This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES
MK-8669
ridaforolimus
tablet
breastcancer

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Phase II Trial of Oral Deforolimus ([redacted] MK-8669), #009 an mTOR Inhibitor, in Combination with Trastuzumab for Patients with HER2-positive Trastuzumab-Refractory Metastatic Breast Cancer

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter 14 sites: United States (8), Chile (1), Czech Republic (3), and France (2). [redacted]

PUBLICATION(S): Ridaforolimus ([redacted] MK-8669) in combination with trastuzumab for patients with HER2-positive trastuzumab-refractory metastatic breast cancer: a multicenter phase 2 clinical trial. (SABCS 2009 Poster) [redacted]

PRIMARY THERAPY PERIOD: 18-Aug-2008 to 11-Jan-2011 **CLINICAL PHASE**: IIb

DURATION OF TREATMENT: The duration of a patient's participation was estimated to be approximately 7.5 months, including a 2-week screening period, six 4-week cycles of study drug administration, and one-month post-treatment follow-up. Participation subsequently involved up to an additional 24 months of survival follow-up, for a total of approximately 31.5 months of participation. The actual duration of each patient's participation varied since patients could continue to receive study drug until documentation of disease progression or other discontinuation criteria were met.

OBJECTIVE(S):

Primary Objective:

To assess the objective response rate by RECIST version 1.0 (Response Evaluation Criteria in Solid Tumors) guidelines of oral ridaforolimus (formally deforolimus) in combination with trastuzumab in patients with HER2-positive (Human epidermal growth factor receptor 2) metastatic breast cancer (MBC) with progression after treatment with at most 2 prior trastuzumab-based regimens.

Secondary Objectives:

Characterize the overall safety and tolerability of oral ridaforolimus administered in combination with standard dose trastuzumab.

Evaluate the clinical-benefit response rate (complete response [CR] or partial response [PR], or stable disease [SD] ≥ six 4-week cycles).

[redacted]

STUDY DESIGN:

The trial was an open-label, non-randomized, single-arm, two-stage, Phase 2 trial designed for initial evaluation of the efficacy of ridaforolimus plus trastuzumab as measured by objective response rate in HER2-positive metastatic breast cancer patients exhibiting trastuzumab resistance. Trastuzumab resistance for this study was defined as disease progression on trastuzumab-containing therapy. Patients may have received at most 2 prior trastuzumab-based regimens. During Stage 1 of the trial, 14 patients were to be assessed for OR, i.e. CR or PR according to RECIST guidelines. Should one or more patients exhibit an OR by the time of the Stage-1 interim analysis, the trial would continue and a total of 33 patients were to be studied. If 5 or more of the 33 patients exhibit an OR by the end of the study, representing an at least 15.2% objective response rate (ORR), then the treatment would be considered effective and the drug would be considered for further study. Patients received study treatment (ridaforolimus plus trastuzumab) until disease progression or other discontinuation criteria were met. If a patient experienced a side effect attributable to trastuzumab alone (e.g., a hypersensitivity reaction), the patient may have continued on single-agent ridaforolimus until disease progression occurred. Disease assessments were to be performed every 8 weeks, and assessed in accordance with modified RECIST guidelines. All patients were to be followed for overall survival at 3-month intervals for up to 24 months after completing the treatment period of the trial. Safety was to be assessed by routine physical and laboratory evaluations and severity of adverse events (AE) were to be graded according to the US NCI (United States National Cancer Institute) Common Terminology Criteria for Adverse Events (CTCAE) version 3.

SUBJECT/PATIENT DISPOSITION:

	MK8669 + Trastuzumab (N=34)
Patients Completed Study	0
Patients Discontinued Study	34
Progressive Disease	21
Clinically Progressive Disease (Physician Judgment)	2
Adverse Event	8
Death	2
Investigator Decision	0
Lost to Follow Up	0
Protocol Violation	0
Patient Withdrew	0
Termination of the Trial by the Sponsor	0
Other	1

Data Source [redacted]

DOSAGE/FORMULATION NOS.: Patients took four tablets once daily of ridaforolimus (10 mg each) for 5 consecutive days every week (40 mg qdx5/week). Trastuzumab was administered as a single intravenous infusion (IV) every week (QW), at an initial loading dose of 4 mg/kg over 90 minutes. Subsequent intravenous doses of 2 mg/kg were administered over 30 minutes QW. The formulation numbers used for ridaforolimus 10 mg was [redacted] All formulations had the same image. The formulation numbers used for Trastuzumab were [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Female patients aged 18 years or older with a documented HER2-positive metastatic breast cancer who had developed trastuzumab resistance, manifested as disease progression on trastuzumab-containing therapy. Measurable disease according to modified RECIST guidelines (histological/cytological confirmation of the neoplastic nature of a solitary lesion was not required in this trial) and an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 [redacted]

EVALUATION CRITERIA:

Efficacy: The primary efficacy endpoint variable was the objective response rate as assessed using modified RECIST guidelines. Additional efficacy endpoint variables included: clinical-benefit response rate, defined as complete or partial response or stable disease ≥ six 4-week cycles (assessed using RECIST guidelines); duration of objective response; time to tumor progression; median progression-free survival; progression-free survival rate at 6 months (26 weeks); best target lesion response, defined as best change in sum of the target lesions from baseline to disease progression ("waterfall" analysis); and overall survival.

Safety: Patient safety was assessed by routine physical examination, interim history, and laboratory assessments [redacted] Adverse events were graded according to the NCI-CTCAE, version 3.0. [redacted]

STATISTICAL PLANNING AND ANALYSIS: This trial was a non-randomized Phase-2 trial utilizing a two-stage design. The study population was women with HER2-positive metastatic breast cancer and progression on trastuzumab-containing therapy who have undergone at most 2 prior trastuzumab-based regimens. During Stage 1 of the trial, 14 patients were assessed for OR, i.e. CR or PR according to RECIST guidelines. Should one or more patients exhibit an OR by the time of the Stage-1 interim analysis, the trial would continue and a total of 33 patients would be studied. If 5 or more of the 33 patients exhibit an OR by the end of the study, representing an at least 15.2% ORR, then the treatment would be considered effective and the drug would be considered for further study. Additional endpoints to be analyzed and included: clinical-benefit response (complete or partial response or stable disease ≥24 weeks) duration of objective response, and overall survival. Time to disease progression and progression-free survival were to be estimated using the Kaplan-Meier procedure.

RESULTS:

[redacted]

Efficacy

Table 1 below provides a summary of key efficacy findings by investigational site assessment. Five patients had a partial response, meeting the minimal efficacy bar for a positive trial, and 7 patients had a stable disease of ≥24 weeks. However, only 3 of the 5 responses were independently confirmed by central assessment (data not shown in table) [redacted]

Table 1

Summary of Best Response
(All Treated Patients)

	MK8669 + Trastuzumab (N=34)	
	n	(%)
Complete Remission	0	(0.0)
Partial Remission	5	(14.7)
Stable Disease	14	(41.2)
≥24 weeks	7	(20.6)
Disease Progression	11	(32.4)
Unknown	4	(11.8)

Data Source: [redacted]

Table 2 summarizes secondary time-to-event outcomes. For the response duration only responders are considered. For survival and progression free survival all patients are included. Five of 34 (14.7%) of patients responded; these 5 had a median response duration of 19.1 weeks with values ranging from 15.9 to 80.1 weeks. Twenty-seven of 34 patients (79.4%) are known to have progressed or died. Median PFS was 23.6 weeks by Kaplan-Meier analysis, duration of PFS observed until and event or censoring of .1 to 88.1 weeks. Sixteen of 34 (47.1%) were known to have died with a median survival time by Kaplan-Meier analysis of 77.0 weeks and a range of survival follow-up from .1 to 112.6 weeks.

Table 2

Summary of Secondary Time-to-Event Variables
(All Treated Patients)

	MK8669 + Trastuzumab (N=34)	
	Event (%)	Median (Range) in Weeks
Response duration by Investigational Site Assessment	5 (14.7%)	19.1 (15.9-80.1)
Progression Free Survival	27 (79.4%)	23.6 (0.1-88.1)
Overall Survival	16 (47.1%)	77.0 (0.1-112.6)

Data Source: [redacted]

Safety

All 34 patients had at least one treatment-emergent adverse event (TEAE) and of the 34 patients, 33 patients had at least one AE that was considered by the investigator to be drug related. Of the 34 patients, Ten (29.9%) patients experienced TEAEs of grade 2 and 17(50.0%) patients experienced TEAEs of grade 3. The most common adverse events were stomatitis (61.8%), nausea (47.1%), and diarrhea (38.2%). [redacted] A total of 3 deaths were reported in this study. [redacted] The investigator reported that this event was possibly related to study drug. [redacted]

Table 3

Clinical Adverse Experience Summary
(All Treated Patients)

	MK-8669 + Trastuzumab	
	n	(%)
Number(%) of patients		
With one or more adverse experiences	34	(100.0)
With no adverse experience	0	(0.0)
With drug-related adverse experiences†	33	(97.1)
With serious adverse experiences	14	(41.2)
With serious drug-related adverse experiences†	8	(23.5)
Who died	3	(8.8)
Discontinued due to adverse experiences	8	(23.5)
Discontinued due to drug-related adverse experiences†	8	(23.5)
Discontinued due to serious adverse experiences	3	(8.8)
Discontinued due to serious drug-related adverse experiences†	3	(8.8)
† Determined by the investigator to be possibly, probably or definitely drug related.		

Data Source: [redacted]

CONCLUSIONS: Data from this study showed that it met the pre-specified criterion for efficacy, (i.e. 5 or more patients exhibited an objective response) based upon investigator's assessment. However, it did not meet the criterion based on assessment by independent radiologic review. In addition, the safety findings were consistent with the known safety profile of ridaforolimus. [redacted].

AUTHORS: [redacted]