in the phase II study, and the modified ITT (mITT) patient population randomized after the clinical hold, who had received concurrent primary chemoradiotherapy. The safety population comprised all patients who received at least one dose of study medication. Subgroup analysis sets were also predefined to include factors such as baseline disease stage and histology, response to primary therapy, biochemistry, immunologic and mutational status, performance status, age, sex and smoking history.

The planned number of 150 patients (100 patients in the investigational arm and 50 in the control arm) was based on an assumed median OS time increase from 24 to 34 months (hazard ratio; HR 0.71), uniform accrual over 18 months, and an expected duration of 48 months until the primary OS time analysis. The trial was not powered to demonstrate statistically significant differences between tecemotide and placebo, but to assess an informative trend toward prolonged OS time.

The primary analysis of OS time used a Cox proportional hazards regression model adjusted for the stratification variables, stage and histology. The stratification variable for concurrent/sequential chemoradiotherapy was not included in the model due to the low number of sequentially pretreated patients. Kaplan–Meier analysis with associated statistics (medians and 95% confidence intervals [CIs]) were calculated. Secondary efficacy endpoints were evaluated using the same methodology. None of the analyses were adjusted for multiplicity. Data were analysed using SAS® software (Statistical Analysis System, SAS Institute, North Carolina, USA), version 9.1.3 or later.

Table 1
Summary of baseline characteristics (intention-to-treat population).

	Tecemotide (n = 114)	Placebo (n = 58)	Overall (N = 172)
Sex, n (%)			
Male	98 (86.0)	47 (81.0)	145 (84.3)
Female	16 (14.0)	11 (19.0)	27 (15.7)
Median age, years (range)	62.0 (33–86)	63.0 (36–81)	63.0 (33–86)
Tobacco use, n (%)			
Former smoker	100 (87.7)	47 (81.0)	147 (85.5)
Current smoker	5 (4.4)	3 (5.2)	8 (4.7)
Never smoked	9 (7.9)	8 (13.8)	17 (9.9)
ECOG PS, n (%)			
0	56 (49.1)	28 (48.3)	84 (48.8)
1	58 (50.9)	30 (51.7)	88 (51.2)
Disease stage at first diagnosis, n (%)			
IIIA	40 (35.1)	20 (34.5)	60 (34.9)
IIIB	74 (64.9)	38 (65.5)	112 (65.1)
Not known	0	1 (1.7)	1 (0.6)
Histology, n (%)			
Adenocarcinoma	68 (59.6)	34 (58.6)	102 (59.3)
Non-adenocarcinoma	46 (40.4)	24 (41.4)	70 (40.7)
Squamous cell	39 (34.2)	23 (39.7)	62 (36.0)
Large cell	1 (0.9)	1 (1.7)	2 (1.2)
Other	7 (6.1)	0	7 (4.1)
EGFR status			
Wild type	63 (55.3)	35 (60.3)	98 (57.0)
Mutant	11 (9.6)	5 (8.6)	16 (9.3)
Not known	40 (35.1)	18 (31.0)	58 (33.7)
Baseline ANA titer[a]			
Positive	42 (36.8)	15 (25.9)	57 (33.1)
Negative	72 (63.2)	43 (74.1)	115 (66.9)
Type of primary chemoradiotherapy, n (%)[b]			
Concurrent	107 (93.9)	55 (94.8)	162 (94.2)
Sequential	7 (6.1)	3 (5.2)	10 (5.8)
Chemotherapy administered, n (%)[c]			
Carboplatin/paclitaxel	23 (20.2)	10 (17.2)	33 (19.2)
Cisplatin/paclitaxel	14 (12.3)	12 (20.7)	26 (15.1)
Cisplatin/gimeracil + oteracil potassium/tegafur	23 (20.2)	7 (12.1)	30 (17.4)
Cisplatin/vinorelbine	51 (44.7)	27 (46.6)	78 (45.3)
Other	9 (7.9)	6 (10.3)	15 (8.7)
Response to primary chemoradiotherapy, n (%)			
Stable disease	19 (16.7)	8 (13.8)	27 (15.7)
Objective response (partial or complete)	95 (83.3)	50 (86.2)	145 (84.3)

ANA, antinuclear antibody; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] An ANA titer <1:40 was considered to be negative.
[b] As recorded in the electronic case report form.
[c] Patients may have received more than one prior chemotherapy regimen.

Table 2
Summary of TEAEs (safety population).

	Tecemotide (n = 114)	Placebo (n = 57)
	n (%)	n (%)
Any TEAE	108 (94.7)	53 (93.0)
Any treatment-related TEAE	55 (48.2)	27 (47.4)
Any serious TEAE	24 (21.1)	12 (21.1)
Any serious treatment-related TEAE	6 (5.3)	3 (5.3)
Any grade 3/4 TEAE	29 (25.4)	10 (17.5)
Any grade 3/4 treatment-related TEAE	10 (8.8)	3 (5.3)

TEAE, treatment-emergent adverse event.

Safety analyses were based on the latest available version of the Medical Dictionary for Regulatory Activities and were presented as descriptive summaries.

3. Results

3.1. Patient characteristics

Between February 2010 and February 2012, 172 patients were randomized to the ITT population, 114 and 58 to the tecemotide and placebo arms, respectively. There were 155 patients in the mITT population (103 tecemotide, 52 placebo), and 171 in the safety population (114 tecemotide, 57 placebo). The mITT population prospectively excluded seven patients randomized prior to the clinical hold and 10 who received primary sequential chemoradiotherapy (according to interactive voice response system data). One patient in the placebo arm was randomized but did not start treatment, and was therefore excluded from the safety population. Data cut-off was on 1 May 2014. At the primary analysis, 95 (83.3%) and 43 (74.1%) ITT patients in the tecemotide and placebo arms, respectively, had discontinued treatment, mostly because of PD (73 [76.8%] and 39 [90.7%] patients, respectively).

Patient disposition is shown in Fig. 1; demographics for the ITT population are shown in Table 1. Key baseline characteristics, including age and sex, were well balanced between treatment arms in the ITT population (Table 1); baseline characteristics were comparable in the mITT population. The majority of patients in the ITT population (94%) had received primary concurrent chemoradiotherapy.

3.2. Treatment

Median treatment exposure time was 35.7 weeks for tecemotide and 27.4 weeks for placebo. Median number of administrations

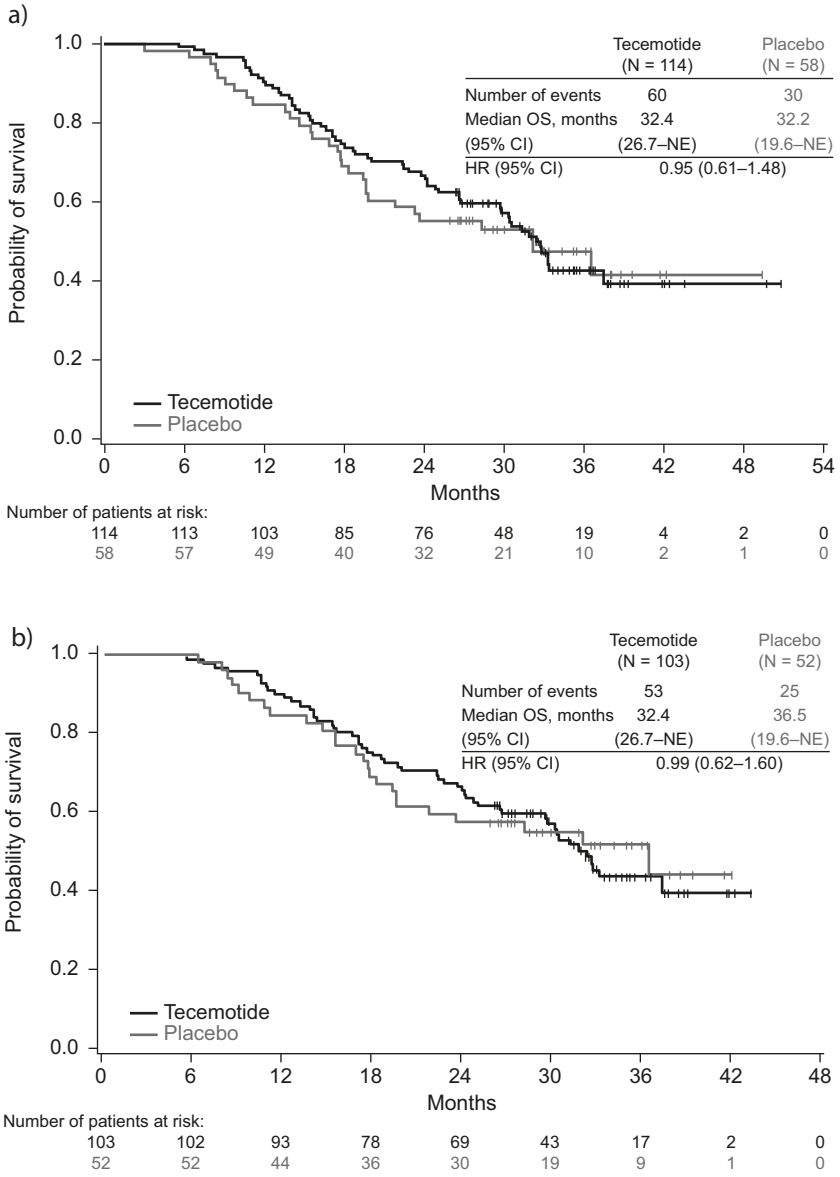

Fig. 2. Kaplan–Meier analysis of overall survival in the (a) intention-to-treat and (b) modified intention-to-treat populations. HRs are based on model adjusted for stratification factors: disease stage and histology, as per interactive voice response system. CI, confidence interval; HR, hazard ratio; NE, non-estimable; OS, overall survival.

were 12.5 and 11.0 for tecemotide and placebo, respectively. Treatment continued for >26 weeks in >50% of patients in both study arms.

3.3. *Efficacy*

There were 90 deaths in the ITT population up to the clinical cut-off date. There was no apparent trend towards improved median OS time with tecemotide over placebo in the ITT population (median 32.4 versus 32.2 months, HR 0.95, 95% CI 0.61–1.48; $p = 0.83$; Fig. 2a). Similarly, no OS time difference was observed between treatment arms in the mITT population (median 32.4 versus 36.5 months, HR 0.99, 95% CI 0.62–1.60; $p = 0.98$; Fig. 2b), or any of the predefined subgroups (Fig. 3).

There were also no clinically relevant differences in PFS time (Fig. 4) or other secondary endpoints for either the ITT or mITT population. For these populations, respectively, HRs with 95% CIs were, for tecemotide versus placebo, 0.95 (0.66–1.37) and 0.99 (0.67–1.46) for PFS time; 0.94 (0.65–1.35) and 1.00 (0.67–1.48) for TTP; and 1.07 (0.75–1.54) and 1.16 (0.79–1.71) for TTF.

3.4. *Safety*

Incidences of TEAEs (94.7% with tecemotide versus 93.0% with placebo; Table 2) and treatment-related TEAEs (48.2% versus 47.4%) were similar in the two treatment arms. Serious TEAE and serious treatment-related TEAE rates were the same in both arms (21.1% and 5.3%, respectively). Tecemotide was associated with a higher incidence of grade 3/4 adverse events than placebo (Table 2), but the incidence of grade 3/4 treatment-related TEAEs was not significantly different between the arms. The most frequent grade 3/4 treatment-related TEAE was lymphopenia (1.8% in both treatment arms; not shown). No new safety signals were identified. Treatment-related ISRs occurred in 19 (16.7%) patients in the tecemotide arm and four (7.0%) patients in the placebo arm; there were no treatment-related grade 3/4 ISRs. Five (4.4%) patients in the tecemotide arm and 1 (1.8%) in the placebo arm were withdrawn

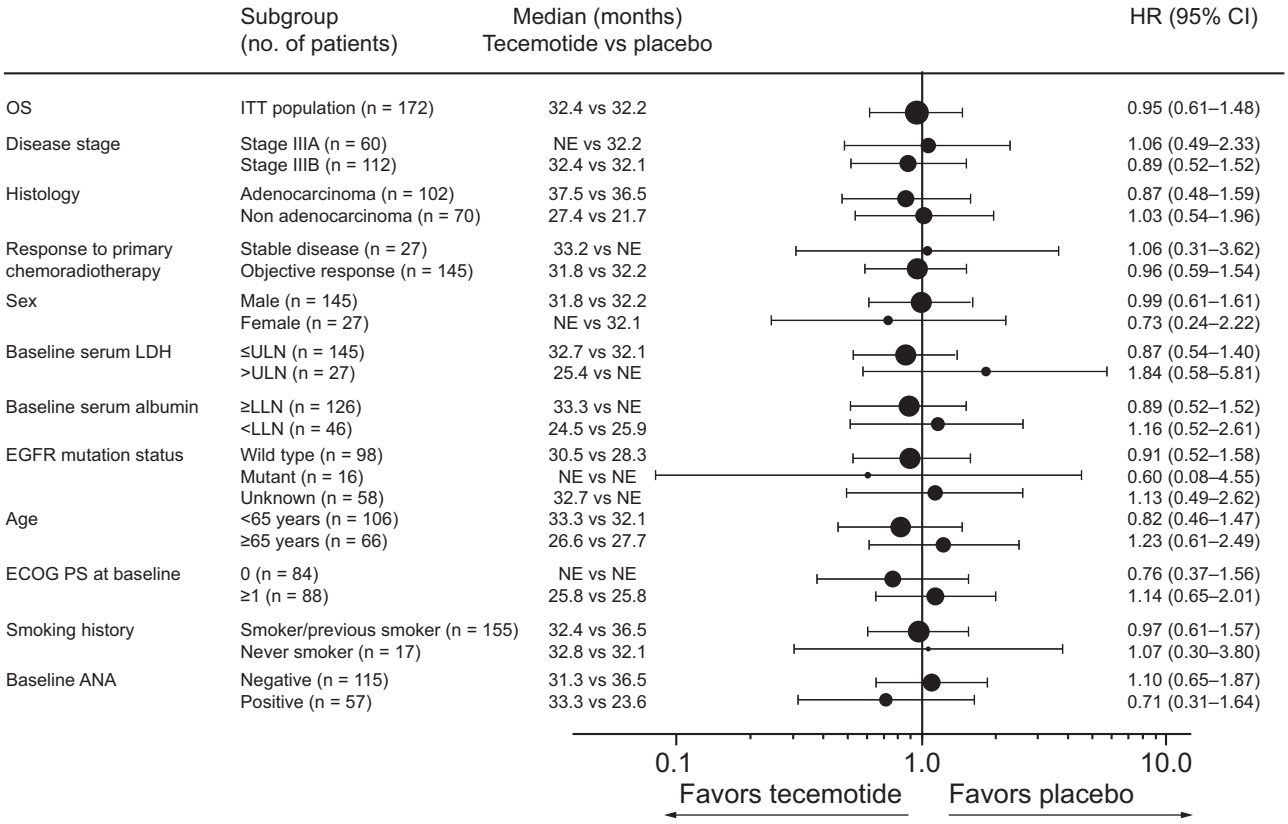

Fig. 3. Forest plot showing overall survival according to predefined subgroups, intention-to-treat population. HRs are based on model adjusted for stratification factors: disease stage and histology, as per interactive voice response system. ANA, antinuclear antibodies; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; LDH, lactate dehydrogenase; LLN, lower limit of normal; NE, non-estimable; OS, overall survival; ULN, upper limit of normal.

from treatment after TEAEs were assessed as related to treatment. There were no deaths resulting from TEAEs.

4. Discussion

This phase II trial did not meet its primary objective of showing a trend towards increased OS time with tecemotide over placebo when used as maintenance therapy in Japanese patients with unresectable stage III NSCLC. There were also no relevant improvements in secondary endpoints (PFS time, TTP or TTF).

The START trial demonstrated OS time improvement with tecemotide in a subgroup of patients receiving primary concurrent chemoradiotherapy [11,12]. A similar finding might have been expected in the present Japanese study, in which the majority of patients (94%) had received concurrent rather than sequential primary chemoradiotherapy; however, no OS time improvement was observed with tecemotide in either the ITT population, or the mITT, in which all patients received concurrent chemoradiotherapy. Reasons for the differences in outcomes between START and this study remain unclear, but may be related to the smaller patient numbers recruited here (the mITT population in START comprised <1200 individuals) and consequently potential underpowering. Another possible contributor to these contrasting results might have been differences between study populations in baseline biomarker levels, including soluble MUC1 (sMUC1) and antinuclear antibody (ANA), which may influence the efficacy of immunotherapy, as noted previously by Mitchell et al. [12] In the placebo group of START, negative prognostic associations with OS time was observed for high (>25 IU/mL) versus low sMUC1 levels, and for high (≥1:160) versus low ANA titers. Correspondingly, OS time was prolonged with tecemotide versus placebo in the high, but not the low, sMUC1 subgroup, and the high, but not the low, ANA titer subgroup [12]. Although a different cut-off for high (>1:40) versus low was used in this Japanese trial, there seems to be a similar trend between ANA levels and outcomes with tecemotide.

Although the overexpression and abnormal glycosylation of MUC1 is well documented in NSCLC [8,9], the expression of MUC1 in patients with NSCLC across ethnic groups does not appear to have been evaluated in any detail. A recent meta-analysis of the prognostic significance of MUC1 in studies of various cancers showed differences in the level of MUC1 expression (by IHC evaluation) between ethnic groups [18]. However, the cut-off values applied in the studies varied from >5% to >75%. Furthermore, several different antibodies for MUC1 staining were used in the studies. Nevertheless, the group of studies with a cut-off value of >5% (eight in Asian and two in Caucasian populations) showed that MUC1 expression was deemed positive/high in 542 of 916 (59%) Asian (Japanese and Chinese) patients compared with 174 of 253 (69%) Caucasian (German) patients. Given the differences in the studies, and in the absence of statistical analysis, no viable conclusions can be drawn as to whether the prevalence of MUC1 in NSCLC patients from different ethnic backgrounds could account for the difference observed between the current trial and START.

Other biomarkers that may have influenced outcomes include imbalances in human leukocyte antigen (HLA) class I and II alleles, which may influence the efficacy of immunotherapy, as noted previously by Mitchell et al. [12] Although differences in the distribution of HLA class I or II allele are known to exist to varying degrees among the different ethnic groups worldwide [19,20], no correlation between HLA status and survival was found in the START trial. Therefore, this was not considered a realistic concern in the current study and thus HLA status was not analysed in these

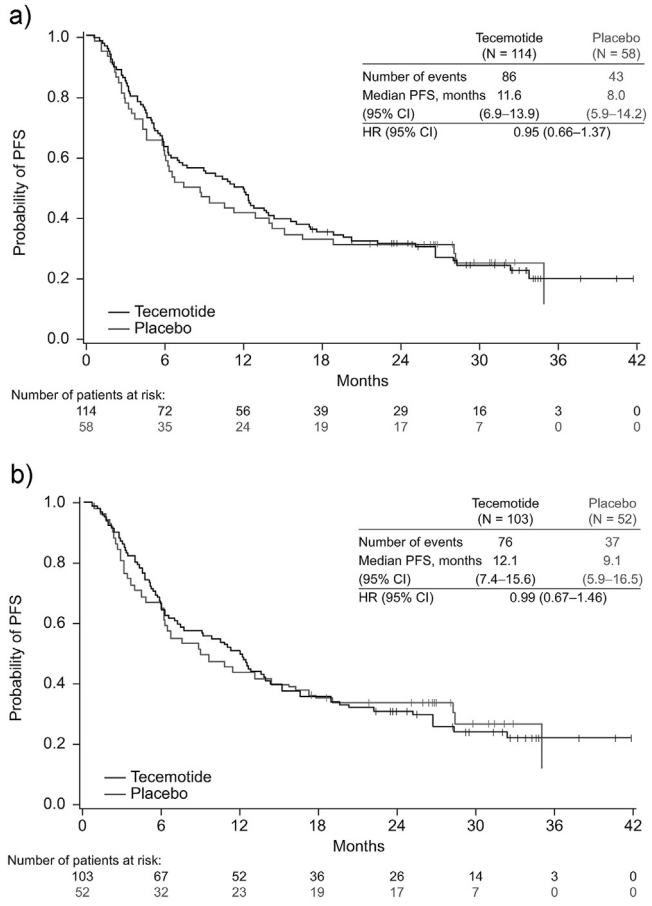

Fig. 4. Kaplan–Meier analysis of progression-free survival in the (a) intention-to-treat and (b) modified intention-to-treat populations. HRs are based on model adjusted for stratification factors: disease stage and histology, as per interactive voice response system. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

patients. Furthermore, it has recently been reported that median PFS with concurrent chemoradiotherapy was significantly shorter in patients with *epidermal growth factor* (*EGFR*)-mutant NSCLC than in those with wild-type disease, despite the overall response rate being similar in the two populations [21]. The data from the current study do not show a similar trend, but limited numbers of patients were known to be *EGFR*-mutant (n = 16). Thus, differences in EGFR mutation status may also explain why our results differ from those of START. The response to chemoradiotherapy in the patient populations entering the two studies should also be considered. Since a higher proportion of patients in the current study versus START achieved response to chemoradiotherapy (84% versus 68%, respectively), it is possible that the patients in this Japanese study already had a lower tumor burden. This may in turn have translated into fewer MUC1-positive tumor cells, and a less potent immune response induced by tecemotide. All of these hypotheses, however, would require further investigation.

Tecemotide was well tolerated with no clinically relevant increase in TEAEs over placebo, and there were no treatment-related deaths. No new safety signals were observed when compared with previous studies [7,11,12,22,23].

5. Conclusions

In conclusion, these results in Japanese patients after long-term follow up do not support the START findings of a potentially greater treatment effect of tecemotide over placebo in individuals who had received primary concurrent chemoradiotherapy, or the future development of the drug for stage III NSCLC. In September 2014, these results triggered Merck Serono to announce the discontinuation of the clinical development of tecemotide in stage III NSCLC.

Conflicts of interest

TH, HN and SA have received research funding from Merck Serono Co. Ltd., Tokyo, Japan. CH is employed by Merck KGaA, Darmstadt, Germany and MW is employed by Merck Serono Co. Ltd., Tokyo, Japan. All remaining authors have declared no conflicts of interest.

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