



Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial

Charles Butts, Mark A Socinski, Paul L Mitchell, Nick Thatcher, Libor Havel, Maciej Krzakowski, Sergiusz Nawrocki, Tudor-Eliade Ciuleanu, Lionel Bosquée, José Manuel Trigo, Alexander Spira, Lise Tremblay, Jan Nyman, Rodryg Ramlau, Gun Wickart-Johansson, Peter Ellis, Oleg Gladkov, José Rodrigues Pereira, Wilfried Ernst Erich Eberhardt, Christoph Helwig, Andreas Schröder, Frances A Shepherd, on behalf of the START trial team*

Summary

Background Effective maintenance therapies after chemoradiotherapy for lung cancer are lacking. Our aim was to investigate whether the MUC1 antigen-specific cancer immunotherapy tecemotide improves survival in patients with stage III unresectable non-small-cell lung cancer when given as maintenance therapy after chemoradiation.

Methods The phase 3 START trial was an international, randomised, double-blind trial that recruited patients with unresectable stage III non-small-cell lung cancer who had completed chemoradiotherapy within the 4–12 week window before randomisation and received confirmation of stable disease or objective response. Patients were stratified by stage (IIIA vs IIIB), response to chemoradiotherapy (stable disease vs objective response), delivery of chemoradiotherapy (concurrent vs sequential), and region using block randomisation, and were randomly assigned (2:1, double-blind) by a central interactive voice randomisation system to either tecemotide or placebo. Injections of tecemotide (806 µg lipopeptide) or placebo were given every week for 8 weeks, and then every 6 weeks until disease progression or withdrawal. Cyclophosphamide 300 mg/m² (before tecemotide) or saline (before placebo) was given once before the first study drug administration. The primary endpoint was overall survival in a modified intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00409188.

Findings From Feb 22, 2007, to Nov 15, 2011, 1513 patients were randomly assigned (1006 to tecemotide and 507 to placebo). 274 patients were excluded from the primary analysis population as a result of a clinical hold, resulting in analysis of 829 patients in the tecemotide group and 410 in the placebo group in the modified intention-to-treat population. Median overall survival was 25·6 months (95% CI 22·5–29·2) with tecemotide versus 22·3 months (19·6–25·5) with placebo (adjusted HR 0·88, 0·75–1·03; p=0·123). In the patients who received previous concurrent chemoradiotherapy, median overall survival for the 538 (65%) of 829 patients assigned to tecemotide was 30·8 months (95% CI 25·6–36·8) compared with 20·6 months (17·4–23·9) for the 268 (65%) of 410 patients assigned to placebo (adjusted HR 0·78, 0·64–0·95; p=0·016). In patients who received previous sequential chemoradiotherapy, overall survival did not differ between the 291 (35%) patients in the tecemotide group and the 142 (35%) patients in the placebo group (19·4 months [95% CI 17·6–23·1] vs 24·6 months [18·8–33·0]), respectively; adjusted HR 1·12, 0·87–1·44; p=0·38). Grade 3–4 adverse events seen with a greater than 2% frequency with tecemotide were dyspnoea (49 [5%] of 1024 patients in the tecemotide group vs 21 [4%] of 477 patients in the placebo group), metastases to central nervous system (29 [3%] vs 6 [1%]), and pneumonia (23 [2%] vs 12 [3%]). Serious adverse events with a greater than 2% frequency with tecemotide were pneumonia (30 [3%] in the tecemotide group vs 14 [3%] in the placebo group), dyspnoea (29 [3%] vs 13 [3%]), and metastases to central nervous system (32 [3%] vs 9 [2%]). Serious immune-related adverse events did not differ between groups.

Interpretation We found no significant difference in overall survival with the administration of tecemotide after chemoradiotherapy compared with placebo for all patients with unresectable stage III non-small-cell lung cancer. However, tecemotide might have a role for patients who initially receive concurrent chemoradiotherapy, and further study in this population is warranted.

Funding Merck KGaA (Darmstadt, Germany).

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, causing about 1·4 million deaths each year.¹ Non-small-cell lung cancer accounts for 80–85% of lung cancer cases and 30% of patients present with stage III disease.² Standard treatment for patients with a good performance status and

unresectable stage III non-small-cell lung cancer is platinum-based doublet chemotherapy and radiotherapy administered with curative intent. A meta-analysis of concurrent versus sequential chemoradiotherapy showed better outcomes with concurrent therapy, but even with concurrent chemoradiotherapy, 5-year overall survival is just 15%.³

Lancet Oncol 2013

Published Online
December 9, 2013
[http://dx.doi.org/10.1016/S1470-2045\(13\)70510-2](http://dx.doi.org/10.1016/S1470-2045(13)70510-2)

See Online/Comment
[http://dx.doi.org/10.1016/S1470-2045\(13\)70572-2](http://dx.doi.org/10.1016/S1470-2045(13)70572-2)

*Listed in the appendix

Cross Cancer Institute, Edmonton, AB, Canada (C Butts MD); UPMC Cancer Pavilion, Pittsburgh, PA, USA (Prof M A Socinski MD); Olivia Newton-John Cancer and Wellness Centre, Austin Hospital, Melbourne, VIC, Australia (P L Mitchell MD); Christie Hospital NHS Trust, Manchester, UK (Prof N Thatcher FRCP); Klinika Pneumologie a Hrudni Chirurgie, Univerzity Karlovy, Prague, Czech Republic (L Havel MD); Maria Curie-Skłodowska Memorial Institute, Warsaw, Poland (Prof M Krzakowski MD); University of Warmia and Mazury, Olsztyn, Poland (S Nawrocki MD); Silesian Medical University, Katowice, Poland (S Nawrocki); Ion Chiricuta Cancer Institute and University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania (T-E Ciuleanu MD); Centre Hospitalier du Bois de l'Abbaye et de Hesbaye, Seraing, Belgium (L Bosquée MD); Hospital Virgen de la Victoria, Málaga, Spain (J M Trigo MD); Virginia Cancer Specialists, Fairfax, VA, USA (A Spira MD); Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada (L Tremblay MD); Sahlgrenska University Hospital, Göteborg, Sweden (J Nyman MD); Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan University of Medical Sciences, Poznan, Poland (R Ramlau MD); Karolinska

University Hospital, Stockholm, Sweden (G Wickart-Johansson MD); Juravinski Cancer Centre, Hamilton, ON, Canada (P Ellis MD); Chelyabinsk Regional Clinical Oncology Dispensary, Chelyabinsk, Russia (O Gladkov MD); Arnaldo Vieira de Carvalho Cancer Institute, São Paulo, Brazil (J Rodrigues Pereira MD); Department of Medical Oncology, West German Cancer Centre, Ruhrlandklinik, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

The mucin 1 (MUC1) glycoprotein is overexpressed and abnormally glycosylated in non-small-cell lung cancer and other cancers.^{4,5} Cancer-associated MUC1 is involved in abnormal interactions with receptor tyrosine kinases and other cell surface receptors. These abnormal interactions trigger inappropriate activation of intracellular signalling pathways and thus promote the growth, proliferation, and survival of cancer cells.⁶⁻¹¹ Tecemotide (L-BLP25) is a MUC1 antigen-specific immunotherapy capable of inducing a T-cell response to MUC1 in both a preclinical MUC1-transgenic lung cancer mouse model¹² and in patients.¹³⁻¹⁵ A National Cancer Institute (NCI) project to prioritise cancer antigens ranked MUC1 very highly on the basis of predefined criteria.¹⁶ In a randomised phase 2 trial of

tecemotide as maintenance therapy versus best supportive care in responding and stable patients with stage IIIB or IV non-small-cell lung cancer, a potential survival benefit with tecemotide in stage IIIB patients was reported.^{13,14} A single-arm phase 2 trial of tecemotide after chemoradiotherapy for unresectable stage III non-small-cell lung cancer showed similar survival results.¹⁵

On the basis of these promising findings, we initiated the START (Stimulating Targeted Antigenic Response To non-small-cell lung cancer) study to assess the efficacy of tecemotide when compared with placebo as a maintenance therapy in patients with stage III non-small-cell lung cancer who have received chemoradiotherapy.

Methods

Study design and participants

START was an international, randomised, double-blind phase 3 trial that recruited patients from 33 countries worldwide. Eligible patients were those aged 18 years or older with histologically or cytologically unresectable stage III non-small-cell lung cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Stage was confirmed and documented by CT, MRI, or PET. We did not require pathological confirmation of mediastinal nodal involvement and we included all histological subtypes of non-small-cell lung cancer. Between 4 and 12 weeks before randomisation, patients had to have completed at least two cycles of platinum-based chemotherapy (given sequentially or concurrently) with a minimum of 50 Gy of radiation, and have received confirmation of stable disease or an objective response after chemoradiotherapy. All patients underwent brain imaging during screening to exclude brain metastases. Exclusion criteria included: having undergone any therapy for lung cancer (other than primary chemoradiotherapy), including surgery; receipt of any immunotherapy 28 days before randomisation; and having metastatic disease or any autoimmune disease. Further details of eligibility and exclusion criteria are listed in the appendix.

The study was done in compliance with the principles of the International Conference on Harmonisation Guidelines on Good Clinical Practice and the Declaration of Helsinki. The trial protocol was approved according to local regulatory requirements and by each study institution's research ethics board. All patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned on a double-blind basis in a 2:1 ratio to receive tecemotide or placebo using a central interactive voice randomisation system (Almac, Craigavon, Northern Ireland, UK); the interactive voice randomisation system staff assigned patients and were not involved in the rest of the trial. Block randomisation was used to ensure balanced populations in 24 prespecified strata consisting of disease stage (IIIA vs IIIB), response

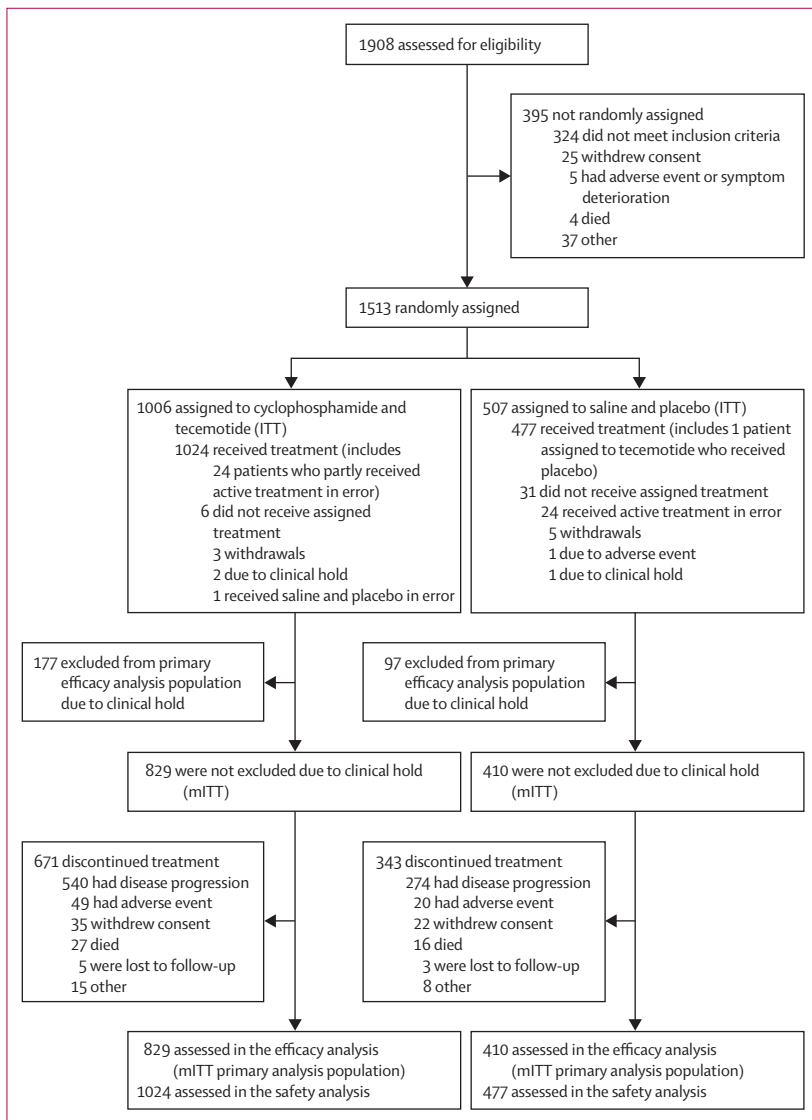


Figure 1: Trial profile

ITT=intention-to-treat population. mITT=modified intention-to-treat population, taking into account the exclusion of patients randomly assigned within the 6 months preceding the clinical hold.

to primary chemoradiotherapy (stable disease vs objective response), type of primary chemoradiotherapy (concurrent vs sequential), and region (North America [Canada, USA] and Australia vs western Europe vs rest of world [Mexico, Central and South America, eastern Europe, and Asia]). To maintain blinding, tecemotide and placebo for the primary and maintenance treatment phases were packaged in identical containers. With the exception of a designated unblinded statistician on the data monitoring board, interactive voice randomisation system staff, a designated pharmacist, and a study monitor for cyclophosphamide drug accountability

records, the randomisation code was masked from the sponsor and to other individuals monitoring the trial. The success of blinding was not formally assessed.

Procedures

After randomisation, and 3 days before administration of study drug, one dose of intravenous cyclophosphamide (300 mg/m², maximum dose 600 mg) was administered to patients assigned to the tecemotide group, and a corresponding intravenous saline infusion to patients assigned to the placebo group. The rationale for incorporating low-dose intravenous cyclophosphamide in the tecemotide schedule is based on a trial by MacLean and colleagues¹⁷ that showed a superior immune response to the STn-KLH (Theratope) vaccine in patients with breast cancer with intravenous versus oral cyclophosphamide. Patients then received tecemotide (contract manufacturer: Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA) or placebo (appendix). Tecemotide consists of the MUC1-derived 25-aminoacid BLP25 lipopeptide, the immunoadjuvant monophosphoryl lipid A, and three liposome-forming lipids (cholesterol, dimyristoyl phosphatidylglycerol, and dipalmitoyl phosphatidylcholine). The placebo consisted only of the three liposome-forming lipids. Initial therapy consisted of eight consecutive weekly subcutaneous injections of tecemotide (806 µg lipopeptide) or placebo. In the absence of progressive cancer or toxicity, maintenance tecemotide or placebo every 6 weeks was continued until disease progression. Temporary suspension of trial treatment because of safety or tolerability concerns was allowed at the discretion of the investigator, but dose adjustments of tecemotide were not permitted.

The primary endpoint was overall survival. Secondary endpoints were: time to disease progression, assessed

(W E Eberhardt MD); MerckKGaA, Darmstadt, Germany (C Helwig Dipl Stat, A Schröder MD); and University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada (Prof F A Shepherd MD)

Correspondence to: Dr Charles Butts, Cross Cancer Institute, Edmonton, AB, T6G 1Z2, Canada charles.butts@albertahealthservices.ca

See Online for appendix

For the trial protocol see http://www.oncology.med.ualberta.ca/AboutUs/FacultyMembers/Documents/CTP%20EMR63325-001-START%206%200_2%20signed.pdf

	Tecemotide (N=829)	Placebo (N=410)
Sex		
Men	566 (68%)	280 (68%)
Women	263 (32%)	130 (32%)
Ethnic origin		
White	764 (92%)	379 (92%)
Asian or Pacific Islander	38 (5%)	19 (5%)
Other or missing	27 (3%)	12 (3%)
Age, years	61.0 (19.0–89.0)	61.5 (24.0–83.0)
Smoking status		
Current	201 (24%)	99 (24%)
Past	578 (70%)	286 (70%)
Never	50 (6%)	25 (6%)
ECOG performance status		
0	398 (48%)	167 (41%)
1	427 (52%)	239 (58%)
Disease stage at first diagnosis		
IIIA	327 (39%)	160 (39%)
IIIB	502 (61%)	250 (61%)
Duration of NSCLC, months		
Median	6.24	6.14
IQR	5.22–7.49	5.13–7.59
Range	2.8–67.1	2.8–18.4
Histology		
Adenocarcinoma	289 (35%)	163 (40%)
Squamous-cell carcinoma	401 (48%)	171 (42%)
Other or unknown	139 (17%)	76 (19%)
Response to initial chemoradiotherapy		
Stable disease	265 (32%)	131 (32%)
Objective response	564 (68%)	279 (68%)
Type of initial chemoradiotherapy		
Concurrent	538 (65%)	268 (65%)
Sequential	291 (35%)	142 (35%)
Region		
North America and Australia	215 (26%)	106 (26%)
Western Europe	319 (38%)	156 (38%)
Rest of world	295 (36%)	148 (36%)

Data are number (%) or median (range), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer.

Table 1: Baseline demographic, clinical, and tumour characteristics

	Tecemotide (N=829)		Placebo (N=410)	
	Concurrent chemoradiotherapy (n=538)	Sequential chemoradiotherapy (n=291)	Concurrent chemoradiotherapy (n=268)	Sequential chemoradiotherapy (n=142)
Procedures for staging lymph node involvement*				
CT	381 (71%)	246 (85%)	187 (70%)	126 (89%)
MRI	5 (1%)	2 (1%)	5 (2%)	1 (1%)
PET	54 (10%)	14 (5%)	26 (10%)	5 (4%)
PET/CT	111 (21%)	34 (12%)	63 (24%)	15 (11%)
Mediastinoscopy	57 (11%)	18 (6%)	26 (10%)	7 (5%)
Other	48 (9%)	10 (3%)	21 (8%)	5 (4%)
Total tumour dose of radiation delivered with initial chemoradiotherapy, Gy				
Mean (SD)	63.4 (5.6)	61.1 (6.5)	63.4 (5.3)	60.8 (5.9)
Median (IQR)	63.8 (60.0–66.0)	60.0 (58.8–66.0)	63.0 (60.0–66.0)	60.0 (58.8–66.0)

Data are number (%) unless otherwise specified. Data are organised by whether patients received concurrent or sequential chemoradiotherapy before enrolment in this trial. *The use of more than one mode for N-staging was permitted for each patient.

Table 2: Procedures for staging lymph node involvement and radiation dose delivered in the modified intention-to-treat population

by investigators according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.0 with timing of follow-up assessments according to the standards of each institution; time to symptom progression, measured with the Lung Cancer Symptom Scale (LCSS); 1 year, 2 year, and 3 year survival; and safety.¹⁸ The LCSS was assessed before treatment, at weeks 2, 5, and 8 of study treatment, and every 6 weeks from week 13 until disease progression. It was assessed again at 6 and 12 weeks after progression and every 12 weeks thereafter. Safety was assessed through monitoring of adverse events, injection-site reactions, vital signs, and laboratory assessments.

The standard definition of serious adverse event was used as described in the protocol. Severity of adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

We calculated sample size on the basis of a hazard ratio (HR) of 0.77 for the primary overall survival outcome with 2:1 randomisation, a one-sided α -error of 0.025, and statistical power of 90%. Two formal interim analyses were planned at 50% and 75% of the planned maximum number of events for the final analysis with stopping boundaries consistent with an O'Brien-Fleming group-sequential design. With these assumptions, we needed 705 deaths for the final analysis. 1322 patients needed to have been enrolled within the scheduled accrual and follow-up to achieve the 705 events. The primary analysis of survival used a Cox proportional hazards regression model adjusted for the four stratification variables and for multiplicity of tests due to the interim analyses. None of the other analyses were adjusted for multiplicity. Subgroup analyses by randomisation strata used a Cox proportional hazards regression model including treatment group only; all other subgroup analyses used a Cox proportional hazards regression model adjusted for the stratification factors.

In March, 2010, clinical trials of tecemotide, including the START trial, were put on hold for enrolment and treatment after a case of encephalitis occurred in a phase 2 trial of tecemotide for multiple myeloma. Subsequent investigations of this patient, an overall safety analysis of the use of tecemotide in non-small-cell lung cancer, and introduction of safety measures by protocol amendment led to the clinical hold being lifted in June, 2010. At the time of the clinical hold, we had randomly assigned 1182 of the planned 1322 patients. We designed a modified intention-to-treat population for the primary analysis by prospectively excluding patients randomly assigned within the 6 months preceding the clinical hold. This approach was based on the assumption that a minimum of eight weekly doses and two 6-weekly doses (corresponding to about 6 months of treatment) were needed for tecemotide to induce an immunotherapeutic effect on survival. As a result, the sample size was adjusted and 274 excluded patients were replaced. Furthermore, the accrual and follow-up periods were extended by the clinical hold so that 1200 patients were needed to observe the anticipated number of events in the modified intention-to-treat analyses. The adjusted total sample size estimation, 1476, included patients excluded from the modified intention-to-treat analysis and replacement patients.

This modification of the intention-to-treat population, which was based purely on the randomisation time (ie, patients were excluded irrespective of whether they were on or off study treatment), left all other aspects of the O'Brien-Fleming group sequential design unchanged and did not introduce bias to the analysis. The US Food and Drug Administration (FDA) and several European regulatory authorities approved the amendment and modification of the intention-to-treat population before the analysis.

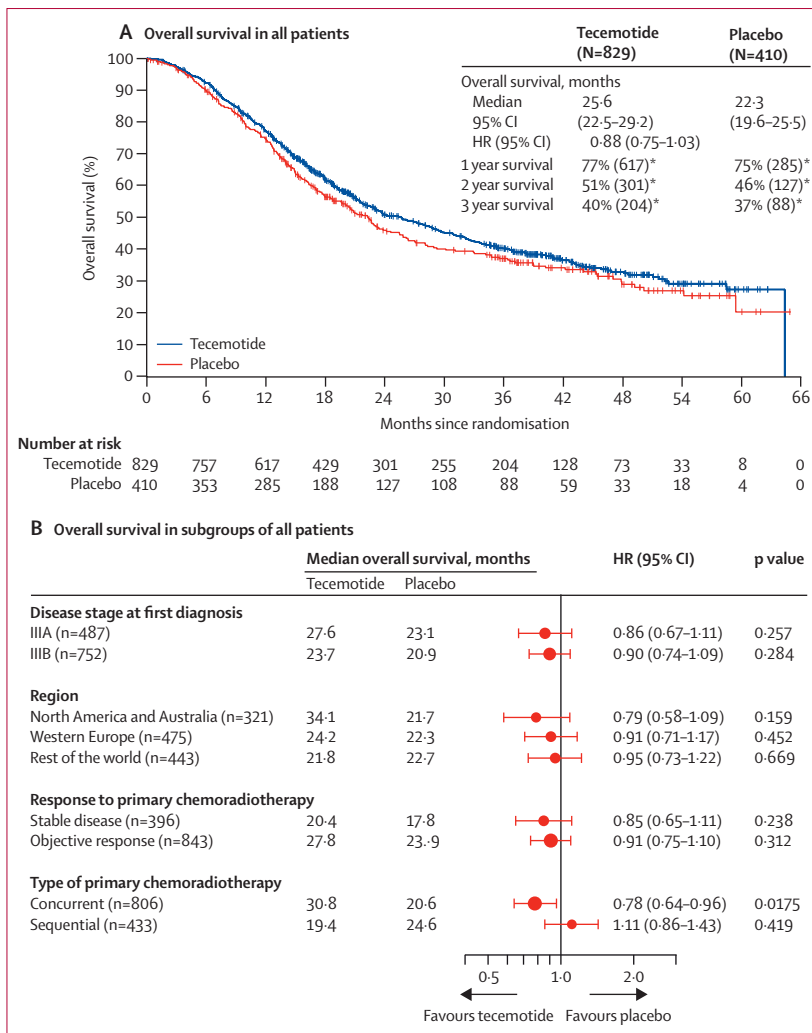


Figure 2: Overall survival in the modified intention-to-treat population, and by randomisation strata (A) Kaplan-Meier curve of overall survival in the primary analysis (modified intention-to-treat) population. (B) Overall survival in each of the four randomisation strata in the modified intention-to-treat population. HR=hazard ratio. *Number in parentheses show number at risk.

We used the statistical analysis system SAS (version 9.1.3) for analyses and S+SeqTrial (version 2) for the adjustment of the results of the primary analysis, accounting for the two interim analyses as part of the group sequential design.

This study is registered with the European Union drug regulating authorities Clinical Trials (EudraCT) database, number 2006-000579-14, and with ClinicalTrials.gov, number NCT00409188.

Role of the funding source

Merck KGaA, the study sponsor, designed the trial in collaboration with the investigators. The sponsor developed the protocol and statistical analysis plan, provided the study drug, coordinated the management of study sites and the clinical data management, did statistical analyses, and participated in the interpretation of data. CB, FAS, AS, and CH had full access to the raw data. CB and FAS wrote the initial draft manuscript and incorporated revisions and had the final responsibility for the decision to submit for publication.

Results

From Feb 22, 2007, until Nov 15, 2011, 1513 patients were enrolled from 264 centres in 33 countries worldwide (figure 1; appendix). The modified intention-to-treat primary analysis population consisted of 1239 patients after exclusion of 274 patients randomly assigned within the 6 months preceding the clinical hold. Only eight (1%) of 1239 patients were lost to follow-up during the treatment phase (figure 1).

At the time of implementation of the clinical hold in March, 2010, 531 patients were receiving study treatment. Although the clinical hold was lifted in June, 2010, resumption of treatment with tecemotide or placebo only started after local regulatory approval of the amended trial protocol after a median suspension of 135 days (IQR 127–174; range 92–358). Of these 531 patients, 180 did not resume treatment.

The two groups were evenly matched for important characteristics such as age, sex, stage at diagnosis, and response to initial chemoradiotherapy (table 1), and procedures for staging of the nodal status and delivery of chemoradiotherapy (table 2), although a numerical difference in histology results was noted.

At the time of the clinical cutoff for data collection of Aug 8, 2012, 469 (57%) of 829 patients in the tecemotide group had died compared with 237 (58%) of 410 patients in the placebo group (modified intention-to-treat population); one death in the tecemotide group was excluded from the efficacy analysis because only the year was reported. Median follow-up was 39.9 months (IQR 21.2–48.7) in the tecemotide group and 37.7 months (19.9–49.7) in the placebo group. The difference in median overall survival between groups was not statistically significant (25.6 months [95% CI 22.5–29.2] in the tecemotide group vs 22.3 months [19.6–25.5] in

the placebo group; HR 0.88 [0.75–1.03], $p=0.123$ [stratified model, multiplicity adjusted]; figure 2A). Survival at year one, year two, and year three are also presented in figure 2A. Although a numerical imbalance was noted between groups on the basis of histology, adjustment for histology did not change the treatment effect (HR 0.88 [95% CI 0.76–1.03]; $p=0.126$).

In the 177 patients in the tecemotide group and the 97 patients in the placebo group who were excluded because of the clinical hold, no benefit in median overall survival was seen with tecemotide (26.4 months [95% CI

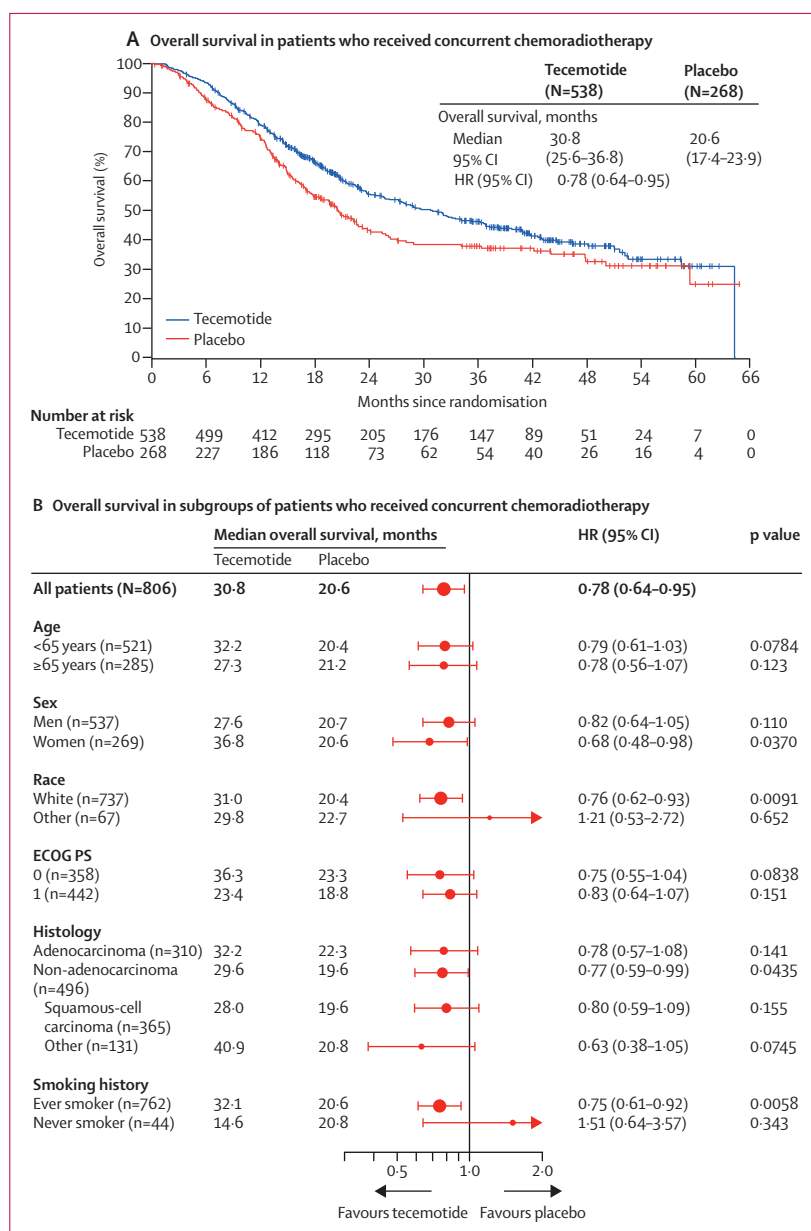


Figure 3: Overall survival in patients who received concurrent chemoradiotherapy (A) Kaplan-Meier curve of overall survival in the subgroup of patients who received initial concurrent chemoradiotherapy. (B) Overall survival by baseline characteristics in the concurrent chemoradiotherapy subgroup. ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio.

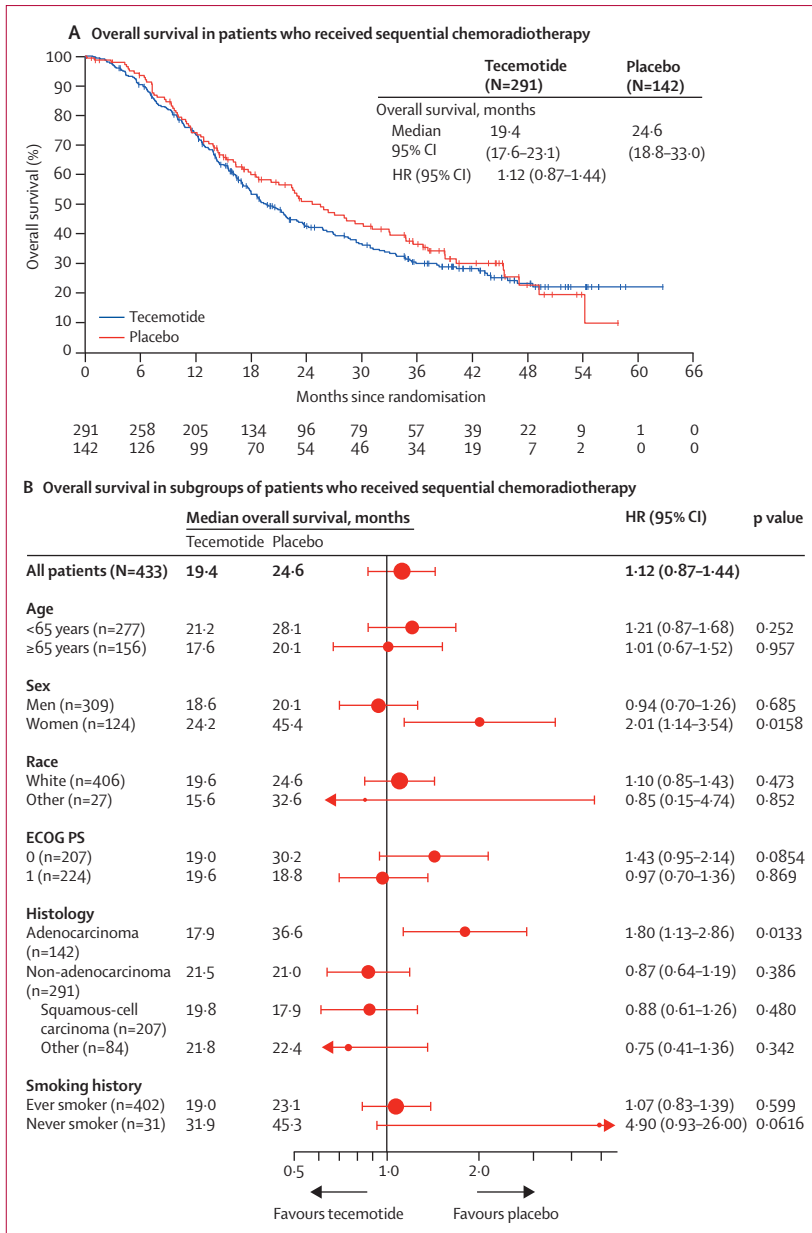


Figure 4: Overall survival in patients who received sequential chemoradiotherapy (A) Kaplan-Meier curve of overall survival in the subgroup of patients who received initial sequential chemoradiotherapy. (B) Overall survival by predefined baseline characteristics in the sequential chemoradiotherapy subgroup. ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio.

21.4–not reached] with tecemotide vs 28.1 [21.7–not reached] with placebo; HR 1.09 [0.75–1.56], $p=0.663$; appendix). Our sensitivity analysis to assess the potential effect of the clinical hold suggested that the hold had a negative impact on the treatment effect of tecemotide in terms of survival that extended beyond the 6 months selected for in the primary analysis population (appendix).

Preplanned subgroup analyses for the stratification variables showed no significant difference between

patients assigned to tecemotide and placebo, except for those patients who received concurrent chemoradiotherapy (figure 2B). Of the 806 patients who received concurrent chemoradiotherapy, median overall survival for the 538 (67%) patients assigned to tecemotide was notably increased compared with the 268 [33%] patients assigned to placebo (HR 0.78 [95% CI 0.64–0.95], $p=0.016$; figure 3A). A benefit from tecemotide was seen in some predefined subgroups (of sufficient size, defined as >100 patients) of patients treated with concurrent chemoradiotherapy (figure 3B; appendix). The interaction test supported the link between delivery of chemoradiotherapy and treatment effect ($p_{\text{interaction}}=0.032$). We noted no difference in median overall survival between treatment groups in the 433 patients who received sequential chemoradiotherapy (HR 1.12 [95% CI 0.87–1.44], $p=0.38$; figure 4A) and subgroup analyses showed heterogeneous results (figure 4B; appendix). The Cox regression analysis of overall survival when adjusted for baseline ECOG performance status and randomisation strata (HR 0.90 [95% CI 0.77–1.06]; $p=0.21$) was not notably different from the primary analysis result adjusted for randomisation strata only (HR 0.89 [0.76–1.04]; $p=0.16$).

Time to symptom progression, as assessed by the LCSS, differed only numerically between the tecemotide group and the placebo group (HR 0.85 [95% CI 0.73–0.98]; $p=0.023$; figure 5A), and the same was true for median time to disease progression (HR 0.87 [0.75–1.00]; $p=0.053$; figure 5B); however, this numerical difference requires confirmation.

The most common treatment-emergent adverse events are shown in table 3, and an overview of all adverse events is presented in table 4. The proportions of adverse events were similar between the tecemotide and placebo groups in nearly every adverse event category. Adverse events of any grade that were more than three percentage points more frequent in the tecemotide group compared with the placebo were cough, back pain, nausea, chest pain, nasopharyngitis, arthralgia, and myalgia (appendix). The reported frequencies of adverse events of special interest, including injection-site reactions and flu-like symptoms, were slightly more frequent in the tecemotide group than in the placebo group and were generally mild to moderate in severity (grade 1 or 2; appendix). Potentially immune-related diseases were infrequent (<3%) and not different between groups (appendix).

One fatal treatment-emergent adverse event of hepatic failure was assessed as being potentially related to study treatment. Two other patients had fatal adverse events that were assessed as being potentially related to study treatment, but occurred more than 42 days after the last dose (one with nervous system disorder, and one with a combination of sepsis, pneumonia, and thrombocytopenia), and there was one death of unknown cause. No safety signal could be established from these events after a review of all safety data.

Treatment delivery was similar between the groups. One patient in each treatment group did not receive the full dose of cyclophosphamide or saline and six patients in each treatment group did not receive tecemotide or placebo after administration of cyclophosphamide or saline. 93 (9%) of 1024 patients who received tecemotide and 45 (9%) of 477 patients who received placebo had a treatment-related adverse event causing temporary discontinuation of trial treatment, and 178 (17%) and 83 (17%) patients in the tecemotide and placebo groups, respectively, had an adverse event leading to permanent discontinuation of trial treatment. 20 (2%) patients in the tecemotide group and seven (1%) in the placebo group had adverse events judged to be related to study drug that led to permanent discontinuation. 160 (16%) and 79 (17%) patients in the tecemotide and placebo groups, respectively, had adverse events that were not regarded as related to study drug but that led to permanent discontinuation.

Discussion

The results of the START trial—the largest done, to our knowledge, in the setting of stage III non-small-cell lung cancer (panel)—showed that the primary endpoint of overall survival in patients who received cyclophosphamide and tecemotide after chemoradiotherapy did not differ significantly from those who received saline and placebo after chemoradiotherapy. However, we noted a favourable effect of tecemotide in patients who received concurrent chemoradiotherapy, with a 10·2 month improvement in median survival. By contrast, no benefit was seen in the sequential chemoradiotherapy subgroup. Therefore, although our primary endpoint was not met, and the null hypothesis was not rejected, our results suggest that tecemotide might have a potential benefit as a maintenance therapy after initial concurrent chemoradiotherapy in patients with non-small-cell lung cancer.

Continuing follow-up will assess the effects of tecemotide on long-term survival. Additionally, a smaller phase 3 trial (INSPIRE),²³ assessing tecemotide in Asian patients with stage III non-small-cell lung cancer, will restrict recruitment to patients receiving concurrent chemoradiotherapy.²³

At the time of the clinical hold, accrual was 90% complete and 531 patients were receiving investigational treatment. By the time the amended protocol was approved by local authorities and treatment could resume, patients had been without study medication for a median of 135 days and a third never resumed study treatment, mostly because of disease progression. We postulated that the interruption of therapy would have the greatest effect in patients who were closest to the primary phase of the immunotherapy at the time of the hold. We defined the primary analysis population prospectively to try to account for the clinical hold by excluding patients randomly assigned within the 6 months preceding the hold, on the basis of theoretical considerations related to the mode of action of tecemotide. This assumption is

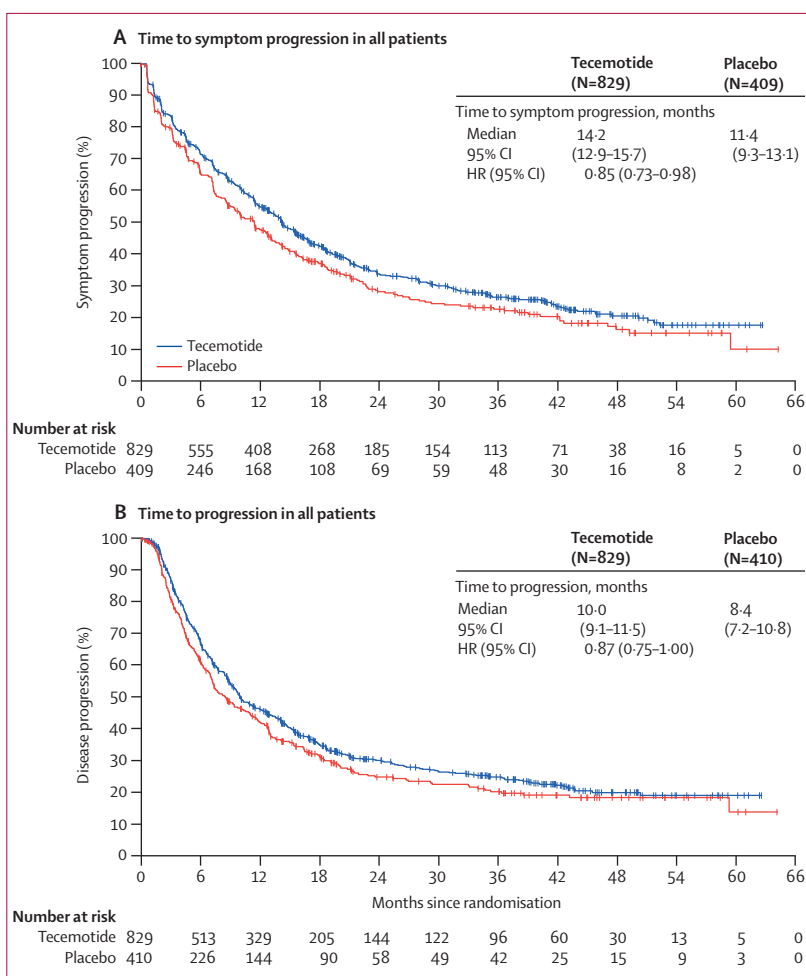


Figure 5: Time to symptom progression and time to progression in the modified intention-to-treat population

Kaplan-Meier curves of the secondary endpoints time to symptom progression (A) and of time to progression (B) in the primary analysis (modified intention-to-treat) population. HR=hazard ratio.

supported by general considerations about treatment time with tumour immunotherapeutics as laid out in the FDA guidance for the development of such compounds.²⁴ Indeed, those patients who were within 6 months of randomisation at the time of the hold had no benefit from tecemotide. However, further sensitivity analyses suggested that, despite these attempts to compensate for the clinical hold, the treatment interruption nonetheless perhaps negatively biased the overall survival results towards an underestimated treatment effect of tecemotide (appendix).

Interpretation of the results of the START trial has limitations inherent to the trial design. START was done on a global scale and therefore allowed for flexibility of inclusion on the basis of variation of standards for the initial treatment of stage III non-small-cell lung cancer in the 33 different countries involved (appendix). As a result, our reported findings take into account the different treatment strategies used

	Tecemotide (N=1024)				Placebo (N=477)			
	Total	Grade 1-2	Grade 3	Grade 4	Total	Grade 1-2	Grade 3	Grade 4
Cough	338 (33%)	323 (32%)	15 (1%)	0	133 (28%)	126 (26%)	7 (1%)	0
Dyspnoea	238 (23%)	189 (18%)	42 (4%)	7 (1%)	112 (23%)	91 (19%)	17 (4%)	4 (1%)
Fatigue	197 (19%)	186 (18%)	11 (1%)	0	102 (21%)	92 (19%)	10 (2%)	0
Back pain	146 (14%)	130 (13%)	14 (1%)	2 (<1%)	53 (11%)	50 (10%)	3 (1%)	0
Nausea	140 (14%)	140 (14%)	0	0	39 (8%)	39 (8%)	0	0
Chest pain	135 (13%)	123 (12%)	11 (1%)	1 (<1%)	45 (9%)	40 (8%)	4 (1%)	1 (<1%)
Nasopharyngitis	128 (13%)	127 (12%)	1 (<1%)	0	44 (9%)	44 (9%)	0	0
Headache	124 (12%)	120 (12%)	4 (<1%)	0	54 (11%)	53 (11%)	1 (<1%)	0
Decreased appetite	109 (11%)	102 (10%)	7 (1%)	0	44 (9%)	42 (9%)	2 (<1%)	0
Arthralgia	108 (11%)	104 (10%)	4 (<1%)	0	34 (7%)	31 (6%)	3 (1%)	0

Data are number of patients who had at least one event (% of patients). Adverse events were classified into grades 1-4; adverse events for which the maximum grade was missing are included in the columns of total grades.

Table 3: Summary of treatment-emergent adverse events occurring in more than 10% of the safety population

	Tecemotide (N=1024)	Placebo (N=477)
Any adverse event	938 (92%)	432 (91%)
Any adverse event related to study drug	353 (34%)	129 (27%)
Any serious adverse event	303 (30%)	151 (32%)
Any serious adverse event related to study drug	16 (2%)	5 (1%)
Any grade 3 or 4 adverse event	342 (33%)	171 (36%)
Any grade 3 or 4 adverse event related to study drug	15 (1%)	5 (1%)
Any adverse event leading to death	46 (4%)	35 (7%)
Any adverse event relating to study drug leading to death	1 (<1%)	0

Data are number of patients who had at least one event (% of patients).

Table 4: Overview of all adverse events in the safety analysis population

in different centres. Additionally, because patients were only eligible after completion of initial chemoradiotherapy, data for radiotherapy schedule and technique, including dose volume data, were not obtained to the same extent as in other chemoradiotherapy trials (eg, RTOG 0617¹⁹) and quality assurance of radiotherapy was not undertaken, with the exception of source data verification. However, the mode of delivery of initial chemoradiotherapy was a stratification variable and a subgroup analysis based on this variable was prespecified in the protocol. Patients enrolled from North America and Australia almost exclusively received concurrent chemoradiotherapy, whereas most patients enrolled from eastern European sites received sequential chemoradiotherapy. At the time START was designed, little information was available about survival of patients with stage III non-small-cell lung cancer who had at least stable disease after initial chemoradiotherapy. To establish a reasonable estimate for survival in the placebo group, more than 200 lung cancer specialists were surveyed. Subsequent reports from the Hoosier Oncology Group²⁰ and the SWOG 0023²⁵ trials suggest that the

20 month median survival estimate for the control group in START was an accurate estimate. Finally, interpretation of these results is affected by the outcome of the clinical hold. For example, the patients who were followed up for longer than planned because of the clinical hold increase the precision of the Kaplan-Meier curve at the later timepoints, whereas the patients recruited later have a relatively short follow-up time with a minimum of about 9 months. We took reasonable steps to define the modified intention-to-treat population without knowledge of the actual survival outcome to minimise any bias introduced by these changes. This prospective change of the primary analysis set was made in consultation with regulatory agencies.

Although the results of this trial need confirmation, a number of hypotheses can be offered as to why active antigen-specific immunotherapy might show a favourable effect in patients treated with concurrent and not sequential chemoradiotherapy. Results of an in-vitro study using a head and neck model cell line²⁶ showed that cytotoxic T-cell mediated lysis directed against MUC1 was enhanced by previous treatment with concomitant chemoradiotherapy compared with either modality alone. Additionally, two studies by similar study teams^{27,28} reported that some chemotherapeutic agents can induce immunogenic cell death whereas others induce tolerogenic cell death. Formenti and Demaria²⁹ recently postulated that the success of concurrent chemoradiotherapy in different solid tumours might be explained by achievement of immunogenic cell death.²⁹ Indeed, our preliminary analysis of benefit by regimen seems to support this hypothesis, suggesting a greater survival benefit from tecemotide than with placebo in the concurrent chemoradiotherapy group with some chemotherapeutic agents (eg, vinorelbine and taxanes) than with others (eg, etoposide; appendix). However, this analysis should be regarded as exploratory only.

Panel: Research in context**Systematic review**

We searched PubMed for phase 3 trials of maintenance or consolidation therapy after chemoradiotherapy in patients with non-small-cell lung cancer. A search with the terms "maintenance", "consolidation", and "NSCLC" found four relevant articles.^{19–22} No language or publication restrictions were used. None of these four trials provided evidence for a survival benefit with maintenance chemotherapy (docetaxel and paclitaxel) compared with observation or placebo after chemoradiotherapy for stage III non-small-cell lung cancer.

Interpretation

To our knowledge, the START trial is the first phase 3 trial of immunotherapy maintenance in patients with stage III non-small-cell lung cancer. Despite not showing a survival benefit with tecemotide in all assigned patients overall, our data suggest that the subgroup of patients who received initial concurrent chemoradiotherapy might benefit from maintenance tecemotide. Considering the lack of effective therapies in this setting and disappointing outcomes in trials of maintenance chemotherapy, this result has some promise. A confirmatory randomised trial of tecemotide after concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer is now being planned.

Patient selection is another possible factor for the differences in overall survival seen in patients receiving concurrent compared to sequential chemoradiotherapy. Patients selected for sequential chemoradiotherapy might have had a poorer performance status at the start of initial treatment and a more compromised immune system than those allocated to concurrent chemoradiotherapy, which requires a good performance status. Data for performance status at the time of initial chemoradiotherapy were not obtained because patients were enrolled only after confirmation of response. The eligibility criteria required only that the performance status at the time of randomisation be 0–1. Patients who received concurrent chemoradiotherapy could have had smaller primary tumours than patients who received sequential chemoradiotherapy, since delivery of concurrent chemoradiotherapy is difficult in the setting of a very large primary tumour. The bulky primary tumour might be a less favourable setting for immunotherapy. Data to support or refute these hypotheses in the context of the START study are not available.

Although RECIST 1.0 had to be followed for classification of disease progression, no formal imaging schedule was required after randomisation in START; rather, it was done according to institutional practice. Symptomatic progression was assessed more formally using the LCSS. Both progression-related endpoints (time to symptom progression and time to progression) differed numerically between patients assigned to

tecemotide and those assigned to placebo; however, these numerical differences need confirmation.

In this trial the safety analysis set consisted of 1024 patients who received tecemotide, 372 (36%) of whom received it for more than 52 weeks. These analyses confirmed the favourable safety and tolerability profile of tecemotide. There were no clinically concerning differences between tecemotide and placebo for any adverse event. Adverse events of special interest such as injection-site reactions or flu-like symptoms were infrequent and rarely greater than grade 2. Potential immune-related diseases or events were seen in less than 3% of patients and with similar frequency in the two groups.

In conclusion, although survival was not significantly prolonged with tecemotide overall in patients with stage III non-small-cell lung cancer, we believe the results seen in the predefined subgroup of patients who received concurrent chemoradiotherapy are suggestive of a benefit of tecemotide in this population and warrant further study. A confirmatory randomised trial of tecemotide is being planned for patients with stage III non-small-cell lung cancer after concurrent chemoradiotherapy.

Contributors

CB, FAS, MAS, PLM, NT, and ASc were involved in the study design, and writing and amendment of the protocol. CB, FAS, MAS, PLM, NT, and ASc were responsible for the running of the trial. FAS, CB, MAS, PLM, NT, LH, MK, SN, T-EC, LB, JMT, ASp, LT, JN, RR, GW-J, PE, OG, JRP, and WEEE participated in data collection and enrolment of patients. CH was responsible for the statistical analysis. FAS, CB, MAS, PLM, NT, CH, and ASc participated in data analysis and interpretation of the results. ASc, CH, and FAS were involved with preparation and writing of the study report. FAS and CB compiled the initial draft and outline of the manuscript and were responsible for manuscript submission. All authors participated in drafting, reviewing, and approval of the final manuscript.

Conflicts of interest

CB has acted in a consultant and advisory role for, and has received honoraria from, Merck KGaA. MAS has received research funding from EMD Serono. PLM has an advisory relationship with, and has received research funding and conference travel remuneration from, Merck KGaA. NT has acted in a consultant and advisory role with, and has received honoraria from, Merck KGaA. JN has received conference travel remuneration from Merck KGaA. WEEE has financial associations with Merck KGaA (speaker's bureau, advisory board, educational lectures), Eli Lilly (speaker's bureau, advisory board, research grants), and Bristol-Myers Squibb (advisory board, speaker's bureau). CH and ASc are employees of Merck KGaA. FAS has an uncompensated consultant and advisory relationship with Merck KGaA. All other authors declare that they have no conflicts of interest.

Acknowledgments

This trial was sponsored by Merck KGaA, Darmstadt, Germany. We thank the patients and their families and the investigators and study teams involved. Medical writing assistance was provided by Paola Accalai (International Medical Press, London, UK) and was funded by Merck KGaA.

References

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893–917.
- 2 Crino L, Weder W, van Meerbeeck J, Felip E. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v103–15.

- 3 Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 2181–90.
- 4 Bafna S, Kaur S, Batra SK. Membrane-bound mucins: the mechanistic basis for alterations in the growth and survival of cancer cells. *Oncogene* 2010; **29**: 2893–904.
- 5 Raina D, Kosugi M, Ahmad R, et al. Dependence on the MUC1-C oncoprotein in non-small cell lung cancer cells. *Mol Cancer Ther* 2011; **10**: 806–16.
- 6 Rahn JJ, Chow JW, Horne GJ, et al. MUC1 mediates transendothelial migration in vitro by ligating endothelial cell ICAM-1. *Clin Exp Metastasis* 2005; **22**: 475–83.
- 7 Yin L, Li Y, Ren J, Kuwahara H, Kufe D. Human MUC1 carcinoma antigen regulates intracellular oxidant levels and the apoptotic response to oxidative stress. *J Biol Chem* 2003; **278**: 35458–64.
- 8 Yin L, Huang L, Kufe D. MUC1 oncoprotein activates the FOXO3a transcription factor in a survival response to oxidative stress. *J Biol Chem* 2004; **279**: 45721–27.
- 9 Acres B, Limacher JM. MUC1 as a target antigen for cancer immunotherapy. *Expert Rev Vaccines* 2005; **4**: 493–502.
- 10 Bafna S, Kaur S, Batra SK. Membrane-bound mucins: the mechanistic basis for alterations in the growth and survival of cancer cells. *Oncogene* 2010; **29**: 2893–904.
- 11 Hollingsworth MA, Swanson BJ. Mucins in cancer: protection and control of the cell surface. *Nat Rev Cancer* 2004; **4**: 45–60.
- 12 Wurz GT, Gutierrez AM, Greenberg BE, et al. Antitumor effects of L-BLP25 antigen-specific tumor immunotherapy in a novel human MUC1 transgenic lung cancer mouse model. *J Transl Med* 2013; **11**: 64.
- 13 Butts C, Murray N, Maksymiuk A, et al. Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer. *J Clin Oncol* 2005; **23**: 6674–81.
- 14 Butts C, Maksymiuk A, Goss G, et al. Updated survival analysis in patients with stage IIIB or IV non-small-cell lung cancer receiving BLP25 liposome vaccine (L-BLP25): phase IIB randomized, multicenter, open-label trial. *J Cancer Res Clin Oncol* 2011; **137**: 1337–42.
- 15 Butts C, Murray RN, Smith CJ, et al. A multicenter open-label study to assess the safety of a new formulation of BLP25 liposome vaccine in patients with unresectable stage III non-small-cell lung cancer. *Clin Lung Cancer* 2010; **11**: 391–95.
- 16 Cheever MA, Allison JP, Ferris AS, et al. The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. *Clin Cancer Res* 2009; **15**: 5323–37.
- 17 MacLean GD, Miles DW, Rubens RD, et al. Enhancing the effect of THERATOPE STn-KLH cancer vaccine in patients with metastatic breast cancer by pretreatment with low-dose intravenous cyclophosphamide. *J Immunother Emphasis Tumor Immunol* 1996; **19**: 309–16.
- 18 Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer* 1993; **29** (suppl 1): S51–58.
- 19 Bradley J, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/- cetuximab for stage IIIa/IIIb non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617 (late-breaking abstract 2). 53rd annual meeting of the American Society of Radiation Oncology; Miami, FL; Oct 2–6, 2011.
- 20 Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008; **26**: 5755–60.
- 21 Jalal SI, Riggs HD, Melnyk A, et al. Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology. *Ann Oncol* 2012; **23**: 1730–38.
- 22 Carter DL, Garfield D, Hathorn J, et al. A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel or observation for patients with locally advanced inoperable non-small-cell lung cancer. *Clin Lung Cancer* 2012; **13**: 205–13.
- 23 Wu YL, Park K, Soo RA, et al. INSPIRE: a phase III study of the BLP25 liposome vaccine (L-BLP25) in Asian patients with unresectable stage III non-small cell lung cancer. *BMC Cancer* 2011; **11**: 430.
- 24 US Food and Drug Administration. Guidance for industry: clinical considerations for therapeutic cancer vaccines, October 2011. <http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm278673.pdf> (accessed April 1, 2013).
- 25 Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008; **26**: 2450–56.
- 26 Gelbard A, Garnett CT, Abrams SI, et al. Combination chemotherapy and radiation of human squamous cell carcinoma of the head and neck augments CTL-mediated lysis. *Clin Cancer Res* 2006; **12**: 1897–905.
- 27 Obeid M, Panaretakis T, Tesniere A, et al. Leveraging the immune system during chemotherapy: moving calreticulin to the cell surface converts apoptotic death from “silent” to immunogenic. *Cancer Res* 2007; **67**: 7941–44.
- 28 Zitvogel L, Kepp O, Senovilla L, Menger L, Chaput N, Kroemer G. Immunogenic tumor cell death for optimal anticancer therapy: the calreticulin exposure pathway. *Clin Cancer Res* 2010; **16**: 3100–04.
- 29 Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst* 2013; **105**: 256–65.