original reports

A First-in-Human Phase I Study of Milademetan, an MDM2 Inhibitor, in Patients With Advanced Liposarcoma, Solid Tumors, or Lymphomas

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abstract

PURPOSE This study evaluated the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of milademetan, a small-molecule murine double minute-2 (MDM2) inhibitor, in patients with advanced cancers.

PATIENTS AND METHODS In this first-in-human phase I study, patients with advanced solid tumors or lymphomas received milademetan orally once daily as extended/continuous (days 1-21 or 1-28 every 28 days) or intermittent (days 1-7, or days 1-3 and 15-17 every 28 days) schedules. The primary objective was to determine the recommended phase II dose and schedule. Secondary objectives included tumor response according to standard evaluation criteria. Predefined analyses by tumor type were performed. Safety and efficacy analyses included all patients who received milademetan.

RESULTS Between July 2013 and August 2018, 107 patients were enrolled and received milademetan. The most common grade 3/4 drug-related adverse events were thrombocytopenia (29.0%), neutropenia (15.0%), and anemia (13.1%). Respective rates at the recommended dose and schedule (260 mg once daily on days 1-3 and 15-17 every 28 days, ie, 3/14 days) were 15.0%, 5.0%, and 0%. Across all cohorts (N = 107), the disease control rate was 45.8% (95% CI, 36.1 to 55.7) and median progression-free survival was 4.0 months (95% CI, 3.4 to 5.7). In the subgroup with dedifferentiated liposarcomas, the disease control rate and median progression-free survival were 58.5% (95% CI, 44.1 to 71.9) and 7.2 months overall (n = 53), and 62.0% (95% CI, 35.4 to 84.8) and 7.4 months with the recommended intermittent schedule (n = 16), respectively.

CONCLUSION An intermittent dosing schedule of 3/14 days of milademetan mitigates dose-limiting hematologic abnormalities while maintaining efficacy. Notable single-agent activity with milademetan in dedifferentiated liposarcomas has prompted a randomized phase III trial (MANTRA).

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

TP53, which encodes the p53 protein and is referred to as the guardian of the genome,[1] is the most frequently (approximately 50%) mutated gene in human cancers.[2,3] In normal cells, p53 functions as a critical tumor suppressor and corrects DNA damage through a myriad of mechanisms that result in cell-cycle arrest and repair or, when irreparable, apoptosis or senescence.[1,4] Tumors that do not harbor *TP53* mutations inactivate wild-type p53 through other mechanisms.[2] One such mechanism is overexpression of murine double minute-2 (MDM2), a negative regulator of p53, through *MDM2* gene amplification or other mechanisms.[2] *MDM2* amplification is found in 3.5%-7.0% of human cancers,[5,6] although there is no accepted copy-number threshold for this alteration. Some tumors, such as dedifferentiated liposarcomas (DDLPS)[5-7] and intimal sarcomas,[8,9] are characterized by *MDM2* gene amplification and lack of *TP53* mutations.[7] Inhibition of MDM2 is a logical target to restore p53 tumor suppressor activity in DDLPS or other tumors with wild-type *TP53* and MDM2-dependency.

Milademetan (RAIN-32) is a selective small-molecule inhibitor of the MDM2-p53 interaction and activates p53 function at nanomolar concentrations in vitro.[10] In preclinical studies, milademetan induced p53-dependent apoptosis in human cancer cell lines and demonstrated antitumor activity in xenograft models of tumors with functional, wild-type p53.[10] This first-in-human study was conducted to evaluate the safety and tolerability of milademetan using various

CONTEXT

Key Objective

To determine the recommended dosing schedule for MDM2 inhibitor milademetan in solid tumors, and which tumor types are responsive to this agent.

Knowledge Generated

This first-in-human phase I clinical trial established a recommended dose and schedule of milademetan 260 mg once daily for three of 14 days that mitigated on-target toxicities associated with MDM2 inhibitors in comparison with more continuous dosing regimens. Milademetan also demonstrated evidence of antitumor activity, particularly in dedifferentiated liposarcoma, which is characterized by the presence of both *MDM2* gene amplification and wild-type *TP53*.

Relevance *(R.G. Maki)*

This phase I trial of an MDM2 inhibitor was novel in its use of an intermittent schedule, and demonstrated acceptable toxicity and activity in comparison with earlier trials of this class of anticancer agents, in which toxicity with continuous administration limited the ability to treat patients. *MDM2* amplification is characteristic in well-differentiated and dedifferentiated liposarcoma and is also observed in a small fraction of other solid tumors, diagnoses that may benefit from this or similar agents.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD.

dosing schedules, as well as the pharmacokinetics, pharmacodynamics, and preliminary efficacy of milademetan in patients with advanced solid tumors or lymphomas. Dose expansion of the phase II dose and intermittent dosing schedule were evaluated in DDLPS.

PATIENTS AND METHODS

Study Design

This two-part, open-label, phase I study of milademetan was conducted at five US institutions (ClinicalTrials.gov identifier: NCT01877382). Part 1 (dose-escalation) investigated the safety and tolerability of milademetan to determine the maximum tolerated dose (MTD) or recommended phase II dose. Secondary objectives were to evaluate tumor response, pharmacokinetics, and pharmacodynamic effects on growth differentiation factor-15 (GDF15). Part 2 (dose-expansion) was conducted to confirm the safety and tolerability of milademetan in patients with advanced melanoma or diffuse large B-cell lymphoma (DLBCL), but was closed after it was determined that it could not meet objectives under the dosing schedule used. Instead, the decision was made to explore alternative dose schedules as part of an expanded dose-escalation phase in DDLPS.

The study Protocol was approved by institutional review boards at participating sites. The study was conducted in compliance with the Declaration of Helsinki, and all patients provided written informed consent before participating in the study.

Patients

Patients were age $\geq$ 18 years with histologically or cytologically documented advanced solid tumors or lymphomas. Patients with tumor types associated with a high prevalence of *MDM2* amplification or overexpression (eg, DDLPS) were preferentially enrolled in part 1. Testing to determine *MDM2* amplification status was not required nor collected. Patients with tumors harboring known *TP53* mutations were excluded. Confirmation of *TP53* status at screening was encouraged, but not required before milademetan dosing. Patients subsequently confirmed to have *TP53* mutations were permitted to remain on study if they were deriving clinical benefit. Patients had an Eastern Cooperative Oncology Group performance status of 0-1, and adequate bone marrow function (platelet count $\geq 100 \times 10^9$/L, hemoglobin $\geq$ 9.0 g/dL, absolute neutrophil count $\geq 1.5 \times 10^9$/L), blood-clotting, and renal and hepatic function.

Treatment

Milademetan was given orally once daily on a 28-day cycle at a starting dose of 15 mg. Extended schedule A (days 1-21) and continuous schedule B (days 1-28) were tested initially, followed by intermittent schedules C (days 1-7) and D (days 1-3 and 15-17; Data Supplement, online only). Methodologic details for dose-escalation, stopping rules for MTD determination, and dose-limiting toxicities (DLTs) are provided in the Data Supplement. Treatment was continued until disease progression, consent withdrawal, or unacceptable toxicity. For patients with adverse events but showing clinical benefit, dose reductions by one dose level were permitted once toxicity had returned to grade $\leq$ 1. Treatment was withdrawn in patients requiring $>$ 4 weeks ($>$ 8 weeks in those showing clinical benefit) to recover from acute toxicities.

Procedures and Outcomes

Methods for tumor and safety assessments, pharmacokinetics, pharmacodynamics, and biomarkers are described in the Data Supplement. Efficacy end points were objective

response rate (ORR), time to response, response duration, disease control rate (DCR), and progression-free survival (PFS); definitions are provided in the Data Supplement.

Statistical Analysis

A Bayesian logistic regression method using escalation with overdose control[11] was used to guide dose selection (Data Supplement). MTDs for each schedule were based on the Bayesian logistic regression model, together with an overall assessment of safety, pharmacokinetic, and pharmacodynamic information. At least 21 patients were required to be evaluable for DLT for an accurate estimate of MTD.[12-14]

The primary analysis was done after final database lock (December 2, 2020), after which the study was closed. Data were analyzed by descriptive statistical methods. Safety and efficacy analyses included patients who had received any amount of milademetan. Exact 95% binomial CIs were provided for response rates. Time-to-event variables were summarized using the Kaplan-Meier method and 95% CIs were computed using the Brookmeyer-Crowley method. For the dose-escalation phase, efficacy end points were further analyzed by dose cohort and by cancer type (ie, DDLPS *v* nonliposarcoma). As a complementary approach in DDLPS, growth rates of target tumors before starting milademetan were analyzed by capturing tumor measurements by local reading of ≥ 2 scans from medical records, if available. All analyses were performed using SAS (version 9.2; SAS Institute Inc).

RESULTS

Between July 2013 and August 2018, 107 patients were enrolled (dose-escalation, n = 87; dose-expansion, n = 20) and received milademetan (Data Supplement). At the time of analysis, all patients had discontinued study treatment, primarily because of disease progression (n = 74; 69.2%). However, five (4.7%) patients who had not progressed at the time of study termination continued treatment with milademetan via a post-trial access program.

Patients were predominantly White (n = 90; 84.1%), with a median age of 61 (range, 25-88) years (Table 1). The most common cancers were DDLPS (n = 53; 49.5%), melanoma (n = 22; 20.6%), and lymphoma (n = 4; 3.7%). Most patients were heavily pretreated; 66 (61.7%) patients had received ≥ 3 prior systemic cancer therapies. Seventy-one (66.4%) patients had *TP53*-wild-type tumors, 13 (12.1%) had confirmed *TP53*-mutant tumors, and the remainder were unknown or unevaluable. Four (3.7%) patients withdrew consent before treatment.

Dose and Extended/Continuous Dosing

Dose-escalation steps for each schedule are depicted in the Data Supplement. Initial dose escalation was performed using extended dosing with short interruptions (21/28 days). No DLTs occurred at 15, 30, or 60 mg, but hematologic DLTs were reported with 120-mg (grade 4 thrombocytopenia, n = 1), 160-mg (grade 4 neutropenia, grade 2 thrombocytopenia, and leukopenia, n = 1; grade 3 nausea and vomiting, n = 1), and 240-mg doses (grade 4 thrombocytopenia, n = 1; Data Supplement); the MTD was determined to be 120 mg. Delayed adverse events requiring prolonged dose interruptions were observed beyond the DLT-assessment period (cycle 1), prompting investigation of a 90-mg dose (schedules of 21/28 days and 28/28 days) to define a hematologically safe regimen. However, myelosuppression and thrombocytopenia leading to dose modifications were also observed at the 90-mg dose.

Dose and Intermittent Dosing

When extended/continuous schedules had excessive toxicity, alternative intermittent dosing schedules were explored (7/28 days and days 1-3 and 15-17/28 days) on the basis of population pharmacokinetics and exposure-toxicity analyses.[15] DLTs occurred with 120 mg once daily on 7/28 days (grade 2 fatigue and malaise, n = 1) and with 340 mg once daily on days 1-3 and 15-17/28 days (grade 3 thrombocytopenia, n = 1). After an evaluation of all available data, the dose of 260 mg once daily for the intermittent schedule of days 1-3 and 15-17 every 28 days was recommended for future development of milademetan.

Safety

The median duration of milademetan treatment was 2.6 (range, 0.1-50.9) months; treatment exposure by schedule is presented in the Data Supplement.

Across all dose schedules (N = 107), the most common drug-related all-grade adverse events were nausea (72.0%), thrombocytopenia (60.7%), fatigue (44.9%), and anemia (35.5%; Table 2). Most nonhematologic adverse events were of mild-to-moderate severity regardless of dosing schedule, whereas the severity of hematologic abnormalities, particularly thrombocytopenia, was dependent on dose density. Respective rates of all-grade and grade 3/4 drug-related thrombocytopenia were 44.7% and 15.8% with intermittent schedules (n = 38) versus 69.6% and 36.2% with extended/continuous schedules (n = 69); similar trends were observed for other hematologic events (Table 2). Dose reductions and dose interruptions for drug-related thrombocytopenia with intermittent schedules were required in eight (21.1%) and six (15.8%) patients, respectively, and with extended/continuous schedules in 16 (23.2%) and 24 (34.8%), respectively. Drug-related serious adverse events were reported in 0% of patients with intermittent versus eight (11.6%) patients with extended/continuous schedules (Data Supplement). There were no reports of severe bleeding with milademetan, or drug-related adverse events associated with a fatal outcome.

For the recommended dose and schedule (260 mg once daily on days 1-3 and 15-17/28 days; n = 20), most adverse events were of mild-to-moderate severity. Drug-related grade 3 thrombocytopenia occurred in three (15.0%) patients, with no grade 4 events. Dose reductions

TABLE 1. Baseline Demographics and Characteristics

Characteristic	DDLPS (n = 53)	All Patients (N = 107)
Age, years	62 (37-88)	61 (25-88)
Sex		
Male	29 (54.7)	54 (50.5)
Female	24 (45.3)	53 (49.5)
Weight, kg	80.5 (42.4-135.3)	75.8 (41.7-146.7)
Race		
White	45 (84.9)	90 (84.1)
Asian	4 (7.5)	9 (8.4)
Black or African American	3 (5.7)	6 (5.6)
Other	1 (1.9)	2 (1.9)
ECOG PS		
0	23 (43.4)	43 (40.2)
1	30 (56.6)	64 (59.8)
Cancer type		
DDLPS	53 (49.5)	53 (49.5)
Melanoma	0 (0.0)	22 (20.6)
Lymphoma	0 (0.0)	4 (3.7)
Osteosarcoma	0 (0.0)	3 (2.8)
Other[a]	0 (0.0)	25 (23.4)
Cancer stage		
I	0 (0.0)	2 (1.9)
II	8 (15.1)	11 (10.3)
III	4 (7.5)	8 (7.5)
IV	40 (75.5)	84 (78.5)
TP53 mutation status[b]		
Wild-type	34 (64.2)	71 (66.4)
Mutant	7 (13.2)	13 (12.1)
Indeterminate/unknown	12 (22.6)	23 (21.5)
No. of prior cancer therapies		
0	17 (32.1)	17 (15.9)
1	7 (13.2)	10 (9.3)
2	8 (15.1)	14 (13.1)
3 or more	21 (39.6)	66 (61.7)

NOTE. Data are number (%) or median (range).

Abbreviations: DDLPS, dedifferentiated liposarcoma; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Included three patients with adenoid cystic carcinoma; two patients each with cholangiocarcinoma, intimal sarcoma, breast cancer, or adenocarcinoma (no primary site); and one patient each with bone sarcoma, leiomyosarcoma, colorectal, esophageal, neuroendocrine, non–small-cell lung cancer, prostate, renal, small-cell lung cancer, synovial sarcoma, maxillary sinus adenocarcinoma, adenocarcinoma of the ampulla, adrenocortical carcinoma, and carcinoid tumor (unspecific site).

[b]*TP53* genotype testing was performed centrally; limit of quantification, 12.5%.

for drug-related adverse events were required in eight (40.0%) patients (thrombocytopenia, n = 7; vomiting, n = 1). Dose interruptions (median duration, 21 days/episode; range, 5-62 days/episode) for drug-related adverse events were required in five (25.0%) patients (thrombocytopenia, n = 2; thrombocytopenia and nausea, n = 1; thrombocytopenia and conjunctivitis, n = 1; neutropenia, n = 1). No drug-related adverse events led to treatment discontinuation. Safety data by cohort are presented in the Data Supplement.

Pharmacokinetics

Milademetan exposure increased in a dose-proportional manner over the 15- to 340-mg dose range (Data Supplement). Pharmacokinetics by schedule on day 1 cycle 1 are summarized in the Data Supplement. For the recommended dose (260 mg once daily on days 1-3 and 15-17/28 days), median time to maximum serum concentration was 3.1 hours. Geometric mean maximum serum concentration and area under the curve$_{0\text{-}24}$ were 1,503 ng/mL and 18,432 ng*h/mL on day 1 of cycle 1, respectively. Geometric mean apparent total clearance was 15.6 L/h and terminal elimination half-life was 10.0 hours (sampling up to 24 hours after dose).

Pharmacodynamics

All 107 patients were included in the evaluation of serum GDF15. Milademetan increased serum GDF15 levels with increasing plasma concentrations across all schedules (Fig 1A). A mean increase of up to 10-fold over baseline in serum GDF15 levels was evident within 24 hours after the first dose.

Depending on the biomarker, 43-50 evaluable tumor samples were available for immunochemistry at baseline (Fig 1B). Milademetan increased expression levels of p53, p21, and MDM2 on day 8 of cycle 1; six evaluable samples were available on day 8 of cycle 1.

Activity

Part 1 (dose-escalation). The dose-escalation population (n = 87), which encouraged enrollment of patients with tumor types with a high prevalence of *MDM2* amplification or overexpression, was stratified by tumor type (DDLPS, n = 53; nonliposarcoma, n = 34). Central testing was performed on a subset of patients to confirm *MDM2* status. Twenty-two of 53 (41.5%) patients with liposarcoma were tested; median *MDM2* copy number was 28.6 (range, 7.5-115.0). All 22/22 (100%) tested patients had *MDM2* gene amplification (*MDM2* copy number > 6), which is consistent with all patients with liposarcoma in the trial having the DDLPS subtype.

Two patients with DDLPS and two patients with nonliposarcoma tumors (synovial sarcoma, n = 1; small-cell lung cancer, n = 1) achieved partial responses (Table 3). ORR and DCR among patients with DDLPS were 3.8% (2/53; 95% CI, 0.5 to 13.0) and 58.5% (95% CI, 44.1 to 71.9), respectively, and among patients with nonliposarcoma tumors were 5.9% (2/34; 95% CI, 0.7 to 19.7) and 32.4% (95% CI, 17.4 to 50.5), respectively. Patients

TABLE 2. Drug-Related TEAEs by Milademetan Dosing Schedule (reported in ≥ 5% of patients)

	Extended/Continuous Schedules[a]		Intermittent Schedules[b]							
	Schedule A or B (n = 69)		Schedule C or D (n = 38)		Schedule D (n = 29)		Schedule D (260 mg)[c] (n = 20)		Total (N = 107)	
Drug-Related TEAE	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Any drug-related TEAE	66 (95.7)	39 (56.5)	33 (86.8)	9 (23.7)	25 (86.2)	5 (17.2)	18 (90.0)	4 (20.0)	99 (92.5)	48 (44.9)
Nausea	50 (72.5)	2 (2.9)	27 (71.1)	0 (0.0)	20 (69.0)	0 (0.0)	16 (80.0)	0 (0.0)	77 (72.0)	2 (1.9)
Thrombocytopenia	48 (69.6)	25 (36.2)	17 (44.7)	6 (15.8)	13 (44.8)	4 (13.8)	9 (45.0)	3 (15.0)	65 (60.7)	31 (29.0)
Fatigue	30 (43.5)	2 (2.9)	18 (47.4)	1 (2.6)	12 (41.4)	0 (0.0)	8 (40.0)	0 (0.0)	48 (44.9)	3 (2.8)
Anemia	30 (43.5)	14 (20.3)	8 (21.1)	0 (0.0)	5 (17.2)	0 (0.0)	4 (20.0)	0 (0.0)	38 (35.5)	14 (13.1)
Decreased appetite	26 (37.7)	1 (1.4)	10 (26.3)	0 (0.0)	9 (31.0)	0 (0.0)	7 (35.0)	0 (0.0)	36 (33.6)	1 (0.9)
Leukopenia	27 (39.1)	8 (11.6)	8 (21.1)	0 (0.0)	7 (24.1)	0 (0.0)	5 (25.0)	0 (0.0)	35 (32.7)	8 (7.5)
Diarrhea	25 (36.2)	0 (0.0)	10 (26.3)	0 (0.0)	9 (31.0)	0 (0.0)	5 (25.0)	0 (0.0)	35 (32.7)	0 (0.0)
Vomiting	19 (27.5)	2 (2.9)	16 (42.1)	1 (2.6)	13 (44.8)	1 (3.4)	10 (50.0)	1 (5.0)	35 (32.7)	3 (2.8)
Neutropenia	22 (31.9)	15 (21.7)	3 (7.9)	1 (2.6)	2 (6.9)	1 (3.4)	2 (10.0)	1 (5.0)	25 (23.4)	16 (15.0)
Dysgeusia	15 (21.7)	0 (0.0)	3 (7.9)	0 (0.0)	3 (10.3)	0 (0.0)	3 (15.0)	0 (0.0)	18 (16.8)	0 (0.0)
Alopecia	8 (11.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (7.5)	0 (0.0)
Constipation	5 (7.2)	0 (0.0)	3 (7.9)	0 (0.0)	3 (10.3)	0 (0.0)	2 (10.0)	0 (0.0)	8 (7.5)	0 (0.0)
Dizziness	4 (5.8)	0 (0.0)	2 (5.3)	0 (0.0)	1 (3.4)	0 (0.0)	1 (5.0)	0 (0.0)	6 (5.6)	0 (0.0)
Dry mouth	5 (7.2)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.6)	0 (0.0)
Lymphopenia	5 (7.2)	4 (5.8)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.6)	4 (3.7)
Stomatitis	5 (7.2)	0 (0.0)	1 (2.6)	0 (0.0)	1 (3.4)	0 (0.0)	1 (5.0)	0 (0.0)	6 (5.6)	0 (0.0)

NOTE. Data are n (%). All patients receiving at least one dose of milademetan were included in the safety analyses.
Abbreviation: TEAE, treatment-emergent adverse event.
[a]Schedule A: milademetan once daily on days 1 to 21 every 28 days; schedule B, milademetan once daily on days 1 to 28.
[b]Schedule C: milademetan once daily on days 1 to 7 every 28 days; schedule D: milademetan once daily on days 1-3 and 15-17 every 28 days.
[c]Recommended dose schedule.

with DDLPS showed clear tumor progression before study entry followed by suppression of growth (or shrinkage) with milademetan in most patients regardless of schedule (Figs 2A and 2B). Median PFS for patients with DDLPS and non-liposarcoma tumors was 7.2 months (95% CI, 3.8 to 10.1) and 3.4 months (95% CI, 1.8 to 5.6), respectively (Fig 3A).

Among patients with DDLPS, outcomes were maintained with intermittent dosing schedules compared with extended/continuous schedules (Data Supplement). Median PFS was 7.2 months (95% CI, 3.8 to 10.1) in the overall DDLPS cohort (n = 53), 6.3 months (95% CI, 3.8 to 10.0) with extended/continuous schedules (n = 30), and 7.4 months (95% CI, 2.7 to 14.6) with intermittent schedules (n = 23; Fig 3B). With the recommended dose and schedule (260 mg once daily on days 1-3 and 15-17/28 days), median PFS was 7.4 months (95% CI, 1.8 to 14.6) in the DDLPS cohort (n = 16; Fig 3B), and 8.0 months (95% CI, 1.8 to 27.7) in patients with previously treated DDLPS (n = 11; Data Supplement).

Exploratory analysis was performed to determine median PFS by line of therapy for all patients with DDLPS, regardless of schedule and dose (n = 53). Previously untreated patients (n = 17) displayed a median PFS of 14.6 months (95% CI, 3.8 to not estimable). Patients with at least one prior therapy (n = 36) demonstrated a median PFS of 5.9 months (95% CI, 3.5 to 10.0; Data Supplement).

Duration of study treatment for each patient with DDLPS is shown in Figure 2C; seven and four patients with intermittent and extended/continuous schedules, respectively, received milademetan for more than 1 year. Waterfall plots by dosing schedule in patients with DDLPS are presented in the Data Supplement.

Exploratory analyses of select biomarkers relevant to DDLPS were performed in a subset of patients with DDLPS. Median PFS did not differ by *MDM2* copy number or *CDK4* copy number (Data Supplement). Median PFS also did not differ by mRNA expression levels of *MDM2*, *CDK4*, or *MDM4* (Data Supplement).

Part 2 (dose-expansion: melanoma and DLBCL). During part 2, 1 (5.6%) of 18 patients with melanoma had a partial response, and eight (44.4%) patients achieved stable disease (Table 3). Both patients with DLBCL were unevaluable.

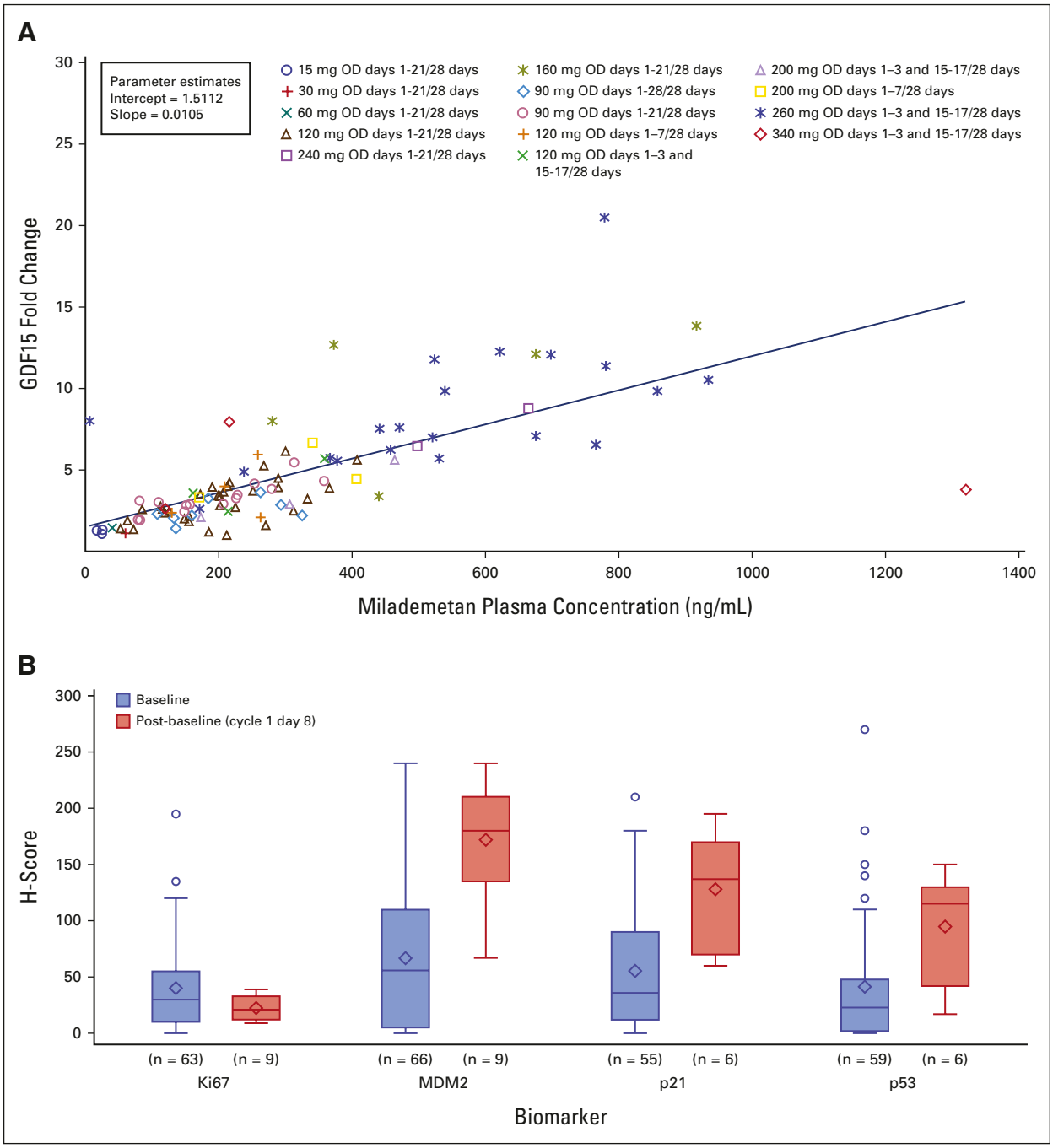

FIG 1. (A) Scatter plot of GDF15 fold change and time-matched milademetan plasma concentration by cohort on cycle 1 day 2 (N = 107) and (B) box plot of exploratory biomarker immunohistochemistry H-scores in dedifferentiated liposarcoma tumor samples at baseline and cycle 1 day 8. In the boxplot, a diamond represents the mean and line within the box represents the median. GDF15, growth differentiation factor-15; MDM2, murine double minute two; OD, once daily; p21, cyclin-dependent kinase inhibitor 1.

ORR for the total dose-expansion cohort (n = 20) was 5.0% (95% CI, 0.1 to 24.9), with a DCR of 35.0% (95% CI, 15.4 to 59.2). Median PFS was 3.2 months (95% CI, 1.6 to 4.0).

DISCUSSION

Despite almost 2 decades of research dedicated to the development of MDM2 inhibitors, none has progressed beyond early-phase clinical trials in patients with solid tumors.[16-21] The main reason for the apparent lack of progress is myelosuppression, an on-target class effect mediated by reactivation of p53. p53 is an integral component of the autoregulatory loop for hematopoietic stem cells, promotes apoptosis of megakaryocyte progenitor cells, and impairs platelet production once activated by MDM2 inhibition.[22] Efforts to control

TABLE 3. Efficacy Summary

End Point	Part 1 (dose-escalation)			Part 2[a] (dose-expansion; n = 20)	Total (N = 107)
	DDLPS (n = 53)	Nonliposarcoma (n = 34)	Total (n = 87)		
Best overall response, No. (%)					
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	2 (3.8)	2 (5.9)	4 (4.6)	1 (5.0)	5 (4.7)
Stable disease	34 (64.2)	14 (41.2)	48 (55.2)	8 (40.0)	56 (52.3)
Progressive disease	12 (22.6)	12 (35.3)	24 (27.6)	5 (25.0)	29 (27.1)
Not evaluable	5 (9.4)	6 (17.6)	11 (12.6)	6 (30.0)	17 (15.9)
ORR, % (95% CI)	3.8 (0.5 to 13.0)	5.9 (0.7 to 19.7)	4.6 (1.3 to 11.4)	5.0 (0.1 to 24.9)	4.7 (1.5 to 10.6)
DCR,[b] % (95% CI)	58.5 (44.1 to 71.9)	32.4 (17.4 to 50.5)	48.3 (37.4 to 59.2)	35.0 (15.4 to 59.2)	45.8 (36.1 to 55.7)
Time to response, months					
Median (95% CI)	10.1 (NE)	2.6 (1.7 to 3.5)	6.8 (1.7 to 10.1)	2.9 (NE)	3.5 (1.7 to 10.1)
Duration of response, months					
Median (95% CI)	NE (NE)	1.8 (1.7 to 1.9)	NE (1.7 to NE)	0.02+[c]	NE (1.7 to NE)
Duration of stable disease, months					
Median (95% CI)	10.0 (6.3 to 14.6)	5.7 (3.5 to NE)	8.0 (5.9 to 13.8)	4.0 (3.2 to NE)	7.4 (5.5 to 13.1)
PFS, months					
Median (95% CI)	7.2 (3.8 to 10.1)	3.4 (1.8 to 5.6)	5.5 (3.5 to 7.4)	3.2 (1.6 to 4.0)	4.0 (3.4 to 5.7)

NOTE. All patients receiving at least one dose of miladematan were included in the efficacy analyses. Note: Best overall response was classified as not evaluable if there were no postbaseline tumor assessments or if the overall response was not evaluable for all postbaseline tumor assessments.

Abbreviations: DCR, disease control rate; DDLPS, dedifferentiated liposarcoma; NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

[a]Included patients with melanoma (n = 18) and diffuse large B-cell lymphoma (n = 2); both patients with diffuse large B-cell lymphoma were not evaluable.

[b]Defined as complete response plus partial response plus stable disease for a minimum of 8 weeks.

[c]Value for one patient; + after the value indicates censoring.

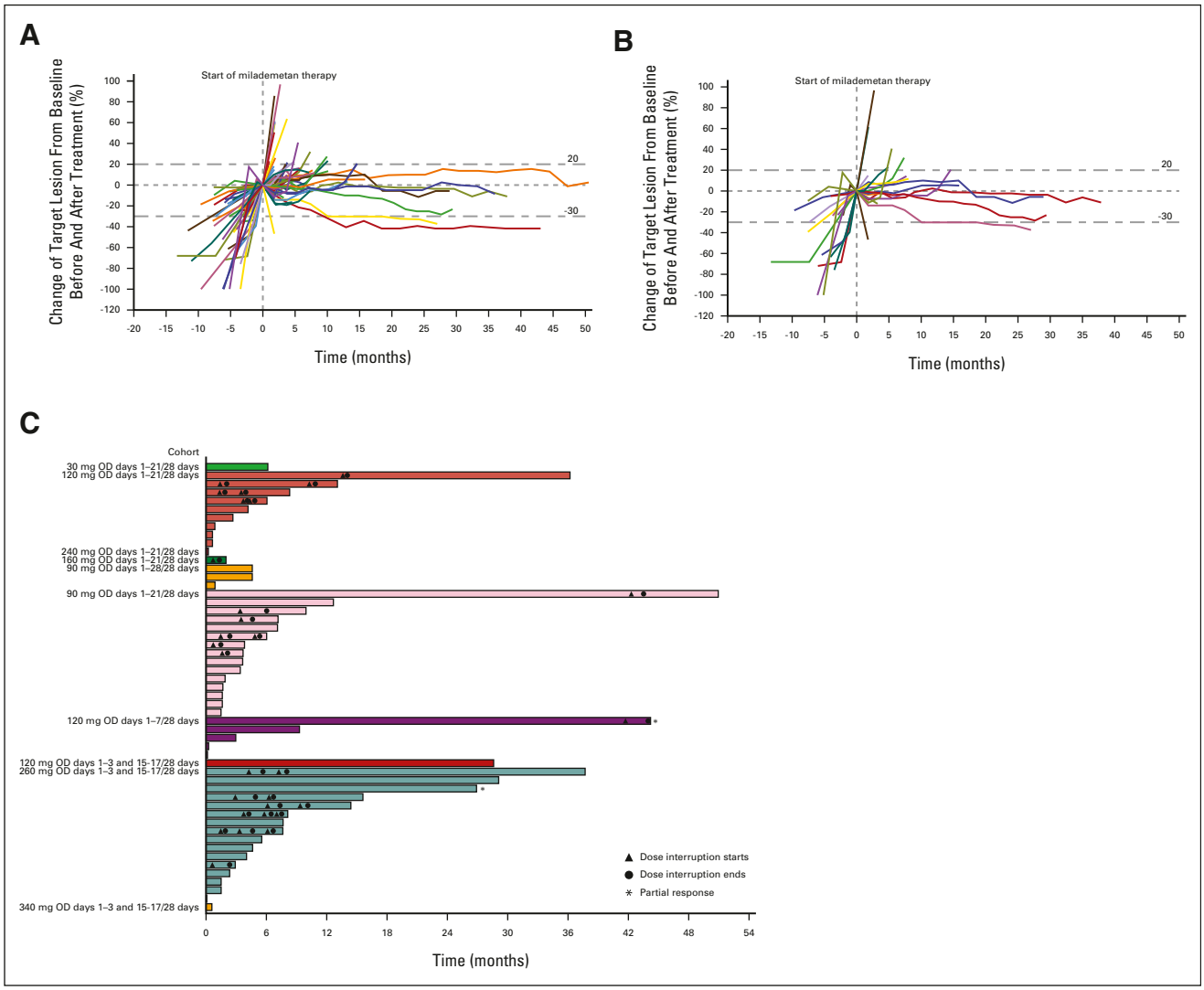

FIG 2. Percent change in sum of diameters from baseline in target lesions before and during miladematan therapy in (A) all patients with DDLPS (n = 53), (B) patients with DDLPS treated with schedule D (days 1-3 and 15-17 once daily every 28 days; n = 18), and (C) swimmer plot of treatment duration in patients with DDLPS by schedule (n = 53). Note: Treatment duration = (last dose date of study drug – first dose date of study drug + 1) * 12/365.25. Only dose interruptions with a duration of 2 weeks or longer are displayed. DDLPS, dedifferentiated liposarcoma; OD, once daily.

myelosuppression with simple dosing adjustments[17,18] or dosing guided by pharmacokinetic/pharmacodynamic modeling[21] have provided insights but no clear solution.

In this first-in-human study of the MDM2 inhibitor miladematan, extended or continuous schedules led to unfavorable myelosuppression, particularly thrombocytopenia, as with other inhibitors from this class.[16-21] Furthermore, the onset of myelosuppression was often delayed and led to dose reductions and prolonged dose interruptions. On the basis of knowledge gained from exposure-toxicity modeling of miladematan,[15] the pathogenesis of p53-driven myelosuppression, and our own clinical experience, we expanded the dose-escalation part of the study to explore alternative intermittent schedules. We found that intermittent dosing, allowing time for bone marrow recovery, markedly reduced the occurrence and severity of thrombocytopenia and other hematologic events. Furthermore, even if toxicities occurred, patients were more likely to continue therapy with fewer dose reductions or prolonged interruptions and maintain clinical outcomes. From this expanded investigation, a 260-mg dose of miladematan given on days 1-3 and 15-17 every 28 days was selected for future clinical development. Notably, several other MDM2 inhibitors in development have also explored intermittent dosing regimens.[18,23,24] Biomarker data confirmed that miladematan reactivated p53 at clinically relevant doses across all schedules, with elevated serum GDF15 levels, a biomarker for p53 reactivation,[25] together with increased tumor expression of p53 and downstream gene products (p21 and MDM2).

Miladematan had single-agent efficacy in the overall study population (DCR; 46%), a result consistent with a smaller

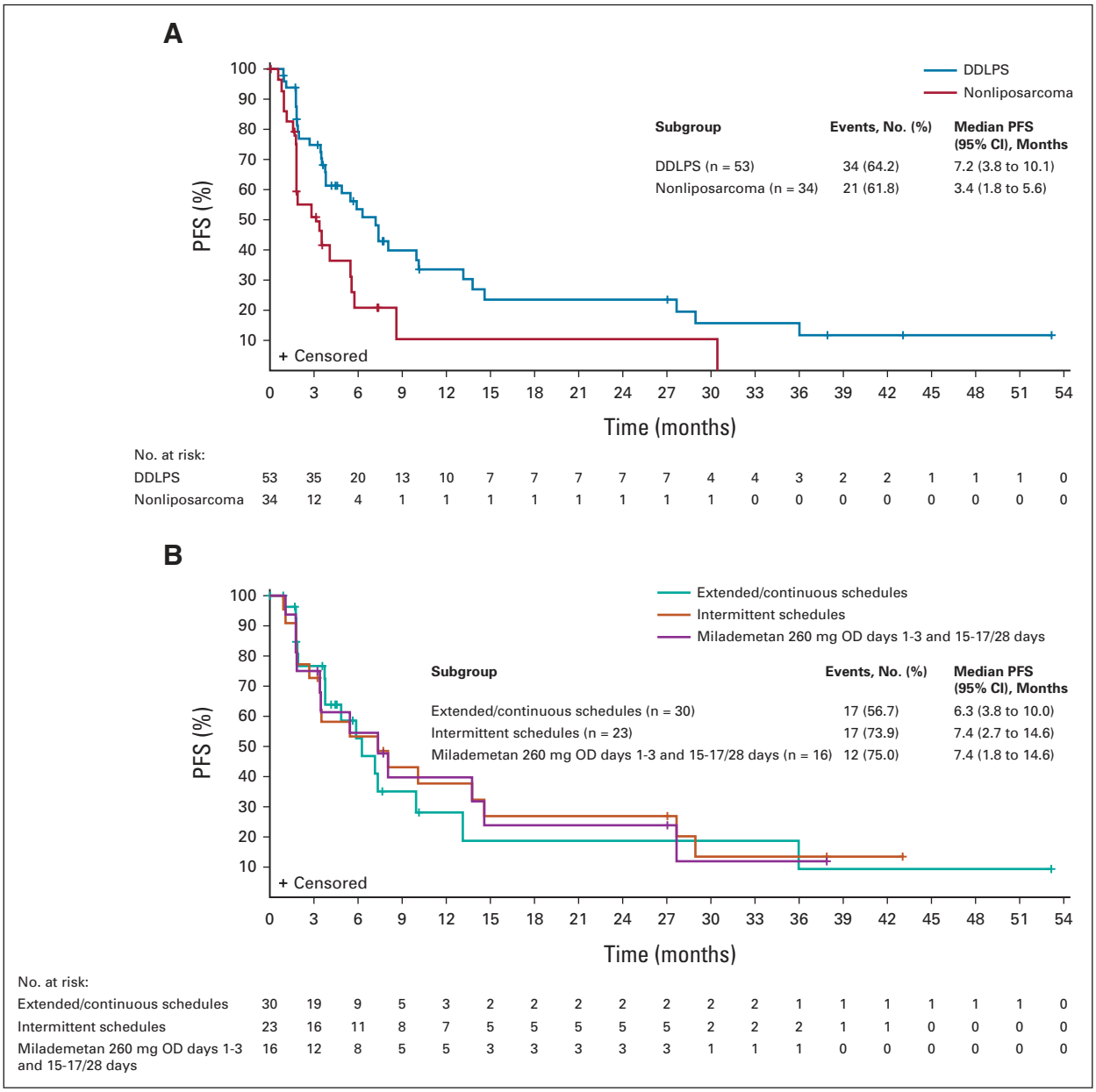

FIG 3. PFS in (A) patients with DDLPS (n = 53) versus nonliposarcoma (n = 34) across all schedules, and (B) in patients with DDLPS by schedule. Extended/continuous: schedule A: milademetan once daily on days 1-21 every 28 days; schedule B, milademetan once daily on days 1-28. Intermittent: schedule C: milademetan once daily on days 1-7 every 28 days; schedule D: milademetan once daily on days 1-3 and 15-17 every 28 days. DDLPS, dedifferentiated liposarcoma; OD, once daily; PFS, progression-free survival.

phase I study of milademetan in Japanese patients with solid tumors (44%).[26] Subsequent expanded enrollment of patients with DDLPS, for which *MDM2* amplification is a hallmark, allowed a more detailed assessment of this tumor type. In this subgroup, the DCR was 59% with prolonged partial responses reported in two patients (ongoing after 17 months) and a median PFS of 7.2 months. In phase I and II studies, it is challenging to evaluate single-arm activity of drugs that induce growth arrest because of selection bias and variable natural histories. To confirm growth arrest in our population, we evaluated tumor growth kinetics before and after initiation of milademetan. Change in tumor growth kinetics is increasingly shown in early- and late-phase clinical trials as a valuable end point to assess activity of drugs that do not necessarily induce apoptosis.[27-29]

DDLPS are relatively resistant to chemotherapy,[30] and systemic treatment options for patients with unresectable or metastatic disease are limited. Trabectedin and eribulin—FDA-approved second-line treatments[31]—have median PFS of 2.2 and 2.0 months, respectively, compared with 1.9 and 2.1 months with dacarbazine in patients with previously

treated DDLPS.[32,33] Inhibitors of CDK4, a protein that is frequently overexpressed in DDLPS in parallel with MDM2, have yielded more promising results than chemotherapy (median PFS: 4.1 months with palbociclib[34,35]; 7.0 months with abemaciclib[36]), but are not approved in this indication. On the basis of our observations, a randomized, phase III registration study (MANTRA; RAIN-3201) of milademetan versus trabectedin in patients with unresectable or metastatic DDLPS with disease progression on ≥ 1 prior systemic therapies has recently started enrolling patients (ClinicalTrials.gov identifier: NCT04979442).[37]

We acknowledge several limitations of our study. Determination of *MDM2* amplification status was not required at study entry and performed only on a minority of patients, although it was notable that 100% of patients with DDLPS tested demonstrated *MDM2* amplification. In the absence of an accepted cutoff for MDM2, a phase II basket study (MANTRA-2) has been initiated to evaluate an *MDM2* copy number ≥ 12 as a potential threshold value in patients with advanced *TP53*-wild-type solid tumors (ClinicalTrials.gov identifier: NCT05012397). Other limitations include the single-arm, open-label study design and no independent central review of scans. The time points for GDF15 blood draw did not accommodate the intermittent dose schedules and thus were not ideal to capture peak GDF15, particularly for the recommended schedule.

In conclusion, we identified an intermittent dosing schedule for the MDM2 inhibitor miladematan (days 1–3 and 15-17, every 28 days), which mitigated the risk of thrombocytopenia and is recommended for future clinical development in solid tumors. Miladematan had notable efficacy in patients with advanced DDLPS, a population that is uniformly enriched for *MDM2* amplification. These findings have provided the foundation for a randomized phase III study of miladematan versus standard of care in DDLPS.

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DATA SHARING STATEMENT

Anonymized individual participant data (IPD) and applicable supporting clinical study documents may be available upon request at https://vivli.org/. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of company and our clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A First-in-Human Phase I Study of Milademetan, an MDM2 Inhibitor, in Patients With Advanced Liposarcoma, Solid Tumors, or Lymphomas

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