The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.
SYNOPSIS

STUDY INFORMATION:

Name of Sponsor:
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA USA 02139
Telephone: +1 (617) 679-7000

Title of Study: A Phase 2 Trial of MLN0264 in Previously Treated Patients With Metastatic or Recurrent Adenocarcinoma of the Stomach or Gastroesophageal Junction Expressing Guanylyl Cyclase C (GCC)

Name of Active Ingredient: MLN0264 (also referred to as TAK-264)

Name of Finished Product: MLN0264 (also referred to as TAK-264)

Investigators: 24 principal investigators enrolled subjects in the Stage 1 portion of the study.

Study Sites: The study was conducted at 24 investigative centers located in the United States (US) and Europe.

Publications Based on the Study: None.

Study Period:
Date first subject signed informed consent form: 04 August 2014
Date of last subject’s last visit/contact 15 January 2016
Date of last subject’s last procedure for collection of data for primary endpoint: 15 January 2016

Phase of Development: Phase 2

Objectives:

Primary:
The primary objective of the study was to evaluate the overall response rate (ORR) of patients with recurrent or metastatic GCC-positive adenocarcinoma of the stomach or gastroesophageal junction treated with MLN0264.

Secondary:
The secondary objectives were:

- To evaluate the safety profile of MLN0264.
- To evaluate progression-free survival (PFS).
- To evaluate duration of response (DOR).
- To evaluate disease control rate (DCR).
- To evaluate overall survival (OS).
- To examine the pharmacokinetics (PK) profile.
- To evaluate tumor size reduction.
- To investigate the association between GCC expression level and antitumor effects of MLN0264.
- To assess immunogenicity of MLN0264.

Methodology: Study C26002 was an open-label, nonrandomized, multicenter, phase 2 study of MLN0264 that was conducted in adult patients with metastatic or recurrent gastric or gastroesophageal junction malignancies expressing GCC. Patients with adenocarcinoma (measurable disease per Response Evaluation Criteria in Solid Tumors
who had been treated with ≥1 prior chemotherapy for advanced or metastatic disease, had adequate renal, hepatic, and hematological function, and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 at baseline were eligible for enrollment.

The study design featured a Stage 1 portion and a Stage 2 portion. However, only the Stage 1 portion was conducted prior to study termination. In Stage 1, at least 12 response-evaluable patients in each of 3 cohorts with high (combined immunohistochemistry [IHC] H-score >250), intermediate (combined H-score 110-249), and low (combined H-score 10-109) GCC expression, respectively, were to be enrolled in parallel. Once enrolled, patients were to receive 1.8 mg/kg MLN0264 intravenously (IV) on Day 1 of 3-week (21-day) cycles for up to 1 year or until disease progression (PD) or unacceptable toxicity occurred. Tumor response assessments were performed at the completion of every other treatment cycle beginning with Cycle 2. Adverse events (AEs) were assessed and laboratory values, vital signs, and electrocardiograms (ECGs) were obtained to evaluate the safety and tolerability of MLN0264. Blood samples were obtained for PK measurements, antitherapeutic antibody (ATA) levels, and peripheral tumor markers. Tumor tissue was evaluated for biomarkers.

An interim analysis for futility was to be conducted in 12 response-evaluable patients in each of the 3 GCC expression groups at the end of Stage 1 to inform whether enrollment into Stage 2 was warranted. If ≥2 responses were observed in the low-, intermediate-, or high-GCC cohorts in Stage 1, Stage 2 was to enroll additional response-evaluable patients into those cohorts in which the responses were observed. Fewer than 2 responses in each cohort would indicate that the study was to be discontinued. Based on the totality of the interim data, the threshold for continued enrollment into the study was not met and Stage 2 was not initiated.

**Number of Subjects:**

Planned: 36 subjects (12 subjects each in the low-, intermediate-, and high-GCC expression level cohorts, respectively).

Screened: 64 subjects

Enrolled in the Stage 1 portion of the study: 38 subjects (9, 15, and 14 subjects in the low-, intermediate-, and high-GCC expression level cohorts, respectively).

**Diagnosis and Main Criteria for Inclusion:** The study population will consist of male or female patients aged 18 years or older with metastatic or recurrent adenocarcinoma of the stomach or gastroesophageal junction expressing GCC who have an ECOG performance status of 0 or 1; adequate hepatic, renal, and hematologic function; and who have been treated with 1 or more prior chemotherapies for advanced or metastatic disease.

**Duration of Treatment:** The study consisted of a screening period, an open-label treatment period with treatment on Day 1 of 3-week cycles for up to 1 year or until disease progression or unacceptable toxicity.

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

<table>
<thead>
<tr>
<th>Study Medication</th>
<th>Product Dose Strength and Form</th>
<th>Study Dosage</th>
<th>Mode of Administration</th>
<th>Drug Product Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLN0264</td>
<td>MLN0264 powder for concentrate for solution for infusion</td>
<td>1.8 mg/kg</td>
<td>IV</td>
<td>Available upon request.</td>
</tr>
</tbody>
</table>

**Criteria for Evaluation:**

Efficacy:

- The primary endpoint was ORR (complete response [CR]+partial response [PR]), based on RECIST Version 1.1.

- PFS, defined as the time from the date of first MLN0264 administration to the date of the first documentation of PD or death.
DOR, defined as the time from the date of first documentation of a confirmed response to the date of first documentation of PD.

DCR, including CR+PR+stable disease (SD) with minimum 12 weeks’ duration. Duration of SD was defined as the time from the date of first MLN0264 administration to the date of first documentation of PD for patients who achieved SD as the best overall response.

OS, defined as the time from the date of first MLN0264 administration to the date of death.

Tumor size reduction.

Pharmacokinetics:

PK parameters.

Efficacy-related pharmacodynamics:

GCC H-score assessed by IHC.

Assessment of ATAs.

Safety:

AEs, serious adverse events (SAEs), clinical laboratory values, and vital sign measurements.

Statistical Methods:

Populations for Analysis:

The Safety population is defined as all patients who receive any amount of MLN0264. This population was used for safety and efficacy analyses.

The Response-Evaluable population is defined as all patients with measurable disease who receive at least 1 dose of MLN0264 and have at least 1 postbaseline response assessment. This population was used for response-related efficacy analyses.

The PK-Evaluable population is defined as all patients who receive at least 1 dose of MLN0264 and who have sufficient MLN0264 concentration–time data to permit reliable estimation of MLN0264 exposure. This population was used for PK analyses.

Efficacy:

The efficacy analysis was based on the Response-Evaluable population and the Safety population. The primary endpoint is the ORR (CR rate+PR rate). For each patient, the best percentage of tumor reduction from baseline in the sum of the diameter was calculated and displayed to show the distribution of response across all patients. Unscheduled visits were also included in such displays. By-patient listings were provided for PFS, DOR, and OS.

All efficacy endpoints were based on evaluations performed by the investigators. The independent central review assessment also conducted the analyses. The number and percentage of patients falling into each response category were descriptively tabulated. Response assessment was based on RECIST Version 1.1 criteria. The DCR was analyzed using similar methods.

Pharmacokinetics:

Serum (MLN0264 and total antibody [TAb]) and plasma (MMAE) concentrations were summarized by postdose sampling time point for the PK-Evaluable population. By-patient listings were also provided.

The relationship between GCC expression and pre-infusion concentration of MLN0264 and TAb at Cycle 2 was explored.
Immunogenicity:

Numbers and percentages of patients were summarized by ATA status according to scheduled time points. ATA statuses were descriptively summarized by response category (separated by high and low titers), and by safety findings such as infusion-related reactions. ATA results were also presented in a by-patient listing.

Patient Reported Outcomes:

European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ) scores were provided in by-patient listings.

Safety:

Safety evaluations were performed using the Safety population and were based on the incidence, severity, and type of AEs, and on clinically significant changes or abnormalities in physical examination, vital signs, and clinical laboratory results. AEs were coded using Medical Dictionary for Regulatory Activities Version 18.0. All AEs and serious adverse events (SAEs) were presented in individual patient listings. Treatment-emergent AEs were tabulated. Event severity was categorized using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

Deaths that occurred either on study or during the follow-up period were included in the AE listing, regardless of treatment-emergent status and causality. An on-study death was defined as one that occurred between administration of the first MLN0264 dose and 30 days following the last dose.

For the purposes of summarization in the tables and listings, all laboratory values were converted to standardized units. Laboratory test results from the local laboratories were summarized according to the scheduled sample collection time point. Change from baseline was also presented. By-patient listings included hematology, clinical chemistry, urinalysis, and coagulation results. Pregnancy testing results were presented in a patient listing. ECG results were presented in a by-patient listing.

The actual values of vital sign parameters were presented in a by-patient listing.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

The patients were 82% male and 95% white; 3% of patients were Black or African American and 3% were Asian. Ethnicity was reported as Not Hispanic or Latino for 92% of patients and Hispanic or Latino for 3% of patients, with 5% not reported. The median age of the patients was 63 years, with a range of 31 to 81 years.

The median time since initial diagnosis was 19 months with a range from 5 to 76 months. The most common histological classification at initial diagnosis was adenocarcinoma (27 patients [71%]). These included not otherwise specified (NOS) (16 patients [42%]), intestinal type (5 patients [13%]), mucinous (4 patients [11%]), and in situ, NOS (2 patients [5%]). Five patients (13%) had signet ring cell carcinoma and 6 patients (16%) had a diagnosis of Other. At initial diagnosis, all 38 patients (100%) had Stage IV disease.

A total of 36 of the 38 patients had at least 1 prior medical condition, as expected in this study population of patients with advanced gastrointestinal (GI) cancer. The number of prior medical conditions ranged from 2 to 21. Fourteen of the 38 patients (37%) had previous surgical procedures. A total of 37 patients (97%) received at least 1 prior anticancer therapy. A total of 12 patients received 2 prior lines of therapy, 9 patients received 3, 5 patients received 1, 5 patients received 4, 3 patients received 5, 2 patients received 6, and 1 patient received 7 prior lines of anticancer therapy. A total of 37 patients (97%) had received platin-based treatments and 27 patients (71%) had received taxein-based treatments. Nineteen of the 38 patients (50%) received prior radiation therapy.

Subject Disposition:

A total of 38 patients were enrolled in the study; 9 patients with low, 15 patients with intermediate, and 14 patients with high GCC expression. All 38 patients (100%) were PK evaluable while 36 patients (95%) were
response-evaluable. The primary reason for leaving study treatment was PD, which occurred in 29 patients (76%). Three patients (8%) left study treatment because of AEs and 2 for patients (5%) study treatment was stopped for other reasons.

End of study implies a termination of the follow-up which is conducted to monitor PFS and OS. For 9 patients (24%), the study was terminated by the sponsor, consistent with the stopping rules for the interim analysis.

Four patients (11%) decided to withdraw from the study.

In the course of the follow-up, 23 patients (66%) died (death/expired/deceased), which represents other reasons for end of the study. Except for Patient: [redacted], all the deaths described as Other occurred during the follow-up period.

**Efficacy Results:**

Efficacy, as measured by ORR based on investigator assessment, was the primary endpoint of Stage 1 of this study. Additional secondary efficacy parameters included PFS, DOR, DCR, OS, and decrease in tumor size.

Based on investigator assessment, the ORR was 6% (2 patients). There were no CRs reported in this study. A PR was achieved by 2 patients (6%), SD was observed in 42% of patients, and PD was observed in 53% of patients.

Overall, PFS ranged from 38 to 427 days. DOR is defined as the time from the date of first documentation of a PR or better to the date of first documentation of PD or relapse. Based on investigator assessment, the DOR of Patient: [redacted] who achieved a PR at Cycle 2, was 90 days (6 cycles). Patient: [redacted] who also achieved a PR at Cycle 2, withdrew from the study after the assessment. DCR, comprising CR+PR+SD of at least 12 weeks’ duration, was 36% based on investigator assessment. OS ranged from 24 to 505 days based on investigator assessment. Overall, 7 patients (20%) had a reduction from baseline in size of the sum of target lesions, while 9 patients (26%) had negligible changes. By contrast, 19 patients (54%) had an increase in tumor size. Percent change from baseline was not calculated for 3 patients.

**Pharmacokinetic Results:**

The mean concentrations of MLN0264 and TAb in serum are steady and time-invariant over cycles of multiple dose administration. In the later cycles (Cycle 9 and later) the concentrations were more variable. However, this may be due to a smaller sample size, as the number of patients who remained on treatment in later cycles was lower.

Although the mean concentration-time profiles of MMAE appear somewhat variable between cycles for the first 3 cycles, at Cycle 6, at which frequent samples were taken, MMAE concentrations were generally similar to those seen in Cycle 1, showing that a steady state was reached. Several later cycles showed consistent steady state concentrations. However, few samples were taken, and as such, a complete profile for MMAE could not be captured in later cycles.

**Efficacy-Related Pharmacodynamic Results:**

MLN0264 and TAb pre-infusion concentrations at Cycle 2 were analyzed by GCC expression. The pre-infusion time point was chosen as a sensitive method of looking at the effect of GCC on the depletion of the antibody-drug conjugate prior to the next dose infusion. When concentrations of MLN0264 in serum at pre-infusion cycle are summarized against GCC H-score categorized into low, medium, and high expression levels, a slight trend is perceivable. Mean serum concentrations of both MLN0264 and TAb appear to be slightly higher for the patients with lowest expression of GCC receptors. An examination of the individual data, however, revealed that this trend is driven by data from a couple of individuals. This is compounded by the extent of variability and the relatively small sample sizes in each group. However, as more clearly shown by the geometric means and median data (which are more appropriate descriptors of central tendency for serum MLN0264/TAb concentrations), there is no observable trend of exposure with GCC expression category.

No correlation was seen with tumor GCC expression levels and response.
Safety Results:
All 38 patients (100%) completed at least 1 cycle of treatment. A total of 95% of patients completed at least 2 cycles, 50% completed at least 3 cycles, and 42% completed at least 4 cycles. A total of 8 patients (21%) completed at least 6 cycles. The maximum number of cycles completed was 14, which was achieved by 1 patient in the low GCC group.

A total of 37 patients (97%) had at least 1 AE. The most commonly reported AEs were observed in the GI system, with 28 patients overall (74%) having at least 1 GI-related AE. Nausea was the most commonly reported GI-related AE (20 patients [53%]). The majority of AEs were Grade 1 or Grade 2. Fourteen of the 38 patients (37%) had at least 1 ≥Grade 3 AE. Ten patients (26%) had at least 1 ≥Grade 3 AE that was assessed by the investigator as related to study drug. Overall, 7 patients (18%) had at least 1 SAE; 1 patient (3%) had SAEs of dysphagia and diarrhea, 1 patient (3%) had SAEs of anemia and upper GI hemorrhage, and 1 patient each (3%) had tumor hemorrhage, hip fracture, bile duct obstruction, gastric cancer, and supraventricular tachycardia. One patient (3%) had an SAE (upper GI hemorrhage) assessed by the investigator as related to study drug. Three patients (8%) had AEs that resulted in study drug discontinuation. These included 1 who had asthenia and liver function alteration, and 1 patient each who had peripheral motor neuropathy and upper GI hemorrhage. The AEs of asthenia, peripheral motor neuropathy, and upper GI hemorrhage were assessed by the investigator as related to study drug. There was 1 on-study death (3%) from gastric cancer that was assessed by the investigator as not related to study drug.

CONCLUSIONS:
This study evaluated 38 patients with gastric or gastroesophageal malignancies to assess the efficacy, safety, and PK of MLN0264. The ORR was 6%, with only 2 patients achieving PR. A total of 8 patients (21%) received 5 or more cycles of treatment. The safety profile of this experimental agent has been found to be manageable, with the majority of patients experiencing Grade 1 and Grade 2 AEs affecting the GI tract. Systemic exposure to MLN0264, TAh, and MMAE were generally maintained during the treatment. In spite of a manageable safety profile, the low efficacy of MLN0264 observed in this study does not support further clinical investigation.

DATE OF REPORT: 08 July 2016