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GENERIC DRUG NAME and/or COMPOUND NUMBER: Tremelimumab/CP-675,206

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not applicable

NATIONAL CLINICAL TRIAL NO.: NCT00312975

PROTOCOL NO.: A3671015

PROTOCOL TITLE: Phase 2 Randomized, Non-Comparative Study of CP-675,206 or Best Supportive Care Immediately Following First-Line, Platinum-Based Therapy in Patients with Stage IIIB (with Effusion) or Stage IV Non-Small Cell Lung Cancer That Has Responded or Remained Stable

Study Centers: A total of 21 centers in 5 countries (United States, United Kingdom, Canada, Czech Republic, and Korea) took part in the study.

Study Initiation and Completion Dates: 03 May 2006 to 03 February 2010

Phase of Development: Phase 2

Study Objectives: The primary objective was to estimate the progression-free survival (PFS) rate at 3 months in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) treated with tremelimumab or best supportive care (BSC) immediately following first-line platinum-based treatment with an outcome of response or stable disease. Secondary objectives were to assess additional evidence of anti-tumor activity as measured by objective response rate (ORR), PFS, overall survival (OS) and 1-year survival; to evaluate the safety and tolerability of tremelimumab when administered after chemotherapy; to obtain pharmacokinetic (PK) data to be evaluated in a future meta-analysis of tremelimumab PK; to monitor for human anti-human antibody (HAHA) response to tremelimumab; to explore whether the cytotoxic T-lymphocyte antigen 4 (CTLA4) genotypes influenced the safety, immune response and/or efficacy of subjects treated with tremelimumab; and to explore health-related quality of life (HRQoL) outcomes.

METHODS

Study Design: This was an open-label, 2 arm, randomized, non-comparative, multicenter, Phase 2 study to evaluate the efficacy and safety of tremelimumab in subjects with locally advanced or metastatic NSCLC. Subjects had been treated with a platinum-based regimen for 4 or more cycles except in the case of a complete response (CR) for which subjects with fewer cycles of first-line treatment were eligible. Previous treatment with bevacizumab or other anti-CTLA4 targeting agents was not permitted.

Subjects were randomized to receive either tremelimumab (Arm A) or BSC (Arm B). Subjects randomized to Arm A received intravenous administration of tremelimumab at a dose of 15 mg/kg on Day 1 of every 90-day cycle (that is, every 90 days [Q90D]). Subjects randomized to Arm B received BSC as needed. Tumor assessments were performed at Baseline, at approximately 3 months after randomization and every 6 weeks thereafter; additional scans were done if clinically indicated.

Subjects randomized to Arm B were offered tremelimumab upon documented evidence of disease progression, provided the subject continued to meet the eligibility criteria except for those related to the time since the last dose of first-line chemotherapy. If subjects in Arm B chose to crossover at the time of disease progression, the data generated from the start of crossover were summarized and analyzed separately (with the exception of OS).

Number of Subjects (Planned and Analyzed): It was planned to enroll 80 subjects in total, 40 subjects in each arm. Eighty-seven subjects were randomized, 44 to Arm A and 43 to Arm B; 15 subjects randomized to Arm B crossed over to Arm A. Overall, 43 subjects from Arm A and 42 subjects from Arm B discontinued. One subject in each of Arm A and B completed the study.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged ≥18 years with histologically or cytologically proven NSCLC at Stage IIIB (locally advanced with effusion) or Stage IV disease at initiation of platinum-based chemotherapy. Subjects were to have completed first-line platinum-based therapy for NSCLC with an outcome of stable disease (SD) or partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST) and were to have received 4 or more cycles of first-line treatment (fewer cycles were acceptable only in subjects achieving a CR in the first-line setting). Subjects must have had Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and adequate bone marrow, hepatic and renal function determined within 14 days prior to enrollment. They must have recovered from all prior treatment-related toxicities to Baseline status or to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE v3.0) Grade of 0 or 1 except for toxicities not considered a safety risk.

Subjects were excluded if there was an interval >6 weeks between last dose of first-line chemotherapy and date of randomization (the last dose of first-line chemotherapy must have been administered at least 3 weeks prior to randomization); if they had received other systemic therapy for NSCLC since last dose of first-line chemotherapy, previous treatment with bevacizumab or other anti-CTLA4 agents, or an immunosuppressive dose of corticosteroids or other immunosuppressive medication within 4 weeks of enrollment (subjects with adrenal insufficiency were allowed to take up to 5 mg of prednisone or equivalent daily and topical and inhaled corticosteroids in standard doses were allowed); if they had symptomatic or uncontrolled brain metastases or uncontrolled pleural effusions, a history of autoimmune disease, current or active psoriasis in the last 3 years, active or chronic hepatitis, history in the last 5 years of inflammatory bowel disease, celiac disease, or other chronic gastrointestinal conditions associated with diarrhea, or current acute colitis of any origin, or any history of diverticulitis or evidence of diverticulitis at Baseline; if they had a diagnosis of any second malignancy within the last 3 years except basal cell carcinoma,

squamous cell skin cancer, or carcinoma in situ of the cervix that had been adequately treated with no evidence of recurrent disease for 12 months.

Study Treatment: Tremelimumab was administered as an open-label, intravenous solution at a dose of 15 mg/kg, followed by observation. Additional doses of tremelimumab were administered every 90 days (±4 days) until disease progression or intolerable toxicity. Dose modifications were only allowed following fluctuations in body weight over time; subjects were weighed within 10 days prior to each cycle. Subjects were allowed to receive up to 4 doses over an approximate 12-month period. Subjects exhibiting clinical benefit (CR, PR, SD) after 12 months were eligible to continue therapy with tremelimumab for up to 4 additional doses or up to a maximum of 24 months after enrollment. After 2 doses of tremelimumab, if there was no evidence that the subject was deriving any benefit from treatment - including objective response (OR), mixed response or SD - the subject was to discontinue treatment. The initiation of a cycle could have been delayed for up to 12 weeks to allow recovery from treatment-related toxicity.

Subjects randomized to Arm B were cared for as deemed appropriate by the treating physician. At the time of documented evidence of disease progression, subjects in Arm B could have been offered tremelimumab at the dose and schedule used for Arm A provided the subject continued to meet the eligibility criteria. Treatment with tremelimumab was to have begun no more than 2 weeks after the investigator documented disease progression.

Two formulations of tremelimumab were used in this study, an original formulation supplied as a sterile solution of 5 mg/mL tremelimumab and commercial formulation supplied as a sterile solution of 20 mg/mL tremelimumab.

Efficacy Evaluations: Radiologic and clinical evaluations were performed within 14 days prior to dosing. On-study tumor assessments were performed 7-10 days prior to Day 90 or the second dose of tremelimumab (this assessment constituted the assessment on which the 3-month PFS rate endpoint was determined) and approximately every 6 weeks thereafter. Tumor responses were confirmed with repeat assessments no less than 4 weeks after the initial observation of response. Subjects were followed for disease progression and survival for 2 years from the date of randomization.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Blood specimens for assay of tremelimumab were obtained just prior to administration of tremelimumab and 1 hour after the end of infusion of tremelimumab in every treatment cycle. In Cycle 1, blood specimens were also collected on Days 30 and 60. Further blood specimens were collected at the end of treatment (EOT) visit and, if possible, at the first follow-up visit.

A blood specimen for HAHA assay was obtained just prior to administration of tremelimumab every treatment cycle, and at the End of Study, and, if possible, at the first follow-up visit.

Health-related quality of life (HRQoL) outcomes were assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30) incorporating QLQ-LC13, the supplementary module for

lung cancer. Subjects were to complete both self-administered questionnaires at Baseline (within 14 days prior to Cycle 1 Day 1), on Day 30 and 60 of Cycle 1 and on Day 1 of Cycle 2 and each subsequent treatment cycle prior to having any tests, receiving any therapy, and prior to any discussion of the subject's progress with their physician. Any subject in Arm B receiving tremelimumab after documented disease progression only needed to complete the HRQoL questionnaire at the EOT visit for the BSC treatment.

A blood sample for polymorphisms of CTLA4, FcgammaRIIa and immunoglobulin G2a was obtained from all randomized subjects on Cycle 1 Day 1. Under a separate informed consent, subjects participating in the study donated an additional single optional blood specimen on Cycle 1 Day 1 for pharmacogenomic analysis (analysis was not performed as the primary efficacy objective was not achieved).

Safety Evaluations: Adverse events (AEs) were recorded throughout the study and safety laboratory tests, medical history, physical examination, height and weight, and vital signs were performed at predefined times.

Statistical Methods:

Primary Endpoint: The PFS rate at 3 months, defined as the proportion of subjects who did not progress at Month 3 relative to the total number of evaluable subjects, based on the per-protocol analysis set. The following null hypothesis was to be tested in Arm A (tremelimumab) and Arm B (BSC) independently with a one-sided exact binomial test at 0.05 level of significance: H_o: PFS rate at 3 months (PFS3mo) did not exceed 50% (H_o:PFS3mo.≤50%). The study was 80% powered for the alternative hypothesis H_1≥70%.

Secondary Endpoints: The ORR was defined as the proportion of subjects with a confirmed CR or PR relative to the total number of response evaluable subjects. Response was defined according to the RECIST guidelines and the 95% CI for the ORR was provided for each treatment arm independently. The duration of OR and CR were evaluated using Kaplan-Meier methodology (median, range), 95% CIs for median OR and CR using Brookmeyer Crowley methodology and Kaplan-Meier plots of duration of OR and CR were provided for each treatment arm independently.

PFS was measured from the date of randomization to date of progression or death, whichever occurred first. PFS was characterized in terms of the median, and the probability of remaining progression-free at 6 months and 12 months (based on Kaplan-Meier methodology) for each treatment arm independently. Range and 95% CI for the estimates were also computed. Brookmeyer Crowley methodology was used to calculate the 95% CI for the median PFS.

OS was measured from date of randomization to date of death due to any cause. One-year survival was also assessed. OS was characterized in terms of the median, and the probability of being alive at 3, 6 and 12 months (based on Kaplan-Meier methodology) for each treatment arm independently. Range and 95% CI for the estimates were also computed. Brookmeyer Crowley methodology was used to calculate the 95% CI for the median OS.

If the primary objective was achieved in both arms (H_o:$PFS_{3mo.}$≤50% was rejected) or the primary objective was not achieved in either arm (H_o:$PFS_{3mo.}$≤50% was not rejected), a pre-planned comparative analysis was to be conducted.

HAHA results and HRQoL outcome data are listed by subject.

Since the primary efficacy objective was not achieved, genotyping of CTLA4, FcgammaRIIa and IgG2a, and the planned statistical analyses to investigate the association between response and polymorphisms of these genes, and the association between AEs and polymorphisms of these genes, were not conducted. Similarly, the analysis of HRQoL data was not performed.

Tremelimumab concentration-time data from this study will be analyzed with PK data from other clinical studies using a population PK approach and reported separately.

AEs were classified using the Medical Dictionary for Regulatory Activities classification system. The severity of the toxicities was graded according to the NCI CTCAE Version 3.0 whenever possible. Descriptive statistics were used to summarize safety data, all subject characteristics, and treatment administration/compliance.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 1. Eighty-seven subjects were randomized, 44 to Arm A and 43 to Arm B, and 15 subjects randomized to Arm B crossed over to Arm A. Thirty-seven (84.1%) subjects from Arm A and 36 (83.7%) subjects from Arm B discontinued due to progressive disease (PD). One (2.3%) subject in Arm A and 3 (7.0%) subjects in Arm B died during the active portion of the study.

All subjects who received treatment were analyzed for AEs (Table 1). All subjects in Arm A and those who crossed over from Arm B to receive tremelimumab were analyzed for laboratory data, reflecting the clinical laboratory test sample collection schedule. Additionally, 12 subjects in Arm B had on-study laboratory data reported.

Table 1. Subject Disposition - All Randomized as Randomized

Number of Subjects (%)	Arm A Tremelimumab 15 mg/kg Q90D	Arm B Best Supportive Care	Crossover[a]
Screened 101			
Assigned to Study Treatment 87			
Treated	44	43	15
Completed	1 (2.3)	1 (2.3)	0
Discontinued	43	42	15
Adverse Event	5 (11.4)	0	
Subject Died	1 (2.3)	3 (7.0)	
Progressive Disease	37 (84.1)	36 (83.7)	
Subject no Longer Willing to Participate	0	3 (7.0)	
Analyzed for Safety:			
Adverse Events	44	43	15
Laboratory Data	44	12	15

Q90D = every 90 days ("quarterly")
[a] Started on best supportive care and crossed over to tremelimumab.

Most subjects were male (75% in Arm A and 60.5% in Arm B). Mean age was similar for both arms, approximately 62 years. All subjects were diagnosed with NSCLC; the mean time since onset was 6.1 and 5.5 months for Arms A and B, respectively. Most subjects had disease Stage IV (88.6% in Arm A and 90.7% in Arm B).

Efficacy Results: Overall, 22.7% of subjects in Arm A (90% confidence interval [CI]: [12.9%, 35.5%]) and 11.9% of subjects in Arm B (90% CI: [4.8%, 23.4%]) were progression-free at 3 months. Neither arm demonstrated a PFS rate at 3 months significantly above 50%.

A summary of the best overall response, as assessed by each investigator, is presented in Table 2. Four subjects (2 in Arm A 1 in the crossover group from Arm B to Arm A, and 1 in Arm B [no crossover to tremelimumab]) achieved an OR, in each case a confirmed PR, all of whom had a pathological diagnosis of squamous cell carcinoma. Nine subjects (20.9%) in Arm A, 5 subjects (11.9%) in Arm B, and 2 subjects (13.3%) in the crossover group had a best overall response of clinical benefit response (CBR [CR, PR or SD]). The duration of response for the 2 responders in Arm A was 11.14 and 12.75 months, and for the responder in Arm B was 11.87 months, measured from the date of randomization to the date of progression or death.

Table 2. Best Overall Response – Evaluable for Response

Number of Subjects (%)	Arm A Tremelimumab 15 mg/kg Q90D (N=43)	Arm B Best Supportive Care (N=42)	Crossover[a] (N=15)
Complete Response (CR)	0	0	0
Partial Response (PR)	2 (4.7)	1 (2.4)	1 (6.7)
Stable Disease (SD)[b]	7 (16.3)	4 (9.5)	1 (6.7)
Progressive Disease (PD)	34 (79.1)	37 (88.1)	13 (86.7)
Number of Subjects with OR (CR or PR)	2 (4.7)	1 (2.4)	1 (6.7)
(95% confidence interval)[b]	(0.6, 15.8)	(0.1, 12.6)	(0.2, 31.9)
Number of Subjects with CBR (CR, PR or SD)	9 (20.9)	5 (11.9)	2 (13.3)
(95% confidence interval)[c]	(10.0, 36.0)	(4.0, 25.6)	(1.7, 40.5)

Q90D = every 90 days ("quarterly"), OR = objective response; CBR = clinical benefit response; N = number of subjects evaluable for response
[a] Started on best supportive care and crossed over to tremelimumab.
[b] Ten weeks criteria is used for stable disease (SD).
[c] Exact two-sided confidence interval.

PFS is summarized in Table 3. Overall, 86/87 subjects (98.9%) had an event (progression or death). The probability estimate for PFS at 3 and 6 months was 0.159 and 0.068, repectively, in Arm A, and 0.047 and 0.023, respectively, in Arm B, with 95% CIs summarized in Table 3. The most common reason for progression was new lesions (21 subjects [48.8%] in Arm A and 19 subjects [45.2%] in Arm B).

Table 3. Progression-Free Survival – All Randomized as Randomized

Kaplan-Meier Estimate	Arm A Tremelimumab 15 mg/kg Q90D (N=44)	Arm B Best Supportive Care (N=43)
Number (%) of subjects with events	44 (100.0)	42 (97.7)
Number (%) of subjects censored	0	1 (2.3)
Median (months)	2.86	2.79
(95% confidence interval)[a]	(2.79, 2.96)	(2.69, 2.92)
Range (months)	(0.59, 14.98)	(0.59, 11.86)
Probability estimate of progression-free survival at 3 months	0.159	0.047
(95% confidence interval)[b]	(0.051, 0.267)	(0.000, 0.109)
Probability estimate of progression-free survival at 6 months	0.068	0.023
(95% confidence interval)[b]	(0.000, 0.143)	(0.000, 0.068)

Q90D = every 90 days ("quarterly"); N = number of subjects evaluable for response
[a] Confidence interval was calculated using the Brookmeyer Crowley method.
[b] 95% confidence interval was calculated using the Greenwood formula.

Median OS was 13.40 months (95% CI : [7.56, 19.42]) in Arm A and 12.52 months (95% CI: [7.06, 22.74]) in Arm B. The 1-year survival rate was 0.520 (95% CI: [0.372, 0.668]) for Arm A and 0.518 (95% CI: [0.366, 0.671]) for Arm B. Any comparison of OS

data for the 2 arms should be treated with caution as 15/43 subjects randomized to BSC crossed over to tremelimumab.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: A total of 57 subjects had evaluable HAHA samples. Of the 162 HAHA plasma samples received and screened, 2 plasma samples were HAHA positive. One subject in Arm A and 1 subject in the crossover group had titers of 8.91 and 6.42, respectively, at the EOT visit. All of the remaining HAHA samples were below detection limit (titer <4.32) suggesting minimal immunogenicity of tremelimumab following intravenous administration at a dose of 15 mg/kg every 90 days.

Safety Results: There were 270 AEs (111 treatment-related AEs) in Arm A, 124 (none of which were considered treatment-related) prior to crossover in Arm B, and 60 (13 treatment-related AEs) following crossover in Arm B.

The most frequently reported treatment-emergent AEs (>15%) for Arm A were diarrhea (14 subjects [31.8%]), decreased appetite (12 [27.3%]), cough (11 [25.0%]), fatigue (10 [22.7%]), rash (10 [22.7%]), dyspnea (8 [18.2%]), nausea (7 [15.9%]), and pruritis (7 [15.9%]), for Arm B were cough (11 [25.6%]), dyspnea (9 [20.9%]), and chest pain (7 [16.3%]), and for the crossover group cough (7 [46.7%]), dyspnea (7 [46.7%]), decreased appetite (3 [20.0%]), chest pain (3 [20.0%]), productive cough (3 [20.0%]), and rash (3 [20.0%]) (Table 4). No treatment-related AEs occurred during infusion.

Table 4. All Causality Treatment-Emergent Adverse Events Occurring in ≥3 Subjects by Treatment Arm, All Cycles – as Treated

Number (%) of subjects MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Arm A (Tremelimumab 15 mg/kg Q90D) (N=44)						
Diarrhea	8 (18.2)	1 (2.3)	5 (11.4)	0	0	14 (31.8)
Decreased appetite	7 (15.9)	4 (9.1)	1 (2.3)	0	0	12 (27.3)
Cough	6 (13.6)	5 (11.4)	0	0	0	11 (25.0)
Fatigue	5 (11.4)	2 (4.5)	3 (6.8)	0	0	10 (22.7)
Rash	5 (11.4)	5 (11.4)	0	0	0	10 (22.7)
Dyspnea	4 (9.1)	2 (4.5)	2 (4.5)	0	0	8 (18.2)
Nausea	4 (9.1)	3 (6.8)	0	0	0	7 (15.9)
Pruritus	5 (11.4)	2 (4.5)	0	0	0	7 (15.9)
Asthenia	1 (2.3)	2 (4.5)	1 (2.3)	1 (2.3)	0	5 (11.4)
Body temperature increased	4 (9.1)	1 (2.3)	0	0	0	5 (11.4)
Headache	4 (9.1)	0	1 (2.3)	0	0	5 (11.4)
Musculoskeletal pain	3 (6.8)	2 (4.5)	0	0	0	5 (11.4)
Productive cough	5 (11.4)	0	0	0	0	5 (11.4)
Pyrexia	3 (6.8)	2 (4.5)	0	0	0	5 (11.4)
Vomiting	1 (2.3)	4 (9.1)	0	0	0	5 (11.4)
Arthralgia	1 (2.3)	2 (4.5)	1 (2.3)	0	0	4 (9.1)
Oropharyngeal pain	4 (9.1)	0	0	0	0	4 (9.1)
Pain	1 (2.3)	2 (4.5)	0	1 (2.3)	0	4 (9.1)
Weight decreased	1 (2.3)	3 (6.8)	0	0	0	4 (9.1)
AST increased	1 (2.3)	1 (2.3)	1 (2.3)	0	0	3 (6.8)
Dizziness	1 (2.3)	2 (4.5)	0	0	0	3 (6.8)
Hypokalemia	2 (4.5)	0	0	1 (2.3)	0	3 (6.8)
Mucosal inflammation	2 (4.5)	1 (2.3)	0	0	0	3 (6.8)
Musculoskeletal chest pain	2 (4.5)	1 (2.3)	0	0	0	3 (6.8)
Myalgia	1 (2.3)	1 (2.3)	1 (2.3)	0	0	3 (6.8)
Arm B (Best Supportive Care) (N=43)						
Cough	4 (9.3)	5 (11.6)	2 (4.7)	0	0	11 (25.6)
Dyspnea	4 (9.3)	4 (9.3)	1 (2.3)	0	0	9 (20.9)
Chest pain	3 (7.0)	4 (9.3)	0	0	0	7 (16.3)
Decreased appetite	4 (9.3)	2 (4.7)	0	0	0	6 (14.0)
Back pain	3 (7.0)	2 (4.7)	0	0	0	5 (11.6)
Fatigue	2 (4.7)	1 (2.3)	1 (2.3)	0	0	4 (9.3)
Productive cough	3 (7.0)	1 (2.3)	0	0	0	4 (9.3)
Bone pain	3 (7.0)	0	0	0	0	3 (7.0)
Bronchitis	1 (2.3)	2 (4.7)	0	0	0	3 (7.0)
Constipation	2 (4.7)	0	1 (2.3)	0	0	3 (7.0)
Insomnia	2 (4.7)	1 (2.3)	0	0	0	3 (7.0)
Crossover[a] (N=15)						
Cough	5 (33.3)	1 (6.7)	1 (6.7)	0	0	7 (46.7)
Dyspnea	3 (20.0)	1 (6.7)	3 (20.0)	0	0	7 (46.7)
Decreased appetite	1 (6.7)	2 (13.3)	0	0	0	3 (20.0)
Chest pain	3 (20.0)	0	0	0	0	3 (20.0)
Productive cough	3 (20.0)	0	0	0	0	3 (20.0)
Rash	3 (20.0)	0	0	0	0	3 (20.0)

MedDRA = Medical Dictionary for Regulatory Activities; Q90D = every 90 days ("quarterly"); N = number of as-treated subjects; AST = aspartate aminotransferase.

[a] Started on best supportive care and crossed over to tremelimumab.

Five subjects in Arm A and 1 subject in the crossover group permanently discontinued due to TEAEs (Table 5).

Table 5. Subjects with Treatment-Emergent AEs Leading to Permanent Discontinuation of Treatment and/or Study, As-Treated Subjects

Subject Gender/Age	Adverse Event (MedDRA v13.0 Preferred Term)	Maximum CTC Grade	AE Start-Stop Cycle Days	Causality	Outcome	SAE
Arm A (Tremelimumab 15 mg/kg Q90D) (N=44)						
M/54	Diarrhea	3	C2D15-C2D19	Study drug	Resolved	No
	Diarrhea	3	C2D19-C2D32	Study drug	Resolved	Yes
M/62	Convulsion	2	C1D21-C1D21	Disease under study	Resolved	No
F/70	Colitis	3	C1D40-C1D90	Study drug	Resolved	Yes
M/64	Diarrhea	3	C1D26-C1D37	Study drug	Resolved[a]	Yes
	Diarrhea	2	C1D38-C1D40	Study drug	Resolved	No
	Diarrhea	1	C1D41-C1D50	Study drug	Resolved	No
	Fatigue	1	C1D14-C1D28	Study drug	Resolved	No
	Fatigue	2	C1D29-C1D37	Study drug	Resolved[a]	No
	Fatigue	3	C1D38-C1D43	Study drug	Resolved	No
	Fatigue	2	C1D44-C1D55	Study drug	Resolved[a]	No
	Fatigue	1	C1D56-C1D62	Study drug	Resolved[a]	No
	Fatigue	3	C1D63-C1D77	Study drug	Resolved	No
	Fatigue	1	C1D78-FUD63	Study drug	Resolved	No
	Fatigue	3	FUD64-FUD291	Study drug	Still present	No
M/60	Diarrhea	3	C3D27-C3D52	Study drug	Resolved	Yes
Crossover[b] (N=15)						
F/63	Hyperamylasemia	4	C2D29-C2D36	Study drug	Resolved	Yes
	Hyperamylasemia	3	C2D37-C2D168	Study drug	Resolved	No

MedDRA =Medical Dictionary for Regulatory Activities; CTC = Common Toxicity Criteria; AE =adverse event; SAE = serious adverse event; Q90D = every 90 days ("quarterly"); N = number of enrolled subjects; M = male; F = female; C = cycle; D = study day; FU = follow-up.
[a] with sequelae.
[b] Started on best supportive care and crossed over to tremelimumab.

Subject deaths are summarized in Table 6. The majority of subjects were followed for 2 years post randomization. During the 2-year follow-up time period, 33 subjects (75.0%) in Arm A and 27 subjects (62.8%) in Arm B died. The cause of death for most subjects was disease under study (ie disease progression). No subject in Arm A died within 30 days of last study dose or within 60 days of randomization (early death).

One Grade 5 (fatal) AE occurred in Arm A (NSCLC progression), 4 in Arm B (NSCLC progression [2 subjects], hemoptysis, and pulmonary embolism) and 1 in the crossover group (NSCLC progression); none of these Grade 5 AEs were considered related to study drug.

Table 6. Summary of Deaths – All Randomized as Randomized

Number(%) of subjects	Arm A Tremelimumab 15 mg/kg Q90D (N=44)	Arm B Best Supportive Care (N=43)
Deaths from all causes	**33 (75.0)**	**27 (62.8)**
Within 30 days of last dose of study drug[a]	0	2 (4.7)
More than 30 days after last dose of study drug	33 (75.0)	25 (58.1)
Causes of death		
Disease under study	31 (70.5)	26 (60.5)
Study drug	0	0
Unknown	0	1 (2.3)
Other	3 (6.8)	0
Early deaths (within 60 days of randomization)	**0**	**1 (2.3)**

More than 1 cause of death may be reported. Unknown cause of death includes not reported
Q90D = every 90 days ("quarterly"); N = number of enrolled subjects
[a] For Arm B, a 90-day treatment period was assumed (ie, the last dose of study drug date was set as 90 days from the randomization date).

SAEs due to any cause are presented in Table 7.

Table 7. Serious Adverse Events

Subject Gender/Age	Adverse Event (MedDRA v13.0 Preferred Term)	Maximum CTC Grade	AE Start-Stop Cycle Days	Causality	Outcome
Page 1 of 2					
Arm A (Tremelimumab 15 mg/kg Q90D) (N=44)					
M/58	Pain	4	C1D81-C1D102	Disease under study	Resolved
M/54	Diarrhea[a]	3	C2D19-C2D32	Study drug	Resolved
	Hypokalemia[a]	4	C2D19-C2D32	Study drug	Resolved
	Acute-prerenal failure[a]	3	C2D19-C2D32	Study drug	Resolved
F/70	Colitis[a]	3	C1D40-C1D90	Study drug	Resolved
	Dehydration	2	C1D40-C1D90	Study drug	Resolved
	Acute prerenal failure	3	C1D40-C1D90	Study drug	Resolved
	Deep vein thrombosis	3	C1D41-C1D90	Study drug	Resolved
	Hypotension	3	C1D40-C1D90	Study drug	Resolved
M/64	Anal fistula	3	FUD22-FUD22	Study drug	Ongoing
	Diarrhea[a]	3	C1D26-C1D37	Study drug	Resolved[b]
	Urinary tract infection	3	C1D92-FUD51	Study drug	Resolved[b]
M/80	Myocardial infarction	3	C1D22-C1D24	Other illness – myocardial infarction	Resolved
M/63	Progression of NSCLC	5	FUD6-FUD6	Disease under study	Resolved
	Pneumonia	4	C1D75-C1D83	Disease under study	Resolved
M/69	Respiratory tract infection	4	C1D55-C1D76	Disease under study	Resolved
M/69	Progression of NSCLC	5	C1D64-C1D64	Disease under study	Resolved
M/60	Diarrhea[a]	3	C3D27-C3D52	Study drug	Resolved
F/39	Pericardial effusion	4	C1D21-C1D23	Disease under study	Resolved[b]
	Pericardial effusion	4	C1D48-C1D51	Disease under study	Resolved
	Fatigue	3	C1D16-C1D30	Disease under study	Resolved
	Hepatic function abnormal	3	C1D22-C1D30	Disease under study	Resolved[b]
	Renal impairment	3	C1D22-C1D26	Disease under study	Resolved
F/71	Small intestinal obstruction	3	C2D26-C2D51	Other illness - adhesions	Resolved
	COPD	4	C2D23-C2D62	Other illness – COPD	Resolved[b]
M/65	Headache	3	C1D43-C1D62	Study drug	Resolved
M/74	Pneumonia	2	C1D11-C1D60	Disease under study	Ongoing
M/70	Pneumonia	4	C1D43-C1D51	Disease under study	Ongoing
Arm B (Best Supportive Care) (N=43)					
F/64	Chest pain	2	C1D34-C1D35	Disease under study	Resolved
	Headache	3	C1D34-C1D35	Other illness – brain metastasis	Resolved
F/65	Progression of NSCLC	5	C1D111-C1D111	Disease under study	Resolved
	Dyspnea	2	C1D15-FUD114[c]	Disease under study	Ongoing

MedDRA = Medical Dictionary for Regulatory Activities; CTC = Common Toxicity Criteria; AE = adverse event; Q90D = every 90 days ("quarterly"); N = number of evaluable subjects; M = male; F = female; C = cycle; D = study day, FU = follow-up; NSCLC = non small cell lung cancer; COPD = chronic obstructive pulmonary disease
[a] Study drug permanently discontinued; [b] with sequelae; [c] According to data provided, the AE was ongoing at the time of death.

Table 7. Serious Adverse Events

Subject Gender/Age	Adverse Event (MedDRA v13.0 Preferred Term)	Maximum CTC Grade	AE Start-Stop Cycle Days	Causality	Outcome
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Arm B (Best Supportive Care) (N=43)					
M/60	Hemoptysis	5	C1D39-C1D39	Disease under study	Resolved
F/58	Progression of NSCLC	5	C1D75-C1D75	Disease under study	Resolved
	Asthma	3	C1D35-C1D36	Other illness – pulmonary obstruction by mucus	Resolved
M/65	Pulmonary embolism	5	C1D80-C1D80	Disease under study	Resolved
Crossover[d]					
F/63	Diarrhea	2	C2D29-C2D36	Study drug	Resolved
	Hyperamylasemia[a]	4	C2D29-C2D36	Study drug	Resolved
M/57	Progression of NSCLC	5	C2D74-C2D74	Disease under study	Resolved
M/60	Meningitis tuberculous	3	C4D23-C4D30	Other illness - tuberculosis meningitis	Ongoing

MedDRA = Medical Dictionary for Regulatory Activities; CTC = Common Toxicity Criteria; AE = adverse event; Q90D = every 90 days ("quarterly"); N = number of evaluable subjects; M = male; F = female; C = cycle; D = study day, FU = follow-up; NSCLC = non small cell lung cancer; COPD = chronic obstructive pulmonary disease
[a] Study drug permanently discontinued; [b] with sequelae; [c] According to data provided, the AE was ongoing at the time of death; [d] Started on best supportive care and crossed over to tremelimumab.

No subjects in Arm B were considered to have experienced a treatment-related AE as they did not receive study drug. None of the subjects in either arm or the crossover group experienced a Grade 5 treatment-related AE. Two subjects in Arm A experienced Grade 4 AEs that were considered related to treatment (hypokalemia and increased lipase). One subject in the crossover group experienced a Grade 4 treatment-related AE of hyperamylasemia.

Seven subjects (15.9%) in Arm A experienced treatment-emergent AEs of maximum Grade 3 that were considered related to treatment during the active phase of the study. These included diarrhea (3 subjects), pruritic rash, myalgia, neuralgia, and exertional dyspnea, colitis, acute prerenal failure, deep vein thrombosis, hypotension, rectal hemorrhage, upper gastrointestinal hemorrhage, fatigue, and skin exfoliation, headache, increased blood lactate dehydrogenase. One subject in the crossover group experienced Grade 3 dyspnea that was considered related to treatment.

Twenty-three (23) of 44 subjects in Arm A and 12 of 43 subjects in Arm B had at least 1 instance of a worsening ECOG on-study. At the end of study 11 subjects in Arm A and 6 subjects in Arm B reported an ECOG of 2 or 3. Of the subjects with worsening performance status on-study, the majority of the subjects worsened between 2 and <4 months after study entry.

There were no clinically significant trends on-study in hematology, clinical chemistry, or urinalysis laboratory assessments. There were no clinically significant median changes in vital signs data.

Conclusions:

- 22.7% of subjects with locally advanced or metastatic NSCLC receiving tremelimumab 15 mg/kg Q90D and 11.9% of subjects receiving best supportive care immediately following first-line platinum-based treatment were progression free at 3 months. Neither arm demonstrated a PFS rate statistically significantly above 50%.

- There was no significant additional evidence of anti-tumor activity as measured by ORR, PFS, OS, and 1-year survival in subjects with locally advanced or metastatic NSCLC receiving tremelimumab 15 mg/kg Q90D.

- The post-infusion safety and tolerability profile of tremelimumab was consistent with that observed to date in other studies which assessed tremelimumab as mono-therapy.