Interrogating Two Schedules of the AKT Inhibitor MK-2206 in Patients with Advanced Solid Tumors Incorporating Novel Pharmacodynamic and Functional Imaging Biomarkers

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Abstract

Purpose: Multiple cancers harbor genetic aberrations that impact AKT signaling. MK-2206 is a potent pan-AKT inhibitor with a maximum tolerated dose (MTD) previously established at 60 mg on alternate days (QOD). Due to a long half-life (60–80 hours), a weekly (QW) MK-2206 schedule was pursued to compare intermittent QW and continuous QOD dosing.

Experimental Design: Patients with advanced cancers were enrolled in a QW dose-escalation phase I study to investigate the safety and pharmacokinetic–pharmacodynamic profiles of tumor and platelet-rich plasma (PRP). The QOD MTD of MK-2206 was also assessed in patients with ovarian and castration-resistant prostate cancers and patients with advanced cancers undergoing multiparametric functional magnetic resonance imaging (MRI) studies, including dynamic contrast-enhanced MRI, diffusion-weighted imaging, magnetic resonance spectroscopy, and intrinsic susceptibility-weighted MRI.

Results: A total of 71 patients were enrolled; 38 patients had 60 mg MK-2206 QOD, whereas 33 received MK-2206 at 90, 135, 150, 200, 250, and 300 mg QW. The QW MK-2206 MTD was established at 200 mg following dose-limiting rash at 250 and 300 mg. QW dosing appeared to be similarly tolerated to QOD, with toxicities including rash, gastrointestinal symptoms, fatigue, and hyperglycemia. Significant AKT pathway blockade was observed with both continuous QOD and intermittent QW dosing of MK-2206 in serially obtained tumor and PRP specimens. The functional imaging studies demonstrated that complex multiparametric MRI protocols may be effectively implemented in a phase I trial.

Conclusions: Treatment with MK-2206 safely results in significant AKT pathway blockade in QOD and QW schedules. The intermittent dose of 200 mg QW is currently used in phase II MK-2206 monotherapy and combination studies (NCT00670488). Clin Cancer Res; 20(22); 5672–85. ©2014 AACR.
Translational Relevance

MK-2206 is a novel, specific, oral inhibitor of AKT, which is deregulated in multiple cancers. The study of different schedules of targeted agents is critical for their optimal application. The maximum tolerated dose (MTD) of MK-2206 was previously established at 60 mg on alternate days (QOD). Because of a long half-life of 60 to 80 hours, MK-2206 was evaluated in a weekly schedule for comparison with QOD dosing in this study. The MK-2206 weekly schedule seemed to be similarly tolerated to QOD dosing, whereas pharmacodynamic studies using novel quantitative electrochemiluminescence assays in serially obtained tumor and platelet-rich plasma (PRP) specimens confirmed significant AKT blockade with both continuous QOD and intermittent schedules of MK-2206. Functional imaging studies demonstrated that complex multiparametric MRI protocols may be effectively implemented in phase I trials. The intermittent weekly MTD of 200 mg of MK-2206 established in this study is currently used in multiple phase II monotherapy and combination studies in defined patient populations.

Preclinical antitumor activity, a phase I dose-escalation study of MK-2206 in 33 patients with advanced solid tumors was carried out, which established the maximum tolerated dose (MTD) at 60 mg on alternate days (QOD) and demonstrated that MK-2206 safely induced significant AKT pathway blockade in tumor and hair follicles, with preliminary evidence of clinical activity (14).

Pharmacodynamic evaluation of AKT blockade may involve the assessment of phosphorylation signals in normal tissue, such as the phosphorylation of pSer473 AKT and downstream substrates in platelet-rich plasma (PRP), as well as in tumor biopsies. Functional imaging can also be utilized to evaluate drug pharmacodynamics, such as through the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), diffusion weighted imaging (DWI), proton magnetic resonance spectroscopy (1H-MRS), and intrinsic susceptibility-weighted MR (ISW-MRI; ref. 15). DCE-MRI is a recognized tool for the characterization of tumor angiogenesis and the quantification of drug effects on tumor vascular permeability and perfusion (16–19). DWI is also emerging as a biomarker of tumor necrosis and/or apoptosis (20, 21). Furthermore, 1H-MRS can detect decreases in phosphocholine content after PI3K–AKT pathway blockade (22, 23). Changes in the imaging parameter for ISW-phosphocholine content after PI3K–AKT pathway blockade in tumor and hair follicles, with demonstrated that complex multiparametric MRI protocols may be effectively implemented in phase I trials. The intermittent weekly MTD of 200 mg of MK-2206 established in this study is currently used in multiple phase II monotherapy and combination studies in defined patient populations.

The study of different schedules of molecularly targeted therapies is critical for their optimal application, but is not often done in randomized phase II trials (25). Thus, an alternative strategy is to undertake this during the expansion phase of a phase I clinical trial. In this study, cohorts of patients with CRPC, advanced ovarian cancer, and those undergoing multiparametric MRI studies were treated with 60 mg QOD of MK-2206. In view of a half-life of 60 to 80 hours observed (14), a QW schedule of MK-2206 was also evaluated to determine the safety and maximum tolerated dose (MTD)/recommended phase II dose (RP2D) of MK-2206, and compared with QOD dosing. In addition, electrochemiluminescence assays were utilized to quantify and compare the pharmacodynamic effects of MK-2206 in serial tumor and PRP specimens between both schedules of MK-2206, in parallel with pharmacokinetic studies.

Patients and Methods

This was an open-label, dose-escalation phase I study (Merck & Co., Inc., Protocol number 002; NCT00670488 www.clinicaltrials.gov) of continuous QOD and QW oral treatment with MK-2206, conducted at three centers [Royal Marsden NHS Foundation Trust (Surrey, UK); South Texas Accelerated Research Therapeutics (START) (San Antonio, TX); and H. Lee Moffitt Cancer Center and Research Institute (Tampa, FL)]. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and approved by relevant regulatory and independent ethics committees.

Eligibility criteria

Study inclusion criteria included written informed consent; age ≥18 years; patients with histologically or cytologically confirmed advanced solid tumors, who failed to respond to established therapies or for whom no proven treatments existed; Eastern Cooperative Oncology Group (ECOG) performance status (26) ≤1; previous surgery or chemotherapy ≥4 weeks; residual toxicities from prior treatment ≤grade (G)1; adequate bone marrow, renal, and hepatic function; fasting serum glucose ≤1.1× the upper limit of normal and HbA1c ≤8%.

Exclusion criteria included diabetic patients on insulin or oral anti-diabetic therapy; oral corticosteroids; pregnancy or breastfeeding; conditions that would impede drug ingestion or absorption; unstable brain metastases; and other significant co-existing medical conditions.

Study design

For the QOD study, MK-2206 tablets were administered at 60 mg QOD in 28-day cycles to fasted patients in three different cohorts, comprising patients with advanced CRPC (n = 14), ovarian cancer (n = 11), and those with tumors suitable for multiparametric MRI studies (n = 16). For the QW study, a two-stage design was utilized. The first stage (dose-escalation phase) followed a
standard 3+3 design. Cohorts of 3 to 6 patients were to be treated at preplanned dose levels of 90, 135, 200, and 300 mg QW; intermediate-dose cohorts were permitted. The second stage (dose confirmation) employed a modification of the toxicity probability interval method (27). The definition of dose-limiting toxicities (DLT) included any MK-2206–related Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (28) ≥G4 hematologic toxicity, ≥G3 neutropenia with fever, or ≥G3 non-hematologic toxicity (except for inadequately-treated G3 nausea, vomiting, or diarrhea).

Safety
Safety assessments were conducted at baseline, days 1, 2, 7, 15, 21, 27, and 28 of cycle 1, weekly in cycle 2, and subsequently every month. Each patient had a full medical history taken and a physical examination, including full ophthalmologic assessment, electrocardiogram, 24-hour cardiac Holter monitoring, hematology and chemistry profiling, and urine analysis. In addition to glucose monitoring, serum c-peptide and whole blood HbA1c were measured at baseline and monthly. Adverse events (AE) and laboratory variables were assessed using CTCAE version 3.0 (28).

Pharmacokinetic analyses
Plasma concentrations were analyzed by noncompartmental pharmacokinetic methods using WinNonLin (Scientific Consultant, Apex, NC; version 5.2.1, Pharsight; Supplementary Materials and Methods).

Biomarker studies
Pharmacodynamic biomarker analyses (pSer473 AKT, pSer9 GSK3β, and pThr246 PRAS40) were undertaken on PRP and tumor, where available, using assays validated to Good Clinical Practice standards on the MesoScale Discovery (MSD) technology and EnVision technology platforms (Supplementary Materials and Methods; ref. 29).

Tumor response
Radiologic assessment of disease status was performed at baseline and every 8 weeks, according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1; ref. 30). Serum cancer antigen 125 (CA125) was assessed according to the Prostate Cancer Working Group criteria (PCWG2; ref. 32). Patients were enrolled into once-weekly cohorts of 90 mg (DLTs: 0/3 patients), 135 mg (DLTs: 0/4 patients), and 200 mg (DLTs: 0/3 patients), before evaluation of a 300 mg cohort where DLTs of G3 rash were observed in 3 of 3 patients. An intermediate dose of 250 mg QW was then explored and deemed to exceed the MTD with G3 rash observed in 2 of 3 patients. Therefore, an additional 3 patients were enrolled at 200 mg QW, where G3 rash was seen in 1 of 3 patients. As only 1 of 6 patients experienced a DLT in the 200 mg cohort during the dose-escalation phase, this dose level was studied in a further expansion cohort of 11 patients. Overall, in this study, 4 of 17 (23.5%) patients at 200 mg QW experienced DLTs (G3 rash in 3 patients; G3 dermatitis acneiform in 1 patient). According to prespecified dose escalation/de-escalation rules, a lower intermediate dose of 150 mg (G3 rash in 1 of 2 patients) was also explored. However, for administrative and nontrial–related reasons, the study was terminated before completion of enrollment to this cohort. Overall, based on review of pharmacokinetic/pharmacodynamic and safety/tolerability data from both the QOD and QW dosing schedules, the MTD/RP2D of MK-2206 was established at 200 mg QW.

No DLTs were reported in patients who received MK-2206 at 90 mg or 135 mg QW. Dose interruptions lasting 2 to 4 weeks were required in patients with DLTs. Two patients withdrew study consent before reinitiation of therapy. One patient in the 200 mg dose cohort resumed therapy at the same dose, whereas dose reduction to the next lower dose level occurred in the remaining 7 patients. No patients discontinued study therapy directly as a result of DLTs. While DLTs fully resolved in 7 of these 10 patients within 1 to 2 weeks of onset, they resolved with sequelae of dry skin in 3 patients. No treatment-related G4–5 toxicities were observed.

Results
A total of 71 patients entered this study between April 2009 and January 2011, and all were included in the safety analysis (Tables 1 and 2). In total, 33 patients received MK-2206 at escalating QW doses of 90 mg (n = 3), 135 mg (n = 5), 200 mg (n = 17), 300 mg (n = 3), and intermediate doses of 250 mg (n = 3) and 150 mg (n = 2). Thirty-eight patients received MK-2206 in three 60 mg QOD MTD expansion cohorts comprising CRPC, ovarian cancer, and multiparametric MRI cohorts.

Safety and tolerability
QW schedule DLTs. Patients were enrolled into once-weekly cohorts of 90 mg (DLTs: 0/3 patients), 135 mg (DLTs: 0/4 patients), and 200 mg (DLTs: 0/3 patients), before evaluation of a 300 mg cohort where DLTs of G3 rash were observed in 3 of 3 patients. An intermediate dose of 250 mg QW was then explored and deemed to exceed the MTD with G3 rash observed in 2 of 3 patients. Therefore, an additional 3 patients were enrolled at 200 mg QW, where G3 rash was seen in 1 of 3 patients. As only 1 of 6 patients experienced a DLT in the 200 mg cohort during the dose-escalation phase, this dose level was studied in a further expansion cohort of 11 patients. Overall, in this study, 4 of 17 (23.5%) patients at 200 mg QW experienced DLTs (G3 rash in 3 patients; G3 dermatitis acneiform in 1 patient). According to prespecified dose escalation/de-escalation rules, a lower intermediate dose of 150 mg (G3 rash in 1 of 2 patients) was also explored. However, for administrative and nontrial–related reasons, the study was terminated before completion of enrollment to this cohort. Overall, based on review of pharmacokinetic/pharmacodynamic and safety/tolerability data from both the QOD and QW dosing schedules, the MTD/RP2D of MK-2206 was established at 200 mg QW.

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QW schedule safety and tolerability. Overall, drug-related AEs were reported in 66.7% (22/33) of patients. The most common (≥10%) drug-related AEs were fatigue in 45.5% (15/33) of patients, rash in 42.4% (14/33) of patients, diarrhea and nausea in 27.3% (9/33) of patients, each, vomiting in 24.2% (8/33) of patients, decreased appetite in 21.2% (7/33) of patients, stomatitis in 15.2%
(5/33) of patients, and pruritus, increased alanine aminotransferase levels, and headaches in 12.1% (4/33) of patients each. The majority of these AEs were G1–2. G1 hyperglycemia was observed in 3.0% (1/33) of patients following 1 cycle of treatment with MK-2206 QW. Elevated blood glucose levels were observed in 57.6% (19/33) of patients who received MK-2206 QW. Elevations were mild and transient with onset occurring with similar frequencies during cycle 1 and subsequent cycles. Post-cycle 1 HbA1c values in all patients assessed were <7%. In 4 of 6 patients assessed, C-peptide levels increased during the first cycle of treatment (range, 65.7%–166.6%).

Three patients discontinued MK-2206 for drug-related AEs of G3 rash (n = 1), G3 complete atrioventricular block (n = 1), and G1 rash (n = 1). Eleven of 33 patients interrupted study therapy due to drug-related AEs. Of these 11 patients, 2 patients resumed therapy at the same dose, 2 patients withdrew consent and did not resume study, and 7 patients required dose reduction to the next lower dose level. Dose interruptions of 1 day to 4 weeks was required before reinitiating study therapy.

QOD schedule DLTs. DLTs occurred in 7 of 38 (18.4%) patients and included G3 rash (n = 5), G3 rash and G3 stomatitis (n = 1), and G3 hyperglycemia (n = 1; Supplementary Table S1). One patient discontinued study treatment due to G3 rash; this resolved within one week of stopping MK-2206. Overall, DLTs resulted in dose interruption in 6 patients. Among these 6 patients, study therapy was resumed within 1 to 2 weeks at the same dose of 60 mg QOD (n = 2), a reduced dose of 30 mg QOD with subsequent dose escalation to 45 mg QOD (n = 2), and a reduced dose of 50 mg QOD (n = 1); dose interruption was followed by MK-2206 discontinuation in one patient due to disease progression. All DLTs resolved to baseline levels within 1 to 2 weeks of drug interruption; the DLT of G3 hyperglycemia was considered to be resolved with sequelae, as this patient with preexisting glucose intolerance remained on metformin treatment.

QOD schedule safety and tolerability. The safety and tolerability of MK-2206 in a QOD schedule have previously been described in the dose-escalation study; thirty-three patients with advanced solid tumors were treated, with G1–2 rash the most common toxicity observed (14). Other MK-2206–associated AEs included fatigue, gastrointestinal toxicities, and hyperglycemia. The QOD expansion cohorts in this study have confirmed that MK-2206 is generally well tolerated in 38 patients at the MTD of 60 mg QOD, with a similar toxicity profile to that observed during dose escalation (Supplementary Table S1; ref. 14).

After the first cycle of treatment, G1–2 hyperglycemia was observed in 7.9% (3/38) of patients, and G3 hyperglycemia was observed in 2.6% (1/38) of patients. While not reported as AEs, blood glucose levels were noted to be elevated in 71.1% (27/38) of patients who received MK-2206 60 mg QOD, with a similar toxicity profile to that observed during dose escalation (Supplementary Table S1; ref. 14).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of all treated patients (N = 71)</th>
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<tbody>
<tr>
<td><strong>60 mg QOD schedule, n = 38</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Median age, y (range)</strong></td>
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<tr>
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<td><strong>All prior therapies¶</strong></td>
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<tr>
<td>1–2</td>
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<td>&gt;2</td>
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</table>

§Includes bile duct carcinoma and leiomyosarcoma (n = 1 each).
¶Includes bronchial carcinoma, leiomyosarcoma, melanoma, neuroendocrine tumor, pancreatic carcinoma, renal cell carcinoma, urothelial carcinoma, uterine carcinoma, and unknown primary carcinoma (all n = 1).

Includes chemotherapy, radiotherapy, hormone therapy, and immunotherapies.
Table 2. Treatment-related adverse events (AE) for the QW dosing cohort

<table>
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<tr>
<th>AE</th>
<th>Cohort</th>
<th>90 mg (n = 3)</th>
<th>135 mg (n = 5)</th>
<th>150 mg (n = 2)</th>
<th>200 mg (n = 17)</th>
<th>250 mg (n = 3)</th>
<th>300 mg (n = 3)</th>
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<td>Gastrointestinal disorders</td>
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<td>Diarrhea</td>
<td>G1</td>
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<td>Nausea</td>
<td>G1</td>
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<td>0 (0)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0 (0)</td>
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<tr>
<td>Vomiting</td>
<td>G1</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0 (0)</td>
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<td>0 (0)</td>
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<td>Fatigue</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Rash^b</td>
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<td>0 (0)</td>
<td>1^c (3)</td>
<td>5 (9)</td>
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</table>

^aAll values shown represent number of AEs occurring in ≥2 patients during first cycle and all cycles (parentheses). If a patient experienced the same AE multiple times (at the same or different grade), the adverse event was counted every time it occurred.

No treatment-related G4–5 AEs were observed during the study.

No treatment-related G2, 3, or 4 AEs were observed in the 90 mg or 135 mg dose cohorts.

^bAll preferred AE terms with *rash* (e.g., rash macular, rash papular, etc.) were collated into the single term of *Rash*.

^cDLT.
patients demonstrating HbA1c levels of ≤6.5% at both time points. In 2 patients with baseline levels ≤6.5%, end of cycle 1 values were 7.3% and 8.3%, respectively. Baseline and end of cycle 1 C-peptide levels were available in 71.1% (27/38) of patients. In 85.2% (23/27) of these patients, C-peptide levels increased during the first cycle of treatment (range, 2.7%–495.5%).

Pharmacokinetics of MK-2206

Weekly (QW) schedule pharmacokinetics. Following administration in a QW schedule, MK-2206 was absorbed with a median time to maximum concentration ($T_{\text{max}}$) of 4 to 6 hours. As gastric emptying occurs within 1 to 2 hours, the median $T_{\text{max}}$ of 4 to 6 hours suggests that MK-2206 absorption probably occurs in both the small intestines and stomach. MK-2206 plasma concentrations declined in a monoexponential manner after administration at 90, 135, 200, 250, and 300 mg QW (Fig. 1A). The absorption and distribution of MK-2206 are consistent with its relatively low solubility, but high permeability across physiologic pH ranges.

MK-2206 plasma concentrations exhibited high interpatient variability with percent coefficient of variations (CV) of area under the concentration–time curve (AUC) and maximum concentration ($C_{\text{max}}$) ranging from 12% to 71%. AUC and $C_{\text{max}}$ increased in a dose-proportional manner within the dose range of 90 to 300 mg QW. Given the high intersubject variability, there was no evidence of deviation from dose proportionality (Figs. 1B and C).

Table 3 summarizes the pharmacokinetic parameters of MK-2206 following the first and last dose of cycle 1 QW dosing. Mean terminal elimination half-lives ($t_{1/2}$) were 71.6, 88.9, and 75.1 hours after administration of 90, 135, and 200 mg doses, respectively, supporting the use of MK-2206 in QW and QOD dosing schedules. Accumulation ratio of MK-2206 expressed as the geometric mean ratios $AUC_{\text{last day}}/AUC_{\text{first day}}$ of $C_{\text{max}}$ at the first dose of cycle 1. QW and QOD schedule pharmacokinetics. The peak plasma concentrations of MK-2206 occurred at median $T_{\text{max}}$ of 4 hours after administration of 60 mg MK-2206 QOD in the expansion cohort and the $t_{1/2}$ was 64 hours, which was comparable with the pharmacokinetic values of patients in the dose-escalation cohorts (Supplementary Table S2; Supplementary Fig. S1; ref. 14). The accumulation ratio of MK-2206, assessed as $AUC_{\text{last day}}/AUC_{\text{first day}}$ ratio, was 3.3,
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**Figure 2.** Tumor biopsies from 5 patients receiving 200 mg QW of MK-2206 (1) showed a rich plasma (PRP) in a QW schedule. The analysis of paired tumor pretreatment samples. Overall, the pSer473 AKT signal decreased to 50.0% (range, 37.5%–60.3%; \( P = 0.0003 \)) of baseline levels on MK-2206 treatment, confirming target modulation.

Pharmacodynamic effects of MK-2206 treatment on pSer473 AKT (n = 11) and pSer9 GSK3β (n = 11) phosphorylation at the 200 mg MTD were assessed sequentially in PRP specimens at multiple time points (Fig. 2A, 2–3). The mean pSer473 AKT signal post-MK-2206 was 19.8% at 24 hours (\( P < 0.0001 \)), 30.6% at 48 hours (\( P < 0.0001 \)), 51.7% at 96 hours (\( P = 0.0015 \)), and 97.4% at 168 hours (\( P = 0.92 \)) of baseline levels (Fig. 2A, 2), while mean pSer9 GSK3β signal was 65.0% at 24 hours (\( P < 0.0001 \)), 82.3% at 48 hours (\( P = 0.012 \)), 91.4% at 96 hours (\( P = 0.56 \)), and 117.2% at 168 hours (\( P = 0.37 \)) of baseline levels (Fig. 2A, 3).

**QOD schedule pharmacodynamics.** Paired tumor biopsies were obtained for biomarker analysis by MSD electrochemiluminescence assays from 3 patients receiving 60 mg QOD of MK-2206 (Fig. 2B, 1). All 3 patients showed a significant suppression of pSer473 AKT when compared with paired pretreatment samples. The mean pSer473 AKT levels decreased to 50.1% (range, 45.3%–56.2%; \( P = 0.004 \)) of baseline levels on MK-2206 treatment, confirming target modulation.

Pharmacodynamic effects in PRP were also assessed serially at multiple time points from 29 patients receiving the MTD of 60 mg QOD of MK-2206 (Fig. 2B, 2–4). The pSer473 AKT signal decreased significantly to mean values at 96 hours (\( P = 0.56 \)), and 117.2% at 168 hours (\( P = 0.37 \)) of baseline levels (3). *, \( P < 0.05 \); **, \( P < 0.01 \); ***, \( P < 0.001 \); paired t test compared with baseline. Points represent the levels of pharmacodynamic biomarkers as a percent of the baseline levels for individual patients and orange lines represent mean of all patients at that time point. (Continued on the following page.)

### Pharmacodynamic biomarker analysis

**Weekly (QW) schedule pharmacodynamics.** The analysis of paired tumor biopsies from 5 patients receiving 200 mg QW of MK-2206 (Fig. 2A, 1) showed a significant suppression of pSer473 AKT when compared with paired pretreatment samples. Overall, the pSer473 AKT signal decreased to 50.0% (range, 37.5%–60.3%; \( P = 0.0003 \)) of baseline levels on MK-2206 treatment, confirming target modulation.

The pharmacodynamic effects of MK-2206 treatment on pSer473 AKT (n = 11) and pSer9 GSK3β (n = 11) phosphorylation at the 200 mg MTD were also assessed sequentially in PRP specimens at multiple time points (Fig. 2A, 2–3). The mean pSer473 AKT signal post-MK-2206 was 19.8% at 24 hours (\( P < 0.0001 \)), 30.6% at 48 hours (\( P < 0.0001 \)), 51.7% at 96 hours (\( P = 0.0015 \)), and 97.4% at 168 hours (\( P = 0.92 \)) of baseline levels (Fig. 2A, 2), while mean pSer9 GSK3β signal was 65.0% at 24 hours (\( P < 0.0001 \)), 82.3% at 48 hours (\( P = 0.012 \)), 91.4% at 96 hours (\( P = 0.56 \)), and 117.2% at 168 hours (\( P = 0.37 \)) of baseline levels (Fig. 2A, 3).

**QOD schedule pharmacodynamics.** Paired tumor biopsies were obtained for biomarker analysis by MSD electrochemiluminescence assays from 3 patients receiving 60 mg QOD of MK-2206 (Fig. 2B, 1). All 3 patients showed a significant suppression of pSer473 AKT when compared with paired pretreatment samples. The mean pSer473 AKT levels decreased to 50.1% (range, 45.3%–56.2%; \( P = 0.004 \)) of baseline levels on MK-2206 treatment, confirming target modulation.

Pharmacodynamic effects in PRP were also assessed serially at multiple time points from 29 patients receiving the MTD of 60 mg QOD of MK-2206 (Fig. 2B, 2–4). The pSer473 AKT signal decreased significantly to mean values at 96 hours (\( P = 0.56 \)), and 117.2% at 168 hours (\( P = 0.37 \)) of baseline levels (3). *, \( P < 0.05 \); **, \( P < 0.01 \); ***, \( P < 0.001 \); paired t test compared with baseline. Points represent the levels of pharmacodynamic biomarkers as a percent of the baseline levels for individual patients and orange lines represent mean of all patients at that time point. (Continued on the following page.)
of 36.3% at 3 hours ($P < 0.0001$), 27.9% at 6 hours ($P < 0.0001$), 44.0% at 24 hours ($P < 0.0001$), and 70.6% at 48 hours ($P = 0.045$) of baseline levels (Fig. 2B). Overall, pSer473 AKT levels decreased significantly by a mean of 55.3%, with maximum inhibition at 6 hours post-MK-2206. This suppression was sustained significantly for 48 hours when the next dose of drug was given.

This inhibition of pSer473 AKT was associated with significant decreases in the phosphorylation of downstream substrates pSer9 GSK3β to mean levels of 76.8% at 3 hours ($P = 0.009$), 67.5% at 6 hours ($P = 0.0051$), 102.9% at 24 hours ($P = 0.87$), and 116.1% at 48 hours ($P = 0.51$) of baseline levels (Fig. 2B, 3); and pThr246 PRAS40 to mean levels of 79.8% at 3 hours ($P = 0.005$), 79.7% at 6 hours ($P = 0.0059$), 86.9% at 24 hours ($P = 0.030$), and 91.4% at 48 hours ($P = 0.42$) of baseline levels (Fig. 2B, 4). With both pSer9 GSK3β substrates and pThr246 PRAS40, the maximum suppression was also at 6 hours post-MK-2206. A single patient was removed as an outlier according to Grubbs test for outliers ($a = 0.01$), resulting in mean levels of 60.1% pSer473 AKT ($P = 0.0004$) and 81.9% pThr246 PRAS40 ($P = 0.0019$) at 48 hours. This confirmed the suppression of pSer473 AKT and its downstream target PRAS40 were significantly sustained to 48 hours in the remaining 28 patients on QOD dosing.
Table 3. Summary of pharmacokinetic parameter values after multiple QW doses of 90, 135, 150, 200, 250, and 300 mg of MK-2206 in male and female oncology patients

<table>
<thead>
<tr>
<th>QW dose</th>
<th>N (day 1, day last)</th>
<th>Day 1</th>
<th>Last day</th>
<th>Last/day ratio</th>
<th>Apparent terminal t½ (h)</th>
<th>Cmax (nmol/L), mean ± SD (%CV)</th>
<th>C_{max} (nmol/L), mean ± SD (%CV)</th>
<th>Tmax (h)</th>
<th>C0–168 h (nmol/L/C2h/L), mean ± SD (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>3, 3</td>
<td>6,510</td>
<td>7,520</td>
<td>10,600</td>
<td>59%</td>
<td>153 ± 81.7 (52%)</td>
<td>42.4 ± 19.6 (4.0–10.0)</td>
<td>87.6 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>135</td>
<td>5, 4</td>
<td>12,000</td>
<td>20,700</td>
<td>8,780</td>
<td>42%</td>
<td>199 ± 35.4 (50%)</td>
<td>79.3 ± 33.7 (4.0–24.0)</td>
<td>88.9 ± 26.9</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>2, 1</td>
<td>20,700</td>
<td>98.0</td>
<td>352</td>
<td>58%</td>
<td>337 ± 34.6 (60%)</td>
<td>158 ± 19.2 (4.0–10.0)</td>
<td>75.1 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>17, 13</td>
<td>16,400</td>
<td>199</td>
<td>345</td>
<td>58%</td>
<td>336 ± 38.5 (80%)</td>
<td>185 ± 16.0 (4.0–24.0)</td>
<td>75.1 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>3, 1</td>
<td>14,000</td>
<td>169</td>
<td>231</td>
<td>57%</td>
<td>231 ± 39.1 (60%)</td>
<td>19.6 ± 7.3 (4.0–24.0)</td>
<td>46.4 ± 12.2</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>3, 0</td>
<td>27,700</td>
<td>169</td>
<td>253</td>
<td>57%</td>
<td>231 ± 39.1 (60%)</td>
<td>19.6 ± 7.3 (4.0–24.0)</td>
<td>46.4 ± 12.2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the concentration-time curve; Cmax, maximum measured plasma concentration; C_{48 h}, plasma concentration 48 hours following dose (trough concentration); Tmax, time from dosing to maximum plasma concentration.

- Median (min – max).
- Harmonic mean ± pseudo SD.
- Geometric mean.

aMedian (min – max).
bHarmonic mean ± pseudo SD.
cGeometric mean.
dSummary statistics not provided due to insufficient data.
Functional imaging cohort

A total of 16 patients were enrolled into the multiparametric MRI cohort, comprising DCE-MRI, DWI, $^1$H-MRS, and ISW-MRI scans over 4 time points (Supplementary Tables S3–S7). Each multiparametric MRI protocol lasted 45 to 50 minutes per patient. Two baseline scans were undertaken at a mean period of 7.4 days apart. Thirteen patients had 2 baseline studies each and were thus included in the reproducibility analysis. Of the 16 patients enrolled into this functional imaging cohort, 4 did not receive MK-2206 due to clinical deterioration (Supplementary Table S3). Of these remaining 12 patients, 1 patient had a nonechogenic lesion and so DCE-MRI analysis was not conducted; 1 patient had no detectable choline and therefore $^1$H-MRS analysis was not performed; and 5 patients had significant artefacts on ISW-MRI, and thus analysis was not undertaken. Therefore, the final evaluable imaging data sets included 11 patients for DCE-MRI, 12 patients for DWI, 11 patients for $^1$H-MRS and 7 patients for ISW-MRI analysis (Supplementary Tables S4–S7).

Overall, the extent of all MRI parameter changes following treatment was within the limits of data variability as determined by the analysis of the reproducibility cohort (Supplementary Fig. S2). There was, however, a statistically significant increase in median tumor ADC in 4 patients on day 7. The increase in ADC was maintained in 2 of these patients on day 21. The baseline imaging measurements in these two patients suggested increased cellularity of the tumors with varying degrees of vascularity, before responding to MK-2206 treatment. In one of these patients (baseline median ADC = $100 \times 10^{-3}$ mm$^2$/s$^{-1}$ and median $k_{\text{trans}} = 0.08$ min$^{-1}$), this response was associated with a moderate reduction in $K_{\text{trans}}$ of 29%, and there was a marginal reduction in the size of the tumor on restaging CT imaging after 6 months of treatment (Supplementary Fig. S3). In the other patient who had a more vascular tumor (baseline median ADC = $97.4 \times 10^{-3}$ mm$^2$/s$^{-1}$ and median $k_{\text{trans}} = 1.14$ min$^{-1}$, $97.4 \times 10^{-5}$ mm$^2$/s$^{-1}$ and median $k_{\text{trans}} = 1.14$ min$^{-1}$), there was a significant increase in ADC values in keeping with areas of necrosis within the enhancing and cellular rim of the tumor, while the central necrotic area of the tumor remained unchanged. This malignant lesion was stable by RECIST measurements on the restaging CT at week 8 of treatment (Supplementary Fig. S4).

Antitumor activity

The median duration of treatment for patients who received MK-2206 in a QW schedule was 8.1 weeks (range, 1.1–24.0 weeks), compared with 13.1 weeks (range, 8.7–28.0 weeks) for those in the QOD cohorts. Antitumor activity was reported in a 43-year-old female with ER/PR-positive, HER2-negative metastatic breast cancer (Fig. 3). Additional molecular characterization demonstrated PIK3CA exon 20 mutation on circulating nucleic acid analysis and low Ki67 proliferation. She had previously received cyclophosphamide, doxorubicin, and radiotherapy. After 8 weeks of treatment with MK-2206 150 mg QW, a 22% reduction in RECIST measurements of target lesions in the liver lesions, celiac axis, and para-aortic lymph nodes was noted. Posttreatment MRI demonstrated intratumoral necrosis of the liver and bone metastases. In addition, an approximate 36% reduction in CA15-3 was observed, and the patient remained on treatment for a total of 24 weeks. Apart from this patient, two patients with CRPC had RECIST SD for >6 months (range, 6.5–7.5 months).

Discussion

The QOD MTD/RP2D of 60 mg of MK-2206 was generally well tolerated in patients with advanced cancers, as demonstrated previously (14). The MTD/RP2D for QW dosing of MK-2206 was established at 200 mg following the observation of DLTs of rash at the 250 mg and 300 mg QW dose levels of MK-2206. This DLT of rash is consistent with previous reports of AKT inhibition with MK-2206 and other PI3K–AKT pathway inhibitors (14, 35, 36). Overall, the MTD/RP2D of the QW schedule of MK-2206 appeared to be similarly tolerated to QOD dosing (Table 2 and Supplementary Tables S1 and S8; ref. 14). The pulsatile QW dosing of MK-2206 resulted in an intermittent rather than sustained blockade of AKT and downstream substrates observed with QOD dosing, thus potentially permitting some recovery of normal cellular function.

The intermittent dosing of MK-2206 is supported by the observation of pharmacokinetic data demonstrating lower trough concentrations after 200 mg QW dosing, in contrast to 60 mg QOD dosing, relieving sustained drug pressure for periods of time during the QW schedule. Pharmacokinetic parameters following the administration of 90–300 mg MK-2206 QW in cycle 1 indicated no autoinduction of MK-2206 metabolizing enzymes as predicted by in vitro pharmacokinetic studies. Importantly, the terminal half-life of MK-2206 (70–90 hours) is supportive of a QW dosing schedule and $C_{\text{max}}$ values up to 250 mg were below the NOAEL obtained in preclinical toxicology studies, while maintaining $C_{48\text{ h}}$ values above the clinical monotherapy pharmacokinetic target for 70% inhibition of pSer473 AKT. Average steady-state trough MK-2206 concentrations at doses of at least 60 mg QOD, and $C_{48\text{ h}}$, concentration of MK-2206 at doses of at least 90 mg QW were on average greater than the concentrations required for 70% inhibition of pSer473 AKT in whole blood (57 nmol/L), a level identified in preclinical models as associated with antitumor activity for both continuous and intermittent dosing schedules, respectively.

In this study, significant AKT inhibition was demonstrated in paired tumor biopsies and PRP specimens with both schedules of MK-2206. To our knowledge, this is the first demonstration of the feasibility of “real-time” serial PRP sampling in a phase 1 trial setting using quantitative electrochemiluminescence assays (MSD) and ELISA assays (EnVision Technology platform) to monitor multiple phosphoprotein changes in response to a novel molecular therapeutic, such as MK-2206. We have previously demonstrated the use of hair follicles as a surrogate tissue for the measurement of pThr246 PRAS40 pharmacodynamic effects, which confirmed AKT pathway blockade with MK-2206 (14).
In addition, there were differential pharmacodynamic effects observed between QOD and QW dosing of MK-2206, specifically with regards to the phosphorylation levels of pSer473 AKT and downstream substrates pSer9 GSK3β and pThr246 PRAS40 in serial PRP sampling (Fig. 2). For example, while continuous blockade of pSer473 AKT was observed at the QOD MTD of MK-2206, with the QW MTD there was an initial suppression of the phosphorylation signal for at least 96 hours, followed by partial recovery by the 168-hour time point before the next QW dosing time point. The establishment of such a pulsatile QW MTD has enabled MK-2206 to be taken forward in an intermittent rather than continuous schedule for combination studies. This schedule minimized potential MK-2206 toxicities and permitted a wider therapeutic window for the codevelopment of different combination regimens. This is especially critical since modest antitumor efficacy has been observed with MK-2206 monotherapy and other PI3K–AKT pathway inhibitors, although anecdotal examples of patient benefit have been observed in this and other studies (Fig. 3; refs. 14, 36–38).

Figure 3. Best responder. A 43-year-old female with ER/PR-positive, HER2-negative metastatic breast cancer treated with 150 mg QW of MK-2206. A, pharmacodynamic studies demonstrated maximal suppression of pSer473 AKT and its substrate pSer9 GSK3β at 24 hours, followed by a gradual recovery of phosphorylation signals from 48 hours in PRP. Points represent the levels of pharmacodynamic biomarkers as a percentage of the baseline levels. Molecular characterization of circulating nucleic acids demonstrated a PIK3CA exon 20 mutation and low Ki67 proliferation. The patient had previously received treatments including cyclophosphamide, doxorubicin, and radiotherapy. B–C, after 8 weeks of treatment with MK-2206 150 mg QW, there was a 22% reduction in RECIST measurements of her target lesions in the liver metastases, celiac axis, and para-aortic lymph nodes. Posttreatment MRI demonstrated intratumoral necrosis in liver and bone lesions, as evidenced by the high signal on anatomical T2 weighted images (D), and the high ADC values on DWI-MRI (overall lymph node mass ADC was 170 × 10^{-3} \text{ mm}^2/\text{s}; the mean ADC in the areas of necrosis was greater than 200 × 10^{-3} \text{ mm}^2/\text{s}; E). Consistent with these findings, CA15-3 levels decreased by 36% (6,853–4,399 U/mL) and the patient remained on treatment for a total of 24 weeks before developing disease progression.
MK-2206–related hyperglycemia and increased C-peptide levels were observed in most patients in both dosing schedules, consistent with pharmacodynamic inhibition of the AKT target and pathway (36). These elevations in glucose were mainly mild and transient, suggesting effective homeostatic compensation with raised pancreatic insulin/C-peptide release in response to decreased glucose transport and metabolism due to AKT inhibition (36). Although the exact mechanism of MK-2206–induced hyperglycemia has not been fully elucidated, blockade of the PI3K pathway with other similar small-molecule targeted inhibitors appears to be associated with peripheral insulin resistance, increased gluconeogenesis, and/or hepatic glycogenolysis (39).

The modest antitumor effects observed in this study with MK-2206 was despite statistically significant AKT blockade demonstrated in tumor and normal tissue at the MTD of both schedules of MK-2206. Nevertheless, signaling through pSer9 GSK3β and pThr246 PRAS40 was less robustly suppressed, suggesting that effective downstream AKT pathway inhibition and biologic effect were not achieved (Fig. 2). The lack of RECIST antitumor responses may also potentially be due to the episodic recovery of AKT pathway signaling during MK-2206 treatment as suggested by the PRP pharmacodynamic data (Fig. 2). Such pulsatile normalization of phosphorylated protein signals towards baseline levels may nevertheless be important for the transient return of normal cellular functions and minimization of MK-2206–related toxicities. Ultimately, it will be important to define the extent and duration of target and signaling pathway inhibition required for optimal antitumor benefit and an acceptable therapeutic window.

Furthermore, the limited antitumor activity observed may be due to signaling pathway crosstalk and/or disruption of feedback loops following the administration of MK-2206 monotherapy, justifying the development of this drug in molecularly defined patient populations and in combination studies with other antitumor agents (25, 40). It is therefore likely that the future development of AKT inhibitors will involve combination strategies with targeted agents against other rational targets including MEK, ER, AR, and the proteasome, as well as chemotherapies for the treatment of solid tumors. The use of an intermittent schedule of MK-2206 may improve tolerability and widen the therapeutic window of combination regimens. The pulsatile dosing of MK-2206 will also permit a higher degree, albeit shorter duration, of target blockade, which may potentially minimize tumor cell adaptation and eventual secondary drug resistance (25).

MK-2206 has now been assessed in combination with the MEK inhibitor selumetinib (AstraZeneca; AZD6244) in patients with advanced solid tumors, including those with RAS-mutant cancers (41). Critically, the pulsatile QW schedule of MK-2206 improved the tolerability of this combination compared with continuous QOD dosing and enabled a RP2D to be established. Importantly, objective antitumor responses were observed in those with advanced KRAS mutant non–small cell lung carcinoma and ovarian cancers following treatment with this novel drug combination.

The functional imaging study demonstrated for the first time that a combined DCE-MRI, DWI, ISW-MRI, and 1H-MRS protocol may be implemented effectively in a phase I trial within a reasonable scanning time of 45 to 50 minutes. The imaging protocol used in our studies also successfully combined DCE-MRI, DWI, and ISW-MRI data acquisition in the same plane through the same tumor volume, permitting the use of a common region of interest across the different modalities included. Such an approach not only potentially reduces the time required for data analysis, but also offers the opportunity to explore tumor heterogeneity using a multiparameter analysis and multisegmentation approach. In our studies, the reproducibility measured was better with the DWI parameter (<10%) in contrast to DCE-MRI, 1H-MRS, and ISW-MRI parameters (all >30%), which is likely to reflect differences in the tumoral characteristics measured and the range of imaging techniques employed.

Individual examples of DWI and DCE-MRI responses were recorded (Supplementary Figs. S3 and S4); however, a statistically significant cohort change in the image-derived parameters Ktrans, ADC, or Cho/Water ratio after administration of MK-2206 was not observed (Supplementary Fig. S2). These observations may be due primarily to the dose of 60 mg QOD of MK-2206 being insufficient to result in alterations in vascular permeability tumor cellularity, as well as total choline and R2* levels that are detectable on the functional imaging undertaken; a higher MTD of 200 mg QW of MK-2206 may be necessary to achieve this. Such imaging studies should thus be considered in ongoing phase II trials evaluating this dose and schedule of MK-2206. The variability in baseline measurements for the imaging parameters could also mean that the sample size was inadequate to detect small changes. Furthermore, most of the lesions selected for MRI evaluation demonstrated a slow increase in overall size during the study, indicating a lack of antitumor response to MK-2206 monotherapy and suggesting that biologically significant AKT inhibition was possibly not achieved.

In conclusion, we have used detailed safety, pharmacokinetic, and pharmacodynamic studies to establish the MTD/RP2D of MK-2206 in a QW schedule, which results in significant tumor cell target and pathway blockade while demonstrating tolerability for utility in different combination regimens. While we have confirmed impressive AKT blockade in pharmacodynamic studies, we have seen little evidence of antitumor activity. This schedule of MK-2206 has now been taken forward into phase I/II trials involving both monotherapy and combination regimens in a wide range of cancers in defined patient populations (42).

Disclosure of Potential Conflicts of Interest
L. Yan and I. Lupinacci are employees of Merck & Co., Inc. E. Tetteh has ownership interest (including patents) in Merck & Co., Inc. R.A. Bedman is an employee of Daiichi Sankyo and a consultant/advisory board member for the Cancer Institute of New Jersey. D.M. Sullivan and J.S. de Bono are consultants/advisory board members for Merck & Co., Inc. A. Tolcher is an employee of AstraZeneca (including patents) and a consultant/advisory board member for Novartis. The Cancer Institute of New Jersey conducted this research in collaboration with the Cancer Institute of New Jersey. No potential conflicts of interest relevant to this article were reported.
a consultant/advisory board member for Abbvie, Ambit, AP Pharma, AstraZeneca, Astellas, Astex, Bayer, Bind, BioMarin, BioMed Valley Discoveries, Blended, Bristol-Myers Squibb Japan, Celator, Clovis, Curis, Daiuchi Sankyo, Dicerna, Eisai, Eli Lilly, Emergent Product Development, Endo, Galapagos NV, Intellikine, Janssen, MedImmune, Merck & Co., Inc., Merus, Micromet, Nanobiotix, Nektar, Neumedicines, Nexus, Novartis, OnconecRx, Onyx, Pfizer, Pharmacies, Pierre Fabre, ProNai, Proximagen, SuperGen, Symphogen, Vaccines, and Zyngenia. No potential conflicts of interest were disclosed by the other authors.

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References


Interrogating Two Schedules of the AKT Inhibitor MK-2206 in Patients with Advanced Solid Tumors Incorporating Novel Pharmacodynamic and Functional Imaging Biomarkers

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