Version 1
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Statistical Plan

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Study of Cirmtuzumab and Paclitaxel for Metastatic or Locally Advanced, Unresectable Breast Cancer

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Purpose of Study

The primary objective of this trial is to determine the safety and tolerability of a fixed dose of cirmtuzumab when administered in combination with weekly standard of care paclitaxel.

Patient Population

Subjects with biopsy-confirmed metastatic or locally advanced surgically unresectable, HER-2 negative and ER/PR-negative or ER/PR-positive breast cancer where standard endocrine therapy has been exhausted and/or cytotoxic chemotherapy is warranted.

Study Overview

Up to 30 subjects were planned for inclusion in the study to obtain 15 subjects evaluable for dose-limiting toxicities (DLTs). Evaluable subjects are defined as subjects who undergo combination therapy for at least two 28-day cycles of study treatment. At the May 24, 2022 data cut-off, 22 subjects signed informed consent, 16 subjects received the investigational product, 6 subjects were screen failures, 1 subject dropped out of the study early. One subject, who was an early screenfailure, was re-consented and treated.

Brief Description of Study Results

Sixteen patients were evaluable for safety and 15 were evaluable for DLTs. A median of 6 prior metastatic therapies (endocrine therapy + chemotherapy) had been received. No discontinuations due to cirmtuzumab toxicity and no DLTs were observed. Adverse events (AEs) were consistent with the known safety profile of paclitaxel. Of 16 patients, 6 (38%) had a partial response (PR) with one patient receiving total treatment duration of 52 weeks and 6/16 (38%) patients had stable disease as their best response. Pharmacokinetic (PK) data were consistent with a drug half-life of approximately 30 days.

The combination of cirmtuzumab and paclitaxel was safe and well-tolerated in heavily pre-treated metastatic breast cancer patients. Further evaluation of ROR1 targeting in breast cancer with cirmtuzumab is warranted. Due to the small number of patients with baseline tumor tissue, the ability to correlate ROR1 staining with clinical outcomes is limited.

Statistical analysis

DLTs were defined as clinically significant adverse events considered by the investigator to be possibly, probably, or definitely related to cirmtuzumab or the combination of cirmtuzumab with paclitaxel within 28 days of investigational treatment initiation. DLTs included Grade 4 hematologic toxicity lasting more than 7 days and nonhematologic toxicity of grade 3 or higher. Patients were enrolled in cohorts of five, and each cohort was assessed for DLTs prior to

enrollment of the next cohort. If two or more patients in the first cohort experienced DLT attributed to cirmtuzumab at full dose, then the next cohort would be enrolled at a 50% dose reduction (300 mg flat dose). If two or more patients in the second cohort experienced DLT attributed to cirmtuzumab at a 50% dose reduction, then the study would be stopped. If fewer than two patients in the first cohort experienced DLT attributed to cirmtuzumab at full dose, but two or more in the second cohort experienced DLT at full dose, then the third cohort would be treated with 50% dose-reduced cirmtuzumab. For adverse events other than DLTs attributed to study treatment, dose and schedule changes were specified in the protocol. The protocol also specified that for Grade > 2 rash, allergy, or infusion reaction, nab-paclitaxel may be substituted at investigator discretion. The intent-to-treat population includes all patients who started at least one dose of cirmtuzumab. Descriptive statistics are used to characterize demographics, safety, toxicities, and anti-tumor activity. Best tumor responses are shown in a waterfall plot, and a swimmer plot is used to show tumor responses for each patient while on study treatment. Confidence intervals of the median progression-free survival (PFS) time are estimated based on Kaplan–Meier estimates, with PFS defined as weeks from the first day of study treatment to first disease progression or death. The duration of partial response (PR) was defined as the time from the first PR assessment to the time of recurrence, progression, or death.