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ORIGINAL ARTICLE

A phase I trial of MK-2206 and hydroxychloroquine in patients with advanced solid tumors

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Abstract

Purpose Given the evidence that coordinate inhibition of AKT induces autophagy, we studied the combination of the AKT inhibitor, MK-2206 with hydroxychloroquine (HCQ) in patients with advanced solid tumors.

Methods Patients were treated with weekly MK-2206 (135 mg or 200 mg) plus HCQ (200 mg, 400 mg or 600 mg BID).

Results Thirty-five patients were enrolled across 5 dose levels. Two DLTs of grade 3 maculo-papular rash were observed at dose level 2 (MK-2206 200 mg weekly plus HCQ at 400 mg BID) and 1 DLT of grade 3 fatigue at dose level 2B (MK-2206 135 mg weekly plus HCQ 600 mg BID). The maximum tolerated dose (MTD) was declared as dose level 2B. The most common adverse events attributed to MK-2206 were hyperglycemia ($N=18$; 51%), fatigue ($N=17$; 49%), maculo-papular rash ($N=16$; 46%), diarrhea ($N=12$; 34%), anorexia ($N=11$; 31%), and nausea ($N=11$; 31%). Patients experiencing adverse events attributed to HCQ were small in number ($N=13$) and primarily included fatigue ($N=5$; 14%) and maculo-papular rashes ($N=3$; 9%). Statistically significant effects on the pharmacokinetic properties of MK-2206 were observed in combination with HCQ. In addition, the plasma concentrations of HCQ in the combination with MK-2206 were significantly higher than the plasma levels of HCQ as monotherapy in prior studies. The best overall response of stable disease was observed in 5/34 (15%) patients.

Conclusion The combination of MK-2206 and hydroxychloroquine was tolerable, but with substantial number of drug-related AEs and minimal evidence of antitumor activity.

Keywords MK-2206 · AKT · Phase I · Hydroxychloroquine · Autophagy

Introduction

The AKT serine/threonine kinases are key regulators of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway, a critical driver of tumor progression, and are one of the most frequently hyperactivated kinases in human cancers [1]. Dysregulation of this pathway, occurring through upstream hyperstimulation by receptor tyrosine kinases, PI3K and AKT mutations or amplifications, and/or loss of PTEN function [2], has been the focus of significant research efforts to identify and develop inhibitory agents [3–6].

MK-2206 is an allosteric inhibitor of AKT and displays antitumor activity in animal models, both as a single agent and in combination with cytotoxic chemotherapeutics or targeted agents [7]. Combination therapies of MK-2206 with other antitumor agents such as chemotherapeutics and targeted therapies have been hypothesized to be more efficacious than monotherapy [8].

The PI3K/AKT pathway plays an essential role in suppressing autophagy, a drug resistance mechanism that facilitates cancer cell survival during metabolic stress or cancer treatments [9]. Thus, AKT inhibitors such as MK-2206 may

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induce autophagy, as an adaptive response to therapy, limiting the efficacy of the agent [10–14]. Reversal of autophagy by hydroxychloroquine (HCQ), a known inhibitor of lysosomal acidification and the degradation of autophagosomes [15], may prevent the induction of the autophagy survival pathway; this coordinated inhibition of AKT and autophagy may improve therapeutic outcomes. In preclinical models, combining inhibitors of autophagy with MK-2206 produced enhanced antitumor effects and is a rationale for combination trial approach [14, 16–18]. We conducted a Phase I trial to determine the safety of the combination of MK-2206 and HCQ, with the secondary endpoint of assessing the pharmacokinetics of the combination MK-2206 alone and in combination with HCQ (NCT01480154).

Materials and methods

Study design and patients

This was an open-label, single institution phase I trial to determine the MTD of MK-2206 in combination with HCQ in patients with advanced solid tumors (NCT01480154). Secondary objectives included determining the adverse effects and activity of the combination, and assessing the pharmacokinetics (PK) of MK-2206 alone and in combination with HCQ.

Eligible patients included those ≥ 18 years of age with advanced solid tumors, who have undergone treatment with at least one regimen of standard therapy, or had a form of cancer for which no therapy exists. Patients must have measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [19], ECOG performance status ≤ 1, an estimated life expectancy of at least 12 weeks, baseline laboratory values within institutional or investigator specified limits, and recovery from toxicities related to prior therapies. Patients were excluded for the following: concurrent treatment with an investigational agent, active CNS metastases, prolonged QTc or ongoing ventricular dysarrhythmias, uncontrolled diabetes, fasting glucose > 150 mg/dL or HbA1c > 7%, and diabetic patients requiring insulin for glucose control. There was no restriction on the number of prior lines of therapy.

This trial was approved by the Institutional Review Board (IRB) of Rutgers, The State University of New Jersey, New Brunswick. All subjects gave written informed consent. Patient enrollment, medication compliance, toxicity monitoring, specimen collection, and correlative studies were carried out in accordance with IRB regulations.

Study procedures

Patients received treatment on an outpatient basis and a cycle was defined as an interval of 21 days. During cycle 1, patients received oral MK-2206 alone on days 1, 8, and 15, to characterize the PK of MK-2206. HCQ was initiated in combination with MK-2206 starting on cycle 2, day 1. Doses of HCQ were administered orally twice a day (BID) for the 21 day cycle with the morning dose on days 1, 8, and 15 taken 2 h after the MK-2206. HCQ doses were administered utilizing a 200 mg tablet, which is equivalent to 155 mg HCQ base and 250 mg of chloroquine phosphate.

Baseline assessments included medical history, vital signs, physical examination, collection of demographic data, ophthalmology assessments, and serum chemistries. Toxicities were evaluated and graded utilizing the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Radiographic assessments were collected at baseline and every 2 cycles of therapy (every 6 weeks). Response and progression were evaluated using RECIST 1.1 [19].

Dose escalation and dose-limiting toxicities

Dose escalation followed a standard 3 + 3 design. Dosing started at dose level 0 (MK-2206 135 mg weekly and HCQ 200 mg BID) and proceeded to dose level 1 and 2. Dose levels 2A and 2B were later implemented (Table 1). Dose-limiting toxicities (DLTs) were assessed beginning in cycle 2 and were defined as any ≥ grade 3 non-hematologic toxicity (excluding transient electrolyte abnormalities lasting less than 96 h) ≥ grade 3 nausea, vomiting, or diarrhea

Table 1 Dose levels, number of patients treated and drug exposure in various dose cohorts

Dose level	MK-2206 weekly (mg)	HCQ BID (mg)	No. patients (*n*)	Number of evaluable patients (*n*)	No. cycles (mean)
0	135	200	5	3	2.6
1	200	200	4	3	3.1
2	200	400	12	9	2.6
2A	135	400	5	3	2.2
2B	135	600	9	5	3.3

Mean number of cycles treatment refers to combined treatment with MK-2206 and HCQ, and does not include the first cycle treatment with MK-2206 alone

uncontrolled by maximal antiemetic/antidiarrheal therapy, grade 4 neutropenia lasting ≥ 7 day, grade 4 neutropenia and fever of > 38.5 °C, grade 3 neutropenia with > grade 3 infection; thrombocytopenia of any grade if associated with clinically significant bleeding (as determined by the PI or resulting in a transfusion of RBCs); grade 4 thrombocytopenia. Patients not evaluable for DLT/MTD were replaced.

Pharmacokinetics

To evaluate the PK of MK-2206, plasma samples were collected in EDTA vacutainer tubes at predose, 1, 2, 3, 4, 5, 6, and 8 h on C1D15, at 24 h on C1D16, at 48 h on C1D17, and on C2D1 prior to dosing of MK-2206. To evaluate the PK of MK-2206 in combination with HCQ, plasma samples were collected at predose, 1, 2, 3, 4, 5, 6, and 8 h on C2D15, at 24 h on C2D16, and at 48 h on C2D17. Additional plasma samples were collected prior to dosing MK-2206 in each subsequent cycle. Plasma concentrations of MK-2206 were analyzed by LC/MS/MS assay by Merck Research Labs, West Point, PA. HCQ quantitation in plasma was performed by a validated HPLC assay modified from Tett et al. [20].

Statistical analysis

The PK parameters of MK-2206 were determined by a standard two-stage approach with non-compartmental analysis using Winnolin 7.0 (Certara, Princeton, NJ). Statistical analysis was performed using mixed effects modeling to compare the MK-2206 steady-state PK parameter on C1D15 and C2D15. Descriptive statistics were used to characterize patient demographics, toxicity, and tumor response.

Results

Patient characteristics, treatment and disposition

Thirty-five patients were enrolled to this phase I study. Table 2 displays the patient baseline disease characteristics. The most common tumor type was colon ($N = 6$; 17%), followed by ovarian ($N = 4$; 11%), cervical ($N = 4$; 11%), and non-small cell lung cancer (NSCLC) ($N = 4$; 11%). All patients had received prior anti-cancer therapy, including prior systemic chemotherapy ($N = 30$; 86%), radiation therapy ($N = 22$; 63%), and biologics and/or targeted therapy ($N = 24$; 69%). Five patients were treated at dose level 0 (MK-2206 150 mg weekly and HCQ 200 mg BID), 4 patients at dose level 1 (MK-2206 200 mg weekly and HCQ 200 mg BID), 12 patients at dose level 2 (MK-2206 200 mg weekly and HCQ 400 mg BID), 5 patients at dose level 2A (MK-2206 135 mg weekly and HCQ 400 mg BID), and 9 patients at dose level 2B (MK-2206 135 mg weekly and HCQ 600 mg BID).

Table 2 Patient demographics

	Patients ($N = 35$)
Gender, *N* (%)	
Male	13 (37)
Female	22 (63)
Race, *N* (%)	
White	29 (83)
Black or African American	4 (11)
Asian	2 (6)
Ethnicity, *N* (%)	
Hispanic	2 (6)
Non-Hispanic	33 (94)
Age (years)	
Median (range)	65 (47–88)
ECOG Performance Status[a], *N* (%)	
0	10 (29)
1	25 (71)
Primary tumor site, *N* (%)	
Colon	6 (17)
Ovarian	4 (11)
Cervical	4 (11)
Non-small cell lung cancer	4 (11)
Melanoma	2 (6)
Sarcoma	2 (6)
Endometrial	2 (6)
Uterine	2 (6)
Breast	2 (6)
Testicular	1 (3)
Prostate	1 (3)
Pancreas	1 (3)
Head and Neck	1 (3)
Liver	1 (3)
Renal	1 (3)
Adenocarcinoma of endometriosis	1 (3)
Prior therapy[b], *N* (%)	
Systemic chemotherapy	30 (86)
Biologics and/or targeted therapy	24 (69)
Radiation therapy	22 (63)
Immunotherapy	3 (9)
Hormonal therapy	6 (17)

[a] *ECOG* Eastern Cooperative Oncology Group

[b] One subject may fall into more than one category

The mean number of cycles was similar across the different dose cohorts (2.2 to 3.3 cycles; range, 0–11 cycles; Table 1). All 35 patients received one cycle of single agent MK-2206 135 mg weekly (dose level 0, 2A and 2B) or 200 mg weekly (dose level 1 and 2) prior to the combination with HCQ. All but 6 patients (29/35) received ≥ 1

cycle (range 1–11) of combination treatment. Supplementary Table 1 shows the disposition of patients in the study. Thirty-one patients (89%) came off treatment because of progressive disease or relapse; 1 subject withdrew consent following a grade 2 muscle weakness; 2 discontinued treatment due to DLT AEs (both grade 3 maculo-papular rash); and 1 patient expired during C1 due to disease progression. The best overall response of stable disease was observed in 5 of the 34 evaluable patients (15%). Twenty-five patients (25/34; 74%) experienced progressive disease (PD) and eventually discontinued treatment due to PD.

Dose-limiting toxicities and recommended dose

Dose escalation proceeded through dose levels 0 and 1 with 0/3 of the evaluable patients in each dose level experiencing a DLT. At the dose level 2 (MK-2206 200 mg weekly combined with HCQ 400 mg BID), 2/5 evaluable patients had a DLT, a grade 3 maculo-papular rash in both cases that resulted in therapy discontinuation in one case, and dose interruption and then reduction in the other. The dose of MK-2206 was de-escalated to 135 mg weekly and HCQ at 400 mg BID (dose level 2A) with 0/3 evaluable patients experiencing a DLT. Subsequently, dose level 2B evaluated MK-2206 135 mg weekly combined with HCQ 600 mg BID, with 1/6 evaluable patients reporting a DLT (grade 3 fatigue). Thus, dose level 2B (MK-2206 135 mg weekly combined with HCQ 600 mg BID) was declared as the MTD.

Adverse events

Thirty-three patients (94%) experienced toxicities considered related to MK-2206 and 13 (37%) patients experienced toxicities considered related to HCQ (Supplemental Table 2). Drug-related AEs experienced by ≥ 5% of patients are displayed in Table 3. The most common AEs attributable to MK-2206 were hyperglycemia ($N=18$; 51%), maculo-papular rash ($N=16$; 46%) and fatigue ($N=12$; 34%). Maculo-papular rashes of a different nature, in a lenticular pattern, were observed in 3 patients (9%) and were attributed to treatment with HCQ. Other HCQ related toxicities include fatigue ($N=5$; 14%), dehydration ($N=2$; 6%), dry mouth ($N=2$; 6%), and diarrhea ($N=2$; 6%). There were no grade > 3 adverse events attributable to MK-2206 or HCQ in this trial. Thirty-one patients (89%) came off treatment due to progressive disease or relapse; 1 patient withdrew consent following grade 2 muscle weakness; 2 patients discontinued treatment due to DLT AEs (both grade 3 maculo-papular rash); and 1 patient expired during C1 due to disease progression. Nine patients expired while on study, due to disease progression.

Table 3 Drug-related adverse events experienced by ≥ 5% of patients

AE	Patients		Attribution	
			MK-2206	HCQ
	(*n*)	(%)	All (grade 3[a])	All (grade 3[a])
All drug-related AEs	33	94	33	13
Hyperglycemia	18	51	18 (2)	–
Fatigue	17	49	12 (2)	5 (2)
Rash maculo-papular	16	46	16 (6)	3 (0)
Diarrhea	12	34	12 (1)	2 (0)
Anorexia	11	31	11 (1)	–
Nausea	11	31	11 (0)	1 (0)
Lymphocyte count decreased	8	26	8 (6)	–
Hypophosphatemia	8	23	8 (1)	1 (0)
WBC decreased	8	23	8 (0)	–
Vomiting	7	20	7 (0)	–
Anemia	6	17	6 (1)	–
Hypomagnesemia	6	17	6 (0)	–
Platelet count decreased	5	14	4 (0)	–
Creatinine increased	4	11	4 (0)	
Dry skin	4	11	4 (1)	1 (0)
Elevated ALT	3	9	2 (0)	1 (0)
Hyponatremia	3	9	3 (1)	–
Hypertension	3	9	3 (1)	–
Hypocalcemia	3	9	3 (0)	1 (0)
Dry mouth	3	9	3 (0)	2 (0)
Weight loss	3	9	3 (0)	–
Pruritus	2	6	2 (0)	–
Hyperkalemia	2	6	2 (0)	–
Hypoalbuminemia	2	6	2 (1)	–
Dehydration	2	6	2 (0)	2 (0)
Elevated AST	2	6	2 (0)	–
Neuropathy	2	6	2 (1)	–
Neutrophil count decreased	2	6	2 (0)	–
Generalized muscle weakness	2	6	2 (0)	–
Hypotension	2	6	0	2

[a]There were no grade 4 or 5 events related to treatment with MK-2206 or HCQ

Pharmacokinetics

Pharmacokinetic data were available for 21 patients treated with MK-2206 monotherapy and 14 patients with subsequent MK-2206 and HCQ combination therapy. Mean plasma concentration vs. time plots for MK-2206 in mono- and combination therapy are shown in Fig. 1a, b, respectively. The PK parameters of single agent MK-2206 at steady state (day 15, prior to 3rd dose in cycle 1) and MK-2206 in combination with HCQ (day 15, cycle 2; prior

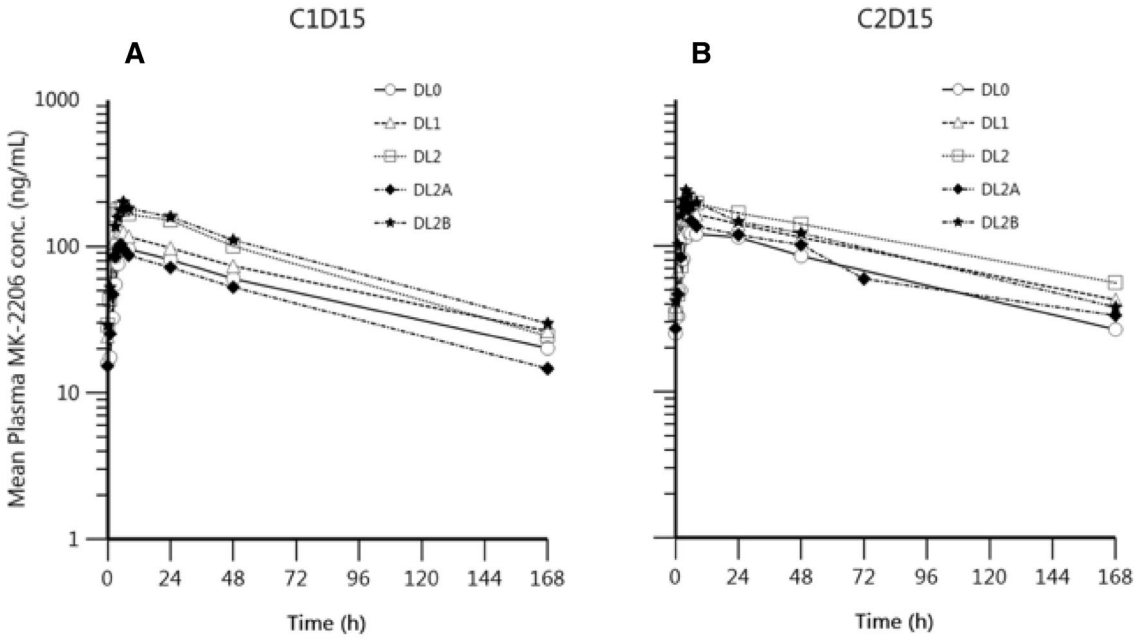

Fig. 1 Plasma MK-2206 concentrations at different dose levels. Pharmacokinetic profiles shown are for **a** MK-2206 monotherapy (C1D15) and **b** MK-2206 in combination with HCQ (C2D15)

to dosing) are shown in Supplementary Table 3. Following weekly administration, MK-2206 was absorbed at a median of 4–7 h to reach C_{max} at different dose levels. No significant difference was observed in T_{max} between monotherapy and combination with HCQ (Supplementary Table 3). There was a large interpatient variability in C_{max} and $AUC_{0-168\ h}$ for MK-2206 in different dose cohorts (data not shown). MK-2206 steady state $AUC_{0-168\ h}$ and C_{max} showed a dose-proportional increase between dose 135 mg and 200 mg dose cohorts. The ratio of $AUC_{0-168\ h}$ geometric means between the combination (C2D15) and monotherapy (C1D15) were 1.26 and 1.46 at the weekly dose of 135 mg and 200 mg, respectively.

The effect of HCQ on MK-2206 PK parameters was assessed with mixed effects modeling on the pooled data of 13 patients with both monotherapy and combination (one patient was excluded from statistical analysis because of MK-2206 dose reduction in treatment). The dose of HCQ (MK-2206 monotherapy vs. combination with HCQ 200, 400, 600 mg BID) had significant effects on C_{max}, terminal $t_{1/2}$, steady state $AUC_{0-168\ h}$ and clearance with the dosage normalization of MK-2206 (p values are 0.012, 0.026, 0.045 and 0.005, respectively). Given the low number of patients in the analysis, more detailed PK studies are needed to confirm the HCQ dose effect on MK-2206 PK parameters. In the MTD dose cohort, the AUCs over the dosing interval at steady state (i.e., $AUC_{0-168\ h}$) were 14,070 ng/mL*h and 16,995 ng/mL*h for MK-2206 monotherapy and MK-2206 in combination with HCQ, respectively.

The mean plasma concentrations of HCQ on C2D15, C2D16, C2D17 and C3D1 at different dose levels are presented in Fig. 2. The steady-state plasma HCQ levels increased in a dose-proportional manner in all dose cohorts (Fig. 2), demonstrating the linear PK characteristics of HCQ in the combination treatment with MK-2206 in cancer patients. At the MTD of the combination, MK-2206 135 mg weekly combined with HCQ 600 mg BID, the steady-state plasma HCQ levels were 584.2 ± 269.2 ng/mL (mean ± SD). There was wide interpatient variability in the plasma HCQ levels (data not shown). In individual patients,

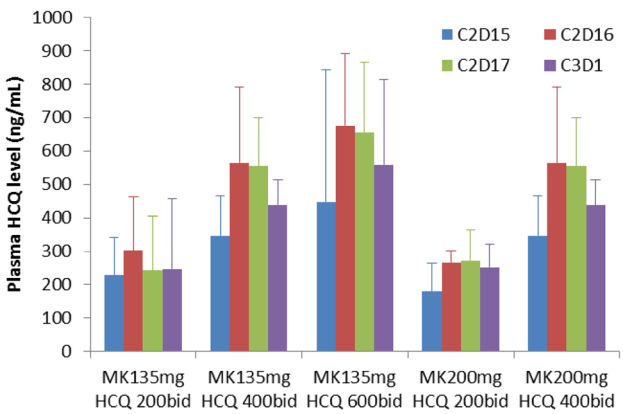

Fig. 2 Plasma HCQ concentrations at different dose levels. Plasma HCQ levels plotted were mean concentrations and the error bars represent standard deviation

the plasma HCQ levels ranged from 100.3 to 1220.5 ng/mL in the dose cohort of MK-2206 135 mg weekly combined with HCQ 600 mg bid. There was no discernable association between drug-related AEs and patients with PK points showing higher concentrations of either drug. For example, AEs experienced by patients with MK-2206 concentrations < 200 ng/mL and ≥ 200 ng/mL were similar in number (112 AEs in 15 patients vs. 58 AEs in 8 patients).

Discussion

As the most commonly activated central pathway in human cancers, several components in the PI3K/AKT/mTOR signaling pathway are highly attractive anti-cancer targets and numerous compounds, including AKT inhibitors, are in clinical development [21]. However, the promise of AKT inhibitors as monotherapy is unrealized due to limited efficacy and narrow therapeutic indices [22]. In phase I clinical trials [23–25], MK-2206 was well tolerated as a single agent with the MTD of 60 mg every other day or 200 mg once weekly. Despite statistically significant AKT blockade in tumor and normal tissue at the MTD of MK-2206, the antitumor effects observed were modest. The limited antitumor activity was hypothesized to be due to signaling pathway crosstalk and/or disruption of feedback loops. Subsequently, MK-2206 has been clinically explored in combination with a variety of antitumor agents [26–30].

To test the hypothesis that blocking autophagy induced by MK-2206 will result in enhanced therapeutic efficacy, we evaluated the combination of MK-2206 and HCQ in patients with a variety of solid tumors. The MTD of the combination in the current study was MK-2206 135 mg weekly and HCQ 600 mg BID. The DLTs observed were grade 3 maculo-papular rash and grade 3 fatigue. The rash associated with the combination in this study is consistent with that of other agents targeting the PI3K-AKT-mTOR pathway and with MK-2206 monotherapy [23–25]. Thus, it is likely the observed rash may represent an on-target effect of AKT inhibition by MK-2206.

The adverse events observed in our study were similar to those reported in prior trials utilizing either MK-2206 [23–25, 31] or HCQ [15, 32, 33]. While there was a significant overlap in AEs with MK-2206 and HCQ, including nausea, vomiting and rash, there was no evidence of exacerbation of expected toxicities in our trial. The most common drug-related adverse events in our study of hyperglycemia ($N = 18$; 51%), fatigue ($N = 17$; 49%), maculo-papular rash ($N = 16$; 46%), diarrhea ($N = 12$; 34% patients), anorexia ($N = 11$; 31%), and nausea ($N = 11$; 31%), were consistent with those reported in studies of MK-2206 as a single agent [23–25, 31] or in combination of with a variety of other agents [26–30, 34–38]. These adverse events were manageable with standard medical and supportive care. The rate of hyperglycemia in the current study is consistent with trials that investigated PI3K/AKT/mTOR inhibitors [39, 40] and may be predicted by the pharmacodynamic inhibition of the AKT target and/or Glut1 transport of glucose into cells [41]. The majority of the treatment related hyperglycemic events were grades 1–2, mostly attributed to MK-2206, but none developed severe metabolic complications.

The PK results of MK-2206 in our study were consistent with data from prior monotherapy or combination studies of MK-2206 [23, 28, 36, 42]. HCQ affected the PK parameters of MK-2206 significantly, suggesting a drug–drug interaction. The mean plasma concentration of HCQ on C3D1 in patients treated with HCQ 200 mg BID in combination with MK-2206 135 mg weekly was 290.77 ng/mL, which is significantly higher than the average HCQ plasma level of 146.26 ± 56.05 ng/mL after 1 cycle treatment of 200 mg BID HCQ as a single agent in patients with hormone-dependent prostate-specific antigen progression after local therapy for prostate cancer [43] and ≥ 3 times higher than the plasma HCQ level (84.58 ng/mL) in the 200 mg BID HCQ alone treatment for 15 days in patients with stage III or IV resectable melanoma (NCT00962845; unpublished data). It is unclear if the drug–drug interaction between MK-2206 and HCQ contributed to the variability, since MK-2206 was reported to be a non-significant inhibitor or inducer of major CYP enzymes ($IC_{50} > 35$ μM for CYP3A4, 2C9 and 2D6) even though CYP450 was involved in the metabolism for both MK-2206 and HCQ [27, 44]. Wide interpatient variability observed in the plasma HCQ level in our study is consistent with such variability reported in single treatment PK studies in rheumatoid arthritis patients [44].

In addition to establishing the maximum tolerated dose of MK-2206 with HCQ, we hoped to gain preliminary evidence of antitumor efficacy using coordinate AKT and autophagy inhibition. However, only 5/35 patients received ≥ 4 cycles of treatment and 30/35 patients were off treatment either due to discontinuation or progressive disease with < 3 cycles of treatment. Though not surprising for a phase I clinical trial population, the high attrition limited our ability to assess the efficacy of MK-2206 combination with HCQ and also precluded analysis of pre-planned autophagy biomarkers in the current study. Nonetheless, our results support the feasibility of safely combining MK-2206 with HCQ at therapeutically relevant doses. While a further exploration of the MK-2206 and HCQ combination in a broader population of cancer patients is not justifiable, it may be worthwhile to consider a limited study in select population using potentially more effective AKT and autophagy inhibitors in tumors, where PI3K/AKT/mTOR pathway aberrations are critical. For example, AZD5363 an ATP-competitive active binding site inhibitor leads to objective responses in clinical trials

of patients whose tumors have E17K AKT1 mutations [45]. It is not clear whether an allosteric ATK inhibitor such as MK-2206 would be effective in trials targeting tumors with AKT1 mutation. However, a future trial of HCQ + AZD5363 might be better than AZD5363 monotherapy for patients whose tumors bear AKT1 mutations. In addition, development of new autophagy targeting drugs that are tolerated better than HCQ and intermittent dosing and/or alternative combinations are key to better understanding of autophagy potential in cancer treatment. However, agents currently available for clinical testing limits the rigorous study of this approach and intermittent schedules have not been tested, to our knowledge, pre-clinically.

In conclusion, the combination of weekly MK-2206 and twice daily HCQ has been shown to be a feasible. Further development of the combination may not be warranted without demonstration of efficacy and significant responses in a limited population defined with autophagy and AKT as key drivers of their tumor.

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Compliance with ethical standards

Conflict of interest JMM: Consulting, Research funding or Advisory Role: Merck, EMD Serono, Pfizer, Genentech. Amgen, Boehringer Ingelheim, Array BioPharma, Immunocore, AstraZeneca, Incyte, Macrogenics, Bristol-Myers Squibb, Sanofi, Novartis and Polynoma; ADK: Research funding or Advisory Role: Novartis and Bayer; JM: Consulting, Research funding or Advisory Role: AstraZeneca, Beyond Spring, Bristol-Myers Squibb, Biohaven, Pfizer; ART: Consulting, Research funding or Advisory Role: Pfizer; JA: on DMC for EMD Serono; RAM: owns stock and employed by Bristol-Myers Squibb; JRB: on the Scientific advisory boards of Prolinx, Oncoceutics and Saladex, and a founder of Xiconic pharmaceutics; EPW: Co-Founder, Vescor Therapeutics; MS: Consulting, Research funding or Advisory Role: Merck, Exelixis, Oncoceutics, Janssen, Medivation/Astellas, Advaxis, Suzhou Kintor, Harpoon, Bristol-Myers Squib, Genocea, Eli Lilly, Nektar, Seattle Genetics and Xencor; All other authors declare that they have no competing interests.

Ethical approval The study was performed in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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