Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

A Phase I Trial of Combined Ridaforolimus and MK-2206 in Patients With Advanced Malignancies

Shilpa Gupta,1 Guillem Argilés,2 Pamela N. Munster,3 Antoine Hollebecque,4 Olav Dajani,5 Jonathan D. Cheng,6 Ruixue Wang,6 Ann Swift,6 Alessandra Tosolini,6 Sarina A. Piha-Paul7

1H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida; 2Vall d’Hebron University Hospital & Vall d’Hebron Institute of Oncology, Barcelona, Spain; 3UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California; 4DITEP, Gustave Roussy, Cancer Campus, Grand Paris, Villejuif, France; 5Oslo University Hospital, Oslo, Norway; 6Merck & Co., Inc., Kenilworth, New Jersey and North Wales, Pennsylvania; and 7The University of Texas MD Anderson Cancer Center, Houston, Texas

Running Title: Ph I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Keywords: Ridaforolimus; mTOR inhibitor; MK-2206; breast cancer; prostate cancer

Financial Support: This study was funded by Merck & Co., Inc., Kenilworth, NJ, USA. Medical editorial assistance, provided by ApotheCom, was funded by Merck & Co., Inc.

Author for Correspondence:
Shilpa Gupta, MD
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Dept. Genitourinary Oncology, H. Lee Moffitt Cancer Center & Research Institute
12902 Magnolia Drive, Tampa, FL 33612 USA
Phone: +1-813-745-3973
Fax: +1-813-745-8494
Email: Shilpa.Gupta@moffitt.org

Conflicts of Interest:
S. Gupta, G. Argilès, P.N. Munster, O. Dajani, and S.A. Piha-Paul have nothing to disclose. J.D. Cheng, R. Wang, A. Swift, and A. Tosolini are employees of Merck & Co., Inc.

Supplemental File 1: Method used for validation of the RAS-147 signature array assay.

Journal: Clinical Cancer Research
Word Count (main text): 4991 (Max 5000)
Number of Tables/Figures: 4/2 (Max 6 total)
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Translational Relevance:

The PI3K/Akt/mTOR pathway plays a critical role in cellular growth and survival, and aberrations in this signaling pathway have been implicated in the occurrence of many cancers. Because of the complex cross-talk between intracellular signaling pathways, therapy with single agents often leads to treatment resistance as other pathways become active through feedback responses. Targeting multiple nodes in a signaling pathway may improve response to therapy. This phase I dose-escalation study identified the dose-limiting toxicities and maximum-tolerated dose for the novel combination of 2 investigational targeted agents, ridaforolimus (an mTOR inhibitor) and MK-2206 (an Akt inhibitor), in patients with advanced solid tumors. In heavily pretreated patients with breast cancer who had biomarker-identified reliance on the PI3K pathway, there was also clinical activity in the form of complete and partial tumor responses and prolonged stable disease, offering the potential for future clinical exploration of this combination therapy for breast cancer.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Abstract (250 words; 250 Max)

Purpose: The PI3K/Akt/mTOR signaling pathway is aberrantly activated in many cancers. Combining ridaforolimus, an mTOR inhibitor, with MK-2206, an Akt inhibitor, may more completely block the PI3K pathway and inhibit tumor growth.

Experimental Design: This phase I study assessed dose-limiting toxicities (DLT) and maximum-tolerated dose (MTD) for the combination of oral ridaforolimus plus oral MK-2206 in patients with advanced solid tumors. Efficacy was evaluated in patients with biomarker-identified estrogen receptor-positive breast cancer (low \emph{RAS} gene signature and high Ki67 index) or castration-resistant prostate cancer (PTEN deficiency) with PI3K pathway addiction.

Results: Thirty-five patients enrolled; 11 patients in part A (3 breast cancer) and 24 biomarker-eligible patients in part B (16 breast cancer, 8 prostate cancer). One patient with breast cancer from part A was also found to be biomarker-eligible when tested after she had clinical response. The MTD was 10 mg/day ridaforolimus 5 days/week + 90 mg/week MK-2206; 1/17 patients experienced DLT (grade 3 rash) at this dose. The most common adverse events at MTD were rash (44.4%), stomatitis (38.9%), diarrhea (27.8%), and decreased appetite (27.8%). By investigator assessment, 2/16 (12.5%) evaluable patients with breast cancer had partial response; by central assessment, 2/14 (14.3%) evaluable patients had complete response. Two patients had durable stable disease (SD) for 416 and 285 days, respectively. No patients with prostate cancer responded; 1 patient had SD for ≥6 months.

Conclusion: Combination ridaforolimus and MK-2206 showed promising activity and good tolerability in heavily pretreated patients with hormone-positive and negative breast cancer exhibiting PI3K pathway dependence.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

**Introduction**

The phosphatidylinositol-3-kinase (PI3K) signaling pathway is important for the growth and survival of cancer cells in many different types of human malignancy, including breast and prostate cancer (1-3). This pathway receives upstream input from ligand-receptor interactions and signals through downstream effectors (4). Mammalian target of rapamycin (mTOR) is a downstream effector molecule that regulates the production of proteins critical for cell cycle progression and other important cellular growth processes (5). Dysregulation of the PI3K axis is common in human cancer, and can be due to several mechanisms including overactive growth factor receptor signaling, activating mutations of PI3K, loss of function of the phosphatase and tensin homolog (PTEN) tumor suppressor, and overactivation of mTOR kinase activity (1).

The PI3K-Akt pathway lies downstream of the most common growth factor tyrosine kinase receptors implicated in cancer, and the pathway is a suspected driver of tumor progression in many cancers (4, 6). Akt protein kinase is activated in the majority of human solid tumors, and appears to play a key role in tumor cell survival, contributing to tumor cell escape of apoptosis induced by cytotoxic, radiation, and targeted therapies (1, 4, 6). Furthermore, constitutive or residual Akt activation is often found in tumor cells that have developed resistance to conventional chemotherapy, radiation, or targeted agents (7). Therefore, inhibition of this critical cell survival pathway by an Akt inhibitor is hypothesized to synergize with multiple cancer treatment modalities to maximize tumor cell killing effect (8, 9).
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Ridaforolimus, a non-prodrug analog of rapamycin that inhibits mTOR, has demonstrated antiproliferative activity in a broad range of human tumor cell lines in vitro and in murine tumor xenograft models (10-13). Ridaforolimus has been evaluated as single-agent or combination therapy for pediatric and adult patients with advanced malignancies by both the intravenous and oral routes of administration (14-24). Ridaforolimus has demonstrated a favorable safety profile, mTOR inhibition, and antitumor activity in a broad range of cancers (3, 11).

MK-2206 is a highly selective, oral allosteric Akt inhibitor, which is equally potent towards purified recombinant human Akt1 and Akt2 and approximately 5-fold less potent against human Akt3 (IC$_{50}$ = 8, 12, and 65 nM, respectively) in enzyme assays, and is well tolerated as a single-agent (25-27). In the first-in-humans clinical trial of MK-2206 in advanced solid tumors, 33 patients received MK-2206 at 30, 60, 75, or 90 mg on alternating days. Dose-limiting toxicities (DLT) included skin rash and stomatitis, establishing the maximum tolerated dose (MTD) at 60 mg every other day (26). In another phase I trial, a once-weekly (QW) schedule of MK-2206 was found to cause dose-limiting rash at 250 and 300 mg, establishing the MTD as 200 mg QW (27).

Combining MK-2206 with other therapies has shown synergistic antitumor effects in vitro (28). The combination of an Akt inhibitor with an mTOR inhibitor was considered a rational duplex to investigate, as mTOR inhibition and Akt inhibition complement each other, and targeting both may produce more complete blockade of the PI3K pathway. Inhibition of Akt could abrogate the feedback induction that results from mTOR complex one (mTORC1) inhibition, and the mTOR inhibition
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

could block distal PI3K pathway signaling at the level of the S6 ribosomal protein that is not effectively inhibited by Akt inhibition alone. In addition, Akt signals through mTOR-independent pathways as well as through mTOR-dependent pathways, and the mTOR-independent signaling is important for tumor cell survival, and thus important to inhibit separately from mTOR.

In the preclinical setting a number of \textit{in vitro} and \textit{in vivo} cancer models, including breast and prostate cancers, have shown increased sensitivity to the combination relative to single agents (29-31). The combination is expected to be most active in tumors with PI3K pathway addiction resulting from mutations in genes such as \textit{PTEN} or \textit{PIK3CA} (which encodes the catalytic subunit alpha of phosphatidylinositol-3-kinase), and in other lesions where RAS/mitogen-activated protein kinase (MAPK) signaling is not constitutively active. It is thus important to identify with use of biomarkers those patients most likely to benefit from treatment with the ridaforolimus/MK-2206 combination. For breast cancer the biomarkers chosen were RAS gene signature and Ki67 analysis, and for prostate cancer \textit{PTEN} loss was analyzed.

The RAS gene expression signature contains 147 genes that are coherently expressed across multiple cell-line models and human tumors (32). A low RAS signature score correlates with high PI3K pathway dependency and better responsiveness to PI3K pathway inhibition (32). Results from human breast cancer tissue have shown that a low RAS gene signature score is associated with the majority of estrogen receptor (ER)-positive breast cancers, whereas the majority of ER-negative breast tumor subtypes (including human epidermal growth factor receptor 2 [HER2] and triple-
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

negative breast cancers) have an elevated RAS gene signature score reflecting increased RAS pathway activity (32).

Within ER-positive breast cancer, the luminal B subset is associated with poor prognosis compared with luminal A tumors (33, 34). Luminal B tumors have higher PI3K pathway activity and are characterized by a high rate of cell proliferation. The Ki67 labeling index has been commonly used to identify a high proliferation subset of patients with ER-positive breast cancer; recently published data have shown that a Ki67 >13.25% is able to distinguish luminal B from luminal A tumors, with a sensitivity of 72% and a specificity of 77% (35). It is therefore possible to enrich the study population with patients who have high proliferation, "luminal B-like" tumors that may be more sensitive to ridaforolimus and MK-2206 combination owing to dependence on the PI3K pathway.

PTEN loss of expression is a suitable biomarker for PI3K pathway–sensitive prostate cancer. Loss or mutations of PTEN and loss of heterozygosity of the PTEN locus occur in a variety of human cancers, and drives PI3K pathway dependence which correlates with advanced disease and poor prognosis in some tumors, including prostate cancer (36, 37). PTEN status has been associated with responsiveness to a number of anticancer agents and treatment outcome (38). In prostate cancer cell lines, PTEN deficiency correlated with enhanced sensitivity to mTOR inhibition (39).

This phase I study was undertaken to define the DLTs and MTD of combination ridaforolimus and MK-2206 in patients with solid tumors, and to explore the
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

antitumor activity of ridaforolimus plus MK-2206 in expansion cohorts of patients with breast and prostate cancer whose tumors were PI3K-pathway dependent.

Patients and Methods

Study Design

This was a multicenter, international, open-label, nonrandomized 2-part phase I study that evaluated the combination of oral ridaforolimus with oral MK-2206 (ClinicalTrial.gov identifier NCT01295632; Protocol 049). Part A comprised dose escalation to define the preliminary MTD for the combination. Part B further evaluated the MTD and assessed preliminary clinical efficacy in a biomarker-defined group of patients with breast cancer or prostate cancer with PI3K pathway addiction. This study included another arm evaluating the combination of the investigational compounds ridaforolimus + MK-0752 (a Notch inhibitor); results will be disseminated in a separate manuscript.

The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines. Patients provided written informed consent.

Patients

The study enrolled male or female adult patients (≥18 years old) with histologically confirmed metastatic or locally advanced solid tumors, who had failed to respond to standard therapy, had progressed despite standard therapy, or for whom standard therapy did not exist. Patients were not permitted to have any medical conditions that
could affect compliance with the protocol, limit interpretation of study results, or pose an unacceptable medical risk. Patients could not be enrolled in more than 1 dose group. Patients with non-Hodgkin lymphoma (NHL) could enroll in part A of the study only, and had to have histologically confirmed relapsed/refractory NHL. There was no limit on the number of prior treatment regimens patients could have received. Other key inclusion criteria for the study were an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate organ (bone marrow, renal, hepatic, cardiac, and pulmonary) function. Patients had to have at least 1 measurable recurrent or metastatic lesion according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) (40), with the exception of patients with prostate cancer, who did not require measurable disease if they had a PSA level >10 ng/mL.

Patients were excluded if they had received chemotherapy or radiotherapy within 4 weeks prior to study day 1, biological therapy (excluding antibodies) within 2 weeks prior to study day 1, or had not recovered (≤ grade 1 or baseline) from adverse events due to agents administered more than 4 weeks earlier. Patients who had known symptomatic or progressing central nervous system (CNS) metastases, prior exposure to related agents, significant or uncontrolled cardiovascular disease, poorly controlled diabetes, known psychiatric or substance abuse disorders that would interfere with study compliance, or who regularly used illicit drugs or had a recent history (within the last year) of drug or alcohol abuse, were human immunodeficiency virus (HIV) positive, or had active hepatitis B or C, were also excluded. Patients who were pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study were excluded.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Patients were eligible to enroll in part B of the study if they had either histologically confirmed prostate cancer that was castration resistant, or histologically confirmed breast cancer that had progressed on standard therapy, or were not candidates for standard therapy. Patients with breast cancer had to have tumor tissue (archival or newly obtained) that demonstrated low RAS gene signature (evaluated by microarray assay); patients with ER-positive (ER⁺) breast cancer also had to demonstrate a high Ki67 index (≥15% by immunohistochemistry). Patients with castration-resistant prostate cancer had to have evidence of PTEN deficiency (H score ≤10) analyzed by immunohistochemistry.

Treatment

In part A of the study, ridaforolimus and MK-2206 were administered in sequentially rising dose levels (3+3 dose-escalation scheme) to establish the preliminary MTD on a schedule of repeating 28-day cycles. The protocol did not permit intrapatient dose escalation. The starting dose level (DL1) was ridaforolimus 20 mg orally (PO) daily for 5 consecutive days (QD×5/wk) followed by 2 days off, plus MK-2206 90 mg PO weekly. The ridaforolimus starting dose was selected to be 50% of the MTD for oral ridaforolimus as a single agent (40 mg PO QD×5/wk) in the phase I/II single-agent, dose-escalation trial (16), and 20 mg PO QD×5/wk was below doses of ridaforolimus that produced minimal to low toxicity as a single agent (16). The starting dose for MK-2206 of 90 mg PO QW was selected as it had not been associated with any DLTs in a previous dose-finding trial (27), and was less than half the single-agent MTD of 200 mg QW, allowing for dose escalation (27).
The 3+3 dose-escalation scheme required an initial cohort of 3 patients to be enrolled at a given dose level. If 0/3 patients developed a DLT, escalation to the next dose level would occur. If 1/3 patients developed a DLT, another 3 patients would be enrolled at that dose level. Providing that 0 of these 3 new patients developed a DLT (to give 1/6 patients with a DLT at this dose level), escalation to the next dose level would occur. If ≥1 of the 3 new patients developed a DLT (to give 2/6 patients with a DLT), the dose-escalation stage of the trial would be terminated and the dose directly below the current dose would be considered the preliminary MTD. If ≥2 of 3 patients developed DLTs, the dose level would not be considered further and a lower dose would be explored. If the highest candidate dose was studied during dose escalation, and 0/3 or ≤1 of 6 toxicities were observed at that dose, then dose escalation would terminate with this finding.

The planned dose-escalation schedule involved 2 additional full dose levels (DL2 and DL3), and also allowed sublevel increments that increased either ridaforolimus or MK-2206. If DL1 was found to be tolerable, simultaneous escalation to DL1.1 (ridaforolimus 20 mg QD×5/wk plus MK-2206 135 mg weekly) and DL1.2 (ridaforolimus 30 mg QD×5/wk plus MK-2206 90 mg weekly) was allowed. Additional planned dose-level increments included DL2 (ridaforolimus 30 mg QD×5/wk plus MK-2206 135 mg weekly), DL2.1 (ridaforolimus 30 mg QD×5/wk plus MK-2206 200 mg weekly), DL2.2 (ridaforolimus 40 mg QD×5/wk plus MK-2206 135 mg weekly), and DL3 (ridaforolimus 40 mg QD×5/wk plus MK-2206 200 mg weekly).
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

DLTs observed in cycle 1 were used to determine escalation to the next dose level. If the current dose was found to be intolerable, lower dose levels could be explored. On this basis, a lower dose of ridaforolimus 10 mg PO QD×5/wk plus MK-2206 90 mg PO weekly was also administered, designated DL-1.

Confirmation of the preliminary MTD was based on enrolling additional patients within disease-specific cohorts (i.e., breast cancer and prostate cancer) to confirm the tolerability of the MTD. Patient recruitment continued until 14 patients were enrolled at 1 dose (Part A patients plus patients from the 2 disease-specific indications in Part B) with ≤3 of 14 patients experiencing a DLT. After MTD confirmation, additional biomarker-eligible patients (target enrollment, \( n = 12 \)) within each disease-specific cohort were enrolled to allow evaluation of tumor response at the MTD.

*End Points and Assessments*

The primary safety end point was the DLT rate. Adverse events were graded and recorded throughout the study according to National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0 (v4.0). Toxicities were characterized in terms of duration, intensity, and time to onset. Assessments included vital signs, electrocardiogram (at screening and 2 hours after dose administration on day 2, cycle 1), ECOG performance status, comprehensive ophthalmologic examination, laboratory measures, and medical history.

Serious adverse events were defined as any adverse event that occurred at any dose that: resulted in death, was life threatening, placed the patient at immediate risk of death from the experience as it occurred, resulted in a persistent or significant
disability or incapacity, resulted in or prolonged an existing inpatient hospitalization, resulted in a congenital anomaly or birth defect in offspring of patient, was a new cancer, or was an overdose (whether accidental or intentional).

The primary efficacy end point for part B in this study was response rate, defined as the proportion of patients whose best response was partial response (PR) or complete response (CR) assessed according to RECIST v1.1 (40). Tumors were imaged using either computed tomography (CT) or magnetic resonance imaging (MRI) at screening, every 2 cycles (±5 days) during treatment, and at the time of treatment discontinuation. Analysis of imaging was undertaken locally by the investigator and centrally by an independent imaging laboratory (ICON Imaging). For patients with prostate cancer, PSA levels were also used for response.

Biomarker Assays

The RAS signature assay utilized the industry-standard Affymetrix platform consisting of its standard hybridization incubator and fluidics wash station as well as the FDA-cleared GeneChip® 3000Dx v.2 scanner (Affymetrix, Inc.). RNA was purified from formalin-fixed, paraffin-embedded (FFPE) tissue samples using standard procedures, and then amplified using a NuGEN Ovation® FFPE amplification system (NuGEN Technologies). A fixed amount of input cDNA (3.5 µg) was hybridized to a Merck custom Affymetrix microarray (Gene Expression Omnibus [GEO] accession number GPL6793). Robust micro-array analysis (RMA) was used on microarray intensity data (CEL files) to perform background adjustment, quantile normalization, and summarization. Validation of the assay was performed at Almac Diagnostics; details of the validation process can be found in Supplement 1.
The assay used for the Ki-67 labeling index was a well-established, widely available clinical assay from Ventana Medical Systems. The anti–Ki-67 primary antibody was a rabbit monoclonal antibody (IgG) directed against the C-terminal portion of Ki-67 antigen. The Ki-67 immunohistochemistry assay had already been validated and was run in a CLIA-approved laboratory (Ventana Medical Systems). Fitness-for-purpose testing using archival (FFPE) breast tumor tissue had previously been performed.

The PTEN immunohistochemistry assay was developed and analytically validated by Ventana Medical Systems for detecting PTEN protein level in multiple tumor tissues. The anti-PTEN primary antibody was a rabbit monoclonal antibody (IgG) directed against C-terminal portion of PTEN antigen. The H-score cutoff for PTEN loss was chosen by analyzing the results of immunohistochemistry staining and florescent *in situ* hybridization (FISH) on the same sample set of prostate tissue samples. As there are multiple factors that can cause PTEN protein deficiency, and the absence of PTEN gene is only 1 of them, it was expected that some samples would be PTEN deficient based on immunohistochemistry, but not by FISH. Based on current data, including receiver operating characteristic curve analysis, an H-score cutoff of ≤10 was selected.

**Statistics**

No formal statistical hypothesis was tested for the primary objective of defining DLT and MTD. Descriptive statistics summarizing the number and percentage of patients who experienced adverse events, as categorized in the NCI CTCAE v4.0, were generated for the overall patient population and by disease-specific cohort.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

The safety analysis population consisted of all patients who received at least 1 dose of study treatment. The primary population for the analysis of efficacy and biomarker data was the full analysis set, consisting of all patients who received at least 1 dose of study treatment and had baseline data for those analyses that required baseline data.

Results

Disposition and Baseline Characteristics

Thirty-five patients were enrolled in the trial from 7 centers in 4 countries (4 in the United States, 1 in France, 1 in Norway, and 1 in Spain). All 35 allocated patients received treatment with 1 of 2 different dose levels of ridaforolimus plus MK-2206: 17 patients received the starting dose of ridaforolimus 20 mg plus MK-2206 90 mg (DL1), and 18 patients received a lowered dose of ridaforolimus 10 mg plus MK-2206 90 mg (DL-1). Patients received a median of 2 (range, 1–10) cycles of both ridaforolimus and MK-2206 at DL1, and 2.5 (range, 1–17) cycles of both ridaforolimus and MK-2206 at DL-1.

Eleven patients were enrolled into part A (dose escalation) of the trial; 7 treated at DL1 and 4 treated at DL-1. For enrollment into part B of the trial (expansion of biomarker-eligible patients), 124 patients with breast cancer and 68 patients with prostate cancer were prescreened. Of the 124 patients with breast cancer, 98 patients had biopsy tissue that was adequately evaluable; of these, 51 (52%) were biomarker eligible, 21 of the eligible consenting patients were screened, and 16 were enrolled into the trial (6 treated at DL1; 10 treated at DL-1). In addition, 1 patient with breast cancer from Part A (treated at DL1) was found to be biomarker eligible when tested after she had a clinical response, and is included in the tumor response results.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

(bringing the total number of breast cancer subjects analyzed for efficacy to 17). Of the 68 prescreened patients with prostate cancer, 40 had tissue that was evaluable, of which 24 exhibited loss of PTEN, and 8 patients were enrolled into the trial (4 at DL1, and 4 at DL-1).

Twenty-three of the 35 allocated patients (65.7%) discontinued from the study because of progressive disease. Five patients (14.3%) discontinued because of an adverse event, 3 patients (8.6%) withdrew consent, and 3 patients (8.6%) discontinued per physician decision. One patient in the DL-1 group continued in the extension phase after database lock for >6 months before discontinuing because of progressive disease.

With the exception of tumor type, baseline characteristics were similar for patients assigned to the 2 different dose levels (Table 1). The median age was 55 (range, 20–84) years old, and the majority of enrolled patients were white (83%). The patient population was heavily pretreated; the median number of prior systemic regimens received was 5 (range, 0–11). Most patients had received previous chemotherapy (91.4%), and many had also received hormonal or biologic therapies (Table 1).

Dose-Limiting Toxicity and Maximum-Tolerated Dose

There were 14 DLT-evaluable patients treated at DL1. Of these, 5 patients experienced a DLT in the first cycle: 1 patient (part A) with grade 4 increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST); 3 patients (1 part A, 1 part B breast cancer, 1 part B prostate cancer) with grade 3 stomatitis; and 1 patient with a DLT of “inability to complete the DLT period” following grade 3...
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

thrombocytopenia that resulted in dose reduction. Of the 17 DLT-evaluable patients treated at DL-1, 1 patient with breast cancer in part B experienced a DLT of grade 3 rash in the first cycle. Per protocol, because there were ≤3 DLTs observed among these patients, DL-1 was selected as the MTD.

Safety

Thirty-three of the 35 treated patients (94.3%) experienced 1 or more drug-related adverse events, including 17 patients (94.4%) treated at DL-1 and 16 patients (94.1%) treated at DL1 (Table 2). Eighteen of the 35 treated patients (51.4%) experienced 1 or more serious adverse events. One patient treated at DL-1 experienced multiple drug-related serious adverse events (grade 2 asthenia and rash, grade 3 stomatitis, and rectal hemorrhage). Two patients treated at DL1 experienced 1 or more drug-related serious adverse events, including grade 3 stomatitis (1 patient) and grade 4 ALT increase and AST increase (1 patient). There was 1 death due to malignant neoplasm progression, which was not considered drug related; this was reported during the safety follow-up period following treatment at DL-1 (Table 2).

The most commonly reported drug-related adverse events at the MTD included rash (44.4%), stomatitis (38.9%), diarrhea (27.8%), decreased appetite (27.8%), fatigue (22.2%), asthenia (22.2%), and nausea (22.2%) (Table 3). Most adverse events were less than grade 3 in severity. Hyperglycemia was rare at the MTD (DL-1), occurring in just 1/18 patients (5.6%), but was observed in 6/17 patients (35.3%) at DL1.

Tumor Response
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Of the 17 enrolled biomarker-eligible patients with breast cancer (16 from part B and 1 from part A), local review by the investigators was possible for 16 patients with evaluable scans, and 14 patients were evaluable by central review. Overall, 3 patients showed a response by either investigator or central review using RECIST v1.1 (Table 4; Fig. 1). By local investigator review, 2/16 patients had an objective response (2 PR, 0 CR). Central radiological assessment found objective responses in 2/14 patients (0 PR, 2 CR). The 2 breast cancer patients reported to have PR by local investigator review were reported as CR and stable disease (SD), respectively by central radiological assessment, and 1 patient assessed to have SD by local investigator review was reported as CR by central radiological assessment (Table 4). While RECIST v1.1 was utilized for both the review assessments, this discrepancy in tumor assessments could be explained by the inter- and intraobserver variability as well as investigators’ bias. The discordance between the local investigator review and central vendor might also be attributed to the choice of target and non-target lesions, including location, size, borders, and shape; presence of confounding factors such as pleural effusion and high density ascites; and clarity of lesions when contrast is not used. Recognizing these well-known limitations, central radiological assessment was utilized in this study to ensure consistency and minimize bias. One patient with breast cancer continued on study for 416 days, until June 2013, and another had a durable PR for 285 days. The maximum change from baseline in the size of target lesions (as assessed by local investigator review, per RECIST v1.1) was determined as a secondary analysis in the 16 evaluable patients with biomarker-eligible breast cancer (Fig. 2A).
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

In the biomarker-eligible prostate cancer group ($n = 8$), SD was observed in 3 patients by local investigator assessment, and durable SD was confirmed in 2 of these 3 patients (162 and 164 days) by independent central radiology review. Both these patients had previously received 3 lines of systemic therapy; 1 had received degarelix, ketoconazole plus hydrocortisone, and leuprolide plus bicalutamide, while the other had received 3 previous treatments with docetaxel over an 18-month period. The maximum change from baseline in the size of target lesions in the 5 patients with prostate cancer with measurable target lesions and evaluable postbaseline scans is shown in Fig. 2B. The prostate cancer arm was closed early due to lack of responses.

No responses were seen in other tumors in part A, although 1 patient with colorectal cancer showed SD for 7 months.

Discussion

This trial established the MTD for this drug combination to be ridaforolimus 10 mg QD×5 days/wk plus MK-2206 90 mg weekly. The combination was generally well tolerated at the MTD, with rash, stomatitis, diarrhea, and decreased appetite being the most common drug-related adverse events; most of these were mild or moderate in severity. Only a small percentage of adverse events were grade 3 or higher. In single-agent trials of ridaforolimus, the most commonly reported adverse events have been mouth sores (including stomatitis, mucositis, and mucosal inflammation), rash, anemia, infection, and fatigue (15-18, 20). Single-agent trials of MK-2206 have reported rash, fatigue, nausea, and vomiting as the most common adverse events, and mild to moderate myelosuppression is also common (25, 26). Both agents have been associated with increased incidence of hyperglycemia (25, 41).
Stomatitis/mucositis was very common at the higher dose level (experienced by approximately 70% of patients at that dose); reducing the dose of ridaforolimus in the combination was associated with a lower incidence of stomatitis. Stomatitis and other oral toxicities are a class toxicity associated with mTOR inhibitors, and are often the DLT (42-44). High incidence rates (56%) of stomatitis or mucositis have also been reported in randomized clinical trials of the approved mTOR inhibitor everolimus in combination treatments for breast cancer (45, 46). Patients should be educated about early detection and maintaining good preventative oral hygiene to minimize the risk of occurrence of this adverse event (41, 47, 48).

Rash was the most commonly reported adverse event at the MTD in this trial, and mild to moderate rash (typically an acne-like dermatitis) has also been frequently reported in trials of mTOR inhibitors (41, 45, 46, 49). Rash appeared to be more common at the lower dose level (44% of patients) than the higher dose level (24% of patients). It is unclear why this inverse relationship occurred, or whether it is a real event or an artifact of the dosing schedule. For example, it is possible that other toxicities that appear earlier than rash could compromise dose intensity in the highest dose level, thus impeding rash appearance.

The MTD identified for this combination requires lower doses of ridaforolimus and MK-2206 than single-agent therapy requires, but both agents have demonstrated activity at lowered levels. Ridaforolimus strongly and rapidly reduces 4E-BP1 protein levels (indicating mTOR inhibition) in peripheral blood mononuclear cells at doses down to 10 mg QD×28 days (16). MK-2206 monotherapy has demonstrated
antitumor activity in hormone-receptor positive breast cancer at a reduced dose of 150 mg QW (27). The need to lower ridaforolimus dose when combining with other agents has been reported previously. In patients with metastatic castration-resistant prostate cancer receiving ridaforolimus with the androgen receptor inhibitor bicalutamide, the starting ridaforolimus dose of 30 mg QD×5/wk had to be reduced in 64% of patients, leading to a median ridaforolimus dose of 21.6 mg QD×5/wk (22). Ridaforolimus pharmacokinetic parameters were not significantly affected by bicalutamide coadministration, suggesting that the toxicity might be due to synergetic pharmacodynamic effects on PI3K/Akt/mTOR pathway inhibition rather than pharmacokinetic drug interactions (22). This is likely to be the case for the ridaforolimus/MK-2206 combination also, as both agents target the PI3K/Akt/mTOR pathway. This may be a limitation for combinations of agents that target the same intracellular pathways.

Despite the low MTD of ridaforolimus plus MK-2206 identified in our trial, the combination showed promising activity in heavily pretreated patients with hormone-positive and -negative breast cancer who exhibited PI3K pathway dependence based on low RAS signature score. Three patients out of 17 (18%) enrolled with biomarker eligibility had either PR or CR based on either investigator or central radiological review. These results in a heavily pretreated patient population offer a rationale for exploring the combination of ridaforolimus and MK-2206 in further studies in PI3K pathway-dependent breast cancer. Use of biomarkers to identify patients most likely to benefit from targeted treatment could help increase response rate and reduce the number of patients who experience the toxicity associated with treatment with no benefit. The RAS pathway signature comprises a 147-gene signature that includes at
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

least 20 genes that are established components of the RAS-MEK-extracellular signal-regulated kinase (ERK) signaling network (32). It has been shown to be superior to KRAS mutation status for predicting response to PI3K and RAS pathway inhibitors (32). RAS pathway activation has been noted in many cell lines and tumor samples in the absence of mutations in KRAS, and the RAS pathway signature can predict sensitivity to inhibition of MEK and resistance to inhibition of Akt in preclinical models of cancer (32). Implementing the low RAS pathway signature threshold in this study ruled out patients with MAPK pathway overactivation (which can lead to PI3K inhibition due to the strong interaction between the pathways), resulting in selection of patients with PI3K dependence who were most likely to get benefit from the combination regimen.

Limited activity (SD) was observed in patients with low PTEN prostate cancer. The lack of objective responses in this patient population mirrored the findings of synergistic antitumor activity observed for this combination in preclinical studies, in which the combination primarily resulted in tumor stasis rather than regression (31). Combination with other agents that target alternative signaling pathways, such as the ERK/MAPK pathway (50), may be feasible to explore for future treatment options.

In conclusion, the combination of ridaforolimus and MK-2206 shows promising activity in heavily pretreated patients with hormone-positive and -negative breast cancer exhibiting PI3K pathway dependence based on low RAS signature score. No responses were observed in patients with low-PTEN prostate cancer, but prolonged SD was seen in 2 patients. The combination was generally well tolerated, with the most common drug-related adverse events being mild to moderate rash, stomatitis,
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

diarrhea, and decreased appetite. These results support further exploration of this combination therapy in breast cancer.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Acknowledgments

Medical writing and editorial assistance was provided by Alison Comer, PhD, of ApotheCom, with funding provided by Merck & Co., Inc. The authors would like to thank Matthew Marton (Merck & Co., Inc) for providing the analytical validation of the RAS-147 gene signature.

Grant Support

This study was supported by Merck & Co., Inc.

Author Contributions

Conception and design: P.N. Munster, J.D. Cheng, A. Tosolini
Development of methodology: P.N. Munster, J.D. Cheng, A. Tosolini
Acquisition of data: G. Argilés, A. Hollebecque, O. Dajani, J.D. Cheng, A. Swift, A. Tosolini, S.A. Piha-Paul
Analysis and interpretation of data: S. Gupta, G. Argilés, P.N. Munster, A. Hollebecque, O. Dajani, J.D. Cheng, R. Wang, A. Swift, A. Tosolini, S.A. Piha-Paul
Writing, review, and/or revision of the manuscript: S. Gupta, G. Argilés, P.N. Munster, A. Hollebecque, O. Dajani, J.D. Cheng, R. Wang, A. Swift, A. Tosolini, S.A. Piha-Paul
Study supervision: S. Gupta, S.A. Piha-Paul
Reference List


Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer


Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer


Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer


Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer


Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer


46. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer


Table 1. Baseline characteristics and demographics

<table>
<thead>
<tr>
<th></th>
<th>Ridaforolimus 10 mg QD × 5 d/wk + MK-2206 90 mg weekly (n = 18)</th>
<th>Ridaforolimus 20 mg QD × 5 d/wk + MK-2206 90 mg weekly (n = 17)</th>
<th>Total (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>12 (66.7)</td>
<td>15 (88.2)</td>
<td>27 (77.1)</td>
</tr>
<tr>
<td>≥65</td>
<td>6 (33.3)</td>
<td>2 (11.8)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>56.5 ± 16.6</td>
<td>54.1 ± 9.5</td>
<td>55.3 ± 13.5</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>60.0 (20-84)</td>
<td>53.0 (35-72)</td>
<td>55.0 (20-84)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (33.3)</td>
<td>7 (41.2)</td>
<td>13 (37.1)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (66.7)</td>
<td>10 (58.8)</td>
<td>22 (62.9)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (83.3)</td>
<td>14 (82.4)</td>
<td>29 (82.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.6)</td>
<td>1 (5.9)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Black or African</td>
<td>1 (5.6)</td>
<td>1 (5.9)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>1 (5.6)</td>
<td>1 (5.9)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>16 (88.9)</td>
<td>14 (82.4)</td>
<td>30 (85.7)</td>
</tr>
<tr>
<td>Not specified</td>
<td>2 (11.1)</td>
<td>2 (11.8)</td>
<td>4 (11.4)</td>
</tr>
</tbody>
</table>
### Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Arm 1 (n=12)</th>
<th>Arm 2 (n=7)</th>
<th>Arm 3 (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>12 (66.7)</td>
<td>7 (41.2)</td>
<td>19 (54.3)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0</td>
<td>2 (11.8)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Prostate</td>
<td>4 (22.2)</td>
<td>4 (23.5)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2 (11.1)</td>
<td>0</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Glioma (anaplastic mixed oligoastrocytoma)</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Ampulla of vater (mucinous carcinoma)</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of prior systemic regimens</th>
<th>Arm 1 (n=12)</th>
<th>Arm 2 (n=7)</th>
<th>Arm 3 (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>5 (0-11)</td>
<td>4 (1-7)</td>
<td>5 (0-11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of prior systemic therapy</th>
<th>Arm 1 (n=12)</th>
<th>Arm 2 (n=7)</th>
<th>Arm 3 (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>17 (94.4)</td>
<td>15 (88.2)</td>
<td>32 (91.4)</td>
</tr>
<tr>
<td>Biologic</td>
<td>4 (22.2)</td>
<td>3 (17.6)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td>Hormone</td>
<td>9 (50.0)</td>
<td>6 (35.3)</td>
<td>15 (42.9)</td>
</tr>
</tbody>
</table>

*Unless otherwise noted.

Abbreviations: QD, once daily; SD, standard deviation.
### Table 2. Safety summary

<table>
<thead>
<tr>
<th>n (%)a</th>
<th>Ridaforolimus 10 mg QD × 5 d/wk + MK-2206 90 mg weekly (n = 18)</th>
<th>Ridaforolimus 20 mg QD × 5 d/wk + MK-2206 90 mg weekly (n = 17)</th>
<th>Total (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE</td>
<td>18 (100.0)</td>
<td>17 (100.0)</td>
<td>35 (100.0)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>17 (94.4)</td>
<td>16 (94.1)</td>
<td>33 (94.3)</td>
</tr>
<tr>
<td>SAE</td>
<td>9 (50.0)</td>
<td>9 (52.9)</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td>Drug-related SAE</td>
<td>1 (5.6)</td>
<td>2 (11.8)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (5.6)</td>
<td>0</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Discontinued because of AE</td>
<td>2 (11.1)</td>
<td>3 (17.6)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Discontinued because of drug-related AE</td>
<td>1 (5.6)</td>
<td>2 (11.8)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Discontinued because of SAE</td>
<td>2 (11.1)</td>
<td>2 (11.8)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Discontinued because of drug-related SAE</td>
<td>1 (5.6)</td>
<td>1 (5.9)</td>
<td>2 (5.7)</td>
</tr>
</tbody>
</table>

aUnless otherwise noted.

Abbreviations: AE, adverse event; QD, once daily; SAE, serious adverse event.
Table 3. Summary of adverse events occurring in ≥10% of patients in one or more treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Ridaforolimus 10 mg QD × 5 d/wk + MK-2206 90 mg weekly (n = 18)</th>
<th>Ridaforolimus 20 mg QD × 5 d/wk + MK-2206 90 mg weekly (n = 17)</th>
<th>Total (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3 or 4</td>
<td>All</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (44.4)</td>
<td>1 (5.6) ( ^\text{a} )</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7 (38.9)</td>
<td>1 (5.6) ( ^\text{a} )</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (27.8)</td>
<td>1 (5.6) ( ^\text{a} )</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (22.2)</td>
<td>1 (5.6) ( ^\text{a} )</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (27.8)</td>
<td>0</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (22.2)</td>
<td>0</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (5.6)</td>
<td>0</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (22.2)</td>
<td>0</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>3 (16.7)</td>
<td>0</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (5.6)</td>
<td>1 (5.6) ( ^\text{a} )</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (11.1)</td>
<td>0</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (11.1)</td>
<td>0</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2 (11.1)</td>
<td>0</td>
<td>2 (11.8)</td>
</tr>
</tbody>
</table>
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 0</th>
<th>Grade 0</th>
<th>Grade 3 (17.6)</th>
<th>Grade 2 (11.8)</th>
<th>Grade 1 (8.6)</th>
<th>Grade 2 (5.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>0</td>
<td>3 (17.6)</td>
<td>2 (11.8)</td>
<td>3 (8.6)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>0</td>
<td>3 (17.6)</td>
<td>1 (5.9)</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>White blood cells decreased</td>
<td>0</td>
<td>0</td>
<td>3 (17.6)</td>
<td>1 (5.9)</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (11.1)</td>
<td>0</td>
<td>1 (5.9)</td>
<td>0</td>
<td>3 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (8.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>2 (11.1)</td>
<td>1 (5.6)</td>
<td>1 (5.9)</td>
<td>0</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>0</td>
<td>0</td>
<td>2 (11.8)</td>
<td>1 (5.9)</td>
<td>2 (5.7)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>0</td>
<td>0</td>
<td>2 (11.8)</td>
<td>1 (5.9)</td>
<td>2 (5.7)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2 (11.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Blood LDH increased</td>
<td>0</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*All grade 3.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; QD, once daily.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Table 4. Responses in biomarker eligible patients with breast cancer, by local investigator assessment or central review (both per RECIST v1.1)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose level</th>
<th>Best response (by RECIST v1.1)</th>
<th>Number of prior lines of therapy</th>
<th>Prior regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local investigator</td>
<td>Central review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ridaforolimus 20 mg QD × 5 d/wk + MK-2206 90 mg weekly</td>
<td>PR</td>
<td>CR</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Ridaforolimus 10 mg QD × 5 d/wk + MK-2206 90 mg</td>
<td>PR</td>
<td>SD</td>
<td>7</td>
</tr>
</tbody>
</table>
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

<table>
<thead>
<tr>
<th>weekly</th>
<th>Ridaforolimus</th>
<th>SD</th>
<th>CR</th>
<th>6</th>
<th>Epirubicin, fluorouracil, cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg QD × 5 d/wk + MK-2206 90 mg weekly</td>
<td></td>
<td></td>
<td></td>
<td>Epirubicin, fluorouracil, cyclophosphamide</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response, QD, once daily; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1; SD, stable disease.
Phase I Trial of Ridaforolimus Plus MK-2206 in Advanced Cancer

Legends for figures:

**Figure 1.** Imaging results for 2 patients with responses. A. Patient 1 was treated with ridaforolimus 20 mg QD × 5 d/wk plus MK-2206 90 mg weekly. Response was assessed as PR by local investigator review, and CR by central review. B. Patient 2 received ridaforolimus 10 mg QD × 5 d/wk plus MK-2206 90 mg weekly. Response was assessed as PR by local investigator review and SD by central review. Abbreviations: CR, complete response; PR, partial response; QD, once daily; SD, stable disease.

**Figure 2.** Maximum change from baseline in the size of target lesions in patients who had at least 1 evaluable postbaseline scan, as assessed per RECIST v1.1 by investigator review. A. Patients with biomarker-positive breast cancer (n = 16). B. Patients with biomarker-positive prostate cancer (n = 5). Abbreviation: RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1.
Figure 2

A

Percent Change from Baseline in Longest Diameter of Target Lesion

Individual Patients with Breast Cancer Treated with Ridaforolimus + MK-2206

B

Percent Change from Baseline in Longest Diameter of Target Lesion

Individual Patients with Prostate Cancer Treated with Ridaforolimus + MK-2206
A Phase I Trial of Combined Ridaforolimus and MK-2206 in Patients With Advanced Malignancies

Shilpa Gupta, Guillem Argiles, Pamela N. Munster, et al.

Clin Cancer Res Published OnlineFirst July 17, 2015.