Results from a First-in-Human Phase I Study of Siremadlin (HDM201) in Patients with Advanced Wild-Type *TP53* Solid Tumors and Acute Leukemia

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ABSTRACT

Purpose: This phase I, dose-escalation study investigated the recommended dose for expansion (RDE) of siremadlin, a p53–MDM2 inhibitor, in patients with wild-type *TP53* advanced solid or hematologic cancers.

Patients and Methods: Initial dosing regimens were: 1A (day 1; 21-day cycle; dose 12.5–350 mg) and 2A (days 1–14; 28-day cycle; dose 1–20 mg). Alternative regimens included 1B (days 1 and 8; 28-day cycle) and 2C (days 1–7; 28-day cycle). The primary endpoint was incidence of dose-limiting toxicities (DLT) during cycle 1.

Results: Overall, 115 patients with solid tumors and 93 with hematologic malignancies received treatment. DLTs occurred in 8/92 patients with solid tumors and 10/53 patients with hematologic malignancies. In solid tumors, an RDE of 120 mg was defined in 1B. In hematologic tumors, RDEs were defined in 1A: 250 mg, 1B: 120 mg, and 2C: 45 mg. More patients with hematologic malignancies compared with solid tumors experienced grade 3/4 treatment-related adverse events (71% vs. 45%), most commonly resulting from myelosuppression. These were more frequent and severe in patients with hematologic malignancies; 22 patients exhibited tumor lysis syndrome. Overall response rates at the RDEs were 10.3% [95% confidence interval (CI), 2.2–27.4] in solid tumors and 4.2% (95% CI, 0.1–21.1), 20% (95% CI, 4.3–48.1), and 22.2% (95% CI, 8.6–42.3) in acute myeloid leukemia (AML) in 1B, 1A, and 2C, respectively.

Conclusions: A common safety profile was identified and preliminary activity was noted, particularly in AML. Comprehensive investigation of dosing regimens yielded recommended doses/regimens for future combination studies.

Introduction

Activation of the tumor suppressor protein p53 induces cell-cycle arrest, promotion of DNA repair pathways, and apoptosis (1–3). Murine double minute-2 (MDM2) is the primary negative regulator of p53 (4, 5). Inhibition of p53 by MDM2 is achieved through binding to the transactivation domain of p53 (6) or by acting as an E3 ubiquitin ligase of p53, resulting in proteasomal degradation (4, 7). *MDM2* is transcriptionally upregulated by p53 activation, thus ensuring, via a negative feedback loop, low p53 activation under normal conditions (8). p53 function is often compromised in tumor cells (1, 9), by either *TP53*-inactivating mutations, amplification, and/or overexpression of *MDM2* (10).

Inhibiting MDM2 to increase wild-type p53 activity is a potentially effective antitumor approach due to the tumor suppressive effect of p53 (11, 12). Several small molecules have been developed with the

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Translational Relevance

Increasing the tumor suppressive activity of the p53 protein through inhibition of the p53–MDM2 interaction represents a potential therapeutic target that could offer patients with cancer new treatment options. Siremadlin, an orally bioavailable, selective inhibitor of the p53–MDM2 interaction, has demonstrated single-agent activity in preclinical studies. In this first-in-human, phase I study, patients with a range of advanced malignancies were treated with escalating doses of siremadlin. Overall, the safety profile of siremadlin did not differ significantly between tumor types and regimens. Thrombocytopenia, believed to be an on-target effect of MDM2 inhibition, was common in line with previous studies of MDM2 inhibitors. Activity was limited in patients with solid tumors, but encouraging in patients with AML. This comprehensive investigation of dosing regimens together with pharmacokinetic/pharmacodynamic modeling of thrombocytopenia yielded recommended single-agent doses and regimens for future combination studies, of which a number are ongoing in an attempt to broaden the efficacy of siremadlin.

ability to inhibit the MDM2–p53 interaction and some are currently under investigation in clinical trials, including idasanutlin, AMG-232, APG-115, BI-907828, and milademetan (13). Data from early-phase trials have demonstrated activity in various hematologic and solid cancers (14–16); however, in some cases, adverse events (AE) have limited the doses that could be administered, with the most common toxicities being gastrointestinal and bone marrow toxicities (15, 17).

Siremadlin, an orally bioavailable, selective inhibitor of the p53–MDM2 interaction, has demonstrated single-agent activity in p53 wild-type cell lines and patient-derived xenograft models (18–20). In preclinical models, fractionated low-dose siremadlin induced p21 expression and delayed accumulation of apoptotic cells, while pulsed high-dose siremadlin induced the pro-apoptotic protein PUMA and promoted rapid apoptosis (21). This first-in-human phase I dose-escalation/-expansion study aimed to determine the recommended dose for expansion (RDE). Secondary endpoints included safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) properties, and preliminary antitumor activity of siremadlin in patients with wild-type *TP53* advanced solid and hematologic malignancies.

Patients and Methods

Patients

Patients were aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and wild-type *TP53* tumor status. Those with solid tumors had treatment-refractory locally advanced or metastatic tumors, or tumors for which no therapy was available. Those with hematologic malignancies had relapsed/refractory acute myeloid leukemia (AML) except for acute promyelocytic leukemia, or previously untreated AML unsuitable for standard induction therapy; relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) or T-cell ALL (including Philadelphia chromosome–positive ALL); or previously untreated ALL unsuitable for standard induction therapy. Patient exclusion criteria are described in the Supplementary Material.

The study adhered to International Council for Harmonisation tripartite guidelines for Good Clinical Practice, the ethical principles of the Declaration of Helsinki, and all applicable local regulations. The study protocol was approved by all Institutional Review Boards, Independent Ethics Committees, and Research Ethics Boards. All patients provided written informed consent.

Study design

This was a first-in-human, phase I, multicenter, open-label, dose-escalation study (NCT02143635). The dose-escalation part determined the RDE of siremadlin. Dose expansion further characterized the antitumor activity of siremadlin in selected regimens.

Six regimens with different dosing schedules and cycle lengths were preplanned. Regimens high-dose 1A (dosing day 1 of a 21-day cycle; starting dose 12.5 mg) and low-dose 2A (dosing days 1–14 of 28-day cycle; starting dose 1 mg) were initially explored. Starting doses and schedules were based on preclinical data suggesting a different mechanism of action between pulsed high-dose and fractionated low-dose regimens (21). If emerging PK or safety data indicated that either regimen was suboptimal, alternative pulsed high-dose (1B: dosing days 1 and 8 of 28-day cycle; 1C: dosing day 1 of 28-day cycle) or fractionated low-dose (2B: dosing days 1–7 of 21-day cycle; 2C: dosing days 1–7 of 28-day cycle) regimens were subsequently explored (Supplementary Fig. S1). Dose escalation of siremadlin in combination with eltrombopag was also explored in a subgroup of patients with solid tumors to determine if eltrombopag could mitigate thrombocytopenia, a known class effect of MDM2 inhibitors. Three eltrombopag-containing regimens were preplanned (Supplementary Fig. S2). Treatment-related toxicities, including myelosuppression, were managed by study treatment interruption, dose reduction, and by appropriate concomitant therapies. These were mainly antifungals, growth factors, antibiotic treatments, and transfusions (for anemia and thrombocytopenia in particular).

The primary objective was to determine the RDE of siremadlin with or without eltrombopag in one or more regimens based on incidence of dose-limiting toxicities (DLT) during cycle 1. The DLT definition differed according to disease type (see Supplementary Table S1). A Bayesian logistic regression model (BLRM; ref. 22) with escalation with overdose control (EWOC) was used to guide dose escalation until the RDE was determined in one or more regimens. At least 6 patients were treated at each dose level. A two-parameter BLRM was fitted on the DLT data (i.e., absence or presence of a DLT) accumulated throughout dose escalation during the first cycle to model the dose–toxicity relationship of siremadlin.

Once the RDE was identified, additional patients were enrolled at the selected dose and regimen of siremadlin into expansion groups. These included approximately 10 patients with *TP53* wild-type liposarcoma (LPS), ∼10 patients with other *TP53* wild-type solid tumors, and ∼20 patients with *TP53* wild-type AML.

Analysis sets and assessments are described in the Supplementary Material.

PK and PK/PD platelet modeling

PK and PK/PD platelet models were established in a two-step approach, where individual PK estimates derived from a previously described population PK model (23) were set as a "regressor", using the interoccasional PK estimates for the subsequent PK/PD modeling of platelets. For details on the modeling methodology and equations, please refer to the Supplementary Material.

Results

Study population

At the data cutoff (October 9, 2018), 115 patients with solid tumors and 93 patients with hematologic tumors had received treatment

(AML: $n = 91$; ALL: $n = 2$). Treatment was discontinued in 203 (98%) patients and 5 (2%) patients continue to receive treatment (all with solid tumors). The main reason for treatment discontinuation was disease progression ($n = 143$; 69%), followed by physician/patient decision ($n = 19$; 9%), AEs ($n = 18$; 9%), death ($n = 17$; 8%), withdrawal of consent ($n = 5$; 2%), and protocol deviation ($n = 1$; 0.4%).

Baseline characteristics of patients with solid tumors and hematologic malignancies are described in **Table 1**.

Dose escalation and RDE determination

Patients with solid tumors received siremadlin in high-dose 1A (every 3 weeks) at 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 350 mg, or at 250 mg + eltrombopag; in low-dose 2A (daily; 2 weeks on/2 weeks off) at 1 mg, 2 mg, 4 mg, 7.5 mg, 15 mg, or 20 mg; in high-dose 1B (once weekly for the first 2 weeks of a 4-week cycle) at 120 mg, 150 mg, 200 mg, or at 150 mg + eltrombopag; and in low-dose 2C (daily; 1 week on/3 weeks off) at 15 mg, 20 mg, or 25 mg (Supplementary Material). No RDEs were determined for high-dose 1A, low-dose 2A, or low-dose 2C; the RDE for high-dose 1B was identified as 120 mg. RDEs were determined by the investigators and sponsor based on the probability of DLTs, and all available safety, efficacy, PK, and PD data. The median duration of exposure for all patients with solid tumors was 9.0 weeks (range, 2–193 weeks). This was quite comparable in all regimens [high-dose 1A: 8.7 weeks (range, 4–128 weeks); high-dose 1B at RDE: 12.1 weeks (range, 5–117 weeks); high-dose 1B at other doses: 10.0 weeks (range, 6–115 weeks); low-dose 2A: 8.1 weeks (range, 2–193 weeks); low-dose 2C: 8.9 weeks (range, 5–89 weeks); high-dose 1B + eltrombopag: 8.0 weeks (range, 2–110 weeks)] except for high-dose 1A + eltrombopag where the median duration of exposure was 4.1 weeks (range, 3–11 weeks). DLTs were assessed in the dose-determining set (Supplementary Material); these were all treatment related and occurred in 8/92 (9%) evaluable patients. DLT occurrence within each dosing cohort is displayed in **Table 2**. Dose escalation of siremadlin in combination with prophylactic eltrombopag was introduced for patients with solid tumors to mitigate dose-limiting thrombocytopenic events. However, a benefit of eltrombopag was not apparent and due to a limited number of patients treated ($n = 10$), the overall interpretation of the results was inconclusive. For high-dose 1A, 1/6 patients treated with 250 mg siremadlin exhibited grade 3/4 thrombocytopenia compared with 1/3 patients treated at this dose and schedule in combination with eltrombopag. In high-dose 1B, 2/8 patients treated with 150 mg siremadlin exhibited grade 3/4 thrombocytopenia compared with 1/7 treated at this dose and schedule in combination with eltrombopag. Therefore, its use was not pursued in either the expansion phase or in patients with hematologic malignancies.

Patients with hematologic malignancies received siremadlin in high-dose 1A at 250 mg, 350 mg, or 400 mg; in low-dose 2A at 20 mg, or 30 mg; in high-dose 1B at 120 mg or 150 mg; and in low-dose 2C at 45 mg (Supplementary Material). No RDE was determined for low-dose 2A; the RDEs for high-dose 1A, high-dose 1B, and low-dose 2C were 250 mg, 120 mg, and 45 mg, respectively. The median duration of exposure for all patients with hematologic tumors was 7.6 weeks (range, 1–36 weeks). This was quite comparable across all regimens [high-dose 1A at RDE: 6.1 weeks (range, 2–23 weeks); high-dose 1A at other doses: 5.4 weeks (range, 1–36 weeks); high-dose 1B at RDE: 7.5 weeks (range, 2–35 weeks); high-dose 1B at other doses: 7.9 weeks (range, 1–23 weeks); low-dose 2A: 7.6 weeks (range, 1–22 weeks); low-dose 2C at RDE: 8.3 weeks (range, 3–27 weeks)]. Grade 3/4 DLTs were all treatment related and occurred in 10/53 (19%) evaluable patients. DLT occurrence within each dosing cohort is displayed in **Table 2**.

Safety

A total of 114 (99%) patients with solid tumors and 92 (99%) patients with hematologic tumors had at least one AE regardless of cause (Supplementary Tables S2 and S3). Overall, 103 (90%) patients with solid tumors and 82 (88%) patients with hematologic malignancies had an AE suspected to be treatment related (**Table 3**). The most common of these were gastrointestinal disorders [nausea (57% solid; 44% heme), vomiting (30% solid; 18% heme), and decreased appetite (24% solid; 17% heme)], hematologic toxicities [anemia (37% solid; 42% heme), neutropenia (24% solid; 28% heme), and thrombocytopenia (33% solid; 43% heme)], and fatigue (30% solid; 13% heme). Tumor lysis syndrome was also reported in 24% of patients with hematologic malignancies, but not in patients with solid tumors. A protocol amendment was introduced during the study requiring risk assessment and safety monitoring for the potential development of tumor lysis syndrome in all patients with hematologic indications (further details are available in the Supplementary Material). For the majority of patients who experienced tumor lysis syndrome (18/22), these events occurred within the first 5 days of treatment. The median duration of tumor lysis syndrome events was 4 days (range, 2–16 days). One patient (in low-dose 2C) experienced grade 4 tumor lysis syndrome; this resolved within 4 days following dose delay and treatment with rasburicase.

Grade 3/4 AEs suspected to be treatment related were observed in 52 (45%) patients with solid tumors and 66 (71%) patients with hematologic tumors (**Table 3**). Hematologic toxicities were the most common grade 3/4 AE for all indications and were more frequent in patients with hematologic tumors compared with those with solid tumors.

A total of 50 (43.5%) patients with solid tumors and 38 (40.9%) patients with hematologic tumors had at least one AE leading to dose adjustment or interruption.

Forty-five patients (39%) with solid tumors had a grade 3/4 serious AE (SAE); in 17 (15%) of these patients, it was suspected of being treatment related. Seventy-two patients (77%) with hematologic tumors had a grade 3/4 SAE; in 42 (45%) of these patients, it was suspected of being treatment related. Six (5%) patients with solid tumors and 2 (2%) patients with hematologic tumors had a grade 3/4 AE suspected of being treatment related that led to treatment discontinuation.

There were 13 (11%) deaths among patients with solid tumors and 34 (37%) deaths among patients with hematologic malignancies during the study treatment and evaluation periods (safety follow-up continued until 30 days after the end-of-treatment visit). In patients with solid tumors, 10 deaths were considered related to underlying disease. Three deaths were considered unrelated to underlying disease: hepatic hemorrhage, hepatic failure, and pneumonia (one patient each). In patients with hematologic malignancies, 22 deaths were considered related to underlying disease. Twelve deaths were considered unrelated to underlying disease: cerebral hemorrhage, sepsis (2 patients each), euthanasia, neutropenic infection, cardiac failure, subarachnoid hemorrhage, acute kidney injury, septic shock, fungal infection, and unknown cause (1 patient each). Of the deaths from AEs in patients with hematologic malignancies, five (neutropenic infection, subarachnoid hemorrhage, acute kidney injury, and both cases of sepsis) were considered related to study treatment.

PK/PD analysis and biomarkers

PK parameters from noncompartmental analysis were summarized by dose regimen irrespective of tumor type. Following oral administration of siremadlin on day 1 of cycle 1, the median time to reach

Table 1. Baseline characteristics of patients with solid tumors or hematologic malignancies (full analysis set).

	Patients with solid tumors						Patients with hematologic malignancies						
	High-dose 1A	High-dose 1B		Low-dose 2A	Low-dose 2C	All patients[b]	High-dose 1A		High-dose 1B		Low-dose 2A	Low-dose 2C	All patients
n (%)[a]	(12.5–350 mg) *N* = 26	RDE (120 mg) *N* = 29	Other doses (150–200 mg) *N* = 11	(1–20 mg) *N* = 20	(15–25 mg) *N* = 19	*N* = 115	RDE (250 mg) *N* = 15	Other doses (350–400 mg) *N* = 13	RDE (120 mg) *N* = 24	Other doses (150 mg) *N* = 6	(20–30 mg) *N* = 7	RDE (45 mg) *N* = 28	*N* = 93
Median age (range), years	61.5 (18–80)	60.0 (19–78)	63.0 (31–75)	59.5 (38–76)	57.0 (37–74)	59.0 (18–80)	70.0 (30–82)	71.0 (23–81)	70.0 (28–83)	70.5 (64–83)	63.0 (26–72)	71.5 (28–85)	70.0 (23–85)
Sex													
Male	9 (35)	16 (55)	6 (55)	15 (75)	13 (68)	64 (56)	7 (47)	9 (69)	17 (71)	1 (17)	7 (100)	17 (61)	58 (62)
Female	17 (65)	13 (45)	5 (45)	5 (25)	6 (32)	51 (44)	8 (53)	4 (31)	7 (29)	5 (83)	0	11 (39)	35 (38)
ECOG performance status													
0	12 (46)	12 (41)	4 (36)	11 (55)	11 (58)	54 (47)	0	2 (15)	3 (13)	0	0	3 (11)	8 (9)
1	14 (54)	16 (55)	7 (64)	9 (45)	8 (42)	60 (52)	13 (87)	10 (77)	16 (67)	5 (83)	4 (57)	23 (82)	71 (76)
2	0	1 (3)	0	0	0	1 (1)	2 (13)	1 (8)	4 (17)	1 (17)	2 (29)	2 (7)	12 (13)
3	0	0	0	0	0	0	0	0	1 (4)	0	1 (14)	0	2 (2)
Prior antineoplastic regimens													
No	0	4 (14)	2 (18)	1 (5)	1 (5)	9 (8)	0	0	0	0	0	0	0
Yes	26 (100)	25 (86)	9 (82)	19 (95)	18 (95)	106 (92)	15 (100)	13 (100)	24 (100)	6 (100)	7 (100)	28 (100)	93 (100)
Number of antineoplastic regimens													
0	0	4 (14)	2 (18)	1 (5)	1 (5)	9 (8)	0	0	0	0	0	0	0
1	7 (27)	10 (34)	3 (27)	1 (5)	1 (5)	23 (20)	6 (40)	5 (38)	8 (33)	0	0	9 (32)	28 (30)
2	7 (27)	4 (14)	3 (27)	7 (35)	5 (26)	28 (24)	4 (27)	1 (8)	6 (25)	2 (33)	1 (14)	7 (25)	21 (23)
3	1 (4)	5 (17)	0	6 (30)	6 (32)	21 (18)	2 (13)	4 (31)	4 (17)	2 (33)	2 (29)	3 (11)	17 (18)
4	3 (12)	2 (7)	2 (18)	2 (10)	2 (11)	12 (10)	2 (13)	1 (8)	5 (21)	1 (17)	2 (29)	1 (4)	12 (13)
≥5	8 (31)	4 (14)	1 (9)	3 (15)	4 (21)	22 (19)	1 (7)	2 (15)	1 (4)	1 (17)	2 (29)	8 (29)	15 (16)
Primary site tumor													
Others[c]	13 (50)	4 (14)	5 (45)	5 (25)	8 (42)	39 (34)							
Sarcoma: others[d]	8 (31)	7 (24)	0	6 (30)	5 (26)	28 (24)							
Liposarcoma	3 (12)	12 (41)	2 (18)	1 (5)	1 (5)	19 (17)							
Uveal melanoma	2 (8)	2 (7)	2 (18)	1 (5)	1 (5)	10 (9)							
Colon	0	1 (3)	0	4 (20)	3 (16)	9 (8)							
Skin melanoma	0	3 (10)	2 (18)	2 (10)	0	8 (7)							
Kidney	0	0	0	1 (5)	1 (5)	2 (2)							
AML							15 (100)	12 (92)	24 (100)	6 (100)	7 (100)	27 (96)	91 (98)
ALL							0	1 (8)	0	0	0	1 (4)	2 (2)
Median time (range) since diagnosis of primary site tumor,[e] months	65.9 (6–229)	32.7 (4–301)	53.2 (10–75)	39.8 (10–116)	42.6 (2–214)	42.9 (2–301)							
Time since diagnosis,[f,g] months													
<1							0	0	1/24 (4)	0	0	0	1 (1)
1–3							3/15 (20)	1/12 (8)	2/24 (8)	0	0	2/27 (7)	8/91 (9)
3–6							2/15 (13)	2/12 (17)	4/24 (17)	2/6 (33)	0	3/27 (11)	13/91 (14)
6–12							3/15 (20)	6/12 (50)	2/24 (8)	1/6 (17)	2/7 (29)	6/27 (22)	20/91 (22)
12–24							6/15 (40)	3/12 (25)	8/24 (33)	3/6 (50)	4/7 (57)	5/27 (19)	29/91 (32)
>24							1/15 (7)	0	7/24 (29)	0	1/7 (14)	11/27 (41)	20/91 (22)

(Continued on the following page)

Table 1. Baseline characteristics of patients with solid tumors or hematologic malignancies (full analysis set). (Cont'd)

	Patients with solid tumors					Patients with hematologic malignancies					
	High-dose 1A	High-dose 1B		Low-dose	All	High-dose 1A		High-dose 1B		Low-dose	All patients
		RDE	Other doses	2A	patients[b]	RDE	Other doses	RDE	Other doses	2A	
n (%)[a]	(12.5–350 mg) *N* = 26	(120 mg) *N* = 29	(150–200 mg) *N* = 11	(1–20 mg) *N* = 20	*N* = 115	(250 mg) *N* = 15	(350–400 mg) *N* = 13	(120 mg) *N* = 24	(150 mg) *N* = 6	(20–30 mg) *N* = 7	*N* = 93
Median time (range) since most recent relapse or recurrence,[e] months	2.0 (0–14)	1.6 (0–12)	1.6 (1–7)	1.9 (0–8)	1.7 (0–19)						
Prior stem cell transplantation											
No						12 (80)	10 (77)	22 (92)	5 (83)	6 (86)	78 (84)
Yes						3 (20)	3 (23)	2 (8)	1 (17)	1 (14)	15 (16)

	Patients with solid tumors					Patients with hematologic malignancies					
	High-dose 1A	High-dose 1B		Low-dose	All	High-dose 1A		High-dose 1B		Low-dose	All patients
		RDE	Other doses	2A	patients[b]	RDE	Other doses	RDE	Other doses	2A	
n (%)[a]	(12.5–350 mg) *N* = 26	(120 mg) *N* = 29	(150–200 mg) *N* = 11	(1–20 mg) *N* = 20	*N* = 115	(250 mg) *N* = 15	(350–400 mg) *N* = 13	(120 mg) *N* = 24	(150 mg) *N* = 6	(20–30 mg) *N* = 7	*N* = 93
Median time (range) since most recent relapse or recurrence,[e] months	2.0 (0–14)	1.6 (0–12)	1.6 (1–7)	1.9 (0–8)	1.7 (0–19)						
Prior stem cell transplantation											
No						12 (80)	10 (77)	22 (92)	5 (83)	6 (86)	78 (84)
Yes						3 (20)	3 (23)	2 (8)	1 (17)	1 (14)	15 (16)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; GU, genitourinary; LPS, liposarcoma; RDE, recommended dose for expansion; WHO, World Health Organization.

[a]Unless specified otherwise.

[b]Includes patients (n = 10) in cohorts receiving eltrombopag.

[c]Others include solid tumors that are not represented in the other categories of the table (including GU, GI, breast, and head and neck cancers).

[d]Sarcoma: others include all non-LPS soft-tissue sarcomas and bone sarcoma.

[e]To start of treatment.

[f]To start of treatment.

[g]Among patients with AML only.

maximum plasma siremadlin concentrations (T_{max}) generally ranged from 2.0 to 8.0 hours, with a median terminal half-life ranging from 6.4 to 31.1 hours. In all regimens, dose–exposure relationships between maximum observed concentration (C_{max}) and area under the concentration–time curve from time 0 to the last measurable concentration (AUC_{last}) were approximately linear after single and repeated doses across the dose range (**Fig. 1**) with no apparent major deviations from dose proportionality. The interpatient variabilities for AUC_{last} and C_{max} were generally moderate. At the defined RDEs of 120 mg (high-dose 1B), 250 mg (high-dose 1A), and 45 mg (low-dose 2C) on cycle 1 day 1, the geometric mean values of C_{max} (ng/mL) were 1,039.5 [51.5 coefficient of variation (CV)%], 2,015.7 (69.5 CV%), and 425.3 (37.9 CV%), respectively, while geometric mean values of AUC_{last} (ng*h/mL) were 18,481.7 (62.7 CV%), 41,422.3 (71.2 CV%), and 5,234.6 (40.7 CV%), respectively (Supplementary Table S4).

PD changes in transcriptional targets of p53 [such as growth/differentiation factor-15 (GDF-15)] were used to measure siremadlin-driven p53 pathway activation, which demonstrated that adequate drug exposures could be achieved (21). Despite limited data, a clear trend was observed for increases in serum GDF-15 with higher exposure (as measured by AUC_{last}) of siremadlin for both high-dose regimens (1A/1B) and low-dose regimens (2A/2C; **Fig. 2**). This exposure-dependent increase in GDF-15 was also maintained on day 2 of treatment cycle 2 (C2D2; Supplementary Fig. S3). High-dose regimens, especially for AUC_{last} >10,000 ng/mL*h, showed > 210-fold changes on an average in GDF-15 for both C1D2 (P = 0.002) and C2D2 (P = 0.009), respectively (**Fig. 2**; Supplementary Fig. S3).

To determine how baseline biomarker status may relate to clinical outcome, next-generation sequencing (NGS) was performed on pretreatment solid tumor samples. Gene alterations in 324 genes were evaluated in 48 patients using the FoundationOne panel (24). Somatic copy-number amplifications in *MDM2* were observed in 16 of 48 patients analyzed (**Fig. 3A**). Although statistically underpowered to robustly detect associations, *MDM2* amplification was more prevalent in patients who achieved either partial response (PR) or stable disease (SD; 9/17 patients with *MDM2* amplification; 53.0%) than in patients with progressive disease (PD; 6/26; 23.0%; **Fig. 3B**). For patients whose tumors had *MDM2* amplification, those with PD also had a higher total number of somatic alterations (range of total alterations: 4–10 in 6 patients) compared with those who had either PR or SD (range, 2–6 in 9 patients; **Fig. 3C**). In patients with PD, concomitant alterations included deletion of *CDKN2A* (2/6 tumors), deletion of *ATRX* (2/6 tumors), amplification of *KRAS* (2/6 tumors), point mutation in *AKT1* (1/6 tumors), and amplification of *CDK6* (1/6 tumors; **Fig. 3A**). These data suggest that the presence of *MDM2* amplification in tumors at baseline may be associated with better clinical outcomes. However, the presence of additional oncogenic alterations in *MDM2*-amplified tumors may be associated with patient progression on treatment.

Semi-mechanistic PK/PD analysis of platelet kinetics in solid tumor patients

A semi-mechanistic PK/PD model modified from Friberg and colleagues (25) was developed to investigate drug action on the time course of platelet in solid tumor patients treated with siremadlin. This model, mimicking the hematopoietic process, was modified from Friberg and colleagues (25) to assume a drug direct action characterized by the parameter (*kr1D*) on proliferating progenitor compartment (*P*1; see Supplementary Fig. S4). For details on the PK/PD modeling methodology and equations, please refer to the Supplementary Material.

Table 2. Dose levels tested and DLTs across the regimens in solid and hematologic tumors.

	Solid tumors			Hematologic tumors		
Regimen	**Siremadlin dose, mg**	***n***	**DLTs, *n***	**Siremadlin dose, mg**	***n***	**DLTs, *n***
High-dose 1A[a]	12.5	1	0	250[b]	15	• 1 pt: G3 cardiac failure • 1 pt: G4 staphylococcal sepsis • 1 pt: G4 hyperuricemia
	25	1	0	350	4	0
	50	4	0	400	9	• 1 pt: G3 chronic GvHD + G3 stomatitis + G3 neutropenic infection • 1 pt: G4 subarachnoid hemorrhage • 2 pts: G4 hypophosphatemia
	100	4	0			
	200	5	0			
	250	6	0			
	350	5	• 1 pt: G4 thrombocytopenia • 1 pt: G3 neutrophil count decreased + G4 platelet count decreased			
	250 + eltrombopag[c]	3	• 1 pt: G4 leukopenia + G4 neutropenia + G4 thrombocytopenia + G3 febrile neutropenia • 1 pt: G3 anemia + G3 platelet count decreased			
High-dose 1B[d]	120[b]	29	0	120[b]	24	0
	150	8	• 1 pt: G3 neutropenia	150	6	• 1 pt: G4 acute kidney injury + G3 hyperkalemia
	200	3	0			
	150 + eltrombopag[e]	7	• 1 pt: G3 platelet count decreased			
Low-dose 2A[f]	1	1	0	20	3	• 1 pt: G3 C-reactive protein increased
	2	2	0	30	4	0
	4	4	0			
	7.5	4	0			
	15	4	0			
	20	5	0			
Low-dose 2C[g]	15	8	0	45[b]	28	• 1 pt: G4 tumor lysis syndrome
	20	6	0			
	25	5	• 1 pt: G4 lipase increased + G4 amylase increased • 1 pt: G3 platelet count decreased			

Abbreviations: DLT, dose-limiting toxicity; G, grade; GvHD, graft-versus-host disease; pt, patient; RDE, recommended dose for expansion.
[a]High-dose 1A: on day 1 of a 21-day cycle.
[b]RDE.
[c]Once daily for 10 consecutive days, starting on day 12 of siremadlin cycle 1 and from cycle 2 onward on the second day after last siremadlin administration.
[d]High-dose 1B: on days 1 and 8 of a 28-day cycle.
[e]Once daily for 10 consecutive days starting on day 19 of siremadlin cycle 1 and from cycle 2 onward on the second day after last siremadlin administration.
[f]Low-dose 2A: on days 1–14 of a 28-day cycle.
[g]Low-dose 2C: on days 1–7 of a 28-day cycle.

In brief, the PK/PD model was able to adequately describe the long-term platelet profiles up to 25 months. Parameter estimates from the final PK/PD model are reported in Supplementary Table S5. In general, all parameters were well estimated with good precision as indicated from relative standard errors, most of them below 50%. A low residual error (additive 12 G/L and proportional 13.6%) was estimated indicating good model description of the data.

The drug effect on early proliferative hematopoietic cells was associated with an estimated mean maturation time (*MMTP*) of 294 hours, reflecting the delayed onset of siremadlin-induced thrombocytopenia and the long platelet recovery time observed in patients. Additionally, assuming an indirect drug effect reducing with time the regulation capacity of the proliferative compartment helped describe the progressive depletion of platelets observed with increasing treatment cycles. Variability on this part of the model was high (IIV of *ke*01 119% and *ke*0 84%), reflecting the broad range of sensitivity across patients in response to bone marrow toxicity.

Individual platelet profile fitting (Supplementary Fig. S5) illustrates model flexibility to capture a diverse array of profiles. Goodness-of-fit diagnostic plots did not show any obvious bias (Supplementary Fig. S6). The predictive performance of the final model was checked by Monte Carlo simulations of the population model and plotting a visual predictive check (Supplementary Fig. S7). Most of the 10th, 50th, and 90th percentiles of the observed platelet data were included in the respective model 90% prediction intervals indicating adequate description by the model. The thrombocytopenia model, together with previously described modeling of tumor growth inhibition by siremadlin (18), provided a consolidated approach to support the selection of dosing regimen(s) for following clinical trials, which allows maximization of the total dose per cycle for efficacy while mitigating the occurrence of severe thrombocytopenia (26).

Table 3. AEs suspected to be related to treatment (occurring in >5% of all patients with solid or hematologic malignancies).

	Patients with solid tumors												Patients with hematologic malignancies											
	High-dose 1A		High-dose 1B				Low-dose 2A		Low-dose 2C		All patients[a]		High-dose 1A				High-dose 1B				Low-dose 2A		Low-dose 2C		All patients	
n (%)	(12.5–350 mg) *N* = 26		RDE (120 mg) *N* = 29		Other doses (150–200 mg) *N* = 11		(1–20 mg) *N* = 20		(15–25 mg) *N* = 19		*N* = 115		RDE (250 mg) *N* = 15		Other doses (350–400 mg) *N* = 13		RDE (120 mg) *N* = 24		Other doses (150 mg) *N* = 6		(20–30 mg) *N* = 7		RDE (45 mg) *N* = 28		*N* = 93	
Grade	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4
Number of patients with ≥ 1 AE	25 (96)	10 (39)	29 (100)	16 (55)	10 (91)	5 (46)	14 (70)	8 (40)	15 (79)	9 (47)	103 (90)	52 (45)	14 (93)	14 (93)	12 (92)	9 (69)	19 (79)	13 (54)	5 (83)	5 (83)	5 (71)	3 (43)	27 (96)	22 (79)	82 (88)	66 (71)
Nausea	17 (65)	0	20 (69)	2 (7)	6 (55)	0	8 (40)	0	8 (42)	0	66 (57)	2 (2)	6 (40)	0	8 (62)	0	6 (25)	0	4 (67)	0	3 (43)	0	14 (50)	0	41 (44)	0
Anemia	10 (39)	3 (12)	15 (52)	6 (21)	5 (46)	1 (9)	6 (30)	4 (20)	4 (21)	3 (16)	43 (37)	18 (16)	8 (53)	5 (33)	5 (39)	4 (31)	8 (33)	4 (17)	2 (33)	2 (33)	3 (43)	2 (29)	13 (46)	9 (32)	39 (42)	26 (28)
Thrombocytopenia	9 (35)	6 (23)	9 (31)	4 (14)	4 (36)	2 (18)	7 (35)	4 (20)	6 (32)	3 (16)	38 (33)	21 (18)	7 (47)	7 (47)	7 (54)	7 (54)	10 (42)	10 (42)	3 (50)	3 (50)	2 (29)	2 (29)	11 (39)	10 (36)	40 (43)	39 (42)
Fatigue	6 (23)	0	9 (31)	0	5 (46)	1 (9)	4 (20)	0	5 (26)	1 (5)	34 (30)	2 (2)	2 (13)	1 (7)	4 (31)	0	1 (4)	0	0	0	0	0	5 (18)	2 (7)	12 (13)	3 (3)
Vomiting	8 (31)	0	12 (41)	1 (3)	3 (27)	0	4 (20)	0	4 (21)	0	34 (30)	1 (1)	2 (13)	0	5 (39)	0	3 (13)	0	0	0	1 (14)	0	6 (21)	0	17 (18)	0
Decreased appetite	8 (31)	1 (4)	8 (28)	0	4 (36)	0	4 (20)	0	3 (16)	1 (5)	27 (24)	2 (2)	3 (20)	1 (7)	4 (31)	0	1 (4)	0	1 (17)	0	1 (14)	0	6 (21)	0	16 (17)	1 (1)
Neutropenia	7 (27)	6 (23)	9 (31)	8 (28)	4 (36)	3 (27)	4 (20)	3 (15)	1 (5)	1 (5)	27 (24)	22 (19)	6 (40)	5 (33)	5 (39)	5 (39)	5 (21)	5 (21)	1 (17)	1 (17)	0	0	9 (32)	8 (29)	26 (28)	24 (26)
Platelet count decreased	3 (12)	2 (8)	9 (31)	3 (10)	2 (18)	0	3 (15)	3 (15)	2 (11)	1 (5)	22 (19)	11 (10)	2 (13)	2 (13)	0	0	1 (4)	1 (4)	0	0	0	0	2 (7)	2 (7)	5 (5)	5 (5)
White blood cell count decreased	5 (19)	2 (8)	7 (24)	2 (7)	2 (18)	0	2 (10)	1 (5)	1 (5)	0	18 (16)	5 (4)	1 (7)	1 (7)	1 (8)	0	0	0	0	0	1 (14)	1 (14)	3 (11)	3 (11)	6 (7)	5 (5)
Diarrhea	4 (15)	0	5 (17)	0	2 (18)	0	2 (10)	0	2 (11)	0	16 (14)	0	5 (33)	0	3 (23)	0	2 (8)	0	0	0	0	0	2 (7)	0	12 (13)	0
Leukopenia	5 (19)	3 (12)	5 (17)	1 (3)	1 (9)	1 (9)	3 (15)	2 (10)	1 (5)	1 (5)	16 (14)	9 (8)	2 (13)	2 (13)	2 (15)	2 (15)	3 (13)	3 (13)	0	0	0	0	2 (7)	2 (7)	9 (10)	9 (10)
Lymphopenia	4 (15)	1 (4)	3 (10)	2 (7)	3 (27)	1 (9)	1 (5)	0	0	0	13 (11)	5 (4)	0	0	0	0	0	0	0	0	0	0	1 (4)	1 (4)	1 (1)	1 (1)
Dysgeusia	3 (12)	0	3 (10)	0	1 (9)	0	2 (10)	0	2 (11)	0	12 (10)	0	0	0	1 (8)	0	0	0	0	0	0	0	1 (4)	0	2 (2)	0
Neutrophil count decreased	2 (8)	2 (8)	2 (7)	2 (7)	3 (27)	1 (9)	2 (10)	1 (5)	2 (11)	1 (5)	12 (10)	8 (7)	0	0	0	0	0	0	0	0	1 (14)	1 (14)	2 (7)	2 (7)	3 (3)	3 (3)
Asthenia	3 (12)	1 (4)	3 (10)	0	1 (9)	0	2 (10)	0	1 (5)	0	10 (9)	1 (1)	2 (13)	1 (7)	1 (8)	0	4 (17)	2 (8)	1 (17)	0	0	0	2 (7)	0	10 (11)	3 (3)
Abdominal pain	2 (8)	1 (4)	2 (7)	0	2 (18)	0	1 (5)	0	0	0	8 (7)	1 (1)	2 (13)	0	1 (8)	0	1 (4)	0	0	0	0	0	0	0	4 (4)	0
Weight decreased	2 (8)	0	2 (7)	0	1 (9)	0	2 (10)	0	1 (5)	0	8 (7)	0	0	0	1 (8)	0	0	0	0	0	0	0	1 (4)	0	2 (2)	0
AST increased	1 (4)	0	0	0	0	0	3 (15)	1 (5)	1 (5)	0	7 (6)	2 (2)	1 (7)	0	0	0	0	0	0	0	0	0	2 (7)	2 (7)	3 (3)	2 (2)
Constipation	3 (12)	0	1 (3)	0	0	0	2 (10)	0	1 (5)	0	7 (6)	0	0	0	0	0	0	0	1 (17)	0	0	0	1 (4)	0	2 (2)	0
Lipase increased	1 (4)	0	2 (7)	0	3 (27)	3 (27)	0	0	1 (5)	1 (5)	7 (6)	4 (4)	0	0	3 (23)	2 (15)	1 (4)	1 (4)	0	0	0	0	1 (4)	1 (4)	5 (5)	4 (4)
Tumor lysis syndrome	0	0	0	0	0	0	0	0	0	0	0	0	8 (53)	7 (47)	5 (39)	5 (39)	5 (21)	5 (21)	0	0	1 (14)	1 (14)	3 (11)	3 (11)	22 (24)	21 (23)
Febrile neutropenia	1 (4)	1 (4)	1 (3)	1 (3)	0	0	0	0	0	0	3 (3)	3 (3)	4 (27)	4 (27)	3 (23)	3 (23)	1 (4)	1 (4)	2 (33)	2 (33)	2 (29)	2 (29)	9 (32)	9 (32)	21 (23)	21 (23)
Hyperuricemia	0	0	0	0	0	0	0	0	1 (5)	0	2 (2)	0	2 (13)	1 (7)	1 (8)	0	1 (4)	0	2 (33)	0	1 (14)	0	2 (7)	1 (4)	9 (10)	2 (2)
Hypocalcemia	0	0	2 (7)	0	1 (9)	0	0	0	0	0	3 (3)	0	3 (20)	1 (7)	2 (15)	0	1 (4)	0	0	0	0	0	3 (11)	0	9 (10)	1 (1)
Amylase increased	0	0	0	0	1 (9)	0	0	0	1 (5)	1 (5)	2 (2)	1 (1)	1 (7)	1 (7)	3 (23)	0	2 (8)	1 (4)	1 (17)	1 (17)	0	0	1 (4)	0	8 (9)	3 (3)
Acute kidney injury	1 (4)	0	0	0	0	0	0	0	0	0	1 (1)	0	0	0	1 (8)	0	1 (4)	0	1 (17)	1 (17)	1 (14)	0	2 (7)	1 (4)	6 (7)	2 (2)
Blood creatinine increased	1 (4)	0	1 (3)	0	0	0	1 (5)	0	1 (5)	0	4 (4)	0	2 (13)	0	1 (8)	0	0	0	0	0	1 (14)	0	2 (7)	0	6 (7)	0
Febrile bone marrow aplasia	0	0	0	0	0	0	0	0	0	0	0	0	2 (13)	1 (7)	0	0	4 (17)	3 (13)	0	0	0	0	0	0	6 (7)	4 (4)
Hyperphosphatemia	0	0	0	0	0	0	0	0	0	0	0	0	2 (13)	0	1 (8)	0	1 (4)	0	1 (17)	0	0	0	1 (4)	0	6 (7)	0
Hypophosphatemia	0	0	1 (3)	0	0	0	1 (5)	0	0	0	2 (2)	0	1 (7)	1 (7)	2 (15)	2 (15)	1 (4)	0	0	0	0	0	2 (7)	1 (4)	6 (7)	4 (4)
Hypotension	2 (8)	1 (4)	0	0	0	0	0	0	0	0	2 (2)	1 (1)	1 (7)	0	1 (8)	0	2 (8)	0	0	0	0	0	2 (7)	1 (4)	6 (7)	1 (1)
Alopecia	2 (8)	0	1 (3)	0	0	0	0	0	0	0	4 (4)	0	1 (7)	0	1 (8)	0	0	0	0	0	0	0	3 (11)	0	5 (5)	0
Blood phosphorus increased	0	0	0	0	0	0	0	0	0	0	0	0	2 (13)	0	1 (8)	0	1 (4)	0	1 (17)	0	0	0	0	0	5 (5)	0
Hyperkalemia	0	0	1 (3)	0	0	0	0	0	0	0	1 (1)	0	3 (20)	1 (7)	0	0	0	0	1 (17)	1 (17)	0	0	1 (4)	1 (4)	5 (5)	3 (3)
Malaise	1 (4)	0	0	0	0	0	0	0	0	0	2 (2)	0	0	0	1 (8)	0	2 (8)	0	0	0	1 (14)	0	1 (4)	0	5 (5)	0
Pyrexia	0	0	2 (7)	0	0	0	0	0	0	0	3 (3)	0	1 (7)	0	3 (23)	0	0	0	0	0	1 (14)	0	0	0	5 (5)	0

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; RDE, recommended dose for expansion.

[a]Includes patients ($n = 10$) in cohorts receiving eltrombopag.

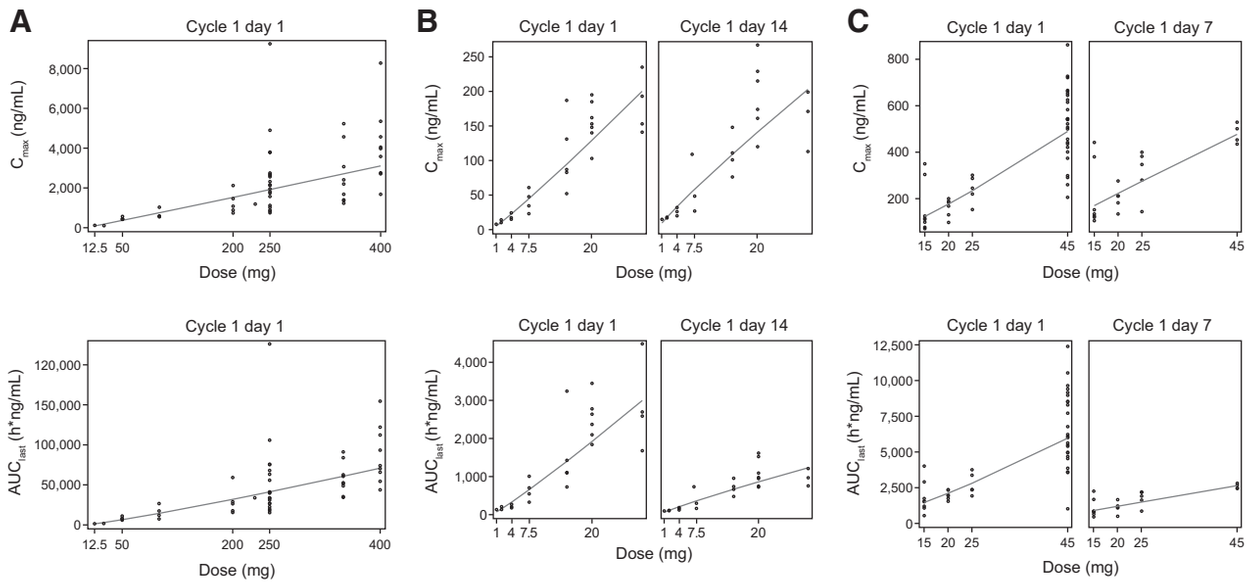

Figure 1.

Relationship between siremadlin dose and noncompartmental PK parameters for cycle 1 day 1 in all patients (PK analysis set). **A,** High-dose 1A (dose range, 50–400 mg) $n = 57$; **B,** low-dose 2A (dose range, 1–30 mg) $n = 27$; **C,** low-dose 2C (dose range, 15–45 mg) $n = 45$. The solid lines shown in the figure are based on the fitted model: PK parameter = exp(alpha)*dose**beta. AUC_{last}: high-dose 1A is represented by 0–48 hour; low-dose 2A cycle 1 day 1 and day 14 by 0–24 and 0–8 hour, respectively; low-dose 2C cycle 1 day 1 and day 7 by 0–24 and 0–8 hour, respectively. AUC_{last}, area under the concentration–time curve from time 0 to last measurable concentration; C_{max}, maximum observed concentration; PK, pharmacokinetic.

Antitumor activity

Among patients with solid tumors, the overall response rate [ORR: complete remission (CR) + PR] was 3.5% [95% confidence interval (CI), 1.0–8.7]; the disease control rate (DCR) was 36.5% (95% CI, 27.7–46.0). Three patients in high-dose 1B and one in high-dose 1A achieved a PR (Supplementary Table S6). Responding patients had tracheal hemangiopericytoma (solitary fibrous tumor; $n = 1$), intimal sarcoma ($n = 2$), or LPS ($n = 1$). Initial responses were achieved at 27,

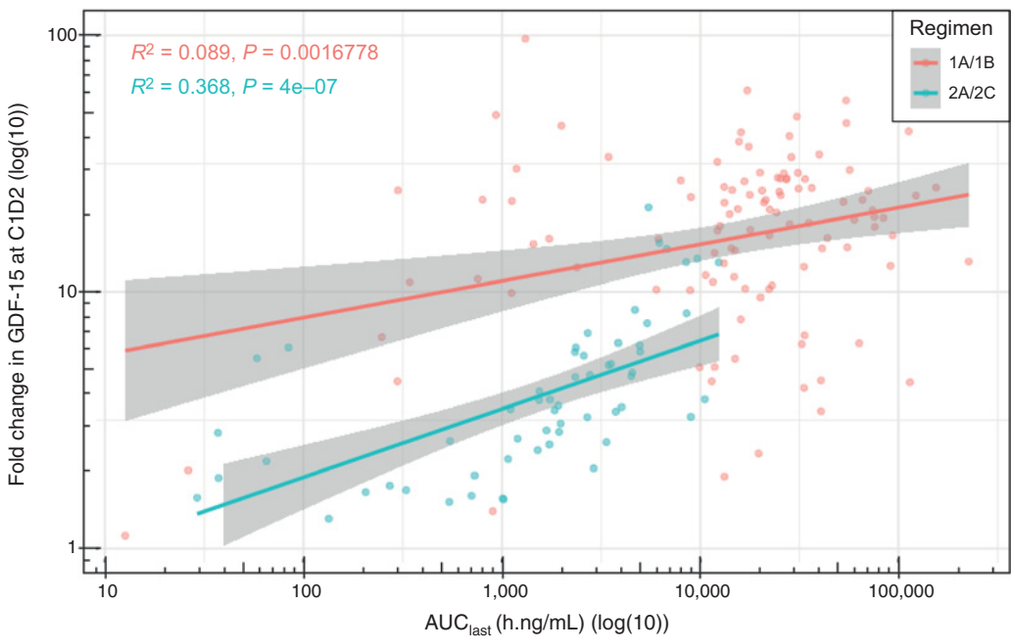

Figure 2.

Representation of individual GDF-15 serum levels expressed as a fold change between predose and 24 hours after dose of siremadlin (C1D2) as it relates to drug serum concentration (AUC_{last}). AUC_{last} calculated on 0–48 hour for high-dose 1A/1B and 0–24 hour for low-dose 2A/2C. All patients irrespective of the cancer type are depicted. AML, acute myeloid leukemia; C1D2, cycle 1, day 2; GDF-15, growth/differentiation factor-15.

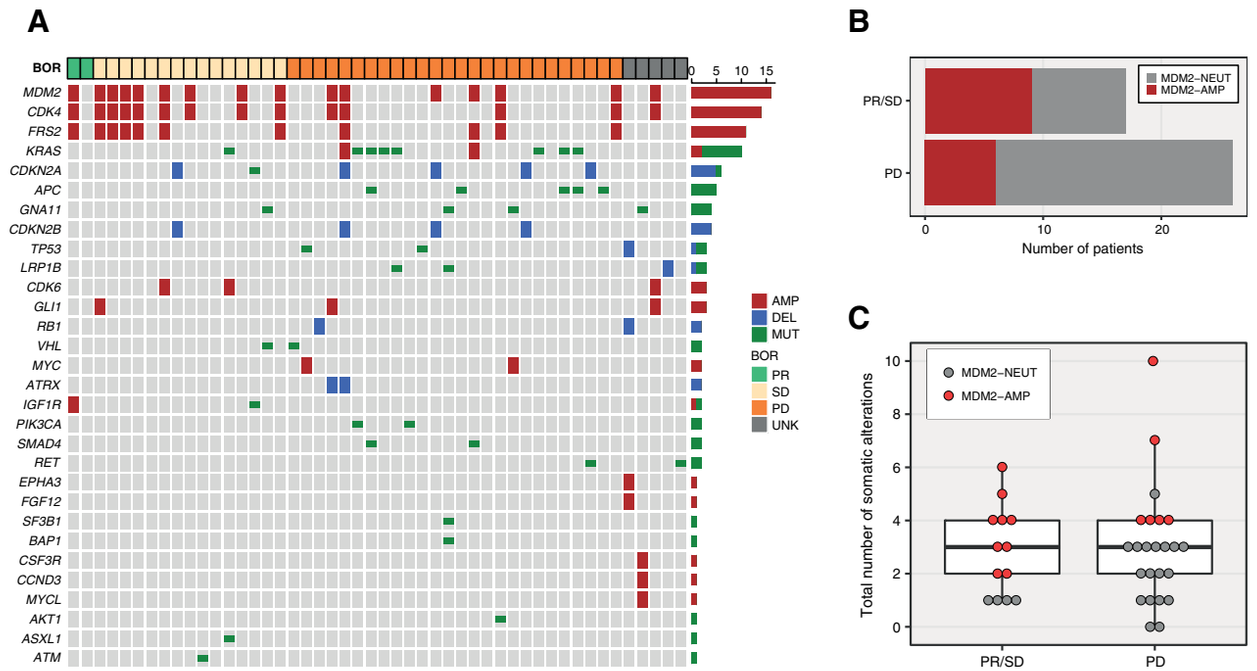

Figure 3.

Genetic alterations detected by NGS in relation to the clinical outcome. **A,** Alterations in 324 cancer-associated genes were evaluated using FoundationOne sequencing in 48 patients with solid tumors. Detected pretreatment somatic alterations of known and likely significance in each patient are depicted together with clinical outcome. Heatmap colors indicate alteration type in the 20 genes most frequently altered across the gene panel. Best overall response (BOR) is also shown for each patient. The numbers and types of alterations identified in each gene are indicated by the bars on the right of the heatmap. Genes with copy number ≥6 were defined as amplified. **B,** *MDM2* status by clinical outcome. The frequency of somatic amplifications in *MDM2* is depicted in patients with better (PR/SD) or worse (PD) clinical outcomes. **C,** Total number of somatic alterations in patients with solid tumors in relation to *MDM2* amplification and clinical outcome. Somatic alterations include copy-number and point mutation events in any of the 324 genes in the FoundationOne panel. Total alteration counts shown here are stratified by patients with better (PR/SD) or worse (PD) clinical outcomes. Points are colored by *MDM2* amplification status. AMP, copy-number amplification; DEL, deletion; MDM2–AMP, MDM2 with copy-number amplification; MDM2–NEUT, MDM2 with neutral copy number; MUT, point mutation; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.

71, 114, and 117 days after treatment began and lasted 79, 92, 452, and 459 days, respectively. No patient achieved CR, but 38 (33%) achieved SD (note that 16/38 patients had LPS, which often has an indolent course). Best percentage change in target lesions from baseline in patients with LPS treated at the RDE is shown in Supplementary Fig. S8. The patient with PR achieved a tumor reduction of 80.84%.

Among the 91 patients with AML, 5 achieved CR (2 patients were treated with high-dose 1A, 1 with high-dose 1B, and 2 with low-dose 2C). CR was achieved at 30, 31, 36, 41, and 50 days of treatment in all responding patients and lasted for 49, 77, and 151 days in 3 patients who eventually relapsed; one patient continues to respond after 141 days and one patient did not have another assessment following initial CR. All 5 responding patients with AML had received at least two prior lines of therapy. In the 4 responding patients with cytogenetic data available, 3 had intermediate risk cytogenetics (trisomy 8, –Y, and normal) and 1 had unfavorable cytogenetics (del7q). The ORR [CR + morphologic CR with incomplete blood count recovery (CRi) + PR] in these patients was 13.2% (95% CI, 7.0–21.9; 5 CR and 7 CRi) overall, and 4.2% (95% CI, 0.1–21.1; 1 CR), 20% (95% CI, 4.3–48.1; 1 CR and 2 CRi) and 22.2% (95% CI, 8.6–42.3; 2 CR and 4 CRi) in those treated at the identified RDEs in high-dose 1B, high-dose 1A, and low-dose 2C, respectively (Supplementary Table S8). There were also patients with a greater than 50% decrease in blast count; however, all necessary criteria for assigning a PR were not met. Two patients, one who had achieved a CRi and one who had not responded (both treated with low-dose 2C), received an allogeneic stem cell transplant following treatment discontinuation. It should be noted that transplantations that occurred later than 30 days after the last treatment dose were not recorded.

Twelve patients with LPS were enrolled and treated with siremadlin at the RDE for high-dose 1B (120 mg) in the dose-expansion phase of the study. Of these, none achieved CR but 1 (8%) achieved a PR and 9 (75%) achieved SD; the DCR in these 12 patients was 83.3% (95% CI, 51.6–97.9). Ten of these patients had a progression-free survival (PFS) event of disease progression and 2 were censored. Median PFS for these 12 patients was 5.6 months (95% CI, 1.9–12.9). Of the 9 patients with SD, 3 patients achieved SD for >6 months.

Discussion

The p53 protein plays a critical role in tumor suppression by inducing growth arrest, apoptosis, and senescence of tumors in addition to blocking angiogenesis (27). Increasing p53 activity represents a potential therapeutic target that could offer patients with a range of different tumor types new treatment options (11, 27, 28). In this study, escalating doses of siremadlin were explored in two fractionated low-dose (2A or 2C) and two pulsed high-dose (1A and 1B) regimens for various indications based on preclinical data (21). Siremadlin displayed linear PK in the tested dose range across all

regimens, with moderate interpatient variabilities for AUC_{last} and C_{max}. Observation of dose-dependent induction of GDF-15 suggested that p53 pathway activation, and therefore biological target engagement, was achieved with siremadlin, in line with previous observations (21). For patients with solid tumors, an RDE of 120 mg was declared with high-dose 1B, while in patients with hematologic malignancies three RDEs were declared: 250 mg, 120 mg, and 45 mg with high-dose 1A, high-dose 1B, and low-dose 2C, respectively. For hematologic malignancies, these RDEs account for different siremadlin regimens: fractionated low dose and pulsed high dose that have been linked preclinically with a different mechanism of action. In addition, they offer a broader range of options for future siremadlin-based combinations.

Overall, the safety profile of siremadlin did not differ significantly between tumor types and regimens. Thrombocytopenia, believed to be an on-target effect of MDM2 inhibition (29), was common in line with previous studies of MDM2 inhibitors (17, 30). Moreover, the delayed onset of siremadlin-induced thrombocytopenia and the long platelet recovery time was likely related to the preferential effect of siremadlin on early proliferative hematopoietic cells. This effect is reflected by the PK/PD model-derived mean maturation time on circulating platelets of 294 hours, which is consistent with that of other MDM2 inhibitors (31), and supportive of short-term high-dose treatment intervals. Furthermore, preclinical and clinical model-based PK/PD analysis showed siremadlin antitumor growth activity not to be regimen-dependent. That is, equivalent antitumor activity could be achieved across regimens providing that the same average concentrations or cumulative dose were achieved per treatment cycle (18). This is of clinical importance as it allows the optimization of dosing regimens to mitigate occurrence of severe myelosuppression that would otherwise be associated with prolonged continuous administration of siremadlin. The reported thrombocytopenia model was used to simulate and guide decisions on dosing regimen(s) selection based on maximizing the total dose per cycle for efficacy while mitigating the occurrence of severe thrombocytopenia (26).

Tumor lysis syndrome was reported in 24% of patients with hematologic malignancies, providing an indication of the antileukemic activity of treatment. It will be necessary to consider the AE and prevention strategies in future development. Other common AEs included gastrointestinal toxicities of lower grade and hematologic toxicities. Compared with patients with solid tumors, more patients with hematologic malignancies had grade 3/4 AEs (71% vs. 45%) and grade 3/4 SAEs (45% vs. 15%). Disease severity at baseline and baseline bone marrow myelosuppression may have contributed to these differences in both severity and incidence of hematologic toxicities. More patients with hematologic malignancies died during study evaluation (37% vs. 11% of patients with solid tumors); however, most deaths were due to underlying disease.

In patients with solid tumors, antitumor activity was limited [ORR = 10.3% (95% CI, 2.2–27.4), comprising 3 PRs] among the 29 patients treated with the RDE, possibly due to tumor heterogeneity. For the 12 patients with *TP53* wild-type LPS enrolled in the expansion group, a DCR of 83.3% (95% CI, 51.6–97.9; comprising 1 PR and 9 SD) was achieved. It should be noted, LPS often presents with an indolent course. However, LPS may be particularly sensitive to siremadlin given the characteristic amplification and/or overexpression of *MDM2* observed in LPS tumors (32, 33). The results for patients with solid tumors highlight the need for combining siremadlin with other agents to potentially improve efficacy.

Among patients with hematologic malignancies treated at the RDEs, antitumor activity was more apparent in high-dose 1A (ORR, 20%; 95% CI, 4.3–48.1, comprising 1 CR and 2 CRis) and low-dose 2C (ORR, 22.2%; 95% CI, 8.6–42.3, comprising 2 CRs and 4 CRis) compared with high-dose 1B (ORR, 4.2%; 95% CI, 0.1–21.1, comprising 1 CR). Five patients with AML across all dosing cohorts of these three regimens achieved CR. This outcome is encouraging given that about one third of patients had received more than three lines of prior therapy and 16% had received prior stem cell transplantation; this compares favorably with other salvage therapies for AML (34, 35).

In 48 patients with solid tumors enrolled based on local assessment of *TP53*, *TP53* sequencing was reassessed centrally using NGS with the FoundationOne panel, whereby alterations were discovered in 3 patients (2 with somatic mutation and 1 with deletion in *TP53*). All 3 patients progressed immediately on treatment. There are several potential reasons for these discrepancies in *TP53* sequencing. They could be due to the sensitivity and ability of different assays to detect mutations with lower allelic frequency. Also, sequencing was done on different biopsy samples, which could have been collected from different lesions, with different *TP53* status. In addition, archival tissue collected months before the study enrollment was allowed for screening. As the incidence of *TP53* mutations may increase with therapy-related genomic instability, this may have contributed to the detection of *TP53* mutations after the patient had been enrolled in the study (36).

In this study, siremadlin demonstrated a tolerable safety profile consistent with previous observations of siremadlin and other MDM2 inhibitors. DLTs of thrombocytopenia were manageable. Efficacy was limited in patients with solid tumors, although patients with LPS in the expansion group achieved excellent disease control. The emergence of *TP53* mutations following treatment with this class of compounds has been previously reported (37); this was not evaluated in the current study, but is planned for investigation in an ongoing study of patients with AML and high-risk myelodysplastic syndromes (MDS; NCT03940352). Siremadlin is being investigated in combination with other agents in an attempt to broaden its efficacy; these include a cyclin-dependent kinase-4 inhibitor for LPS (NCT02343172), anti–programmed cell death protein-1 for colorectal cancer and renal cell carcinoma (NCT02890069), and a Janus kinase 1/2 inhibitor for myelofibrosis (NCT04097821). Combinations with an anti-TIM3 and with B-cell lymphoma-2 (Bcl2) inhibitor for AML and high-risk MDS (NCT03940352) are also being explored.

Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described at www.clinicalstudydatarequest.com.

The sequencing data described in this publication will be made available for any qualified request. To submit a request, please contact: novartis.datasharing@novartis.com.

Authors' Disclosures

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