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2.0 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 1/2 Trial of MLN0264 in Previously Treated Asian Patients with Advanced Gastrointestinal (GI) Carcinoma (Phase 1) or Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma (Phase 2) Expressing Guanylyl Cyclase C (GCC)

Name of Active Ingredient: MLN0264 antibody drug conjugate comprising 5F9 human monoclonal antibody conjugated to monomethyl auristatin E (MMAE) via a peptide linker, maleimido-caproyl-valine-citrulline (vc) which targets GCC

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

Investigator: 4 principal investigators enrolled subjects in the phase 1 portion.

Study Sites: The study was conducted at 4 investigative centers located in Korea, Japan, and Taiwan.

Publication Based on the Study: None

Study Period:
Date first patient signed informed consent form: 01 December 2014.
Date of last patient’s last visit/contact (from the Clinical database): 07 October 2015.
Date of last patient’s last procedure for collection of data for primary endpoint: 07 October 2015.

Phase of Development: Phase 1 [the phase 2 portion of the protocol was not initiated]

Objectives: This abbreviated Clinical Study Report focuses on the objectives that pertain to the phase 1 portion because the phase 2 portion of the study protocol was not initiated. Please refer to Protocol Amendment 3 for the list of objectives that had been planned for the phase 2 portion.

Primary:
The phase 1 primary objectives were:

- To assess the safety profile, including dose-limiting toxicities (DLTs) of MLN0264 administered as an intravenous (IV) infusion every 3 weeks (q3w) to Asian patients with advanced GI malignancies expressing GCC.
- To determine the recommended phase 2 dose (RP2D) of MLN0264 administered to Asian patients in a q3w dosing schedule.
- To characterize the pharmacokinetic (PK) profiles of MLN0264, total antibody (TAb; conjugated and unconjugated), and MMAE.

Secondary:
The phase 1 secondary objectives were:

- To evaluate immunogenicity of MLN0264 (antitherapeutic antibody [ATA] development).
- To explore the antitumor activity of MLN0264.
Methodology: Study C26004 is an open-label, nonrandomized, multicenter study conducted in Asian patients. The study design featured a phase 1 dose-escalation portion and a phase 2 portion. However, only the phase 1 dose-escalation portion was conducted prior to study termination. For information regarding the phase 2 portion, please see Protocol Amendment 3.

Phase 1 Dose Escalation

In the course of the dose-escalation portion of the study, MLN0264 doses of 1.2, 1.5, 1.8, 2.1, 2.4, and 2.7 mg/kg were to be administered IV on Day 1 of 3-week cycles for up to 1 year or until disease progression (PD) or unacceptable toxicity occurred. A conventional 3+3 dose-escalation scheme was applied, as detailed in Section 6.3 of Protocol Amendment 3. It was planned that at least 1 Japanese patient would be included in each of the 6 dose groups, if possible. If Asian patients dosed at 1.8 mg/kg did not show DLT, the totality of the interim data, including PK data, were to be examined in order to determine any further escalation. If the interim results were considered acceptable, dose escalation was to then proceed according to the dose increments specified above. DLT was defined in Protocol Amendment 3, Section 6.2. Toxicity was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing or previously tested dose level were permissible following discussions between the sponsor and the investigators, if such measures were needed for patient safety or for a better understanding of the dose–related toxicity, exposure, or PK of MLN0264.

Number of Subjects:

Planned: 28 subjects
Screened: 12 subjects
Enrolled in the phase 1 portion: 12 subjects

Diagnosis and Main Criteria for Inclusion: The study population consisted of male or female Asian patients 18 years of age or older (or minimum age of legal consent consistent with local regulations) who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate hepatic, renal, and hematologic function; and who had been treated with prior chemotherapies for advanced or metastatic disease. Patients in the phase 1 portion of the study had advanced GI malignancies expressing GCC and had exhausted standard-of-care treatment options.

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>Planned doses were 1.2, 1.5, 1.8, 2.1, 2.4, and 2.7 mg/kg</td>
<td>IV</td>
<td>Available upon request.</td>
</tr>
</tbody>
</table>

Criteria for Evaluation:

Efficacy:

- Disease response based on the investigator’s assessment using the modified Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 guidelines.

Pharmacokinetics:

- PK parameters of MLN0264, total antibody (conjugated and unconjugated), and MMAE.
Safety-related pharmacodynamics:
- Assessment of ATAs.

Safety:
- Adverse events (AEs), serious adverse events (SAEs), DLTs, assessment of clinical laboratory values and vital sign measurements.
- RP2D.

Statistical Methods:

Populations for Analysis:

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

The Response-Evaluable population included all patients with measurable disease who received at least 1 dose of MLN0264 and had at least 1 postbaseline response assessment. This population was used for response-related efficacy analyses.

The PK-Evaluable population included all patients who received ≥1 dose of MLN0264 and had sufficient MLN0264 concentration–time data to permit reliable estimation of MLN0264 exposure. This population was used for PK analyses.

The DLT-Evaluable population included all patients who either experienced DLT during Cycle 1 or received their scheduled Cycle 1 dose and completed all study procedures in Cycle 1 without DLT. This population was used to determine the RP2D.

Efficacy:

Efficacy analyses were based on the Response-Evaluable population and the Safety population. Efficacy information including response and progression-free survival (PFS) were presented as by-patient listings. Disease response or PD was determined by the investigator using the modified RECIST Version 1.1 guidelines.

Pharmacokinetics:

PK analyses were based on the PK-evaluable population.

Descriptive statistics (eg, number of patients, arithmetic mean, geometric mean, standard deviation, median, percentage of coefficient of variation, minimum, and maximum) were used to summarize MLN0264, TAb, and MMAE concentrations at each time point. The mean concentration-time profiles of MLN0264 were plotted for all cycles. Similar plots were provided for TAb and MMAE. Individual patient concentration data were listed over time.

Noncompartmental analyses for the determination of PK parameters such as area under the concentration-time curve from time 0 to infinity (AUC_{inf}), maximum (peak) observed concentration (C_{max}), terminal disposition half-life (t_{1/2z}), and time to reach C_{max} (t_{max}) were performed for MLN0264, TAb, and MMAE as data permitted.

PK parameters such as C_{max}, AUC_{inf}, t_{1/2z}, and single-dose first time to reach C_{max} (t_{max}) were summarized. Summary statistics comprised N, mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, and geometric mean. Individual patient values of the parameters were listed by treatment cycle.

Safety–Related Pharmacodynamics:

Numbers and percentages of patients were summarized by ATA status at scheduled time points. In patients with ATA positivity, the ability to neutralize MLN0264 was to be summarized, if available. 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.
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.

The incidence of DLTs was listed for each dose group in the phase 1 portion of the study. The DLT-Evaluable population was used for the analysis of DLT.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:
All of the patients were Asian. The age of the patients ranged from 45 to 78 years. Approximately 42% (5/12) of the patients were women. Out of a total of 12 patients, 7 patients were Korean, 4 were Japanese, and 1 was Chinese. The 2 lower dose groups (1.2 mg/kg and 1.5 mg/kg) consisted of 2 Korean patients and 1 Japanese patient each, while the higher dose group (1.8 mg/kg) consisted of 3 Korean patients, 2 Japanese patients, and 1 Chinese patient.

The time since initial diagnosis ranged from approximately 1 to 8 years. The patient population comprised 12 patients with colon, pancreatic, rectal, and gastric cancers (3 patients each).

All 12 patients had at least 1 prior medical condition, as expected in this study population of patients with advanced GI carcinoma. The number of prior medical conditions ranged from 1 to 11. Eight of 12 patients had previous surgical procedures. The number of surgical procedures among the 8 patients ranged from 1 to 3.

All 12 patients received at least 1 prior anticancer therapy. A total of 3 patients received 2, 3 patients received 3, and 3 patients received 4 different prior anticancer therapies. One patient received 1, 1 patient received 5, and 1 patient received 6 different prior anticancer therapies. Two of the 12 patients received prior radiation therapy.

Subject Disposition:
A total of 12 patients were enrolled in the study and all 12 patients were response evaluable. The reason for discontinuation of treatment for all patients was progressive disease. One patient (29001-404) had a secondary reason for discontinuation, a Grade 3 tumor hemorrhage SAE that was considered not related to MLN0264.

Efficacy Results:
Efficacy was a secondary objective of the phase 1 portion of the study. Efficacy parameters included disease response based on the investigator’s assessment, PFS, dates of response and progression/death. There was no evidence of complete response (CR) or partial response (PR). The number of cycles completed ranged from 1 to 10, with a majority of the 12 patients (8 patients) completing 2 cycles. The duration of each treatment cycle was 3 weeks. A total of 3 patients completed more than 2 cycles. Of 3 patients each with rectal cancer, 1 patient completed 4 cycles, 1 patient completed 6 cycles, and 1 patient completed 10 cycles. Patient reported outcomes and quality of life assessments were exploratory objectives for the phase 2 portion of the study, which was not conducted. Although these data were collected, they were not analyzed. The findings from the phase 1 portion of the study are consistent with the results observed in a study conducted in Western patients with advanced gastric carcinoma (C26002). Inclusively, these data suggest that further evaluation of additional Asian patients would not provide critical data to better understand the clinical potential of this experimental agent. Therefore, continued investigation of MLN0264 in Asian patients with gastric carcinoma is not justifiable.

Pharmacokinetic Results:
A primary objective of the phase 1 portion of the study was to determine the PK profiles of MLN0264, TAb, and MMAE. Serum concentrations of MLN0264 and TAb, and plasma concentrations of MMAE all increased with dose. Similar observations were made for AUC for all 3 analytes. The half-life of TAb is slightly longer than that of MLN0264, while that of MMAE is shorter than that of MLN0264. However, the $t_{\text{max}}$ for MMAE is much longer than that of the other components. $t_{\text{max}}$ for MMAE occurred approximately 2 days after infusion of MLN0264, compared to immediately after the infusion for TAb and MLN0264.
Safety-Related Pharmacodynamic Results:

There was no apparent relationship between the preinfusion concentrations of MLN0264 or TAb and GCC H-score seen in this study.

Safety Results:

Part 1 of this study comprised a total of 12 patients who participated in 3 dose cohorts: 3 patients each treated at 1.2 mg/kg and 1.5 mg/kg, and 6 patients treated at 1.8 mg/kg. The primary objectives of Part 1 of the study were to evaluate the safety of MLN0264 administered as an IV infusion q3w to Asian patients with advanced GI malignancies expressing GCC. These objectives included assessing DLT and determining the RP2D. None of the 12 patients experienced DLT. Consequently, an evaluation of these 12 patients did not establish RP2D. All 12 patients enrolled received at least 1 dose of study drug. Overall, 10 of the 12 patients in the Safety population experienced 66 AEs. Twenty of the 66 AEs, as reported by 7 patients, affected the GI system, with nausea and vomiting and diarrhea the most commonly reported AEs. The majority of AEs were Grade 1 or Grade 2. As assessed by the investigator, a majority of AEs (73%) were considered not related to study drug. A total of 4 patients experienced 5 SAEs, none of which were assessed by the investigator as related to study drug. These SAEs consisted of tumor hemorrhage and ascites in 1 patient, and asthenia, abdominal distension, and adrenal insufficiency, respectively, in 1 patient each. During the course of treatment and within the protocol-specified 30 days post-treatment, no patient died. One patient discontinued treatment due to an SAE of tumor hemorrhage that was assessed by the investigator as not related to study drug. Other patients discontinued due to progression of their disease. Overall, a manageable safety profile was observed throughout this study.

CONCLUSIONS:

This study evaluated a total of 12 patients with GI malignancies to assess the safety, PK, and preliminary efficacy of MLN0264 when escalating doses are administered to defined cohorts of patients. Systemic exposure to MLN0264, TAb, and MMAE are generally dose-dependent. The data suggest that dose escalation beyond 1.8 mg/kg is not recommended. Grade 3 neutropenia was observed in the 1.8 mg/kg dose cohort, which indicated further dose escalation is not appropriate. 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. The clinical experience with MLN0264 in Asian patients is comparable to observations in Western patients, as assessed throughout 3 earlier clinical studies. When the overall clinical experience with MLN0264 is considered, continuation of clinical investigation in Asian patients is not expected to provide new critical insight about MLN0264. Therefore, continuation of the study is not warranted.

DATE OF REPORT: 05 May 2016