SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor:	Geron Corporation
Name of Finished Product:	GRN163L (Imetelstat Sodium for Injection)
Name of Active Ingredient:	Imetelstat
Study Number:	CP14B012
Study Title:	A Randomized Phase II Study of Imetelstat as Maintenance Therapy after Initial Induction Chemotherapy for Advanced Non-Small Cell Lung Cancer (NSCLC)
Phase of Development:	II
Investigators:	Multicenter (32 investigators; list to be provided in final clinical study report)
Study Centers:	Multicenter (31 study centers in the Unites States, Canada, and Germany; list to be provided in final clinical study report)
Publications (Reference):	Chiappori A, Kolevska T, Burington B, et al. A randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced non-small cell lung cancer. Third AACR International Conference on Frontiers in Basic Cancer Research - September 18-22, 2013; National Harbor, MD. Poster presentation: Abstract 4669. Chiappori A, Bassett, K, Burington B, et al. Improved progression-free survival (PFS) in patients with short tumor telomere length: subgroup analysis from a randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced NSCLC. Third AACR International Conference on Frontiers in Basic Cancer Research - September 18-22, 2013; National Harbor, MD. Poster presentation: Abstract 2378.
Study Period:	13 July 2010 – 20 August 2013
Date of this Report:	30 June 2014

OBJECTIVES

Primary Objective

- To obtain a preliminary estimate of efficacy, as defined by progression-free survival (PFS), for patients with advanced non-small cell lung cancer (NSCLC) who received four to six cycles of induction chemotherapy and were randomized to receive treatment with either:
  - Imetelstat maintenance therapy in addition to standard of care (bevacizumab or observation)
  - Standard of care alone (bevacizumab or observation)

Secondary Objectives

- To assess the safety and tolerability of imetelstat as part of maintenance therapy following initial induction chemotherapy in patients with advanced NSCLC
- To obtain a preliminary estimate of the response rate when imetelstat was used as part of maintenance therapy in patients with advanced NSCLC

Exploratory Objectives

- To obtain a preliminary estimate of 6-month survival rate when imetelstat was used as part of maintenance therapy in patients with advanced NSCLC
- To obtain a preliminary estimate of efficacy, as defined by progression-free survival, for patients with advanced NSCLC who received four to six cycles of induction chemotherapy, including bevacizumab, and were randomized to receive either:
  - Bevacizumab and imetelstat maintenance therapy
  - Bevacizumab alone
- To obtain a preliminary estimate of efficacy, as defined by progression-free survival, for patients with advanced NSCLC who received four to six cycles of induction chemotherapy, without bevacizumab, and were randomized to receive either:
  - Imetelstat maintenance therapy alone
  - No additional therapy
- To assess the correlation of biologic markers in tumors with outcomes in each of the treatment groups

METHODOLOGY

This open-label, multicenter, randomized Phase II study was designed to evaluate the efficacy and safety of treatment with imetelstat plus standard of care, versus standard of care alone, for patients with advanced NSCLC who have not progressed after completing four to six cycles of induction chemotherapy.

Patients received induction treatment consisting of any platinum-based chemotherapy doublet regimen. If eligible, patients received bevacizumab on Day 1 of a 21-day cycle. Patients were entered into the registration period of the trial at any time prior to, during receipt of, or within

42 days following completion of induction chemotherapy (defined as the last dose of chemotherapy within the last cycle).

Patients who completed four to six cycles of chemotherapy without evidence of progression were eligible for a 2:1 randomization to treatment with imetelstat (9.4 mg/kg, Days 1 and 8 of a 21-day cycle) in addition to standard of care (bevacizumab or observation) vs. standard of care alone (bevacizumab or observation). Randomization was to occur within 42 days from the last dose in the last cycle of induction chemotherapy. Day 1 commenced within 3 days of randomization. Patients were stratified based on whether they received bevacizumab with their induction chemotherapy and were willing and able to continue on bevacizumab (Day 1 of a 21-day cycle). Patients who received bevacizumab therapy but were unable or unwilling to continue to receive this therapy were not randomized. All patients may have received supportive care. Imetelstat and/or standard of care continued until disease progression or unacceptable toxicity was observed. Patients on the imetelstat + bevacizumab treatment arm who discontinued bevacizumab or imetelstat due to reasons other than disease progression continued to receive treatment with either single agent imetelstat or bevacizumab.

After the baseline evaluation prior to randomization, tumor status was assessed every 6 weeks (from first dose) for 36 weeks, then every 9 weeks for the remainder of the study. Responses were assessed using the investigator's assessment based on the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), and confirmation of a partial or complete response was required at least 3 weeks after initial documentation. No formal interim analyses for efficacy were planned. For patients who withdrew from the study for any reason other than disease progression, imaging studies were obtained at the end of study visit, unless the last imaging studies were performed within 30 days of the last dose of study drug. For patients who were withdrawn from the study due to clinical evidence of disease progression, imaging studies were performed for confirmation of progression by RECIST v1.1.

At the time of disease progression, patients who were randomized to the standard of care only arm had the option to cross-over to receive imetelstat. Treatment with single agent imetelstat occurred either within 3 weeks of determination of disease progression by RECIST v1.1 or within 3-4 weeks following the discontinuation of a standard second-line therapy and continued up to 1 year. The decision to cross-over, however, should have occurred within 3 weeks following determination of disease progression.

Patients were followed for safety assessments from the time of randomization until 30 days after their last infusion of study drug, or until initiation of alternative therapy for their NSCLC (whichever occurred first). Patients who participated in the optional post-maintenance phase of the study who received imetelstat monotherapy were followed until 30 days after their last infusion or until initiation of alternative therapy for their NSCLC (whichever occurred first).). Patients in the standard of care arm of the study, who subsequently crossed-over to receive imetelstat, were followed until 30 days after their last infusion of imetelstat or until initiation of alternative therapy for their NSCLC (whichever occurred first). A safety committee internal to Geron reviewed the safety data approximately every 3 months or every 25 patients, whichever occurred first.

Optional archived tumor samples (10-20 unstained slides), serum, and peripheral blood mononuclear cells (PBMCs) were collected following randomization. Archived tumor samples were provided to Geron at any time between randomization and termination from study. These

samples were used to explore the impact of pre-treatment tumor characteristics on the clinical outcome of all treatment arms in this study.

Number of Patients (Planned and Analyzed)

A total of 116 patients were enrolled in the study and randomized to the study as follows: 50 patients to imetelstat alone, 27 to imetelstat + bevacizumab, 26 to observation only, and 13 to bevacizumab only.

Overall, 114 (98.3%) of the randomized patients received study treatment or, in the observation-only control arm, attended a Cycle 1 Day 1 visit as follows: 52 in imetelstat alone (45.6%), 24 in imetelstat + bevacizumab (21.1%), 26 in observation only (22.8%), and 12 in bevacizumab only (10.5%). Two randomized patients (Patients 807-0001 and 122-0007) did not receive study treatment because laboratory assessments performed after randomization (at the Cycle 1 Day 1 visit) disqualified them for treatment. These 2 patients were excluded from both the efficacy and safety analyses, so that these two population samples have identical patient memberships. Two patients who were stratified into the imetelstat + bevacizumab group did not receive bevacizumab on study and were included in the imetelstat alone group for safety and efficacy analyses; since bevacizumab use was not randomized, analyses according to the actual treatment received does not alter the intent-to-treat properties of the imetelstat randomization.

Diagnosis and Main Criteria for Inclusion

Patients with advanced NSCLC (Stage IV according to the 7th edition of AJCC, or recurrent locally advanced disease who were not amenable to chemoradiation) who were eligible for induction chemotherapy with a platinum-based doublet regimen or who were currently receiving this therapy were registered into this study. Patients must not have progressed after completing four to six cycles of induction chemotherapy (i.e. stable disease or better). Patients were either not eligible for maintenance treatment with pemetrexed or epidermal growth factor receptor (EGFR) inhibitors or chose not to receive these maintenance treatments. Patients who had received, or were scheduled to receive pemetrexed or erlotinib as maintenance therapy were not eligible.

Test Product, Dose, and Mode of Administration

Imetelstat was the investigational product in this study and was administered at a dose of 9.4 mg/kg as a 2-hour IV infusion (± 10 min) on Days 1 and 8 of a 21-day cycle. For patients who received bevacizumab, imetelstat was infused prior to bevacizumab.

Reference Therapy, Dose, and Mode of Administration

Bevacizumab was administered according to the FDA-, Health Canada-, or EMA-approved dose in NSCLC. Bevacizumab was administered on Day 1 of each 21-day cycle. Refer to the Avastin® package insert (U.S.), product monograph (Canada) or summary of product characteristics (EU) for details on dosage and administration.

Duration of Study Treatment

Imetelstat and/or standard-of-care treatment continued until disease progression or unacceptable toxicity was observed. Patients on the imetelstat + bevacizumab treatment arm who discontinued bevacizumab or imetelstat due to reasons other than disease progression continued to receive treatment with either single agent imetelstat or bevacizumab. At the time of disease progression,

patients who were randomized to the standard-of-care arm had the option to cross-over to receive imetelstat. Treatment with single agent imetelstat occurred within 3 weeks after determination of disease progression by RECIST v1.1 or within 3-4 weeks following a standard second-line therapy and continued up to 1 year.

CRITERIA FOR EVALUATION

Efficacy

Patients who were randomized and received at least one dose of study treatment (or in the observation arm, completed the Cycle1, Day 1 visit) were included in the efficacy evaluation of this study. Efficacy data were analyzed based on the treatment arm to which patients were randomized.

Safety

Patients who were randomized and received at least one dose of study treatment (or in the observation arm, completed the Cycle1, Day 1 visit) were included in the safety evaluation of this study.

STATISTICAL METHODS

Efficacy Endpoints

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from randomization to documented disease progression, as determined by the investigator's assessment according to RECIST v1.1, or death from any cause, whichever occurred first.

Secondary efficacy endpoint was response rate, defined as the proportion of patients with a partial response (PR) or complete response (CR), as determined by the investigator's assessment according to RECIST v1.1, compared to baseline tumor measurements taken after the chemotherapy induction period and prior to randomization.

Safety Endpoints

The safety and tolerability of imetelstat maintenance was assessed by the frequency, severity, and nature of adverse events (AEs), laboratory abnormalities, and vital signs.

SUMMARY AND CONCLUSION

Efficacy Conclusions

Efficacy data from this study suggest that in patients with advanced NSCLC who have not progressed after completing four to six cycles of induction chemotherapy, efficacy of treatment with imetelstat alone or in combination with bevacizumab was not significantly different from standard of care (observation or bevacizumab alone) for patients who were not eligible to receive or declined to receive pemetrexed or erlotinib. Maintenance therapy with imetelstat as a single agent or combined with bevacizumab did not improve PFS or OS compared with standard of care.

- Median PFS was 2.76 months in the imetelstat arms and 2.57 months in the control arms. Compared with the control arm, the HRs were: 0.708 (95% CI, 0.46, 1.09) for stratified RECIST, p-value = 0.1126; 0.784 (95% CI, 0.51, 1.20) for unstratified

RECIST, p-value = 0.2597; and 0.786 (95% CI, 0.51, 1.21) for stratified clinical or radiologic progression, p-value = 0.2689.

- Median overall survival was 14.31 months (95% CI, 9.90, 18.36) in the imetelstat arms and 12.04 months (95% CI, 7.57, 16.09) in the control arms, with a median follow-up of 11.23 and 11.28 months, respectively. Compared with the control arm, the HR was 0.796 (95% CI, 0.49, 1.30), p-value = 0.3568.
- The 6-month survival rate was 81.3% (95% CI, 70.5, 88.5) in the imetelstat arms vs. 75.0% (95% CI, 57.5, 86.1) in the control arms.
- The objective response rates were 3.0% in the imetelstat arms (n = 2, both were PRs) and 0% in the in the control arms; p-value = 0.3209. Due to the maintenance setting, high rates of additional response after the induction response were not expected.

Safety Conclusions

Imetelstat alone or in combination with bevacizumab was generally well tolerated, although incidences of AEs were generally higher in the imetelstat arms (imetelstat alone and imetelstat + bevacizumab) compared with the control arms (observation and bevacizumab alone). Liver biochemistry abnormalities, the majority of which were Grade 1, were identified as a safety signal possibly attributable to imetelstat, based on review of the data from this study. Two patients also experienced serious AEs (SAEs) with hepatic manifestations (acute reversible transaminitis with concurrent ascites in one patient). This signal is currently under evaluation.

- Of the 114 treated patients in this trial, 107 (93.9%) experienced at least one treatment-emergent AE, regardless of attribution. The most common reported AEs (occurring in ≥ 50% of patients in any arm) observed in this study were thrombocytopenia (34.2% overall) and nausea (33.3% overall). As with previous imetelstat studies, higher incidences of thrombocytopenia (50%), nausea (43.4%), and fatigue (42.1%) were observed in the imetelstat arms compared with the control arms (2.6%, 13.2%, and 15.8%, respectively). The majority of the nausea and fatigue events were Grade 1 or 2.
- A higher percentage of patients experienced treatment-emergent Grade ≥ 3 AEs in the imetelstat arms (63.2%) compared with the control arms (26.3%). The most common reported Grade ≥ 3 AEs were thrombocytopenia (27.6% in the imetelstat arms vs. 0% in the control arms), neutropenia (17.1% in the imetelstat arms vs. 0% in the control arms), and platelet count decreased (9.2% in the imetelstat arms vs. 0% in the control arms).
- The percentage of patients who experienced at least one treatment-emergent SAE in the imetelstat arms (22.4%) was slightly higher than the control arms (15.8%). The most common SAEs (occurring in ≥ 2 patients in any arm) observed in this study were pneumonia (5.3% in the imetelstat arms and 5.3% in the control arms) and thrombocytopenia (4.0% in the imetelstat arms compared with 0% in the control arms).
- More patients (22.4%) discontinued imetelstat because of AEs compared with patients who discontinued bevacizumab (13.9%) due to AEs

- Two patients (2.6%) died due to an AE in the imetelstat arms compared with 2 patients (5.3%) in the control arms, although one death (in a patient in the bevacizumab only arm) occurred after the patient had crossed over to imetelstat maintenance treatment.
- The incidences of all cytopenias (based on the maximum post-baseline grade in laboratory values) were higher in the imetelstat arms compared with the control arms. The most common cytopenias of all grades observed were thrombocytopenia (85.5% in imetelstat arms vs. 15.8% in the control arms) followed by anemia (82.9% in imetelstat arms vs. 76.3% in the control arms). The most common Grade ≥ 3 cytopenias were thrombocytopenia (46.1% in imetelstat arms vs. 0% in the control arms) followed by neutropenia (34.2% in imetelstat arms vs. 0% in the control arms).
- Higher rates of liver biochemistry abnormalities (based on the maximum post-baseline grade in laboratory values) were observed in the imetelstat arms compared with control arms. The most common liver biochemistry abnormalities were increased aspartate aminotransferase (AST; 55.3% in imetelstat arms vs. 10.5% in the control arms), followed by increased alkaline phosphatase (ALP; 47.4% in imetelstat arms vs. 18.4% in the control arms), increased alanine aminotransferase (ALT; 39.5% in imetelstat arms vs. 7.9% in the control arms), and increased bilirubin (18.4% in imetelstat arms vs. 0% in the control arms). The majority of these events were Grade 1; Grade ≥ 3 abnormalities were only reported in the imetelstat arms and included: 5 (6.6%) increased ALT, 2 (2.6%) increased AST, and 1 (1.3%) increased bilirubin. There were no Grade ≥ 3 events of increased ALP. Two patients experienced SAEs with hepatic manifestations as summarized below.
  - Patient 807-0008 experienced an SAE (hospitalization) of acute transaminitis (Grade 4, considered to be related to imetelstat by the investigator) with concurrent ascites and thrombocytopenia, diagnosed as liver insufficiency. The patient had no other signs of liver failure. Imetelstat was discontinued. The transaminases resolved to Grade 1 and the patient improved clinically. The patient subsequently developed sepsis and acute renal failure. Laboratory culture of ascites fluid noted MRSA. He died due to sepsis; an autopsy showed mediastinitis as a possible cause of the sepsis.
  - Patient 018-0005 experienced an infusion-related reaction (SAE; hospitalization) including abdominal pain, shortness of breath, and hypertension during the Cycle 3, Day 1 infusion of imetelstat. The patient developed acute onset of very severe chest pain with associated nausea and an acute rise in aminotransferases (Grade 4) and was in a decompensated state. Imetelstat was discontinued. The patient was discharged 2 days later and the liver biochemistry levels normalized over the following 3 weeks.

Overall Conclusions

Median PFS rate was 2.76 months in the imetelstat arms and 2.57 months in the control arms (HR = 0.784, p = 0.2597), with a median follow-up of 2.3 and 2.6 months, respectively. Response rates were based on post-induction baseline assessments and imetelstat was studied for its potential to maintain induction response; therefore, high rates of further response compared to

post-induction baseline were not expected in this study. Median OS was 14.31 months (95% CI, 9.90, 18.36) in the imetelstat arms and 12.04 months (95% CI, 7.57, 16.09) in the control arms, (HR = 0.796, p = 0.3568), with a median follow-up of 11.23 and 11.28 months, respectively. Although statistical significance was not demonstrated for OS in this small Phase II study, the results suggest a trend toward a survival benefit for imetelstat as maintenance therapy, with or without bevacizumab, when compared with standard of care (observation or bevacizumab alone) in bevacizumab when compared with standard of care (observation or bevacizumab alone) in patients with advanced NSCLC who were not eligible to receive or declined to receive maintenance therapy with pemetrexed or erlotinib. Superior efficacy was observed with pemetrexed maintenance therapy in a similar patient population (Ciuleanu et al. 2009; Scagliotti et al. 2008).

In terms of safety, imetelstat alone or in combination with bevacizumab was generally well tolerated, although incidences of overall AEs, Grade ≥ 3 AEs, SAEs, and AEs leading to study drug discontinuation were generally higher in the imetelstat arms compared with the control arms. The most frequent increased toxicities in the imetelstat arm were hematologic, predominantly neutropenia and thrombocytopenia. Constitutional symptoms (e.g., fatigue, dizziness), gastrointestinal symptoms (e.g., nausea, vomiting), low-grade infections, and biochemical liver function tests were also increased in the imetelstat arm.