A Phase 1 Study of Milademetan in Combination With Quizartinib in Patients With Newly Diagnosed (ND) or Relapsed/Refractory (R/R) *FLT3*-ITD Acute Myeloid Leukemia (AML)

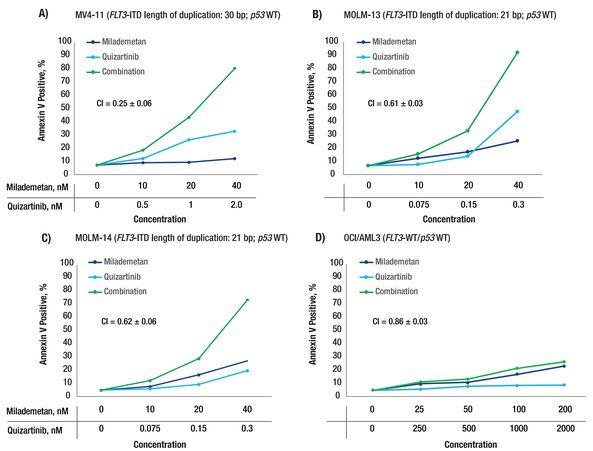
Naval Daver,[1] Weiguo Zhang,[1] Richard Graydon,[2] Vikas Dawra,[2] Jingdong Xie,[2] Prasanna Kumar,[2] Michael Andreeff[1]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Daiichi Sankyo, Inc, Basking Ridge, NJ

BACKGROUND

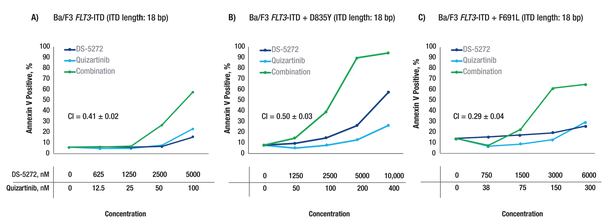
- Fms-related tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutations occur in ≈ 25% of patients with AML and are associated with a poor prognosis[1-3]
- Quizartinib is an oral, highly potent and selective type II FLT3 inhibitor[4]
  - In the phase 3 QuANTUM-R trial, quizartinib prolonged overall survival vs salvage chemotherapy in patients with R/R *FLT3*-ITD AML[4]
- MDM2 downregulates the p53 tumor suppressor protein and is upregulated in patients with AML. Inhibiting MDM2 may restore p53 activity in patients with AML with wild-type *p53*[5]
- Milademetan, a novel and specific oral MDM2 inhibitor, showed activity in an ongoing phase 1 trial in patients with AML or myelodysplastic syndromes (MDS)[6]
- Preclinical studies have shown that quizartinib in combination with milademetan acts synergistically to target *FLT3*-ITD and restore p53 activity in *FLT3*-ITD/*p53* wild-type AML, in quizartinib-resistant cell lines and in sorafenib- and venetoclax-resistant patient-derived xenograft (PDX) models (*FLT3*-ITD positive + D835 mutated) (**Figures 1-4**)[6,7]

Figure 1. Quizartinib Plus Milademetan Treatment Exerted Highly Synergistic Apoptotic Activity in *FLT3*-ITD–Positive/*p53* Wild-Type AML Cell Lines



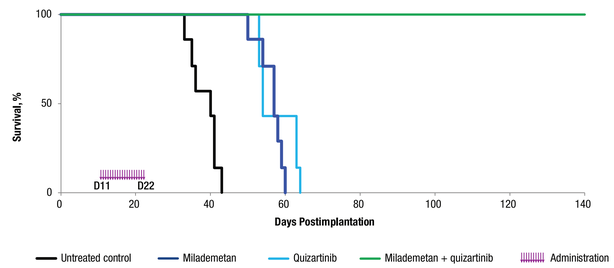
bp, base pair; CI, combination index; WT, wild type.
Cells were treated for 48 to 72 hours in triplicate wells. Apoptosis was measured by flow cytometry with annexin V staining in (A) MV4-11 (derived from blast cells of a 10-year-old male patient with biphenotypic B-myelomonocytic leukemia), (B) MOLM-13 (human cell line derived from the peripheral blood of a patient with AML evolved from MDS), (C) MOLM-14 (human cell line derived from the peripheral blood of a patient with AML evolved from MDS), and (D) OCI/AML3 cells (negative control; derived from the peripheral blood of a 57-year-old male patient with AML). CI < 1 indicates synergism, CI = 1 indicates an additive effect, and CI > 1 indicates antagonism.

Figure 2. Quizartinib Plus the Murine MDM2 Inhibitor DS-5272 Synergistically Induced Apoptosis in Quizartinib-Resistant *FLT3*-ITD–Positive/TKD-Mutant Murine AML Cells



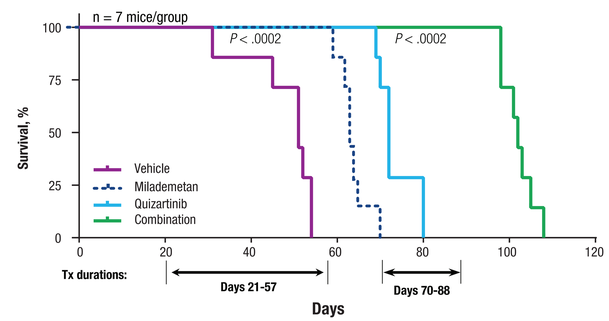
TKD, tyrosine kinase domain.
(A) *FLT3*-ITD–positive/*p53* wild-type, (B) *FLT3*-ITD + D835Y/*p53* wild-type, or (C) *FLT3*-ITD + F691L/*p53* wild-type murine leukemia cells (Ba/F3) were treated with increasing concentrations of single-agent DS-5272 or quizartinib or quizartinib plus DS-5272 for 48 hours. Quizartinib plus DS-5272 synergized to induce apoptosis in *FLT3*-ITD–positive/*p53* wild-type Ba/F3 cells (A). The combination treatment abrogated the prevention of apoptosis induction in quizartinib-resistant, wild-type *p53* Ba/F3 cells co-expressing TKD mutations (B and C). CI < 1 indicates synergism, CI = 1 indicates an additive effect, and CI > 1 indicates antagonism.

Figure 3. Quizartinib Plus Milademetan Improved Overall Survival in an MV4-11 Intravenous Xenograft Model (*FLT3*-ITD positive/*p53* wild type)



NSG mice were inoculated with MV4-11 cells on day 0 and administered treatment (single-agent quizartinib or combination of oral quizartinib 3 mg/kg and oral milademetan 50 mg/kg) once daily for 12 days, starting on day 11.

Figure 4. Quizartinib Plus Milademetan Improved Overall Survival in a PDX Murine Model of Sorafenib- and Venetoclax-Resistant AML (*FLT3*-ITD positive + D835 mutation/*p53* wild type)



Tx, treatment.
Survival curve for xenografted mice. NSG mice were intravenously implanted with xenografts from a patient with AML who harbored *FLT3*-ITD + D835 mutations and relapsed after sorafenib and venetoclax treatments. Oral administration of single-agent quizartinib 5 mg/kg or milademetan 50 mg/kg or quizartinib plus milademetan was initiated on day 21 (~ 1% leukemic cell engraftment). The median survival rates were 51, 63, 72, and 102 days in the vehicle, milademetan, quizartinib, and combination groups, respectively. *P* values (from left to right) represent milademetan vs vehicle and combination vs quizartinib.

OBJECTIVE

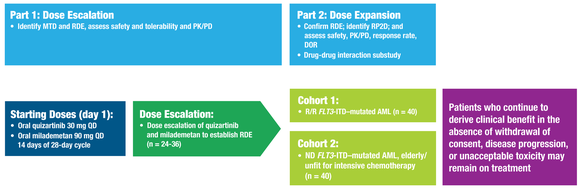
- To evaluate the safety, pharmacokinetics (PK), and preliminary efficacy (tumor response) of the FLT3 inhibitor quizartinib in combination with the MDM2 inhibitor milademetan in patients with ND or R/R *FLT3*-ITD–positive AML

METHODS

Study Design

- Open-label, 2-part, phase 1 study with dose escalation (part 1) and expansion (part 2) portions (NCT03552029; **Figure 5**)
  - The expansion part consists of 2 cohorts: adult patients with R/R *FLT3*-ITD–positive AML (≥ 3% *FLT3*-ITD/total *FLT3*) and elderly or unfit patients with ND *FLT3*-ITD–positive AML
- During dose escalation, quizartinib will be administered once daily in 28-day cycles, with 3 proposed levels: 30, 40, and 60 mg. Milademetan will be administered on days 1 to 14 of each 28-day cycle, with 3 proposed initial dose levels: 90, 120, and 160 mg
- Milademetan in alternative dosing schedules, such as on days 1 to 7 or on days 1 to 3 and 15 to 17 of each 28-day cycle, may also be explored
- The milademetan dose will be escalated first, followed by the quizartinib dose with no simultaneous escalation, guided by a Bayesian logistic regression model (BLRM) with overdose control
- In patients receiving concomitant treatment with strong cytochrome P450 3A (CYP3A) isozyme inhibitors, the milademetan dose will be reduced to half the intended dose, and the quizartinib doses will be reduced from 60 mg to 30 mg, and from 40 and 30 mg to 20 mg
- The dose escalation will be conducted at ≈ 15 sites in the United States, and the dose expansion may be extended to an additional ≤ 15 sites worldwide as needed

Figure 5. Phase 1 Study of Milademetan in Combination With Quizartinib in Patients With R/R or ND *FLT3*-ITD–Positive AML Who Are Unfit for Intensive Chemotherapy: Study Design



DOR, duration of response; MTD, maximum tolerated dose; PD, pharmacodynamics; QD, once daily; RDE, recommended dose for expansion; RP2D, recommended phase 2 dose.

Table 1. Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Part 1 and cohort 1 in part 2 • Patients with *FLT3*-ITD–positive (≥ 3% *FLT3*-ITD/total *FLT3*) AML (primary AML or secondary to MDS) who have experienced failure of any prior induction therapy or have relapsed after prior induction/consolidation therapy[a,b] • Age ≥ 18 years • ECOG PS of 0-2[a] • Adequate renal, hepatic, and clotting function **Additional criteria for cohort 2 in part 2** • No prior treatment for AML • Ineligible for intensive induction chemotherapy due to ≥ 1 of the following criteria: – Age ≥ 75 years with ECOG PS of 0-2 – Age ≥ 18 years and known congestive heart failure, ECOG PS of 3, or any other comorbidity judged to be incompatible with conventional intensive chemotherapy	• CNS leukemia[c] • Acute promyelocytic leukemia (AML subtype M3) • Uncontrolled or significant cardiovascular disease or QTcF interval > 450 ms • Unresolved toxicities from prior AML therapies • Prior treatment with MDM2 inhibitors • Receipt of strong CYP3A inducers (within 14 days of treatment initiation) and during therapy • Clinically significant GVHD • Known HIV infection or active hepatitis B or C virus infection

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GVHD, graft-vs-host disease; QTcF, corrected QT interval per Fridericia's formula.
[a] Patients in cohort 2 in part 2 do not need to meet this criteria; [b] No time restraints were specified for duration of previous response in patients with relapse; [c] Patients with adequately controlled CNS leukemia may participate with sponsor approval.

Table 2. Trial Endpoints

Primary Endpoints	Secondary Endpoints
Safety, including: • Serious adverse events • Treatment-emergent adverse events • Dose-limiting toxicities (DLTs) • Physical examination findings • Vital sign measurements • Clinical laboratory parameters • QTc parameters **Efficacy (Part 2 only), including:** • CRc rate • DOR • Morphologic leukemia-free state • PR and SD rates	**Pharmacokinetics** **Preliminary efficacy (Part 1 only), including:** • CRc rate (CR + CRi) • CRh • PR and SD rates • Morphologic leukemia-free state • DOR **Exploratory Endpoints** • EFS • OS • Transplant rate • Transfusion independence

CR, complete remission; CRc, composite complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; OS, overall survival; PR, partial remission; SD, stable disease.

Statistical Design

- Sample size for the dose-escalation part of this study was based on prior assumptions and simulations of BLRM. Approximately 24 to 36 DLT-evaluable patients are needed to determine the MTDs and RDE
- Dose escalation is guided by BLRM with overdose control, with cohorts of 3 to 6 patients undergoing sequential escalation
- The RDE will be determined based on overall assessment of safety and preliminary efficacy data
- The dose-expansion part will enroll 2 parallel cohorts of ≈ 40 patients each using Simon 2-stage design with futility boundary
- Statistical analysis will occur after all patients from both dose escalation and dose expansion have either completed or discontinued the study or received ≥ 6 months of therapy
- For response rates (CRc, overall response rate, etc), point estimates and 95% exact binomial confidence levels will be calculated
- Time to event endpoint (DOR) will be summarized using the Kaplan-Meier method
- PK parameters will be estimated using noncompartmental analysis

Enrollment

- This trial is registered at ClinicalTrials.gov (NCT03552029)
- As of May 21, 2019, 3 patients have been enrolled in part 1
- Enrollment is ongoing at several participating institutions (**Table 3**)

Table 3. Participating Institutions in Part 1[a]

Participating Institution	Location
Emory University Winship Cancer Institute	Atlanta, Georgia
The University of Kansas Cancer Center	Fairway, Kansas
University of Michigan Rogel Cancer Center	Ann Arbor, Michigan
Roswell Park Comprehensive Cancer Center	Buffalo, New York
Duke University Cancer Center	Durham, North Carolina
The University of Texas MD Anderson Cancer Center	Houston, Texas
Thomas Jefferson University Sidney Kimmel Cancer Center	Philadelphia, Pennsylvania
Case Western Reserve University Cancer Center	Cleveland, Ohio
UCLA Ronald Reagan Medical Center	Los Angeles, California

[a] Study locations per ClinicalTrials.gov, as of October 7, 2019.

REFERENCES

1. Levis M, *Hematology Am Soc Hematol Educ Program*. 2013;2013:220-226.
2. Kottaridis PD, et al. *Br J Haematol*. 2003;122(4):523-538.
3. Daver N, et al. *Leukemia*. 2019;33(2):299-312.
4. Cortes JE, et al. *Lancet Oncol*. 2019;20(7):984-997.
5. DiNardo CD, et al. *Blood*. 2016;128(22) [abstract 593].
6. Andreeff M, et al. *Blood*. 2018;132(suppl_1) [abstract 2720].
7. Andreeff M, et al. *HemaSphere*. 2018;2(S1):63 [abstract PF219].

ACKNOWLEDGMENTS

Preclinical data and this study were developed in collaboration between The University of Texas MD Anderson Cancer Center and Daiichi Sankyo, Inc. The authors would like to thank the patients and their families for participating in this study. Medical writing support was provided by Jamie King, PhD, of SciMentum, Inc, a Nucleus Global company, and was funded by Daiichi Sankyo, Inc. Editorial support was provided in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

DISCLOSURES

N. Daver—Consultancy: Agios, Astellas, Celgene, Forty-Seven, Jazz Pharmaceuticals, Otsuka; Consultancy & Research Funding: AbbVie, Bristol-Myers Squibb, Daiichi Sankyo, Genentech, Immunogen, Incyte, Karyopharm, Novartis, Pfizer, and Sunesis; Research Funding: Glycomimetics and Nohla. **W. Zhang**: None. **R. Graydon**, **V. Dawra**, **J. Xie**, **P. Kumar**—Employees of Daiichi Sankyo, Inc. **M. Andreeff**—Consultancy: AstraZeneca, Celgene, Jazz Pharmaceuticals, and 6 Dimensions Capital; Research Funding: Breast Cancer Research Foundation, Cancer Prevention and Research Institute of Texas, and National Institutes of Health/National Cancer Institute (NCI); Equity Ownership: Aptose, Eutropics, Oncoceutics, Oncolyze, and Reata; Membership on an Entity's Board of Directors or Advisory Committees: Bioline Rx, Cancer UK, Center for Drug Research & Development, Chronic Lymphocytic Leukemia Foundation, German Research Council, Leukemia & Lymphoma Society, NCI Cancer Therapy Evaluation Program, and NCI Rare Diseases Clinical Research Network; Equity Ownership & Membership on an Entity's Board of Directors or Advisory Committees: Senti Bio; Consultancy, Patents, & Royalties (patents licensed, royalty bearing and research funding): Daiichi Sankyo, Inc.

To download a copy of this poster:
Scan QR code via a barcode reader application

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASH and the authors of this poster.