DSP-5336: A Promising MENIN-MLL Inhibitor for Precision Medicine in Acute Myeloid Leukemia

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The 11q23 abnormalities involving mixed lineage leukemia (MLL) gene are frequently found in adult and pediatric patients with acute leukemia. MLL rearrangements (MLL-r) are often associated with poor prognosis and show poor response to currently available therapies; thus, developing more effective therapies is urgently required. The leukemogenic activity of MLL fusion proteins, the products of the chimeric genes of MLL and its fusion partners generated by MLL-r, is critically dependent on direct interaction with MENIN. Therefore, we have generated a MENIN-MLL interaction inhibitor (DSP-5336), which showed durable anti-leukemogenic activity against acute leukemia with MLL-r or NPM1 mutations in non-clinical studies. DSP-5336 is an ongoing Phase I/II clinical trial that aims to fulfill unmet medical needs for acute leukemia.

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Introduction

Leukemia, a type of blood cancer, results from gene mutations in hematopoietic cells, primarily in the bone marrow. It is characterized by the autonomous proliferation of immature hematopoietic cells (blasts) that have lost their ability to differentiate. Leukemia is broadly classified into chronic leukemia (chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL)) and acute leukemia (acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL)). Recent research has elucidated the etiology and pathology of leukemia at the chromosomal and genetic levels, revealing that specific genetic abnormalities are related to the prognosis of leukemia treatment. Research is ongoing on the classification of leukemia types based on genetic abnormalities and the establishment of optimal treatments for each classification[1),2)]. Almost all cases of CML involve the constant activation of the BCR-ABL tyrosine kinase encoded by the BCR-ABL fusion gene. The development of tyrosine kinase inhibitors, such as Gleevec, which inhibits this function, has dramatically improved the five-year survival rate to over 95%[3),4)]. Meanwhile, several carcinogenic driver gene abnormalities, including transcription factors and chromatin regulators, observed in acute leukemia are difficult to target with therapeutic drugs. Further, the wide variety of gene mutations has delayed the development of molecularly targeted drugs, making chemotherapy the first-line treatment for many cases of acute leukemia. Cases of acute leukemia are divided into good, intermediate, and poor prognosis groups depending on the type of gene mutation. The poor prognosis group has a low response rate to chemotherapy and an extremely low five-year survival rate of about 30%[5),6)]. In this study, we used non-clinical pharmacological data and some of the latest clinical data to demonstrate the efficacy and future potential of the MENIN-MLL binding inhibitor (DSP-5336). This inhibitor was developed as an innovative treatment for cases of leukemia with mixed lineage leukemia (MLL) gene translocations, which belong to the poor prognosis group, and is currently in the clinical development stage.

Discovery of MENIN-MLL protein binding

Chromosome 11q23 translocations are relatively frequent, occurring in about 10% of all adult acute leukemia cases and 80% of infant acute lymphoblastic leukemia cases[7)–9)].

Acute leukemia with chromosome 11q23 translocation is characterized by rapid disease progression and a high relapse rate, even after treatment with strong anticancer drugs or hematopoietic stem cell transplantation, leading to an extremely poor prognosis. Therefore, there is a strong demand for innovative treatments[10]. Chromosome 11q23 translocations are reciprocal translocations with the MLL gene located on the long arm of chromosome 11 (11q23.3) as the breakpoint. This results in the generation of an MLL fusion gene where the N-terminal region of the MLL gene is fused in-frame with a partner gene, leading to leukemia[11]. Yokoyama, a collaborator of one of the authors, reported the molecular mechanism by which the MLL fusion protein expressed by the MLL fusion gene interacts with a co-factor called MENIN to cause leukemia[12]. Subsequent research has shown that the MLL fusion protein binds to MENIN and activates the expression of a group of genes involved in leukemia development by binding to a specific transcriptional control region (HOXAS9/MEIS1 promoter, *etc.*), where another protein, LEDGF, is present[13]. That report demonstrated that the deletion of the MENIN gene in cells that develop leukemia because of the MLL fusion gene results in the leukemic cells losing their undifferentiated state and inducing differentiation. It has also been shown that the deletion of the MENIN gene in a leukemic model mouse created by expressing the MLL fusion gene in hematopoietic cells results in the remission of fatal leukemia. These results led to the idea that low-molecular-weight compounds inhibiting the intermolecular binding between MLL and MENIN could inhibit the transcriptional activation of MLL-dependent carcinogenesis-related factors and act as molecularly targeted drugs (**Fig. 1**, upper panel).

Meanwhile, recent research has shown the molecular mechanism by which wild-type MLL leads to leukemia in some cases without MLL gene translocations[14]. One example is leukemia with NPM1 gene mutations (NPM1c). NPM1 gene mutations belong to the intermediate prognosis group, but most patients with this mutation also have FLT3, IDH1/2, DNMT3A, and other mutations, worsening the prognosis[15]. The treatment policy differs depending on the concomitant gene mutation, but hematopoietic stem cell transplantation is recommended in cases with concomitant poor prognosis factors, indicating a high unmet medical need. Cases of leukemia with NPM1 gene mutations have been reported to exhibit NPM1c acting as a transcriptional activator through binding with wild-type MLL, inducing the expression of leukemia-related genes such as HOXA9 and MEIS1 and resulting in disease onset[16]. This molecular mechanism involves the binding of wild-type MLL to MENIN and coupling with LEDGF, which activates the expression of genes involved in leukemia development by binding to transcriptional control regions (*e.g.*, HOXA9/MEIS1 promoter). This suggests that MENIN-MLL binding inhibitors are also effective against cases of leukemia that highly express HOX genes through the function of the wild-type MLL/MENIN complex (**Fig. 1**, lower panel).

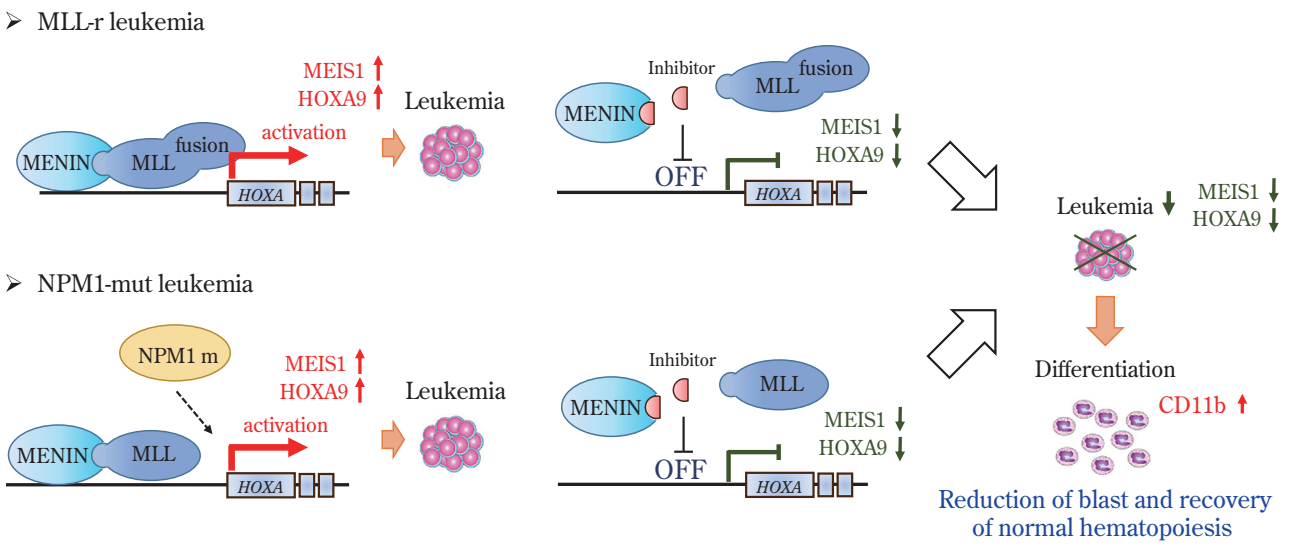

Fig. 1 MENIN-MLL inhibitor turns off the leukemic gene transcription in AML cells with MLL-r/NPM1 mutation and induces terminal differentiation.

New MENIN-MLL binding inhibitor: DSP-5336

Creation of DSP-5336

DSP-5336, a MENIN-MLL binding inhibitor, was developed as a next-generation protein–protein interaction (PPI) molecularly targeted drug, specifically targeting the PPI between MLL and MENIN[17]. Low-molecular-weight compounds typically inhibit protein function by targeting the pocket structure originally present in the protein that binds to low-molecular-weight substrates.

Many previously approved molecularly targeted anticancer drugs are inhibitors that target the active site of enzymes with deep pocket structures. For example, Gleevec, a drug for CML, exhibits its pharmacological effect by competitively binding with adenosine triphosphate (ATP) to the tyrosine kinase active site of BCR-ABL[18]. However, MENIN proteins lack enzymatic functions and deep pocket structures, making them difficult targets for drug discovery. Research by our collaborators showed a binding mode in which a short peptide sequence called RXRFP, present at the N-terminal of the MLL protein, is recognized by a wide region on the MENIN side[12]. Crystal analysis results further showed that MENIN-MLL binding is a druggable target, exhibiting a lock-and-key binding mode where MENIN binding domains (MBDs) containing the RXRFP sequence bind to a relatively wide and shallow pocket structure in the MENIN protein[19]. Based on this, our unique *in silico* approach and drug discovery research targeting the shallow pocket structure of the MENIN protein led to the discovery of a new compound binding site on the MENIN protein surface. This resulted in the identification of compounds that selectively and strongly inhibit MENIN-MLL binding. Additionally, we modified the MLL fusion gene to create unique leukemia cells in which the MLL transcription pathway was activated without MENIN binding. This was used as a counter assay in compound screening, leading to the creation of a clinical candidate compound, DSP-5336, which has low cytotoxicity because of its nonspecific action.

Pharmacological effects of DSP-5336

A) *In vitro* pharmacological effects

- Cell-free evaluation system: MENIN-MLL binding inhibition evaluation

The MENIN-MLL binding inhibitor DSP-5336, developed as a next-generation PPI molecular targeting drug, was confirmed to have a strong affinity

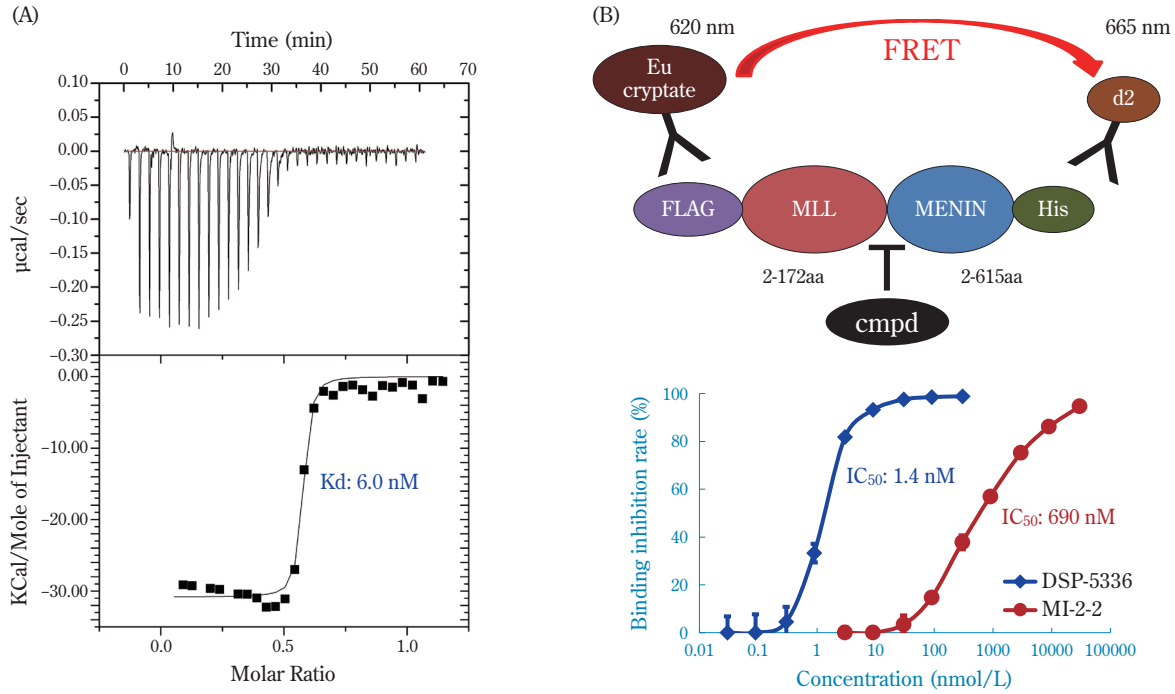

Fig. 2 DSP-5336 directly bound to MENIN and inhibited the MENIN-MLL interaction.
(A) Binding isotherm from ITC for DSP-5336 binding to MENIN protein, demonstrating binding affinity (*Kd*).
(B) Inhibition of the MENIN-MLL interaction separates the Europium cryptate donor from the d2 acceptor and decreases the HTRF ratio (emission intensity at 665 nm/emission intensity at 620 nm). Binding inhibition rates were calculated using the HTRF ratio and IC_{50} values were calculated by logistic curve fitting. Three independent tests were conducted.

(*Kd* = 6.0 nM) for the MENIN protein in an isothermal titration calorimetry (ITC) test (**Fig. 2**A). The MENIN-MLL binding inhibition ability was evaluated using a time-resolved fluorescence resonance energy transfer (FRET) TR-FRET (HTRF) assay. This assay system uses the FRET signal resulting from the binding of the MENIN protein and MLL protein (N-terminal region) bound to different fluorescent dyes. In this assay system, DSP-5336 was shown to inhibit MENIN-MLL interactions at an extremely low concentration, that is, a median inhibitory concentration (IC_{50}) ≤ 50 nM (**Fig. 2**B). These results demonstrate that DSP-5336 strongly inhibits protein interactions with MLL by binding to MENIN.

- Cellular evaluation system: Selective pharmacological effects on leukemia cells

The pharmacological effects of DSP-5336 at the cellular level have been examined in various human leukemia cell lines. DSP-5336 shows inhibitory effects on proliferation at low concentrations (IC_{50}: 10–30 nM) against three human leukemia cell lines with MLL gene translocations (MLL-AF4 positive cells: MV4-11, MLL-AF9 positive cells: MOLM-13, MLL-ENL positive cells: KOPN-8) but did not inhibit proliferation in three human leukemia cell lines without MLL gene translocations (HL-60, MOLT-4, and Reh) (**Table 1**). DSP-5336 also showed inhibitory effects on proliferation against OCI-AML3 cells (without MLL gene translocation) carrying NPM1 gene mutations (NPM1c), suggesting a pharmacological effect against leukemia cells that proliferate through the wild-type MLL function (**Table 1**). These results indicate that DSP-5336 selectively inhibits the proliferation of MENIN-MLL binding-dependent leukemia cells (leukemia cells with MLL translocation or NPM1 mutation).

Table 1 DSP-5336 selectively inhibited the cell growth of human leukemia cell lines

Cells were seeded in 96-well plates and DSP-5336 at a range of concentrations was added. After incubating for 7 days, cell viabilities were measured using PrestoBlue Cell Viability Reagent. IC_{50} values were estimated based on the cell viability data, using the sigmoid Emax model.

Cell line	*MLL-r/NPM1* mutation	IC_{50} (nM)
MV4-11	*MLL-AF4*	10.2
MOLM-13	*MLL-AF9*	14.7
KOPN-8	*MLL-ENL*	30.8
OCI-AML3	*NPM1* mutation	15.3
HL-60	None	> 10000
MOLT-4	None	> 10000
Reh	None	> 10000

Proof of mechanism (POM) in new drug development requires a pharmacodynamics (PD) marker as an indication of efficacy based on the molecular mechanism of action of the drug. DSP-5336 inhibits the expression of leukemia-related genes by inhibiting MENIN-MLL binding, thereby inhibiting the proliferation of leukemia cells (blasts) and inducing differentiation. Therefore, we confirmed the change in PD markers arising from DSP-5336 treatment using MV4-11 cells, a human AML cell line with MLL-AF4 translocation. The results showed a DSP-5336 concentration-dependent decrease in the expression of undifferentiated marker genes (leukemia-related genes)

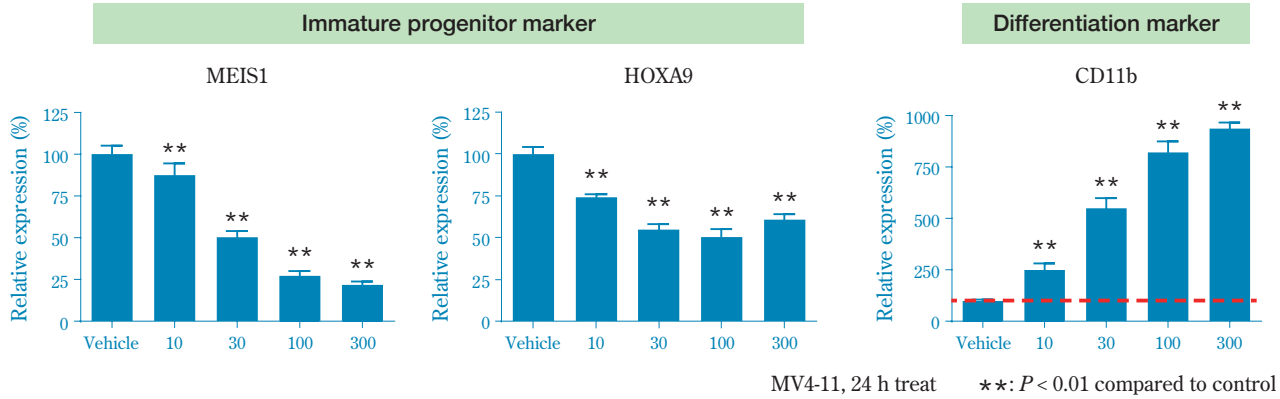

Fig. 3 DSP-5336 modulates the expression of MENIN-MLL-associated PD markers in the MV4-11 cell line.

RT-qPCR was performed on MV4-11 cells after treatment with DSP-5336 for 24 hours. The expression levels of HOXA9, MEIS1, and CD11b were normalized to GAPDH and referenced to the vehicle-treated control. Values are presented as mean ± S.D. (n = 6). ** P < 0.01 vs vehicle (the Dunnett's test).

such as HOXA9 and MEIS1, which are expressed in association with the MENIN-MLL interaction. A DSP-5336 concentration-dependent increase was also confirmed in the expression of CD11b, a terminal differentiation marker in myeloid cells (**Fig. 3**). These results suggest that DSP-5336 inhibits MENIN-MLL protein binding, suppressing the expression of undifferentiated marker genes deeply involved in leukemia development and inducing differentiation.

B) *In vivo* pharmacological effects

DSP-5336 has been developed as an oral drug, and a favorable pharmacokinetic (PK) profile (sufficient blood exposure for exerting pharmacological effects) has been confirmed in a PK study using mice. A pharmacological efficacy study using a tumor-bearing model [cell line-derived xenograft (CDX) model] in which a human AML cell line (MV4-11 cells) with MLL gene translocation was subcutaneously transplanted into nude mice demonstrated complete tumor regression in all test subjects (5/5 cases) 10 days after drug administration at a dose of 50 mg/kg/BID (p.o.), a dose at which no toxic findings were observed. Significant tumor growth inhibition was observed in a dose-dependent manner, even at the low dose of 25 mg/kg/BID (p.o.) (**Fig. 4**A).

PD marker changes in the residual tumor tissue were analyzed in this pharmacological study, and results demonstrated a significant decrease in the expression of gene markers (HOXA9 and MEIS1) that indicate the undifferentiated nature of the tumor in a drug dose-dependent manner (**Fig. 4**B), as well as a significant increase in the expression of the terminal differentiation marker (CD11b) in monocytic and granulocytic cells (**Fig. 4**B, right). These demonstrate that DSP-5336 exhibits a pharmacokinetic profile sufficient for demonstrating pharmacological effects *in vivo* in mice, and that the drug inhibits the proliferation and promotes the differentiation of human leukemia cells carrying the MLL fusion gene at drug concentrations that did not show significant toxic findings.

Translational research: Efficacy in human clinical specimens

An essential component of new drug development before clinical trials in patients is non-clinical trials using model animals such as mice. However, the discrepancy between the results of non-clinical trials using laboratory animals and clinical trials in patients is a significant issue in new drug development[20]. This issue is thought to arise from differences between the "cancer cell lines" used in non-clinical trials and "cancer cells in clinical practice." The "cancer cell lines" commonly used in non-clinical trials are selected as clones with high proliferation ability suited for culture conditions. These cells acquire

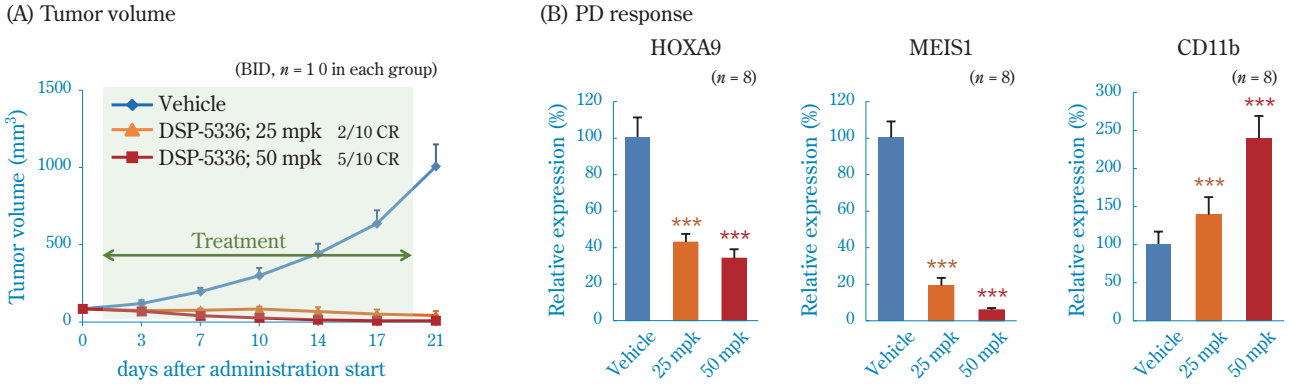

Fig. 4 DSP-5336 demonstrated antitumor activity with a corresponding PD response in a subcutaneous MV4-11 xenograft model.

(A) MV-4-11 cells were subcutaneously inoculated into NOD/SCID mice. The dosing formulations were administered orally twice daily for 20 days. Values are presented as mean ± S.D. (n = 10). *** P < 0.001 vs vehicle group (the Dunnett's test). CR, complete remission.

(B) MV-4-11 cells were subcutaneously inoculated into NOD/SCID mice. The dosing formulations were administered orally twice a day on days 1 and 2, and once a day on day 3. After administration on day 3, the tumors were collected, and RT-qPCR was performed. The expression levels of HOXA9, MEIS1, and CD11b were normalized to GAPDH and referenced the vehicle-treated group. Values are presented as mean ± S.D. (n = 8). *** P < 0.001, ** P < 0.01 vs vehicle group, (the Dunnett's test).

genetic mutations and epigenetic changes during long-term culture, so they do not necessarily maintain the properties of cancer cells in clinical practice. Therefore, when developing DSP-5336, we conducted translational research using acute leukemia patient specimens held by the National Cancer Center to increase the accuracy of clinical trials.

A) *Ex vivo* pharmacological evaluation using leukemia clinical specimens

Seeding bone marrow mononuclear cells collected from AML patients on a semi-solid medium (containing stem cell factor (SCF), interleukin-3 (IL-3), and granulocyte-macrophage colony-stimulating factor (GM-CSF)) resulted in the formation of leukemia cell colonies because of the strong proliferation of leukemia stem cells contained in the clinical specimens (colony formation assay). This assay system was used to investigate the pharmacological effect of DSP-5336 on AML patient specimens carrying the MLL-AF6 fusion gene. The results showed the significant inhibition of leukemia colony formation when DSP-5336 was treated at 100 nM (**Figs. 5**A & B). A characteristic of the leukemic colonies was the formation of large colonies (blast colonies) composed of morphologically undifferentiated cells. However, DSP-5336 treatment caused the disappearance of blast colonies and their transformation into small colonies (granulocyte/macrophage (G/M) colonies) composed of differentiated granulocytic cells (**Figs. 5**A & C). Furthermore, gene expression changes in colony formation cells showed a decrease in the expression of genes (HOXA9, MEIS1) that indicate tumor undifferentiation, which are PD markers, and an increase in the expression of terminal differentiation markers (CD11b) in monocytic and granulocytic cells (**Fig. 5**D). These results indicate that DSP-5336 has sufficient efficacy against leukemic cells in clinical practice, and its mechanism of action is the inhibition of proliferation and induction of differentiation in leukemic cells.

Changes in PD markers were also observed in clinical samples based on the mechanism of action, suggesting the usefulness of DSP-5336 as a PD marker in clinical trials.

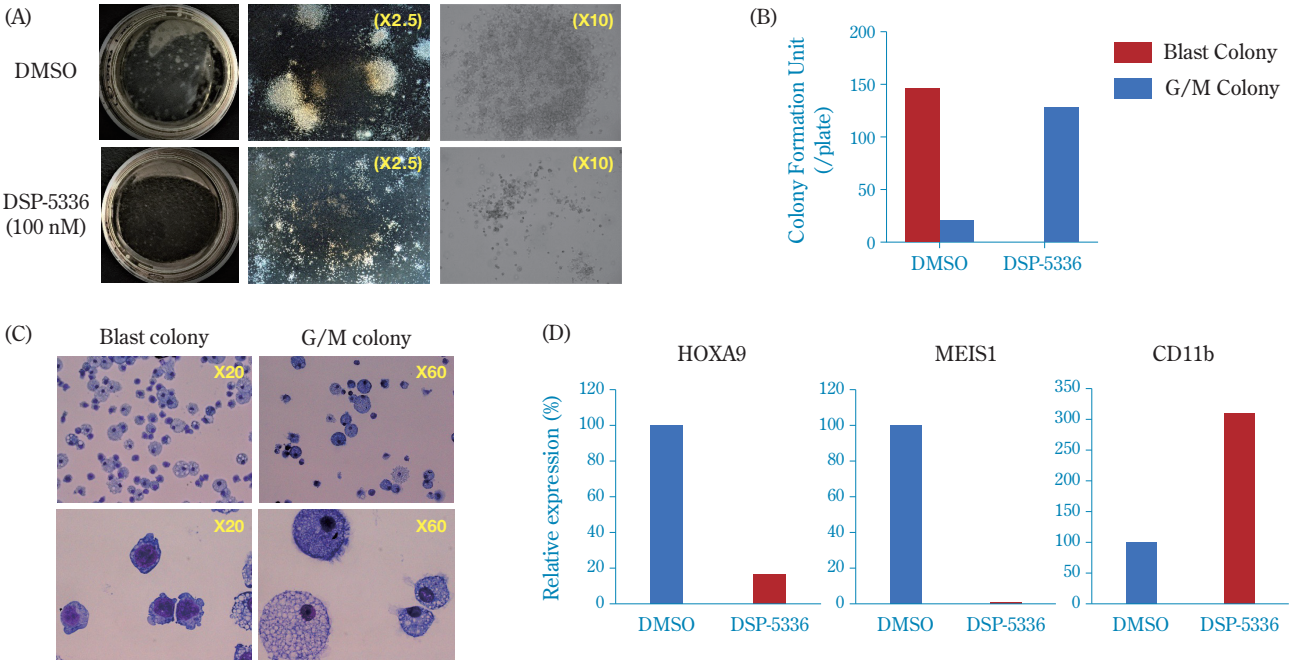

Fig. 5 DSP-5336 showed *ex vivo* efficacy in primary patient samples with MLL-AF6.
Primary patient samples were treated with DSP-5336 (100 nM) or DMSO for 10 days.
Representative images of colonies (A) and Wright-Giemsa-stained cytospin (C) for primary patient samples with MLL-AF6.
The number of blast and G/M colony formation units was counted (B).
RT-qPCR was performed on primary patient samples after treatment with DSP-5336 for 10 days. The expression levels of HOXA9, MEIS1, and CD11b were normalized to GAPDH and referenced to DMSO-treated controls (D).

B) Pharmacological evaluation in a patient-derived xenograft (PDX) model

The PDX model, created by transplanting bone marrow cells from AML patients into severely immunodeficient mice, is a disease model that reflects the pathology of human AML[20),21)]. The cell line-derived xenograft (CDX) model, in which leukemia cell lines were transplanted subcutaneously into immunodeficient mice, is a simple test but has limitations. For example, it does not exhibit phenotypes characteristic of human leukemia, such as the appearance of leukemic blasts in peripheral blood, inhibition of normal hematopoiesis accompanied by leukocytosis and anemia, and hepatosplenomegaly. Nevertheless, the PDX model is a high-level model that mimics the clinical circumstances of human AML cases. In this model, human AML stem cells are engrafted in the optimal microenvironment in the mouse bone marrow for disease onset. Conducting pharmacological tests using the PDX model is expected to result in high clinical predictability in actual human leukemia cases. DSP-5336 was administered for 28 days at a dose (100 mg/kg/BID (p.o.)) at which no toxic findings were observed in a PDX model created using specimens from AML patients carrying the MLL-AF4 fusion gene. The results revealed that the control group developed fatal AML accompanied by abnormal proliferation of leukemic blasts (human CD45-positive cells) in the peripheral blood, whereas the DSP-5336 treatment group achieved complete hematological remission (disappearance of leukemic blasts (human CD45-positive cells) in the peripheral blood) and exhibited significant extension of survival (**Figs. 6**A & B). DSP-5336 was also administered for 28 days at doses of 25, 50, and 100 mg/kg/BID (p.o.) in a PDX model created by transplanting bone marrow cells from an AML patient with gene mutations in NPM1 and FLT3/IDH2/DNMT3A. The results indicate that leukemic blasts were eliminated in the peripheral blood, and remission of fatal leukemia was induced (**Figs. 6**C & D). In this model, complete remission was induced even at a low dose of 25 mg/kg/BID (p.o.), confirming the strong pharmacological effect of this drug. These results indicate the high

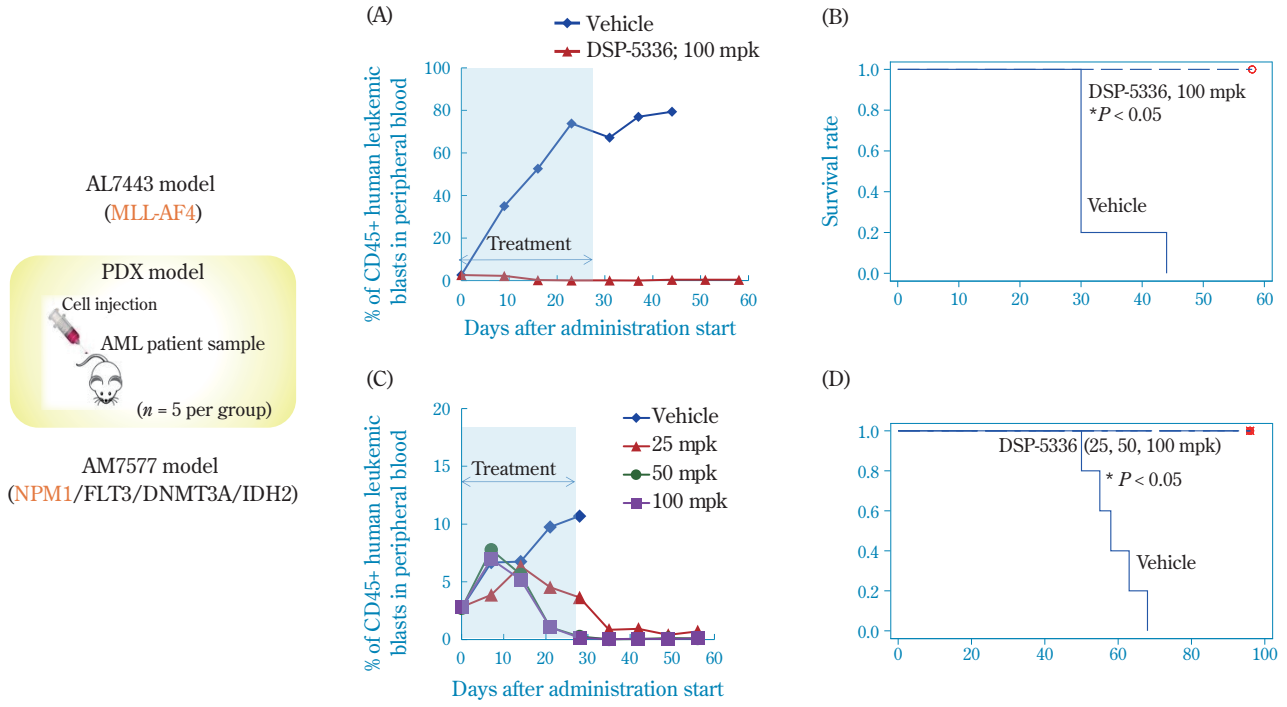

Fig. 6 DSP-5336 induced complete remission and significantly prolonged of survival in the PDX models.
Primary patient-derived leukemia cells with MLL-AF4 or NPM1 mutations were transplanted into NOD/SCID mice, and the tumor burden was determined by the frequency of human CD45-positive cells in peripheral blood using flow cytometry. Dosing was initiated when the mean tumor burden was approximately 3%. The dosing formulations were administered orally twice daily for 28 d.
(A and C) The tumor burden in the peripheral blood was analyzed weekly. Values represent mean (n = 5).
(B and D). Kaplan-Meier survival curves of vehicle- or DSP-5336-treated mice in the PDX model. * P = 0.0037 vs vehicle group, (log-rank test).

efficacy of DSP-5336 against human leukemia and suggest a high therapeutic effect may be expected in clinical trials.

Clinical trials

Clinical trial applications for DSP-5336, a new MENIN-MLL binding inhibitor, were submitted globally based on the results of various non-clinical studies. Applications were accepted in the United States of America (July 2021), Japan (December 2021), and Canada (February 2022), with clinical Phase I/II trials currently underway.

An overview of these clinical trials shows that the initial human dose was set at 80 mg/day based on the results of preclinical safety assessment studies, and the maximum dose in the Phase I portion was set at 1,480 mg/day. Considering the potential impact of azole antifungals, commonly used for infection prophylaxis in leukemia patients, on the metabolic stability of DSP-5336, a dose-escalation study was incorporated into the Phase I portion. All relapsed/refractory (R/R) acute leukemia patients were divided into two arms (A and B) based on azole antifungal use. In Phase I, the recommended Phase-II dose (RP2D) was determined based on safety, efficacy, PD marker changes, and OK values, considering the effects of azole antifungals.

The Phase-II portion is designed to assess efficacy and safety in two arms: MLL gene translocation-positive R/R AML and NPM1 mutation-positive R/R AML (**Fig. 7**). As of the data cutoff, the pharmacological

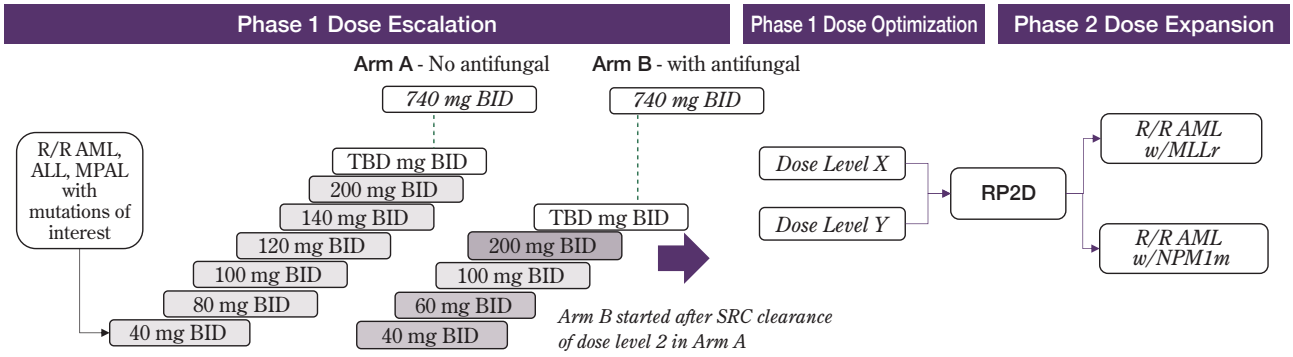

Fig. 7 Clinical study design of DSP-5336
- Dose escalation is guided by a Bayesian Logistic Regression Model
- Phase 1 was narrowed to include only patients with mutations of interest (*e.g.*, MLLr or NPM1m), as documented by the standard of care testing prior to enrollment.

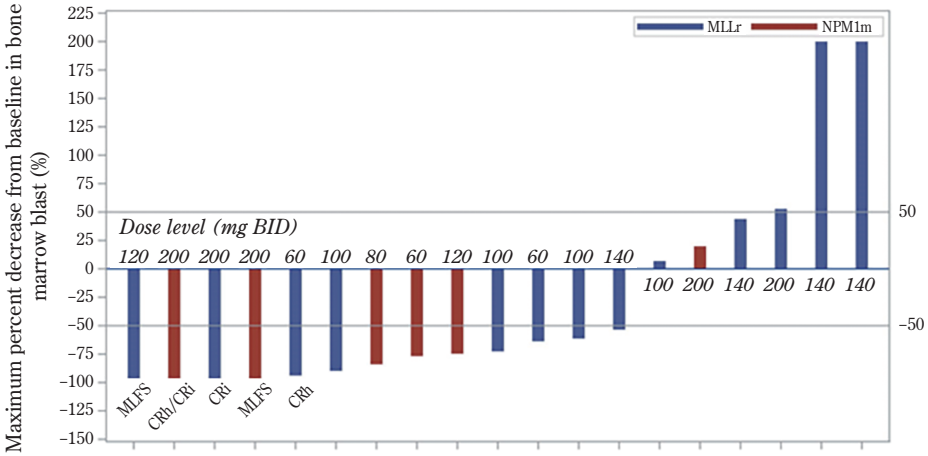

Fig. 8 Clinical activity in Phase I part
- 17 patients had MLLr, 9 pts had NPM1m, and 17 had other genetic subtypes
- At 200 mg BID/Arm B (highest dose tested), there were 4 evaluable patients at the cut-off (3 w/NPM1m, 1 w/MLLr)
- 1 achieved CRh/CRi, 1 achieved CRi, 1 achieved MLFS, all patients cleared peripheral blasts, and all are ongoing
- 2 additional patients with MLLr also achieved responses per ELN 2017 at lower doses (CRh/CRi and MLFS)

effect of DSP-5336 has been evaluated in a subset of treated patients (n = 43), including those with MLL-translocation-positive (n = 17) and NPM1-mutation-positive (n = 9) AML (**Fig. 8**). Notably, among four patients (one MLL-translocation-positive and three NPM1-mutation-positive) receiving 400 mg (200 mg BID) daily in the azole antifungal arm (arm B), three achieved complete clearance of peripheral blood leukemic blasts. Responses in these three cases included hematological remission without recovery of normal hematopoiesis (CRh/CRi and CRi: two cases) and morphological leukemia-free state (MLFS; one case) based on bone marrow examination. The efficacy of DSP-5336 in the treatment of leukemia with MLL translocation and NPM1 mutation was further demonstrated through dose escalation (**Fig. 8**). No dose-limiting toxicities have been observed in previous dose-escalation studies, suggesting that further dose optimization may yield more pronounced efficacy.

Conclusions

AML with MLL gene translocation is characterized by a poor response to chemotherapy and an extremely poor prognosis. MLL translocation is also frequently detected in pediatric leukemia, highlighting the need for targeted therapies that minimize long-term adverse effects. Previous drug discovery efforts have attempted to target leukemia-related factors such as MLL fusion proteins resulting from MLL gene rearrangements, as well as HOXA9 and MEIS1, whose expression is induced by MLL fusion proteins. However, developing small-molecule drugs targeting these transcription factors has proven challenging. Our research focused on the molecular mechanism by which MLL fusion proteins interact with MENIN to promote leukemogenesis. We successfully developed DSP-5336, a small-molecule inhibitor of the protein–protein interaction between MENIN and MLL. DSP-5336 demonstrates potent activity specifically against AML cell lines with MLL translocation and NPM1 mutations. The clear mechanism of action and associated pharmacodynamic markers, validated for use in clinical trials, suggested strong potential for clinical efficacy at the preclinical stage. Our non-clinical pharmacological research incorporated translational approaches to enhance the probability of clinical success. Efficacy was demonstrated in primary AML patient samples with MLL rearrangements and NPM1 mutations before initiating clinical studies. This comprehensive preclinical research program was based on a collaborative project with Kyoto University (DSK project), involving Dr. Akihiko Yokoyama (currently at the National Cancer Center Tsuruoka), who discovered the MENIN-MLL protein interaction. The program progressed through collaboration with Dr. Issei Kitabayashi (National Cancer Center Tsukiji) in translational research and was supported by the AMED Acceleration Transformative Research for Medical Innovation (ACT-M) program and other initiatives[22]. DSP-5336, developed and optimized through these processes, is currently undergoing Phase I/II clinical trials. Preliminary efficacy in AML patients with the target gene alterations is being observed during the dose-escalation phase of the study.

There is no effective treatment for AML with MLL translocations and NPM1 mutations (*i.e.,* with concomitant gene mutations). Therefore, DSP-5336 is expected to change the current treatment strategy as an innovative treatment to improve patient prognosis dramatically.

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