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

Shilpa Gupta1, Guillem Argilés2, Pamela N. Munster3, Antoine Hollebecque4, Olay Dajani5, Jonathan D. Cheng6, Ruixue Wang6, Ann Swift6, Alessandra Tosolini6, and Sarina A. Piha-Paul7

Abstract

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 RAS gene signature and high Ki67 index) or castration-resistant prostate cancer (PTEN deficiency) with PI3K pathway addiction.

Results: Thirty-five patients were enrolled: 11 patients in part A (three breast cancer) and 24 biomarker-eligible patients in part B (16 breast cancer, eight 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/d ridaforolimus 5 d/wk + 90 mg/wk MK-2206; 1 of 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 of 16 (12.5%) evaluable patients with breast cancer had partial response; by central assessment, 2 of 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; one patient had SD for ≥6 months.

Conclusions: 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. Clin Cancer Res; 21(23):5235–44. ©2015 AACR.

Introduction

The 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). 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 PTEN tumor suppressor, and overactivation of mTOR kinase activity (6).

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).

Ridaforolimus, a non-prodrug analogue 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 toward purified recombinant human Akt1 and Akt2 and approximately 5-fold less potent against...
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 1 dose-escalation study identified the dose-limiting toxicities and maximum tolerated dose for the novel combination of two 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.

human Akt3 (IC50 = 8, 12, and 65 nmol/L, 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 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 in vitro and 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 PTEN or PIK3CA (which encodes the catalytic subunit of PI3K) 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, 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-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 LOH of the PTEN locus occur in a variety of human cancers and drive PI3K pathway dependence that 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 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 1 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 article.

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 RECIST version 1.1 (40), with the exception of patients with prostate cancer, who did not require measurable disease if they had a prostate-specific antigen (PSA) level > 10 ng/mL.

Patients were excluded if they had received chemotherapy or radiotherapy within 4 weeks prior to study day 1, biologic 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 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.

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+ 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 (per os) daily for 5 consecutive days (QD × 5/week) followed by 2 days off, plus MK-2206 90 mg per os weekly. The ridaforolimus starting dose was selected to be 50% of the MTD for oral ridaforolimus as a single agent (40 mg per os QD × 5/week) in the phase I/II single-agent, dose-escalation trial (16), and 20 mg per os QD × 5/week 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 per os 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 of 3 patients developed a DLT, escalation to the next dose level would occur. If 1 of 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 of 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 of 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 of 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/week plus MK-2206 135 mg weekly) and DL1.2 (ridaforolimus 30 mg QD × 5/week plus MK-2206 90 mg weekly) was allowed. Additional planned dose-level increments included DL2.1 (ridaforolimus 30 mg QD × 5/week plus MK-2206 135 mg weekly), DL2.2 (ridaforolimus 30 mg QD × 5/week plus MK-2206 200 mg weekly), DL2.3 (ridaforolimus 40 mg QD × 5/week plus MK-2206 200 mg weekly).

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 per os QD × 5/week plus MK-2206 90 mg per os 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 cohorts 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.

Endpoints and assessments
The primary safety endpoint 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 endpoint 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 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 used the industry-standard Affymetrix platform consisting of its standard hybridization incubator and fluids 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 Supplementary Data S1.

The assay used for the Ki67 labeling index was a well-established, widely available clinical assay from Ventana Medical Systems. The anti-Ki67 primary antibody was a rabbit monoclonal antibody (IgG) directed against the C-terminal portion of Ki67 antigen. The Ki67 immunohistochemical 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 immunohistochemical 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 immunohistochemical staining and 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 on the basis of immunohistochemistry, but not by FISH. On the basis of current data, including receiver operating characteristic curve analysis, an H-score cutoff of ≤10 was selected.

Statistical analysis
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.

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 rifadinaforolimus plus MK-2206: 17 patients received the starting dose of rifadinaforolimus 20 mg plus MK-2206 90 mg (DL1) and 18 patients received a lowered dose of rifadinaforolimus 10 mg plus MK-2206 90 mg (DL-1). Patients received a median of 2 (range, 1–10) cycles of both rifadinaforolimus and MK-2206 at DL1 and 2.5 (range, 1–17) cycles of both rifadinaforolimus 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 17 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 (bringing the total number of breast cancer patients 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%) continued 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).

DLT and MTD
There were 14 DLT-eligible 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, and 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 thrombocytopenia that resulted in dose reduction. Of the 17 DLT-eligible 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

Table 1. Baseline characteristics and demographics

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<th>Ridaforolimus 10 mg QD×5 d/week + MK-2206 90 mg weekly (n = 18)</th>
<th>Ridaforolimus 20 mg QD×5 d/week + MK-2206 90 mg weekly (n = 17)</th>
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*Unless otherwise noted.

Table 2. Safety summary

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<th>Ridaforolimus 20 mg QD×5 d/week + MK-2206 90 mg weekly (n = 17)</th>
<th>Total (N = 35)</th>
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<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>

Abbreviations: AE, adverse event; SAE, serious adverse event.

*Unless otherwise noted.
Hyperglycemia was rare at the MTD (DL-1), occurring in just 1 of 18 patients (5.6%), but was observed in 6 of 17 patients (35.3%) at DL1.

Tumor response

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 of 16 patients had an objective response (2 PR, 0 CR). Central radiologic assessment found objective responses in 2 of 14 patients (0 PR, 2 CR). The 2 patients with breast cancer reported to have PR by local investigator review were reported as CR and stable disease (SD), respectively, by central radiologic assessment, and 1 patient assessed to have SD by local investigator review was reported as CR by central radiologic assessment (Table 4).

Table 3. Summary of adverse events occurring in >10% of patients in one or more treatment groups

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>All Grade 3 or 4</th>
<th>All Grade 3 or 4</th>
<th>All Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>1 (5.6)</td>
<td>3 (17.6)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (11.1)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (11.1)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (11.1)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (5.6)</td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (11.1)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (11.1)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1 (5.6)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (11.1)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertiglyceridemia</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>White blood cells decreased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Alopeica</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Blood LDH increased</td>
<td>0</td>
<td>2 (11.8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: LDH, lactate dehydrogenase.

*All grade 3.

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>1</td>
<td>Ridaforolimus 20 mg QD × 5 d/week + MK-2206 90 mg weekly</td>
<td>PR, CR</td>
<td>5</td>
<td>Epirubicin, fluorouracil, cyclophosphamide, Tamoxifen</td>
</tr>
<tr>
<td>2</td>
<td>Ridaforolimus 10 mg QD × 5 d/week + MK-2206 90 mg weekly</td>
<td>PR, SD</td>
<td>7</td>
<td>Epirubicin, fluorouracil, cyclophosphamide, Liposomal doxorubicin, Paclitaxel, Tamoxifen, Letrozole, Exemestane, Letrozole, Anastrozole, Fulvestrant, PI3K inhibitor (unspecified)</td>
</tr>
<tr>
<td>3</td>
<td>Ridaforolimus 10 mg QD × 5 d/week + MK-2206 90 mg weekly</td>
<td>SD, CR</td>
<td>6</td>
<td>Epirubicin, fluorouracil, cyclophosphamide, Tamoxifen, Letrozole, Dasatinib, Fulvestrant, Epirubicin, fluorouracil, cyclophosphamide</td>
</tr>
</tbody>
</table>
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 radiologic assessment was used 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).

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, whereas 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/week 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 were rash, stomatitis, diarrhea, and decreased appetite being 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 ~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/week had to be reduced in 64% of patients, leading to a median ridaforolimus dose of 21.6 mg QD × 5/week (22). Ridaforolimus pharmacokinetic parameters were not significantly affected by bicalutamide coadministration, suggesting that the toxicity might be due to synergistic 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 of 17 (18%) enrolled with biomarker eligibility had either PR or CR based on either investigator or central radiologic 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 least 20 genes that are established components of the RAS/MEK/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, diarrhea, and decreased appetite. These results support further exploration of this combination therapy in breast cancer.

Disclosure of Potential Conflicts of Interest
J.D. Cheng has ownership interest (including patents) in Merck. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: P.N. Munster, J.D. Cheng, A. Tosolini, S.A. Piha-Paul
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Swift
Study supervision: S. Gupta, P.N. Munster, J.D. Cheng, A. Tosolini, S.A. Piha-Paul

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

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


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