Phase I Trial of the Human Double Minute 2 Inhibitor MK-8242 in Patients With Advanced Solid Tumors

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ABSTRACT

Purpose

To evaluate MK-8242 in patients with wild-type *TP53* advanced solid tumors.

Patients and Methods

MK-8242 was administered orally twice a day on days 1 to 7 in 21-day cycles. The recommended phase II dose (RP2D) was determined on the basis of safety, tolerability, pharmacokinetics (PK), and by mRNA expression of the p53 target gene pleckstrin homology-like domain, family A, member 3 (*PHLDA3*). Other objectives were to characterize the PK/pharmacodynamic (PD) relationship, correlate biomarkers with response, and assess tumor response.

Results

Forty-seven patients received MK-8242 across eight doses that ranged from 60 to 500 mg. Initially, six patients developed dose-limiting toxicities (DLTs): grade (G) 2 nausea at 120 mg; G3 fatigue at 250 mg; G2 nausea and G4 thrombocytopenia at 350 mg; and G3 vomiting and G3 diarrhea at 500 mg. DLT criteria were revised to permit management of GI toxicities. Dosing was resumed at 400 mg, and four additional DLTs were observed: G4 neutropenia and G4 thrombocytopenia at 400 mg and G4 thrombocytopenia (two patients) at 500 mg. Other drug-related G3 and G4 events included anemia, leukopenia, pancytopenia, nausea, hyperbilirubinemia, hypophosphatemia, and anorexia. On the basis of safety, tolerability, PK, and PD, the RP2D was established at 400 mg (15 evaluable patients experienced two DLTs). PK for 400 mg (day 7) showed C_{max} 3.07 μ M, T_{max} 3.0 hours, $t_{1/2}$ (half-life) 6.6 hours, CL/F (apparent clearance) 28.9 L/h, and Vd/F (apparent volume) 274 L. Blood *PHLDA3* mRNA expression correlated with drug exposure ($R^2 = 0.68$; $P < .001$). In 41 patients with postbaseline scans, three patients with liposarcoma achieved a partial response (at 250, 400, and 500 mg), 31 showed stable disease, and eight had progressive disease. In total, 27 patients with liposarcoma had a median progression-free survival of 237 days.

Conclusion

At the RP2D of 400 mg twice a day, MK-8242 activated the p53 pathway with an acceptable safety and tolerability profile. The observed clinical activity (partial response and prolonged progression-free survival) provides an impetus for further study of HDM2 inhibitors in liposarcoma.

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INTRODUCTION

p53 protects cells from malignant transformation and is negatively regulated by the product of the mouse double minute 2 (*MDM2*/*HDM2*) gene.¹ *HDM2* amplification is observed in a variety of tumors, including > 90% of well-differentiated (WD) and dedifferentiated (DD) liposarcoma (LPS) as well as other sarcomas and carcinomas.^{2,3} Restoring p53 function through pharmacologic blockade of the HDM2/p53

protein-protein interaction may represent an anticancer therapeutic strategy.⁴ Tumors that contain wild-type (WT) p53 and overexpress *HDM2* represent ideal candidates for evaluating the clinical potential of HDM2/p53 protein-protein interaction inhibitors.

An exploratory proof-of-mechanism trial demonstrated adequate safety, tolerability, p53 activation, antiproliferative activity, and preliminary antitumor efficacy of the investigational HDM2 inhibitor RG7112 in patients with LPS.⁵ Although promising, the findings were limited by

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the small sample size and overall short duration of treatment. Thus, more definitive studies are needed to further assess the clinical potential of HDM2 inhibitors.

MK-8242 (formerly SCH 900242) is a potent, orally bioavailable, small-molecule inhibitor of the HDM2/p53 protein-protein interaction.⁶ This article describes a phase I dose-ranging study designed to establish the recommended phase II dose (RP2D) of MK-8242 on the basis of safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) in adults with advanced solid tumors with WT *TP53* gene.

PATIENTS AND METHODS

Study Design

This multicenter, nonrandomized, open-label study (Merck & Co., Kenilworth, NJ; Protocol MK-8242-006) was conducted at four centers (three in the United States, one in the United Kingdom) between December 2011 and March 2015. This study had two parts: part 1, dose escalation ($n = 26$) and part 2, RP2D dose confirmation/expansion ($n = 21$); only the dose-escalation and dose-confirmation cohorts were enrolled. The study was terminated in June 2014 for nonsafety reasons (ie, change in oncology portfolio).

Human exposure was determined from a previous phase I trial conducted in healthy volunteers. The selection of the starting dose in this study was on the basis of area under the curve (AUC) comparisons derived from the severely toxic dose in 10% of rodents established in previous studies in rats. The AUC at the severely toxic dose in 10% of rodents was $45.7 \mu\text{M} \cdot \text{hour}$; therefore, one-tenth of this exposure ($4.57 \mu\text{M} \cdot \text{hour}$) was used to define the starting dose. For 60 mg twice a day, considering the accumulation ratio of 1.44 (on the basis of data at 160 mg, assuming that PK is independent of time), the $\text{AUC}_{0-24\text{hour}}$ at steady state was estimated to be $3.1 \mu\text{M} \cdot \text{hour}$; this value is still less than the original estimated exposure of $4.57 \mu\text{M} \cdot \text{hour}$ at 30 mg once daily. Therefore, the starting dosage was established at 60 mg twice a day.

MK-8242 was administered orally at dosages of 60 to 500 mg twice a day on days 1 to 7 of a 21-day cycle until withdrawal criteria were met (Data Supplement). Single-patient cohorts were initially treated with escalating MK-8242 doses in increments of approximately 100%.⁷ The accelerated dose escalation continued until a patient experienced one or more dose-limiting toxicity (DLT), at which point escalation converted to a 3 + 3 design.⁸ In the 3 + 3 portion, dose escalations were done at approximately 40%. The starting dose in the 3 + 3 portion was 120 mg and therefore subsequent doses were 170, 250, 350 mg, and so on. Dose escalation continued until preliminary maximum tolerated dose (MTD) identification, which was based on toxicities observed during cycle one, defined as the highest dose at which fewer than two of six patients experienced a DLT. Part 2 included a dose-confirmation/expansion phase.⁸

All patients provided written informed consent. The protocol was approved by institutional review boards and/or ethics review committees and conducted in accordance with the guidelines on Good Clinical Practice and ethical standards established by the Declaration of Helsinki.

Patients

Eligible patients included men and women at least 18 years of age with histologically confirmed advanced solid tumors lacking effective standard therapies. Major inclusion, exclusion, and withdrawal criteria are listed in the Data Supplement. Patients in part 2 or the 3 + 3 escalation portion of part 1 had tumors with confirmed WT *TP53* (AmpliChip p53 Assay; Roche Molecular Systems, Pleasanton, CA).^{9,10} In addition, all patients had Eastern Cooperative Oncology Group performance status of 0 to 1, adequate organ function, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.¹¹ Patients with LPS who were enrolled in the dose-confirmation phase were required to have confirmed WD or DD histology. Patients with any tumor

type were eligible for the dose-confirmation phase, although the protocol required at least 15 patients with WD- or DD-LPS. Patients who discontinued for nontoxicity reasons were replaced if they did not complete the DLT evaluation period (cycle one).

End Points

The primary end point was to identify DLTs and establish the RP2D. Secondary end points were objective radiologic response rate as defined by RECIST 1.1 and PK/PD profile.¹¹

Assessments

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. DLTs were derived during the first cycle for each dose. A DLT was any grade (G) ≥ 3 , which included drug-related hematologic toxicity lasting ≥ 1 week, thrombocytopenia with bleeding, neutropenia with infection, or nonhematologic toxicity that required medical intervention, led to hospitalization, or persisted ≥ 1 week. The DLT criteria were modified by an amendment to the protocol, which allowed for 72 hours of maximal supportive care measures before G3 nausea, vomiting, diarrhea, or dehydration were considered a DLT. Before this amendment, any G3-or-higher nonhematologic toxicity was considered a DLT; nausea and vomiting were excluded only if untreated.

The preliminary MTD was the highest dose at which $< 33\%$ of patients experienced a DLT. Dose escalation (part 1) continued until a MTD was established, then dose confirmation (part 2) began, followed by response assessment. The RP2D was determined during the dose-confirmation stage and was the dose at which 14 patients were enrolled with ≤ 5 DLTs.

AEs were followed for ≥ 30 days following the last dose of medication through cycle 12. After cycle 12, only serious AEs (SAEs) and events of clinical interest were reported. Patients who discontinued treatment because of AEs were followed until AE resolution and/or stabilization.

The PK profiles of MK-8242 and M16 (an MK-8242 metabolite with similar in vitro potency) were characterized in plasma samples collected on days 1 and 7 of cycle one at 0, 0.5, 1, 2, 4, 6, 8, and 12 hours after the morning dose. On day 7, only one dose was given, with additional samples collected at 24 and 48 hours postdose. Sample handling and analysis were performed as described.⁶

Response Methodology

Computed tomography scans of the chest, abdomen, and pelvis were performed within 28 days before the first dose and before every third cycle. Changes in tumor size were evaluated by RECIST 1.1.¹¹

PD

Optional pre- and post-treatment blood samples and tumor biopsies were collected to evaluate exploratory biomarkers. mRNA expression of the p53 target gene pleckstrin homology-like domain, family A, member 3 (*PHLDA3*) was assessed as a potential biomarker of response.¹²

Statistics

Safety and tolerability were assessed by clinical review of relevant parameters, including AEs. Toxicities were analyzed by dose and grade. AEs were summarized as counts and frequencies by dose. The preliminary MTD was the highest dose at which $< 33\%$ of patients experienced a DLT. Dose escalation (part 1) continued until a MTD was established; then dose confirmation (part 2) began, followed by response assessment. The RP2D was determined during the dose-confirmation stage and was the dose at which 14 patients were enrolled with five or fewer DLTs (Data Supplement).

Response rates were summarized with point estimates and 95% exact CIs using binomial distribution. Progression-free survival (PFS) was the

Table 1. Baseline Demographic Data and Disease Characteristics in Treated Population

Characteristic	No. (%)
No. of patients treated	47
Sex (male)	28 (59.6)
Mean age years $\pm$ SD	61.6 $\pm$ 10.6
ECOG performance status	
0	23 (48.9)
1	24 (51.1)
Race	
White	44 (93.6)
Black or African American	3 (6.4)
<i>TP53</i> mutation status	
Wild type	45 (95.7)
Unknown	2 (4.3)
Primary diagnosis	
Liposarcoma	27 (57.4)
WD	9 (19.1)
DD*	17 (36.2)
Unknown	1 (2.1)
Other tumor†	20 (42.6)

Abbreviations: DD, dedifferentiated; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; WD, well differentiated.

*Includes one patient with DD liposarcoma/sarcomatoid renal cell carcinoma and one patient with DD/WD liposarcoma diagnoses at baseline.

†Includes two patients with unknown tumor diagnoses at baseline.

time from treatment to disease progression or death from any cause. PFS by tumor type (ie, LPS) was estimated by the Kaplan-Meier method.

Role of the Funding Source

Merck & Co. funded this study and was involved in the study design, conduct, data collection, and data analysis.

RESULTS

Patient Characteristics

At the time of trial termination, 48 patients with advanced/refractory solid tumors were enrolled and 47 received treatment across eight doses (Table 1). Twenty-seven patients (57.4%) had a diagnosis of LPS and all except two patients without LPS had a tumor with confirmed WT *TP53*. Of the 47 treated patients, 27 (57.4%) were diagnosed with LPS tumors at baseline: nine patients

(19.1%) and 17 patients (36.2%) were determined to have WD and DD histology, respectively; one patient had an unknown LPS type.

Patient Disposition

Patients were treated with MK-8242 orally twice a day at 60 mg (n = 1), 120 mg (n = 6), 170 mg (n = 3), 250 mg (n = 7), 300 mg (n = 3), 350 mg (n = 6), 400 mg (n = 15), or 500 mg (n = 6). Twelve patients (26%) discontinued as a result of AEs (Data Supplement). All AEs resolved by the end of the follow-up period or before last contact, except for two G3 events of thrombocytopenia (at 250 mg and 350 mg), one event of G4 neutropenia, and one event of G3 hypophosphatemia. One patient with hyperbilirubinemia at the end of treatment was lost to follow-up before bilirubin normalized.

AE Summary

All patients had at least one AE and 46 of 47 patients experienced at least one drug-related AE. Common drug-related AEs included nausea (76.6%), fatigue (70.2%), decreased appetite (48.9%), diarrhea (48.9%), vomiting (38.3%), thrombocytopenia (34.0%), and neutropenia (31.9%). Also, 21 (44.7%) of 47 patients experienced at least one G3 or G4 drug-related AE, including three patients in the 250-mg group (42.9%), three patients in the 350-mg group (50.0%), 10 patients in the 400-mg group (66.7%), and five patients in the 500-mg group (83.3%; Data Supplement). G3 and G4 drug-related AEs included fatigue (10.6%), decreased appetite (2.1%), diarrhea (6.4%), vomiting (2.1%), thrombocytopenia (17.0%), and neutropenia (25.5%).

Sixteen patients (34.0%) experienced an SAE; four of 16 (8.5% of all treated patients) experienced drug-related SAEs. One patient in the 250-mg group who experienced two drug-related G3 SAEs of fatigue and decreased appetite required hospitalization. One patient in each of the 400-mg and 500-mg groups experienced drug-related SAEs of febrile neutropenia, which resulted in hospitalization. One patient who received a dose of 500 mg experienced a drug-related SAE of vomiting that did not require hospitalization. There were no drug-related deaths or other drug-related G4 SAEs.

DLT Summary

Six patients developed DLTs under the original protocol-defined DLT criteria: G2 nausea at 120 mg (missed > 20% dose

Table 2. Number (%) of Patients With DLTs Summarized by Grade and MK-8242 Dosage (N = 47)

Grade	MK-8242 Dosage, Twice a Day								Total No. of Patients With DLTs Within Each Grade Across All Dosages
	60 mg (n = 1)	120 mg (n = 6)	170 mg (n = 3)	250 mg (n = 7)	300 mg (n = 3)	350 mg (n = 6)	400 mg (n = 15)	500 mg (n = 6)	
1	0	0	0	0	0	0	0	0	0
2	0	1 (16.7)	0	0	0	1 (16.7)	0	1 (16.7)	3 (6.4)
3	0	0	0	1 (14.3)	0	0	0	2 (33.3)	3 (6.4)
4	0	0	0	0	0	1 (16.7)	2 (13.3)	2 (33.3)	5 (10.6)
5	0	0	0	0	0	0	0	0	0
Total no. of patients with DLTs at each dosage, across all grades									
	0	1 (16.7)	0	1 (14.3)	0	2 (33.3)	2 (13.3)*	5 (83.3)*	11

NOTE. Toxicity grade is on the basis of Common Terminology Criteria for Adverse Events, version 4.0. Only the highest reported grade for a given DLT was counted for each patient. All values are expressed as the number of subjects (%).

Abbreviation: DLT, dose-limiting toxicity.

*There were two DLTs observed under the revised criteria: two DLTs at 400 mg and two DLTs at 500 mg.

Fig 1. Geometric mean plasma concentration time curves for MK-8242 and metabolite M16 following treatment on days 1 and 7 of cycle one. Only one dose was administered on day 7 to support characterization of pharmacokinetics.

in cycle one); G3 fatigue at 250 mg; G2 nausea at 350 mg (missed > 20% dose in cycle one); G4 thrombocytopenia at 350 mg; and G3 vomiting and G3 diarrhea at 500 mg (Table 2). The DLT criteria were subsequently revised via protocol amendment to permit medical management of GI toxicities < 72 hours before they were considered to be DLTs. Under the new criteria, four patients developed an additional five DLTs: G4 neutropenia at 400 mg (n = 1), G4 thrombocytopenia at 400 mg (n = 1), G4 thrombocytopenia and G2 neutropenia (n = 1, with two DLTs), and G4 thrombocytopenia (n = 1) at 500 mg. The dose of 400 mg was identified as

the protocol-defined RP2D, because only two DLTs were observed in 15 treated patients (using the revised GI DLT criteria).

PK and PD

The MK-8242 and M16 PK profiles are shown in Fig 1 and the Data Supplement. The PK exposure goal of $25.0 \mu\text{M} \cdot \text{hour}$ for MK-8242 ($2 \times$ day 7 geometric mean $\text{AUC}_{0-12\text{hour}}$) was exceeded for doses of 350 mg (projected daily exposure of $26.2 \mu\text{M} \cdot \text{hour}$), 400 mg ($33.0 \mu\text{M} \cdot \text{hour}$), and 500 mg ($26.9 \mu\text{M} \cdot \text{hour}$), and additionally at 300 mg ($25.2 \mu\text{M} \cdot \text{hour}$) for MK-8242 plus M16 (active metabolite).

Fig 2. Individual exposure relationships between plasma pharmacokinetics (PK) and plectroin homology-like domain, family A, member 3 (*PHLDA3*) mRNA expression in plasma on day 7 for MK-8242 and MK-8242 plus M16. Linear model fits (blue line) and 95% CI (light blue shading) are shown for illustration purposes only. Vertical and horizontal gold lines represent the preclinically established exposure targets for PK and pharmacodynamics (PD), respectively. AUC, area under the curve.

Fig 3. Swimmer plot for the 47 treated patients, with time since treatment (months) shown for each patient. Blue lines indicate patients with LPS; gray lines indicate patients with non-LPS tumor types. Stable disease, partial response, and progressive disease are denoted by blue, gold, and gray circles, respectively. The time of treatment discontinuation is noted by red open circles. The open red circles denote discontinuation of treatment. The dose level for each patient and type of LPS (WD or DD) is juxtaposed next to the relevant bars. DD, dedifferentiated; LPS, liposarcoma; WD, well differentiated.

On day 7, the $AUC_{0-12\text{hour}}$ increased supra-proportionally versus dose for MK-8242 and MK-8242 plus M16 (Data Supplement). The accumulation ratio from day 1 to day 7 was 1.04 for MK-8242 and 2.26 for M16. The ratio of M16 to MK-8242 exposure was 0.26 on day 1 and 0.54 on day 7. Two patients in the 500-mg group were co-administered dexamethasone as an antiemetic, and the MK-8242 $AUC_{0-12\text{hour}}$ decreased by 53% and 34%, respectively, from day 1 to 7, presumably as a result of induction of *CYP3A4*. The use of dexamethasone was subsequently prohibited in this study.

In the 300-, 400-, and 500-mg groups, mRNA expression of the p53 target gene *PHLDA3* was well correlated with MK-8242 ($R^2 = 0.68$; $P < .001$) and MK-8242 plus M16 ($R^2 = 0.71$; $P < .001$) exposure (Fig 2). On day 7, 12 of 15 patients met the *PHLDA3* exposure target of 90-fold·hour, including 11 of 13 patients who received 400 mg. For patients with both valid PK and PD on day 7, 12 of 14 exceeded both their PK and PD exposure goals.

Tumor Response

Postbaseline tumor measurements were obtained in 41 patients. Six patients did not have postbaseline scans as the result of

discontinuation of dosing within 7 days of the first dose for the following reasons: AEs ($n = 3$); progressive disease ($n = 1$); protocol violation ($n = 1$); and withdrawal ($n = 1$).

Three partial responses (PRs) were observed in the 47 patients who received at least one dose of MK-8242 (Fig 3). The overall response rate was 6.4% for the entire study population (95% CI, 1.3 to 17.5) and 11.1% in the 27 patients with LPS (95% CI, 2.4 to 29.2). One PR at 400 mg was maintained for at least 121 days; no response assessment data were collected after cycle 11 and the patient remained on study for 17 cycles. In total, five patients with WD LPS had prolonged stable disease ($n = 4$) or prolonged PR ($n = 1$), ranging from 231 to 419 days. In addition, one patient with WD LPS had stable disease until discontinuation from the study as the result of thrombocytopenia in day 56 of cycle three, but subsequently developed a confirmed PR at day 130 in the absence of additional treatments. Tumor progression rates for these patients before study entry were not assessed because of the variability in imaging frequency and prior treatments.

Kaplan-Meier curves of PFS for the overall treated population and the subgroup of patients with LPS are shown in Fig 4. The

median PFS was 3.4 months (95% CI, 3.2 to 7.8) for the overall population, 7.8 months (95% CI, 3.3 to not-estimable) for patients with LPS, and 2.9 months (95% CI, 1.2 to 3.3) for patients without LPS. The median PFS for the DD LPS cohort was 5.5 months (95% CI, 2.1 to not-estimable), whereas the median PFS for the WD LPS cohort was not reached in this study.

DISCUSSION

MK-8242 monotherapy had an acceptable safety and toxicity profile in patients with advanced solid tumors. Six patients developed six DLTs during cycle one of treatment across the dosing range, including fatigue (250 mg), diarrhea (500 mg), nausea (120 mg and 350 mg), vomiting (500 mg), and thrombocytopenia

(350 mg). After revision of the DLT criteria to permit medical management of GI-related toxicities before considering such AEs as DLTs, four patients developed five DLTs of neutropenia and thrombocytopenia at 400 mg and 500 mg. The protocol-defined RP2D was identified as 400 mg because only two of 15 patients treated at this dose had DLTs under the new GI-management criteria.

Overall, the observed pattern of GI and hematologic toxicity was consistent with previous studies of MK-8242 and other HDM2 inhibitors.^{13,14} The most common drug-related AEs were lower than G3 and manageable; however, there was one drug-related SAE of vomiting (500 mg), two drug-related SAEs of febrile neutropenia (400 mg and 500 mg), and two G3 drug-related SAEs of decreased appetite and fatigue in one patient at the 250-mg dose. There were no G5 toxicities.

Fig 4. Kaplan-Meier estimates of progression-free survival are presented for the overall population and the subgroup of patients with LPS. The inset shows Kaplan-Meier estimates of progression-free survival for the WD and DD LPS cohorts. (*) The upper bound of median survival time could not be reliably estimated. DD, dedifferentiated; LPS, liposarcoma; WD, well differentiated.

Exposure of MK-8242 and its active metabolite, M16, were supra-dose-proportional (greater than linear); the M16 accumulation ratio and ratio to MK-8242 indicate a significant role for this metabolite. Adequate PK and PD exposure for single-agent activity, on the basis of preclinical models, was achieved. The daily PK exposure target was exceeded for MK-8242 at doses of 350 mg, 400 mg, and 500 mg, and at 300 mg for MK-8242 plus M16. At the 300 mg, 400 mg, and 500 mg doses, *PHLDA 3* expression exceeded target for 12 of 15 patients and was well correlated with PK exposure. Taken together, these findings indicate that MK-8242 doses $\geq$ 300 mg activate the p53 pathway and corroborate the selection of 400 mg as the RP2D.

This study demonstrated modest single-agent activity of MK-8242, specifically in patients with LPS with a confirmed WT *TP53* gene. Among 41 evaluable patients, the best objective responses included PRs in three patients with LPS (two WD, one DD) who were administered doses of 250 mg, 400 mg, and 500 mg. In addition, five patients with LPS who received 400 mg had prolonged stable disease for at least seven cycles.

The median PFS for patients with LPS was 7.8 months (approximately 34 weeks or 237 days). However, considering that one-third of patients with LPS had WD tumors, for which the median PFS was not reached, it is difficult to determine whether this prolonged disease control rate is an effect of MK-8242 or reflects the potentially indolent nature of this tumor subtype. Although prestudy progression rates were not available for reference, the median PFS of patients with DD LPS (5.5 months) suggests that MK-8242 treatment contributed, at least in part, to prolonged disease control. Acknowledging that direct comparisons cannot be made across studies because of variations in study designs and patient populations, it is notable that the median PFS for patients with progressive WD or DD LPS in two phase II studies of a CDK4 inhibitor was only 18 weeks (approximately 126 days).¹⁵⁻¹⁸ Taken together, the results of this MK-8242 study confirm and extend those of a prior study,⁵ demonstrating preliminary evidence of antitumor activity of HDM2/p53 protein-protein inhibitors in patients with LPS.

Although the preclinical target exposure was reached and there was induction of expression of *PHLDA3*, a biomarker of p53 transcriptional activity, the degree of clinical activity was less than was expected on the basis of preclinical models, particularly in terms of tumor regression. This discordance may be the result of any of many factors. For example, prior treatment of the study population may have selected for a more resistant disease state; intratumoral exposure may be less than the exposure determined by plasma assays; and although the dose and schedule may have permitted induction of p53 transcriptional activity, it may have

been insufficient for p53-mediated induction of apoptosis. Furthermore, it is unclear if MK-8242 may show greater efficacy when administered in combination with other traditional chemotherapeutic agents.

In conclusion, evidence of single-agent clinical efficacy was observed in patients with LPS. Using a 7 days-on/14 days-off dosing schedule, MK-8242 was generally safe at doses up to 400 mg; the RP2D was 400 mg twice a day on the basis of the observed safety, tolerability, and PK/PD profiles. The potential for GI and hematologic toxicities, particularly neutropenia and thrombocytopenia, should be considered when designing future clinical studies. Tolerance and activity of MK-8242 in combination with conventional chemotherapeutic agents or following alterations in monotherapy schedule (including lower doses/longer term or higher doses/shorter term) are important. Future studies are needed to more thoroughly evaluate the potential clinical activity, safety, and tolerability of HDM2 inhibitors in patients with advanced solid tumors. Particularly important for combination therapy studies is careful attention to hematologic toxicities because similar effects are elicited by standard chemotherapeutic agents and may be exacerbated when administered with HDM2 inhibitors. The results of this study should aid in improving future trial designs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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