Synopsis

Sponsor: **Human Genome Sciences, Inc.**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**

Name of Finished Product: **Volume:**

Mapatumumab

Name of Active Ingredient: **Page:**

Recombinant, fully human, IgG1λ monoclonal antibody to TRAIL-R1

Study Title:

A Phase 2, Randomized, Multi-center, Open-label Study to Evaluate the Efficacy and Safety of Mapatumumab ([HGS1012], A Fully Human Monoclonal Antibody to TRAIL-R1) in Combination with Carboplatin and Paclitaxel as First Line Therapy in Subjects with Advanced Non-small Cell Lung Cancer (NSCLC)

Investigators and Study Centers: Multi-center (22 sites; 13 United States, 4 Germany, 3 Hungary, 2 Romania).

Publication (reference): Von Pawel J, Harvey JH, Spigel DR, et al. A randomized phase II trial of mapatumumab, a TRAIL-R1 agonist monoclonal antibody, in combination with carboplatin and paclitaxel in patients with advanced NSCLC. [abstract] J Clin Oncol (Meeting Abstracts) 2010;28 (18_suppl):LBA7501.

Studied Period:

21 November 2007 (first subject informed consent) to
17 December 2010 (last subject for final database lock in February 2011) to
29 March 2012 (last subject last visit)

Study Phase: 2

Objectives:

Primary:

- To evaluate the efficacy of mapatumumab in combination with paclitaxel and carboplatin in subjects with Stage IIIB/IV NSCLC.

Secondary:

- To evaluate the safety and tolerability of mapatumumab in combination with paclitaxel and carboplatin.
- To determine serum mapatumumab concentrations.

Methodology: This was a Phase 2 randomized, multi-center, open-label study designed to evaluate the efficacy and safety of mapatumumab in combination with carboplatin and paclitaxel as 1st-line therapy in the treatment of advanced NSCLC (Stage IIIB or IV).

Approximately 105 subjects were planned to be randomly assigned in a 1:1:1 ratio to 1 of

3 treatment arms and treated with either the 2-agent combination of carboplatin and paclitaxel or the 3-agent combination of carboplatin, paclitaxel, and mapatumumab as indicated:

- Arm A: Paclitaxel 200 mg/m2 intravenous (IV) over 3 hours on Day 1 of a 21-day treatment cycle, followed by carboplatin area under the curve (AUC) 6.0 mg·min/mL IV over 30 to 60 minutes.
- Arm B: Paclitaxel 200 mg/m2 IV over 3 hours on Day 1 of a 21-day treatment cycle, followed by carboplatin AUC 6.0 mg·min/mL IV over 30 to 60 minutes. Mapatumumab 10 mg/kg (based on actual body weight) was administered IV over 1 hour on Day 1 of each cycle following the completion of chemotherapy administration.
- Arm C: Paclitaxel 200 mg/m2 IV over 3 hours on Day 1 of a 21-day treatment cycle, followed by carboplatin AUC 6.0 mg·min/mL IV over 30 to 60 minutes. Mapatumumab 30 mg/kg (based on actual body weight) was administered IV over 1 hour on Day 1 of each cycle following the completion of chemotherapy administration.

The planned duration of each treatment cycle was 21 days. Randomization was stratified according to cancer stage (IIIB vs IV) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1).

After discontinuation of treatment, subjects continued to be followed every 6 weeks until documented disease progression (if not previously documented) and then every 3 months thereafter for survival. Subjects had an end of treatment visit at least 30 days after the last dose of the study agent.

Number of Subjects (Planned and Analyzed):

Approximately 105 subjects were planned; 111 subjects were enrolled and randomized; 109 subjects received at least 1 dose of any study agent and were analyzed for safety and efficacy.

At the time of database lock in February 2011, 3 subjects (2 in Arm B and 1 in Arm C) who had completed 40 cycles continued to receive mapatumumab monotherapy under the provisions of protocol amendment 03. One subject in Arm B completed 2 additional cycles before discontinuing mapatumumab due to lack of efficacy, one subject in Arm C completed 13 additional cycles before discontinuing due to subject request, and the other subject in Arm B completed an additional 27 cycles before discontinuing due to AE (see Safety below).

Diagnosis and Main Criteria for Inclusion:

Eligible adult subjects (18 years or older) had histologically or cytologically confirmed Stage IIIB (T4 due to malignant pericardial or pleural effusions as indicated by positive cytology, exudative effusion and lactate dehydrogenase [LDH] > 200 IU with effusion/serum LDH ratio 0.6 [“Wet IIIB”] or any N3, M0 who were not candidates for standard combined modality therapy) or Stage IV advanced primary non-small cell lung carcinoma. Eligible subjects were required to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), adequate hematological function and bone marrow reserve, adequate hepatic and renal function, and adequate performance status.

Test Product, Dose and Mode of Administration, Lot Number:

Mapatumumab, 10 mg/kg and 30 mg/kg, administered IV; Lot No. 71026, 71056, and 71058.

Duration of Treatment: All subjects received paclitaxel IV over 3 hours on Day 1 of a 21-day treatment cycle, followed by carboplatin IV over 30 to 60 minutes. For subjects randomized to Arms B and C, mapatumumab was administered IV over 1 hour on Day 1 of each cycle following the completion of chemotherapy administration.

Subjects in Arm A completed up to 6 cycles of treatment if there was no evidence of disease progression or unacceptable toxicity during Cycles 1 through 6. Subjects in Arm B and Arm C who did not have evidence of documented disease progression (stable disease [SD], partial response [PR] or complete response [CR]) or unacceptable toxicity following the 6^{th} cycle were allowed to receive additional treatment with mapatumumab alone every 21 days until disease progression.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Paclitaxel, 200 mg/m^2, administered IV; carboplatin, AUC 6.0 mg · min/mL administered IV; commercially available supplies were used.

Criteria for Evaluation:

Efficacy:

Clinical response was evaluated according to RECIST, Version 1.0.Clinical decisions regarding subject treatment were made by the investigator using local readings of the imaging scans; however, the primary endpoint was based on blinded independent central review (BICR) of these images.

Safety:

Safety was assessed by evaluation of type, frequency, and severity of adverse events (AEs), changes in clinical laboratory tests (hematology and clinical chemistry), immunogenicity, and physical examinations. All AEs and laboratory toxicities were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0, 09 August 2006). If an AE did not have an NCI-CTCAE grading, the severity grades in Section 8.5 of the protocol were used.

Pharmacokinetics:

Blood samples were obtained from subjects in Arms B and C at multiple time points for serum mapatumumab concentration measurements. See Report HGS1012-C1072.PK.

Pharmacodynamics:

Blood samples were collected for exploratory analysis of rheumatoid factor (RF) titer (before dosing Cycle 1 Day 1 only) and quantification of B and T lymphocyte subsets (on Day 1 [before dosing] and Day 15 of Cycles 1 and 2).

From subjects who consented to participate in a biomarker research sub-study, tissue sample from previous biopsy, if available, and several blood samples for examination of biomarkers in peripheral blood were obtained (see Report AB22125.ONC.0.074). In addition, samples were requested from subjects who underwent a biopsy during the treatment period.

Statistical Methods:

The co-primary analyses were an estimate of overall response rate (CR+PR) for each arm, reported with 95% confidence intervals (CI) and an estimate of median progression free survival (PFS) for each arm, using Kaplan-Meier methods. The focus of this study was estimation of response rate and PFS, and all statistical comparisons are considered secondary analyses.

The secondary efficacy analysis of disease control and overall survival (OS) included estimates of the disease control rate and median overall survival. PFS was tested with a stratified log-rank test. Secondary analyses included an estimate of the difference in response rates between Arms A and B and between Arms A and C reported with a 95% CI and tested for significance with a Pearson chi-square test. Results from Arm B and Arm C were also pooled and the pooled response rate estimated with a 95% CI and tested for significance vs Arm A.

For frequency and severity of AEs and laboratory toxicity grading, counts and rates were presented.

Summary of Results

Efficacy:

The overall response rate (CR + PR) was 31% in Arm A, 14% in Arm B, and 36% in Arm C. No statistically significant difference was observed between the treatment arms. Disease control (CR+PR+SD) rates were comparable across the treatment arms (75% Arm A, 68% Arm B, 64% Arm C). No statistically significant difference was observed in PFS or OS between the treatment arms. No benefit was observed by adding mapatumumab to paclitaxel and carboplatin in subjects with Stage IIIB or Stage IV advanced primary NSCLC.

Safety:

All subjects had at least 1 treatment-emergent AE during the study. The proportion of subjects with severe AEs was higher in Arm B compared with Arms A and C; however, the proportion of subjects with severe mapatumumab-related AEs was similar between the 2 mapatumumab treatment arms (Arms B and C). In the 3 subjects who remained on treatment with mapatumumab monotherapy following database lock in February 2011, 1 SAE was reported in 1 subject (Arm B) during the additional cycles of treatment. This SAE occurred 16 days after the subject's 67^{th} dose of mapatumumab when she was hospitalized for general physical health deterioration (Grade 4), considered not related to mapatumumab by the investigator. The subject died off study (45 days after last dose of study agent). The most frequently reported AEs (≥ 25% of all subjects) were peripheral sensory neuropathy, fatigue, nausea, neutropenia, anemia, alopecia, dyspnea, constipation, decreased appetite, and diarrhea. Peripheral sensory neuropathy was the most frequently occurring AE, with more cases reported in subjects who received mapatumumab in combination with chemotherapy. None of the cases of peripheral sensory neuropathy in mapatumumab-treated subjects were considered related and severe, and severe cases were evenly distributed between the treatment arms (2 in Arm A, 3 in Arm B, and 1 in Arm C). Twenty-five subjects (25/109; 23%) discontinued study agent(s) due to AE; 6 subjects in Arm A, 10 in Arm B, and 9 in Arm C. Rates of discontinuation of mapatumumab, mapatumumab and chemotherapy, or chemotherapy due to AE were similar for Arms B and C. There were 8 deaths among the 109 treated subjects

during treatment or within the 30-day follow-up period due to respiratory failure (n=3), pulmonary embolism (n=2), cardiac arrest (n=1), pneumonia (n=1), and disease progression (n=1). None of the deaths were considered related to any study agent by the investigator. Shifts of at least 2 grades from baseline to Grade 3 or Grade 4 lymphopenia occurred in more subjects who received mapatumumab, 10 subjects in Arms B and C compared with 1 subject in Arm A. Grade 3 and Grade 4 lymphopenia was transient in nearly all cases and lymphocyte counts returned to baseline within a few weeks. There was no apparent evidence of other hematologic, hepatic, or renal toxicity associated with mapatumumab in combination with paclitaxel and carboplatin. Anti-mapatumumab antibodies were detected in 2 subjects.

Pharmacokinetics:

See Report HGS1012-C1072. PK.

Pharmacodynamics:

Data and discussion of the exploratory analysis of RF subset for mapatumumab from subjects enrolled in this study will be reported separately.

An exploratory analysis of B and T lymphocyte subsets was performed to assess the effect of mapatumumab treatment on lymphocyte subpopulations. Levels of CD4 T cells, CD8+ T cells, CD28+ T cells and CD19+ B cells were examined by flow cytometry. No noticeable trends were observed that would suggest mapatumumab treatment had any effect on lymphocyte subpopulations at the time points examined.

See Report AB22125.ONC.0.074 for data and discussion of the analysis of potential biomarkers in blood.

Results of the immunohistochemistry analysis for TRAIL-R1 expression on tumor specimens are on file.

Conclusions:

Efficacy Conclusion:

The overall response rate (CR + PR) was not statistically significant different between the treatment arms. No benefit was observed by adding mapatumumab to paclitaxel and carboplatin in subjects with Stage IIIB or Stage IV advanced primary NSCLC.

Safety Conclusions:

Mapatumumab 10 mg/kg and 30 mg/kg in combination paclitaxel and carboplatin were well tolerated. There was no apparent evidence that mapatumumab exacerbated AEs associated with paclitaxel and carboplatin.

Twenty-five subjects (25/109; 23%) discontinued study agent(s) due to AE; 6 subjects in Arm A, 10 in Arm B, and 9 in Arm C. Rates of discontinuation of mapatumumab, mapatumumab and chemotherapy, or chemotherapy due to AE were similar for Arms B and C.

There were 8 deaths among the 109 treated subjects during treatment or within the 30-day follow-up period due to respiratory failure (n=3), pulmonary embolism (n=2), cardiac arrest (n=1), pneumonia (n=1), and disease progression (n=1). None of the deaths were considered related to any study agent by the investigator.

Shifts of at least 2 grades from baseline to Grade 3 or Grade 4 lymphopenia occurred in more

subjects who received mapatumumab compared with Arm A. The lymphopenia was transient in nearly all cases and lymphocyte counts returned to baseline within a few weeks. There was no apparent evidence of other hematologic, hepatic, or renal toxicity associated with mapatumumab in combination with paclitaxel and carboplatin.

Anti-mapatumumab antibodies were detected in 2 subjects.

Final Date: 15 June 2012

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