# A novel regimen for relapsed/refractory adult acute myeloid leukemia using a *KMT2A* partial tandem duplication targeted therapy: results of phase 1 study NCI 8485

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## ABSTRACT

*KMT2A* partial tandem duplication occurs in approximately 5-10% of patients with acute myeloid leukemia and is associated with adverse prognosis. *KMT2A* wild type is epigenetically silenced in *KMT2A* partial tandem duplication; re-expression can be induced with DNA methyltransferase and/or histone deacetylase inhibitors *in vitro*, sensitizing myeloid blasts to chemotherapy. We hypothesized that epigenetic silencing of *KMT2A* wildtype contributes to *KMT2A* partial tandem duplication-associated leukemogenesis and pharmacologic re-expression activates apoptotic mechanisms important for chemoresponse. We developed a regimen for this unique molecular subset, but due to relatively low frequency of *KMT2A* partial tandem duplication, this dose finding study was conducted in relapsed/refractory disease regardless of molecular subtype. Seventeen adults (< age 60) with relapsed/refractory acute myeloid leukemia were treated on study. Patients received decitabine 20 milligrams/meter$^2$ daily on days 1-10 and vorinostat 400 milligrams daily on days 5-10. Cytarabine was dose-escalated from 1.5 grams/meter$^2$ every 12 hours to 3 grams/meter$^2$ every 12 hours on days 12, 14 and 16. Two patients experienced dose limiting toxicities at dose level 1 due to prolonged myelosuppression. However, as both patients achieved complete remission after Day 42, the protocol was amended to adjust the definition of hematologic dose limiting toxicity. No further dose limiting toxicities were found. Six of 17 patients achieved complete remission including 2 of 4 patients with *KMT2A* partial tandem duplication. Combination therapy with decitabine, vorinostat and cytarabine was tolerated in younger relapsed/refractory acute myeloid leukemia and should be explored further focusing on the *KMT2A* partial tandem duplication subset. (*clinicaltrials.gov identifier 01130506*).

## Introduction

Though acute myeloid leukemia (AML) is considered a curable disease, the majority of patients will succumb to their diagnosis. Prognosis has been based primarily on age and cytogenetic/molecular mutations at diagnosis with younger patients (<60 years) faring better, in particular those with European LeukemiaNet

**Table 1.** Treatment Dose and Schedule.

| Dose level | Decitabine (mg/m²/day) Days 1-10 | Vorinostat (mg/day) Days 5-10 | Cytarabine (g/m²/q12hr) Days 12,14,16 | Number treated | Number of DLTs |
|---|---|---|---|---|---|
| 1 | 20 | 400 | 1.5 | 6 | 2 |
| 2 | 20 | 400 | 2 | 3 | 0 |
| 3 | 20 | 400 | 2.5 | 3 | 0 |
| 4 | 20 | 400 | 3 | 5 | 0 |

DLTs: dose limiting toxicities.

(ELN) favorable risk subtypes.[1] Despite recent advances in understanding of leukemogenesis, the initial treatment for most AML patients remains largely unchanged over the past 30 years and salvage regimens also remain similar in their use of a cytarabine backbone. However, targeted therapeutics for specific molecular subsets of AML are beginning to emerge including inhibitors for patients with *FLT3*-ITD/TKD, *IDH1* or *IDH2* mutations.[2,3] Another potential targetable population in AML includes patients with partial tandem duplication (PTD) in the lysine methyltransferase 2A (*KMT2A*) gene which was formerly known as mixed lineage leukemia 1 (MLL1). The *KMT2A* gene is located on Chromosome 11q23 and *KMT2A* PTD occurs in a single allele of this gene. This alteration occurs more commonly in AML with normal cytogenetics and trisomy 11 and is associated with an adverse prognosis.[4-6] Multiple mechanisms are attributed to these adverse outcomes including hypermethylation of gene promoters leading to the silencing of potential tumor suppressors.[7,8]

Our published data show that the *KMT2A* wild type (WT) allele is epigenetically silenced in AML with *KMT2A* PTD.[9] We have shown that re-expression of the *KMT2A* WT allele can be induced with DNA methyltransferase (DNMT) and/or histone deacetylase (HDAC) inhibitors.[10,11] Indeed, we demonstrated that epigenetic silencing of *KMT2A* WT contributes to *KMT2A* PTD-associated leukemogenesis and that pharmacologic re-expression of this gene with DNMT and HDAC inhibitors attenuates the *KMT2A* PTD leukemogenic potential and activates apoptotic mechanism important to enhance chemosensitivity, *in vitro*. Re-expression of *KMT2A* WT following exposure to decitabine, followed by an HDAC inhibitor, was associated with a lower apoptotic threshold and sensitized *KMT2A* PTD cells to chemotherapy-induced cytotoxicity. In order to develop a regimen that might be effective in the subset of patients with AML and *KMT2A* PTD, we conducted a phase 1 study of a novel regimen of combined epigenetic and chemotherapies in relapsed and refractory AML patients. Because of the relatively low frequency of *KMT2A* PTD AML, the initial dose finding portion of this study was conducted in any patient with relapsed/refractory AML regardless of their molecular subtype but was enriched for *KMT2A* PTD.

## Methods

### Eligibility criteria

Eligible patients were adults (≥18 and <60 years) with relapsed/refractory non-M3 AML with adequate organ function and ECOG performance status ≤2. Patients with previous exposure to high-dose cytarabine were eligible. Patients with previous history of neurological toxicity with cytarabine or vorinostat were ineligible (See Appendix 1 for full Eligibility Criteria). Informed written consent approved by The Ohio State University Humans Studies Committee was obtained on all patients prior to enrollment, in accordance with the Declaration of Helsinki.

### Treatment

The regimen consisted of epigenetic priming with decitabine followed by vorinostat, then high dose cytarabine (which was dose-escalated). The dosing regimen was based on pre-clinical data showing the myeloid apoptotic threshold decreased most significantly compared to other therapeutic sequences. Decitabine was given intravenously over 1 hour at a dose of 20mg/m²/day on Days 1-10. Vorinostat was given orally at a dose of 400mg/day on Days 5-10. Cytarabine was administered intravenously over 2 hours every 12 hours on Days 12, 14, and 16 for 6 doses total. Cytarabine was dose escalated as follows: dose level 1, 1.5g/m²/q12hr; dose level 2, 2g/m²/q12hr; dose level 3, 2.5g/m²/q12hr; and dose level 4, 3g/m²/q12hr (Table 1). The study was designed in classic 3+3 phase I design schema to determine the maximum tolerated dose (MTD) and define dose limiting toxicity (DLT). Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0. Responses were defined according to International Working Group (IWG) Criteria for AML, including complete remission (CR) and CR with incomplete count recovery (CRi), partial remission (PR), and treatment failure.[12] Next generation sequencing using MiSeq platform assessed over 80 AML-associated gene mutations as previously described.[13] *KMT2A* PTD and *FLT3*-ITD mutations were performed by PCR testing.[14,15]

### Definition of dose limiting toxicity

Grade 4 non-hematological toxicity attributable to any of the therapeutic agents, with exception of line-associated venous thrombosis, infection, fatigue, or nausea and vomiting controllable with anti-emetic therapy were defined as DLT. Hematologic toxicity was initially defined as failure to recover peripheral blood counts by Day 42 in patients with <5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of disease by flow cytometry in the bone marrow. However, 2 patients at dose level 1 experienced delayed count recovery (beyond day 42) meeting the hematological DLT definition but both patients achieved CR with no long-term sequelae. It was felt disadvantageous to reduce chemotherapy doses due to high risk nature of the disease, and the protocol was modified to extend duration of hematologic DLT to Day 56 with G-CSF permitted to hasten neutrophil recovery in patients with hypoplastic bone marrow after treatment.

### Statistical analysis

A standard method 3 + 3 phase I design of dose escalation using 3 patients per dose level cohort and a minimum of 6 patients at the MTD was performed. As an exploratory, phase I study, no infer-

ential statistical tests of hypotheses were planned. Data collected are descriptive and provide limited estimates of variability given the small patient sample size at each dose level.

## Results

### Patient characteristics and treatment groups

Seventeen adults with relapsed/refractory AML were treated on this phase I study. The median age of patients was 46 years (range, 21-59 years). Median white blood cell count and bone marrow blast percentage was 3.5 x $10^3/\mu L$ (range, 0.4-75.8) and 66% (range, 4-87%), respectively. The median number of prior induction therapies was 2 (range, 1-4). All patients had previous anthracycline exposure, and 15 patients had previous high-dose cytarabine exposure. Twelve patients had relapsed disease, with 8 patients having prior CR1 duration of less than 1 year and 4 patients experiencing CR1 ranging from 16-38 months. Five patients had primary refractory disease;

**Table 2.** Patient Characteristics.

| Patient | Age/ Sex | # of prior inductions | Pretreatment karyotype | *KMT2A* PTD | Initial WBC | Initial blast count | Dose Level | Length of 1st CR (mos) |
|---|---|---|---|---|---|---|---|---|
| 1 | 58/F | 1 | 46,XX,t(12;22)(q13;q13)[15]/42-45,XX,-2,add(3)(p25),del(3)(p24),-11,-17,add(17)(p11.2),der(19)t(17;19)(q21;p12),+mar1,+mar2[4]/46,XX[1] | n/a | 40.9 | 81 | 1 | 6 |
| 2 | 45/F | 3 | 46, XX [19]/nonclonal[1] | n/e | 3.5 | 79 | 1 | 17 |
| 3 | 46/M | 2 | 47,XY,+11 [2]/47, idem, t(16;21)(p11.2;q22)[18] | n/e | 3.3 | 77 | 1 | 10 |
| 4 | 25/M | 4 | 45,XY,der dic(13;18)(q21;p11.3)ins(13;?)(q21;?)[13]/45,idem,t(10;12)(p13;q13)[cp2]/46,XY[5]/nonclonal[2] | n/a | 3.2 | 40 | 1 | n/a |
| 5 | 58/F | 1 | 47,XX,t(16;16)(p13.1;q22),+22[14]/nonclonal w/clonal abnormalities [1]/46,XX[7] | PTD+ | 2.2 | 22 | 1 | 18 |
| 6 | 54/M | 1 | 46,XY[19]/nonclonal[1] | neg | 1.3 | 36 | 1 | 16 |
| 7 | 50/M | 2 | 43,XY,del(4)(q31),-5,-12,del(13)(q12q14),-15,add(17)(q25),add(18)(q12),add(19)(p13.3),add(20)(q13.3),add(21)(q22)[1]/ 42-44,sl,-Y,add(6)(p21),+i(8)(q10)[cp3]/ 43,sdl1,-add(6),+del(6)(p23)[cp6]/ 42-44,sl,+8,add(22)(q22)[cp4]/ 43,sl,-Y,+5,- | n/e | 5.9 | 8 | 2 | n/a |
| 8 | 42/F | 2 | 45,XX,-7[20] | neg | 22.1 | 66 | 2 | n/a |
| 9 | 26/F | 2 | 46,XX,t(1;16)(p32;p13.1),der(3)t(3;17)(q29;q11.2),der(5)t(5;9)(q11.2;q21),add(8)(q22),-9,add(12)(q13),der(12)t(12;12)(p13;q13)ins(12;17)(p13;q11.2q21),+16,der(16)t(1;16),-17,-17,-18,add(22)(q13),+mar1,+mar2,+mar3[12]/45,sl,-der(16)t(1;16)(p32;p13.1),+der(16)t(1;16)(p32;p13.1)add(1) (p36.3)[2]/46,sl,del(6)(q13q25)[1]/nonclonal w/clonal abnormalities[1]/46,XX[4] | PTD+ | 2.0 | 51 | 2 | n/a |
| 10 | 59/M | 4 | 45,XY,t(3;12)(q26;p13),t(4;5)(q21;q31),del(5)(q15q35),-7,t(10;21)(q22;q22)[cp1] | neg | 3.2 | 4 | 3 | 38 |
| 11 | 24/F | 3 | 46,XX,del(11)(p13p15.1)[16]/nonclonal w/clonal abnormalities[4] | neg | 75.8 | 82 | 3 | 2 |
| 12 | 42/M | 2 | 46,XY,der(12)t(12;21)(p12;q11.2)[19]/nonclonal[1] | neg | 4.0 | 87 | 3 | 10 |
| 13 | 27/F | 4 | 46,XX,dup(2)(q21q31),t(8;21)(q22;q22)[18]/nonclonal w/clonal abnormalities[1]/46,XX[1] | PTD+ | 0.4 | 66 | 4 | 11 |
| 14 | 21/F | 3 | 47,XX,der(10)t(10;11)(p11.2;q13)inv(11)(q13q23),der(11)t(10;11)(p11.2;q13),+mar1[cp7]/47,idem,add(X)(q26),add(8)(q24.1),add(13)(p11.2),-15,add(18)(p11 2),+21,-mar1,+mar2[cp15]/nonclonal w/clonal abnormalities[2] | PTD+ | 17.8 | 82 | 4 | 3 |
| 15 | 58/M | 1 | 46,XY,t(3;15)(p13;q13)[16]/47,idem,+13[2]/46,XY[1]/nonclonal[1] | n/a | 30.5 | 83 | 4 | 10 |
| 16 | 58/F | 2 | 46,XX,del(12)(p11.2p13)[1]/45,sl,del(19)(q13.3),-20,add(21)(q22)[3]/45,sdl1,-7[2]/45,sdl2,-20[2]/46,XX[12] | neg | 2.1 | 69 | 4 | n/a |
| 17 | 57/M | 2 | 45,X,-Y[20] | neg | 36.6 | 66 | 4 | 6 |

CR: cytogenetic remission; F: female; M: male; mos: month; n/a: not applicable; n/e: not evaluable; WBC: white blood.

each one entered the study after failure of at least 2 conventional regimens. One patient had undergone prior allogeneic stem cell transplant and 2 patients had undergone autologous transplant in CR1 (on study protocols). Two patients had secondary or therapy-related AML, 14 patients had abnormal karyotypes and 4 patients were found to have *KMT2A* PTD molecular subtype. Clinical as well as pre-treatment cytogenetic and molecular characteristics of enrolled patients are summarized in Tables 2 and 3.

## Dose escalation and treatment

Six patients were treated at dose level 1 due to prolonged myelosuppression in 2 patients requiring dose expansion. However, both patients achieved CR after toxicity "cut-off" and the protocol was amended to allow further time for count recovery as well as G-CSF to hasten count recovery. Three patients were treated on dose levels 2 and 3; 5 patients were treated on dose level 4. No other DLTs were observed.

## Toxicities

As this treatment approach was intensive, patients experienced universal pancytopenia and toxicities as expected in this poor risk cohort of patients. Treatment overall was well tolerated. Diarrhea, nausea, fatigue, febrile neutropenia and elevated alanine aminotransferase were the most common occurrences for all grade toxicities occurring in 41%, 29%, 29%, 35%, and 35% of patients respectively. With regards to Grade 3 or greater toxicities, febrile neutropenia and catheter-related infections were most common at 35% and 24% of patients and are common complications that occur in this patient population. A summary of all Grade toxicities and Grade 3 or greater non-hematological toxicities possibly attributable to the treatment are listed in Table 4.

## Clinical responses

The overall response rate was 35% (6/17 patients) as seen in Table 3. All 6 responses by IWG criteria were CR; 3 of these 6 patients had abnormal cytogenetics and all 3 achieved a cytogenetic CR (Patients 5, 7 and 9). The median number of prior therapies for patients with CR was 2 (range 1-3). Response duration assessment is compromised due to 4 patients subsequently receiving allogeneic transplantation (Patients 2, 5, 7, and 9). However, all patients with CR on study except one (Patient 5) eventually relapsed and succumbed to complications of their underlying disease including patients who underwent allogeneic transplantation.

Count recovery for the 6 patients who achieved CR was prolonged with average absolute neutrophil count (ANC) recovery of 45 days (range Day 39-55) and average platelet recovery of 52 days (range Day 34-67). Four of the 6 patients received G-CSF to aid in count recovery with 3 patients receiving this therapy on dose level 1 and 1 patient on dose level 2. No patients had a serious adverse event (SAE) felt related to prolonged count recovery. None of the patients who were considered treatment failures received any G-CSF support.

Of the 4 patients known to have *KMT2A* PTD mutations, 2 patients responded achieving cytogenetic CRs. It is interesting to note one of the *KMT2A* PTD responders also had a *TP53* mutation with a high variant allele frequency (VAF), but this response may not be due to the regimen examined, considering recent findings with a 10-day decitabine schedule in *TP53* mutated AML patients.[13] It is also of interest that 2 *KMT2A* PTD patients (1 responder and 1 non-responder) were associated with favorable karyotypes as this has not been commonly reported. It was difficult to make any other definitive conclusions about responders and non-responders with other concurrent mutations with such a small number of patients.

**Table 3.** Patient molecular mutations and responses.

| Responders | *KMT2A* PTD | Other gene mutations (VAF) | Best response |
|---|---|---|---|
| Patient 2 | | FLT3-TKD, PTPN11 (0.3), U2AF1 (0.23) | CR |
| Patient 5 | + | None | CRc |
| Patient 6 | | DDX41 (0.5), ASXL1 (0.19) | CR |
| Patient 7 | | None | CRc |
| Patient 9 | + | TP53 (0.53) | CRc |
| Patient 17 | | FLT3-ITD (heterozygous), NRAS (0.36) | CR |
| Non-Responders | | | |
| Patient 1 | | NPM1 (.54), FLT3-ITD (hemizygous), FLT3-TKD, TET2 (0.47) | |
| Patient 3 | | None | |
| Patient 4 | | NPM1 (0.35), FLT3-ITD (heterozygous) | |
| Patient 8 | | PTPN11 (0.52), RUNX1 (0.41), NRAS (0.2) | |
| Patient 10 | | PTPN11 (0.14), SF1 (0.13) | |
| Patient 11 | | NPM1 (0.42), FLT3-ITD (hemizygous), WT1 (0.64), SF3A1 (0.49) | |
| Patient 12 | | IDH2 (0.21), KRAS (0.19) | |
| Patient 13 | + | FLT3-ITD (heterozygous) | |
| Patient 14 | + | RUNX1 (0.39) | |
| Patient 15 | | None | |
| Patient 16 | | TP53 (0.5) | |

CR: morphologic Complete Remission; CRc: morphologic and cytogenetic Complete Remission; VAF: variant allele frequency.

## Discussion

Epigenetic deregulation is felt to contribute to the underlying pathobiology of AML and both aberrant DNA methylation and histone acetylation have been explored as potential therapeutic targets in this disease.[16] Monotherapy with hypomethylating agents, azacitidine and decitabine, that target DNMTs have shown some success in regards to clinical activity and are currently used in the treatment of AML, though neither are considered curative therapies in this patient population.[17] These agents have become the standard of care for elderly patients who are unfit to undergo intensive induction chemotherapy. With regards to HDAC inhibition, though preclinical findings in AML have been exciting, these results have yet to translate into significant clinical responses in AML both as monotherapy and in combination with hypomethylating agents or with cytotoxic chemotherapy.[18-21] However, priming with both hypomethylating agents and HDAC inhibitors prior to salvage chemotherapy has shown some promise.[22]

A dose-finding study of decitabine and valproic acid in 25 patients in both relapsed/refractory and untreated, unfit AML populations has been previously performed. Due to the major DLT of the study of encephalopathy in older patients attributed to valproic acid, this current study of combination therapy with HDAC inhibitors was limited to those <60 years old. It was also felt a different HDAC inhibitor, such as vorinostat, might be better tolerated.[23]

As mentioned, vorinostat has also been studied in combination with other agents in AML, including hypomethylating agents and cytotoxic chemotherapies. Kirschbaum, *et al*. randomized patients with untreated (n=31) and relapsed/refractory AML (n=29) along with myelodysplastic syndrome (MDS) (n=31) to concurrent decitabine plus vorinostat *versus* sequential decitabine followed by vorinostat. Both schedules were felt to be well-tolerated but more objective responses (CRs plus PRs) were seen in the concurrent schedule (46% *vs.* 14% in untreated AML, 15% *vs.* 0% in relapsed/refractory AML, and 60% *vs.* 0% in MDS).[24] Gojo *et al*. assessed the ability to add vorinostat prior to etoposide and cytarabine in relapsed/refractory AML or acute lymphoblastic leukemia, newly diagnosed secondary AML, or chronic myeloid leukemia in accelerated or blastic phase failing or intolerant of tyrosine kinase inhibitor therapy. The MTD was found to be vorinostat 200mg orally twice a day (Days 1-7) followed by cytarabine and etoposide on Days 11-14 with DLTs of hyperbilirubinemia/septic death and anorexia/fatigue at higher dosing. In the 21 patients treated, there were 7 CRs (n=5) or CRi's (n=2) all in the AML population (2 newly diagnosed high-risk and 5 relapsed/refractory patients).[25] A phase II trial combined vorinostat 500mg orally 3 times a day (Days 1-3) followed by idarubicin and cytarabine induction chemotherapy in younger untreated AML and higher-risk MDS patients and saw no excess in vorinostat-related toxicities with an overall response rate of 85% including 76% CR and 9% CRi rates.[20] A Phase III randomized intergroup study assessed the benefit of vorinostat in addition to high dosed cytarabine-based induction chemotherapy *vs.* induction chemotherapy alone and did not show any differences in CR, event-free survival, or overall survival with the addition of vorinostat. Toxicity was considered similar between groups.[26] However, the effect of epigenetic priming, particular for subsets of disease that may be sensitive to the approach, remains an area of interest for clinical development.

In this phase I study, we evaluated the combination of decitabine and vorinostat priming prior to high-dose cytarabine in a cohort of younger AML patients with relapsed or refractory AML. We developed a regimen for subsequent phase 2 testing in the select population that may be sensitive to the approach (*KMT2A* PTD). The treatment was generally well-tolerated with exception of the initial prolonged myelosuppression identified in dose level 1 and there were otherwise no DLTs. The most common toxicities seen including febrile neutropenia, nausea, and diarrhea are all common side effects that can be seen with high-dose cytarabine alone. Neurotoxicity that was seen previously with valproic acid in combination with decitabine was not seen in this patient population.[23] This combination therapy resulted in CR in 6 patients with an overall response rate of 35%. Although the small number of patients limits the interpretation of these findings, prior

**Table 4.** Non-hematological toxicities possibly attributable.

| Toxicity | All grades number of events | Grade 3 or greater number of events |
|---|---|---|
| Diarrhea | 7 | 2 |
| Nausea | 5 | |
| Fatigue | 5 | |
| Catheter-related infection | 4 | 4 |
| Lung infection | 2 | 2 |
| Hypoxia | 1 | 1 |
| Febrile neutropenia | 6 | 6 |
| Blood bilirubin increased | 1 | |
| Peripheral sensory neuropathy | 1 | |
| Dyspnea | 2 | |
| Lymph node pain | 1 | |
| Abdominal pain | 2 | |
| Colitis | 1 | 1 |
| Dry mouth | 1 | |
| Mucositis oral | 1 | |
| Proctitis | 1 | |
| Rectal pain | 1 | |
| Vomiting | 1 | |
| Sinusitis | 1 | 1 |
| Prolonged PTT | 1 | |
| Increased ALT | 6 | 1 |
| Increased AST | 3 | 1 |
| Creatinine increased | 1 | |
| Anorexia | 4 | |
| Urinary incontinence | 1 | |
| Cough | 2 | |
| Weight loss | 1 | |
| Headache | 1 | |
| Proteinuria | 1 | |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; PTT: partial thromboplastin time.

high dose cytarabine exposure does not appear to preclude a response to this combination therapy. With regards to patients with *KMT2A* PTD mutations, as noted, 2 patients were able to obtain response to this combination therapy while the other 2 were refractory to this treatment with no definitive features to explain difference in outcomes. In conclusion, we successfully determined the recommended phase 2 dose for this novel treatment regimen. The regimen had modest toxicities beyond uncomplicated (though prolonged) myelosuppression, and we propose that the study provides a framework for larger efficacy studies for AML patients with the uncommon but biologically distinct molecular feature of *KMT2A* PTD.

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