A Phase I Trial of the Human Double Minute 2 Inhibitor MK-8242 in Subjects with Advanced Solid Tumors

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ABSTRACT

Purpose

Evaluate MK-8242 in subjects with wild-type (WT) *TP53* advanced solid tumors.

Patients and Methods

MK-8242 was administered p.o. BID, days 1-7 in 21-day cycles. The recommended phase 2 dose (RP2D) was determined based on safety/tolerability, pharmacokinetics (PK), and by mRNA expression of the p53 target *PHLDA3*. Other objectives were characterizing PK/pharmacodynamic (PD) relationship, correlation of biomarkers with response, and tumor response.

Results

47 subjects received MK-8242 across 8 doses ranging from 60-500 mg. Initially, 6 subjects developed DLTs (G2/nausea at 120 mg; G3/fatigue at 250 mg; G2/nausea and G4/thrombocytopenia at 350 mg; G3/vomiting and G3/diarrhea at 500 mg). DLT criteria were revised to allow for management of gastrointestinal toxicities and dosing was resumed at 400 mg, and 4 additional DLTs were observed (G4/neutropenia and G4/thrombocytopenia at 400 mg; G4/thrombocytopenia [2 subjects] at 500 mg). Other drug-related G3-4 events included anemia, leukopenia, pancytopenia, nausea, hyperbilirubinemia, hypophosphatemia, and anorexia. Based on safety/tolerability, PK, and PD, the RP2D was established at 400 mg (i.e., 2 DLTs/15 evaluable subjects). PK for 400 mg (Day 7) showed C_{max} 3.07 μM, T_{max} 3.0 hr, $t_{1/2}$ 6.6 hr, CL/F 28.9 L/hr, and Vd/F 274 L. Blood *PHLDA3* mRNA expression correlated with drug exposure (R^2=0.68, P<0.001). In 41 subjects with post-baseline scans, 3 achieved PR (all with liposarcoma, at 250 mg, 400 mg and 500 mg), 31 showed SD, 8 had PD. In total, 27 subjects with liposarcoma had a median progression-free survival of 237 days.

Conclusions

At the RP2D of 400 mg BID, MK-8242 activates the p53-pathway with an acceptable safety/tolerability profile. The observed clinical activity (PR and prolonged PFS) provides impetus for further study of HDM2 inhibitors in liposarcoma. (ClinicalTrials.gov NCT01463696)

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) liposarcomas (LPS) as well as other sarcomas and carcinomas.[2,3] Restoring p53 function through pharmacologic blockade of HDM2:p53 protein-protein interaction may represent an anti-cancer therapeutic strategy.[4] Tumors that contain wild type (WT) p53 and also 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, anti-proliferative activity and preliminary anti-tumor efficacy of the investigational HDM2 inhibitor RG7112 in patients with LPS.[5] Although promising, the findings were limited by small size and overall short treatment duration. 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 report describes a Phase I dose-ranging study designed to establish the recommended phase 2 dose (RP2D) of MK-8242 based on safety/tolerability/pharmacokinetics (PK)/pharmacodynamics (PD) in adults with advanced solid tumors with WT *TP53* gene.

PATIENTS AND METHODS

Study Design

This multi-center, non-randomized, open-label, study (Merck & Co., Inc., Kenilworth, NJ; Protocol MK-8242-006; NCT01463696) was conducted at 4 centers (3 USA, 1 United Kingdom) between

December 2011 and March 2015. This study had 2 parts: dose escalation (Part 1; N=26) and RP2D dose confirmation/expansion (Part 2; N=21); only the dose escalation and dose confirmation cohorts were enrolled. The study was terminated in June 2014 for non-safety reasons (i.e., 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 based on area under the curve (AUC) comparisons derived from the severely toxic dose in 10% of rodents (STD10) established in previous rat studies. The AUC at the rodent STD10 was 45.7 uM*hr; therefore, 1/10 of this exposure (4.57 uM*hr) was used to define the starting dose. For 60 mg BID, considering the accumulation ratio of 1.44 (based on data at 160 mg, assuming PK is time-independent), the $AUC_{0\text{-}24hr}$ at steady state was estimated to be 3.1 uM*hr; a value that is still less than the original estimated exposure of 4.57 uM*hr at 30 mg QD. Therefore, the starting dose was established at 60 mg BID.

MK-8242 was dosed orally at doses from 60-500 mg BID on days 1-7 of a 21-day cycle until withdrawal criteria were met (**Appendix Fig A1**). Single subject cohorts were initially treated with escalating MK-8242 doses in increments of approximately 100%.[7] The accelerated dose escalation continued until a subject experienced ≥1 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 ~40%. The starting dose in the 3+3 portion was 120 mg and therefore subsequent doses were 170, 250, 350 mg, etc. Dose escalation continued until preliminary MTD identification based on toxicities observed during Cycle 1, defined as the highest dose at which <2/6 subjects experienced a DLT. Part 2 included a dose confirmation/expansion phase.[8]

All subjects 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.

Subjects

Eligible subjects included males and females, ≥18 years with histologically confirmed advanced solid tumors lacking effective standard therapies. Major inclusion/exclusion/withdrawal criteria are shown in **Appendix Table A1**. Subjects 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 (ECOG) performance status of 0-1, adequate organ function, and at least one measurable lesion as defined by RECIST 1.1.[11] Patients with LPS who were enrolled in the dose confirmation phase were required to have confirmed WD or DD histology. Subjects with any tumor type were eligible for dose confirmation phase, although the protocol required ≥15 subjects with WD/DD LPS. Subjects discontinued for non-toxicity reasons were replaced if they did not complete the DLT evaluation period (Cycle 1).

Endpoints

The primary endpoint was to identify DLTs and establish the RP2D. Secondary endpoints were objective radiological response rate as defined by RECIST v1.1 and PK/PD profile.[11]

Assessments

AEs were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) v4.0. DLTs were derived during the first cycle for each dose. A DLT was any ≥G3 drug-related hematological toxicity lasting ≥1 week; thrombocytopenia with bleeding; neutropenia with infection; or non-hematological toxicity requiring medical intervention/leading to hospitalization/persisting for ≥1 week. The DLT criteria were modified by an amendment to the protocol which allowed for 72 hrs of maximal supportive care measures before Grade 3 nausea, vomiting, diarrhea,

or dehydration were considered a DLT. Prior to this amendment, any non-hematologic toxicity ≥ Grade 3 was considered a DLT; nausea and vomiting were excluded only if untreated.

The preliminary MTD was the highest dose at which <33% of subjects experienced a DLT. Dose escalation/Part 1 continued until an MTD was established then the 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 last dose of medication through Cycle 12. After Cycle 12, only serious AEs (SAEs) and events of clinical interest were reported. Subjects discontinued due to AEs were followed until AE resolution/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 1 at 0, 0.5, 1, 2, 4, 6, 8, and 12hr after the morning dose. On Day 7, only one dose was given, with additional samples at 24 and 48hr post-dose. Sample handling and analysis were performed as described.[6]

Response Methodology

CT scans of the chest, abdomen, and pelvis were performed within 28 days prior to the first dose and prior to every third cycle. Changes in tumor size were evaluated by RECIST 1.1.[11]

Pharmacodynamics

Optional pre-/post-treatment blood samples and tumor biopsies were collected to evaluate exploratory biomarkers. mRNA expression of the p53 target Pre-Homology-Like Domain, Family A, Member 3 (*PHLDA3*) was assessed as a potential biomarker of response.[12]

Statistics

Safety/ tolerability were assessed by clinical review of relevant parameters including AEs. Toxicities were analyzed by dose/grade. AEs were summarized as counts and frequencies by dose. The preliminary MTD was the highest dose at which <33% of subjects experienced a DLT. Dose escalation/Part 1 continued until an MTD was established then the 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. [Refer to **Appendix, Supplemental Methods** for additional information.]

Response rates were summarized with point estimates and 95% exact confidence intervals (CI) using binomial distribution. PFS was the time from treatment to disease progression or death from any cause. PFS by tumor type (i.e., LPS) was estimated by Kaplan-Meier method.

Role of the Funding Source

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

RESULTS

Subject Characteristics

At the time of trial termination, 48 subjects with advanced/refractory solid tumors were enrolled and 47 received treatment across 8 doses (**Table 1)**. Twenty-seven subjects (57%) had a diagnosis of LPS and all but 2 non-LPS subjects had a tumor with confirmed WT *TP53*. Of the 47 treated patients, 27 (57.4%) were with LPS tumors at baseline: 9 (19.1%) and 17 (36.2%) were determined to have WD and DD histologies, respectively while 1 patient had an unknown LPS type.

Subject Disposition

Subjects were treated with MK-8242 orally BID at 60 (n=1), 120 (n=6), 170 (n=3), 250 (n=7), 300 (n=3), 350 (n=6), 400 (n=15), or 500 mg (n=6). Twelve subjects (26%) discontinued due to AEs (**Appendix Table A2**). All AEs resolved by the end of the follow-up period/before last contact, except for 2 G3 events of thrombocytopenia (250 mg and 350 mg), 1 event of G4 neutropenia and 1 event of G3 hypophosphatemia. One subject with hyperbilirubinemia at treatment end was lost to follow-up before bilirubin normalized.

AE Summary

All subjects had ≥1 AE and 46/47 subjects experienced ≥1 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, 21/47 subjects (44.7%) experienced ≥1 G3-4 drug-related AE, including 3 subjects each in the 250 mg (42.9%) and 350 mg (50.0%) groups, 10 subjects in the 400 mg group (66.7%) and 5 subjects in the 500 mg group (83.3%) (**Appendix Table A3**). Grade 3-4 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 subjects (34.0%) experienced an SAE; 4/16 (8.5%) experienced drug-related SAEs. One subject in the 250 mg group experienced 2 drug-related G3 SAEs of fatigue and decreased appetite requiring hospitalization. One subject in each of the 400 mg and 500 mg groups experienced drug-related SAEs of febrile neutropenia resulting in hospitalization. One subject dosed at 500 mg experienced a drug-related SAE of vomiting not requiring hospitalization. There were no drug-related deaths or other drug-related G4 SAEs.

DLT Summary

Initially, 6 subjects developed DLTs (G2/nausea [missed >20% dose in Cycle 1] at 120 mg; G3/fatigue at 250 mg; G2/nausea [missed >20% dose in Cycle 1] and G4/thrombocytopenia at 350 mg; G3/vomiting and G3/diarrhea at 500 mg) under the original protocol-defined DLT criteria (**Table 2**). The DLT criteria were subsequently revised via protocol amendment to permit medical management of gastrointestinal toxicities <72 hrs prior to considering such toxicities as DLTs. Under the new criteria, 4 subjects developed an additional 5 DLTs (G4/neutropenia [n=1] and G4/thrombocytopenia [n=1] at 400 mg; G4/thrombocytopenia and G2/neutropenia [n=1 with 2 DLTs]; G4/thrombocytopenia [n=1] at 500 mg). The 400 mg dose was identified as the protocol-defined RP2D, since only 2 DLTs were observed in 15 treated subjects (using the revised gastrointestinal DLT criteria).

Pharmacokinetics/Pharmacodynamics

The MK-8242 and M16 PK profiles are shown in **Fig 1**; **Appendix Table A3**. The PK exposure goal of 25.0 uM*hr for MK-8242 (2xDay 7 geometric mean [GM]$AUC_{0\text{-}12hr}$) was exceeded for doses of 350 mg (projected daily exposure of 26.2 µM*hr), 400 mg (33.0 µM*hr), and 500 mg (26.9 µM*hr), and additionally at 300 mg (25.2 µM*hr) for MK-8242+M16 (active metabolite). On Day 7, $AUC_{0\text{-}12hr}$ increased supra-proportionally versus dose for MK-8242 and MK-8242+M16 (**Appendix Fig A2**). The

accumulation ratio from Day 1 to 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 subjects were co-administered dexamethasone as an antiemetic in the 500 mg group, and MK-8242 $AUC_{0\text{-}12hr}$ decreased 53% and 34%, respectively, from Day 1 to 7, presumably due to induction of *CYP3A4*. 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<0.001) and MK-8242+M16 (R^2=0.71; P<0.001) exposure (**Fig 2)**. On Day 7, 12/15 patients met the *PHLDA3* exposure target of 90 fold*hr including 11/13 patients receiving 400 mg. For patients with both valid PK and PD on Day 7, 12/14 exceeded both their PK/PD exposure goals.

Tumor Response

Post-baseline tumor measurements were obtained in 41 subjects; 6 did not have post-baseline scans due to discontinuation of dosing within 7 days of first dose (n=3 due to AE; n=1 progressive disease; n=1 protocol violation; n=1 withdrawal).

Three PRs were observed in the 47 subjects who received ≥1 dose of MK-8242 (**Fig 3**). ORR was 6.4% for the entire study population (95% CI: 1.3, 17.5), and 11.1% in the 27 subjects with LPS (95% CI: 2.4, 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 subject remained on study for 17 cycles. In total, 5 subjects with WD LPS had prolonged stable disease (n=4) or prolonged PR (n=1) ranging from 231 to 419 days. In addition, one subject with WD LPS had stable disease until discontinuation from the study due to thrombocytopenia in Cycle 3/Day 56, but subsequently developed a confirmed PR at Day 130 while not receiving additional treatments. Tumor progression rates for these subjects prior to 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 subjects with LPS are shown in **Fig 4**. Median PFS for the overall population was 3.4 months (95% CI: 3.2, 7.8), 7.8 months (95% CI: 3.3, 'not estimable') for subjects with LPS, and 2.9 months (95% CI: 1.2, 3.3) for subjects without LPS. The PFS for the DD LPS cohort was 5.5 months (95% CI: 2.1, 'not estimable') while 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 subjects developed 6 DLTs during Cycle 1 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 gastrointestinal-related toxicities prior to considering such AEs DLTs, 4subjects developed 5 DLTs of neutropenia and thrombocytopenia at 400 mg and 500 mg. The protocol-defined RP2D was identified as 400 mg since only 2 out of 15 subjects treated at this dose had DLTs under the new gastrointestinal-management criteria.

Overall, the observed pattern of gastrointestinal and hematologic toxicity was consistent with previous studies of MK-8242 and other HDM2 inhibitors.[13,14] The most common drug-related AEs were <G3 and manageable; however, there was 1 drug-related SAE of vomiting (500 mg), 2 drug-related SAEs of febrile neutropenia (400 mg and 500 mg), and 2 G3 drug-related SAEs of decreased appetite and fatigue in one subject at the 250 mg dose. Of note, there were no G5 toxicities.

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/PD exposure for single agent activity, based on preclinical models, were achieved. The daily PK exposure target was exceeded for MK-8242 at 350 mg, 400 mg, and 500 mg doses; and at 300 mg for MK-8242+M16. At the 300 mg, 400 mg, and 500 mg doses, *PHLDA 3* expression exceeded target for 12/15 patients, and was well correlated with PK exposure. Taken together, these findings indicate that MK-8242 doses at 300 mg and above activate the p53 pathway, and corroborate the selection of the 400 mg dose as the RP2D.

This study demonstrated modest single-agent activity of MK-8242, specifically in LPS subjects with a confirmed WT *TP53* gene. Among 41 evaluable subjects, the best objective responses included

PRs in 3 subjects with LPS (2 WD,1 DD) dosed at 250 mg, 400 mg, and 500 mg. Additionally, 5 subjects (LPS receiving 400 mg) had prolonged stable disease for ≥7 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 pre-study 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 DDLPS in two phase 2 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 anti-tumor activity of HDM2:p53 protein-protein inhibitors in LPS patients.

Although the preclinical target exposure was reached and there was induction of expression of *PHLD3A*, a biomarker of p53 transcriptional activity, the degree of clinical activity was less than expected based on preclinical models, particularly in terms of tumor regression. This discordance may be due to 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 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 summary, evidence of single-agent clinical efficacy was observed in LPS patients. Using a 7 day-on/14 day-off dosing schedule, MK-8242 was generally safe at doses up to 400 mg and the RP2D

was 400 mg BID based on the observed safety/tolerability, PK and PD profiles. The potential for gastrointestinal and hematological 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 needed to more thoroughly evaluate the potential clinical activity and safety/tolerability of HDM2 inhibitors in patients with advanced solid tumors. Particularly important for combination therapy studies is careful attention to hematologic toxicities since similar effects are elicited by standard chemotherapeutic agents and may be exacerbated when administered together with HDM2 inhibitors. The results of this study should aid improved trial design for future studies.

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Table 1. Baseline demographics and disease characteristics in treated population

	n (%)
Number treated	**47**
Gender (male)	28 (59.6%)
Age (years) - mean ± SD	61.6 ± 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%)
TP53 Mutation status	
Wild-Type	45 (95.7%)
Unknown	2 (4.3%)
Primary Diagnosis	
Liposarcoma	27 (57.4%)
WD	9 (19.1%)
DD[a]	17 (36.2%)
Unknown	1 (2.1%)
Other Tumor[b]	20 (42.6%)

DD= dedifferentiated; ECOG= Eastern Cooperative Oncology Group; WD = well differentiated

[a]Includes 1 subject with 'DD liposarcoma/sarcomatoid renal cell carcinoma' and 1 subject with 'DD/WD liposarcoma' diagnoses at baseline

[b]Includes 2 subjects with unknown tumor diagnoses at baseline

Table 2. Number (%) of subjects with DLTs[a] summarized by Grade and MK-8242 dose

MK-8242 dose	**60 mg BID n=1**	**120 mg BID n=6**	**170 mg BID n=3**	**250 mg BID n=7**	**300 mg BID n=3**	**350 mg BID n=6**	**400 mg BID n=15**	**500 mg BID n=6**	**Total no. subjects with DLTs within each Grade, across all dose levels N=47**
Grade 1	0	0	0	0	0	0	0	0	0
Grade 2	0	1 (16.7%)	0	0	0	1 (16.7%)	0	1 (16.7%)	3 (6.4%)
Grade 3	0	0	0	1 (14.3%)	0	0	0	2 (33.3%)	3 (6.4%)
Grade 4	0	0	0	0	0	1 (16.7%)	2 (13.3%)	2 (33.3%)	5 (10.6%)
Grade 5	0	0	0	0	0	0	0	0	0
Total no. of subjects with DLTs at each dose level, across all Grade	**0**	**1 (16.7%)**	**0**	**1 (14.3%)**	**0**	**2 (33.3%)**	**2 (13.3%)[b]**	**5 (83.3%)[b]**	**11**

DLT= dose limiting toxicity; Grade= toxicity grade based on CTCAE version 4.0
[a]Only the highest reported grade for a given DLT is counted for each individual subject
[b]There were 2 DLTs observed under the revised criteria: 2 DLTs at 400 mg and 2 DLTs at 500 mg

Figure Legends

Fig 1. Geometric mean plasma concentration-time curves for MK-8242 and metabolite M16 following treatment on Days 1 and 7 of Cycle 1. Only one dose was administered on Day 7 to support characterization of pharmacokinetics (PK).

Fig 2. Individual exposure relationships between plasma pharmacokinetics (PK) and PHLDA3 mRNA expression in plasma on Day 7 for MK-8242 and MK-8242+M16. Linear model fits (black line) and 95% CI (shaded gray) are shown for illustration purposes, only. Vertical and horizontal dotted lines represent the pre-clinically established exposure targets for PK and pharmacodynamics (PD), respectively.

Fig 3. Treatment response: Swimmer plot for the 47 treated patients, with time since therapy (months) shown for each patient. Blue line indicates LPS patient; orange line indicates non-LPS tumor types. Stable disease, partial response and progressive disease are denoted by filled pink, green, and red dots. The last completed cycle of treatment prior to discontinuation is noted in red font. The open blue circles denote discontinuation of treatment. The dose level for each subject and type of LPS (WW/DD) is juxtaposed next to the relevant bars.

Fig 4. Kaplan-Meier estimates of progression-free survival (PFS) presented for the overall population and the subgroup of patients with LPS. The inset shows Kaplan-Meier estimates of PFS for the WD and DD LPS cohorts.

Table legends

Table 1. Baseline demographics and disease characteristics

Table 2. Number (%) of subjects with DLTs[a] summarized by Grade and MK-8242 dose

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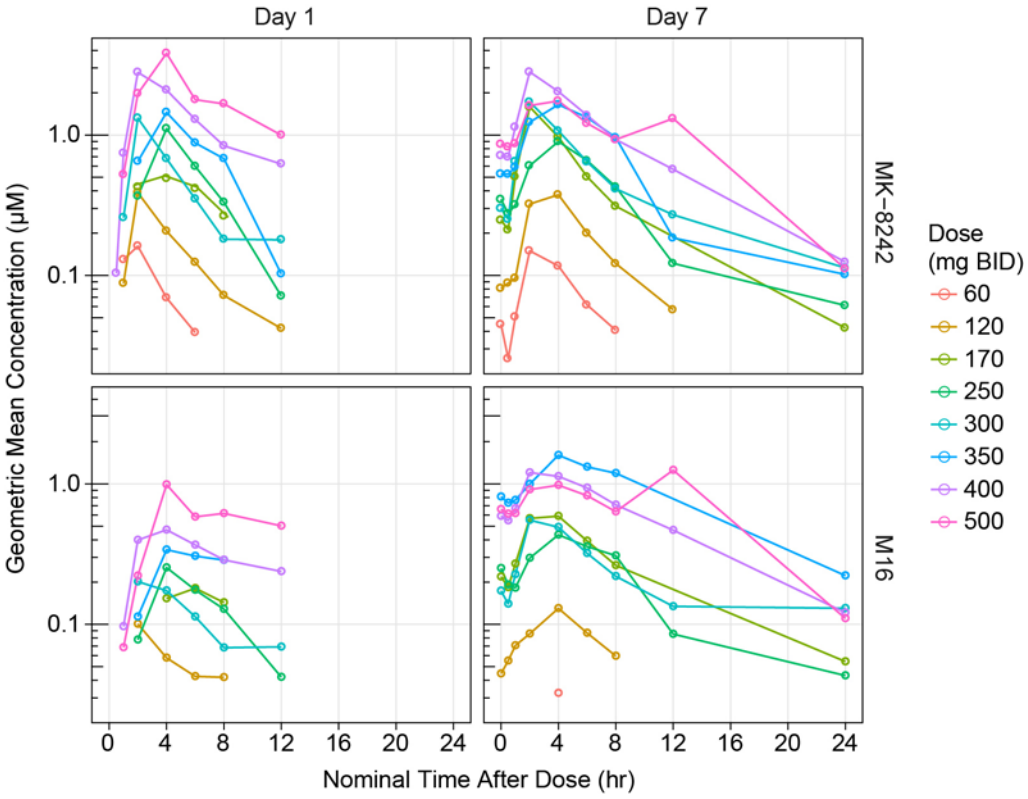

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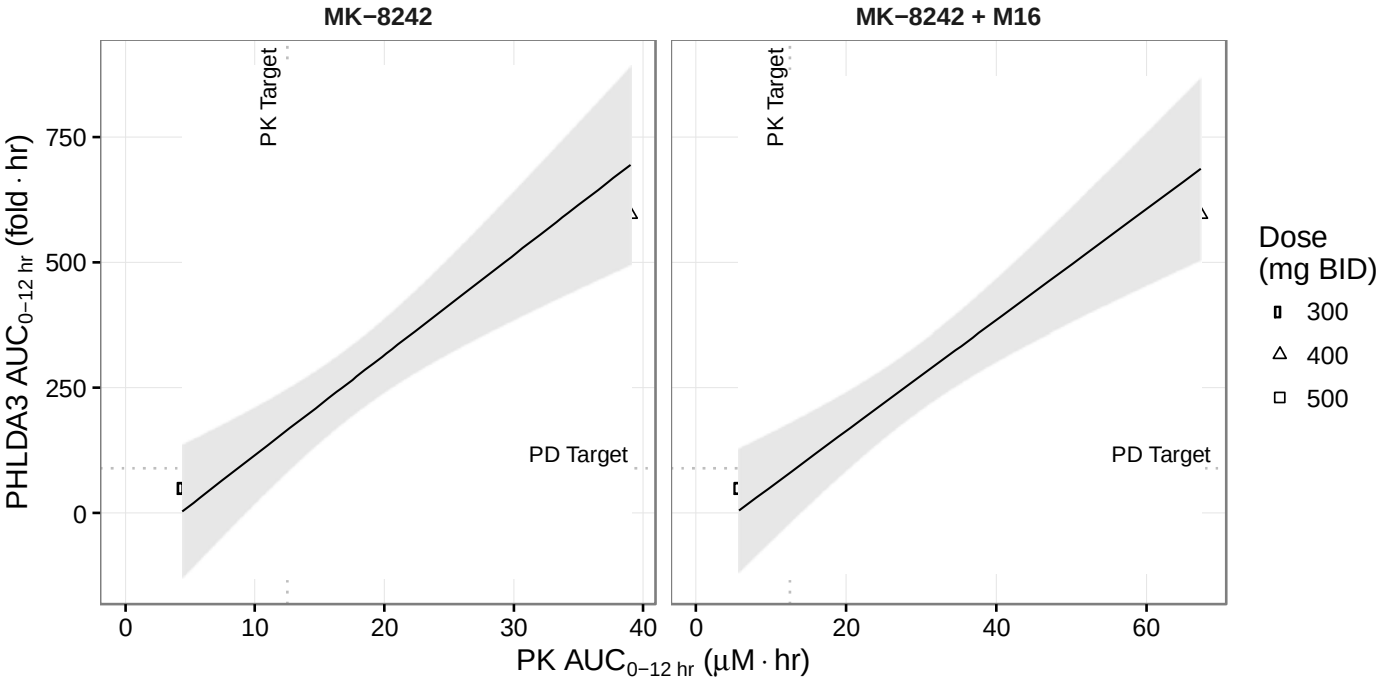

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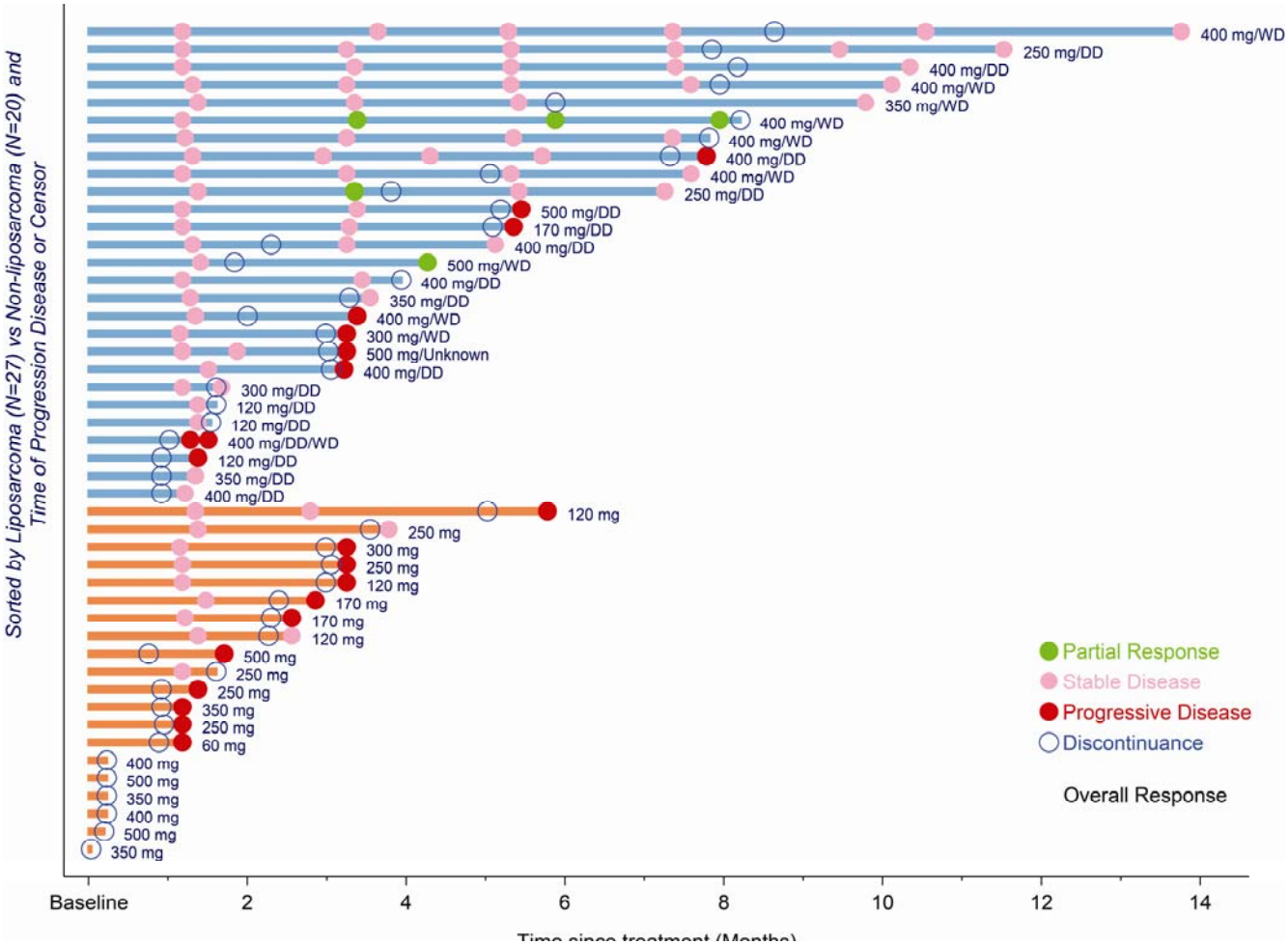

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