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A Phase I Study of the Myeloid Cell Leukemia 1 (MCL1) Inhibitor Tapotoclax (AMG 176) in Patients with Myelodysplastic Syndrome After Hypomethylating Agent Failure

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INTRODUCTION

MYELODYSPLATIC SYNDROMES (MDS)

- Heterogeneous group of malignant clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, bone marrow dysplasia, and propensity to transform into acute myeloid leukemia (AML)
- Frontline standard-of-care for many remains hypomethylating agents: azacitidine, decitabine, decitabine/cedazuridine (PO)
- Therapeutic benefits of HMA transient with low durable response rates
- **HMA failure**: patients who are refractory to or have lost response to HMA therapy with dismal survival
- No FDA-approved treatment options for the majority of patients with HMA failure
- Development of innovative therapeutic strategies for patients with HMA failure MDS remains a pressing need

MYELOID CELL LEUKEMIA 1

- Anti-apoptotic member of B-cell lymphoma/leukemia 2 (BCL2) protein family promoting cell survival
- Expressed in a range of human and mouse tissues with overexpression implicated in the development of hematologic malignancies and therapy resistance
- **Tapotoclax (AMG 176)**: first in class, small molecule therapeutic candidate that disrupts protein-protein interactions between MCL1 and pro-apoptotic members of the BCL2 family
  - Directly induces apoptosis in cells dependent on MCL1 for survival
  - Highly specific for MCL1
- In vivo studies revealed sensitivity of AML xenograft models to tapotoclax monotherapy and combination with HMA
- Clinical study investigating tapotoclax in patients with relapsed/refractory multiple myeloma or AML with no concerning safety events or dose-limiting toxicities

HYPOTHESIS

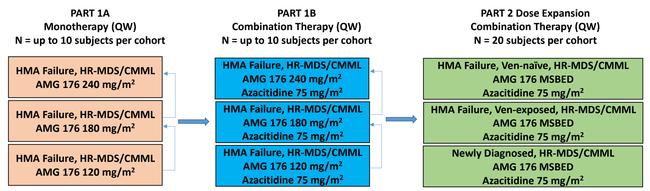
- Tapotoclax may be safe and clinically active in patients with HMA failure MDS

METHODS

- Phase I study evaluating safety and tolerability of tapotoclax in HMA failure MDS
- Included adult patients with HMA failure MDS, defined as:
  - Not responding to HMA after 4 or more cycles
  - Progression/relapse at any time during HMA therapy

TRIAL DESIGN

FIGURE 1. ORIGINAL STUDY DESIGN



CMML = chronic myelomonocytic leukemia; HMA = hypomethylating agent; HR-MDS = higher-risk myelodysplastic syndrome; MSBED = minimum safe and biologically effective dose; QW = once weekly; Ven = venetoclax

- Primary endpoint: safety and tolerability of tapotoclax (incidence of dose-limiting toxicities [DLTs] and adverse events [AEs])
- Secondary endpoints: overall response rate by IWG 2006 criteria, pharmacokinetic parameters for tapotoclax
- BM aspiration and/or biopsy at baseline, after cycles 1 and 2, and then after every other cycle or more frequently as clinically indicated
- Trial terminated due to lack of clinical activity during exploratory dose-finding portion with tapotoclax monotherapy

RESULTS

- Trial accrued from October 2022 through December 2023
- 9 patients enrolled and 7 treated with tapotocolax
  - 4 patients: tapotoclax 120 mg/m^2
  - 3 patients: tapotoclax 240 mg/m^2
  - Tapotoclax 180 mg/m^2 dose level omitted due to safety demonstrated in the relapsed/refractory multiple myeloma and AML study

TABLE 1. PATIENT CHARACTERISTICS AT STUDY ENTRY

Pt #	Age	Gender	t-MDS	# Prior Tx	# HMA Cycles	Previous Response to HMA	WBC [x10^9/L]	ANC [x10^9/L]	Hgb [g/dL]	Plt [x10^9/L]	BM Blasts [%]	CG	Mutations	IPSS-R Risk Category	IPSS-M Risk Category
1	79	M	Yes	4	13	No	5.4	2.82	6.9	107	11	i(17q)	*ASXL2, DNMT3A, ETNK1, NF1, SRSF2, TET2, TP53*	Very High	Very High
2	72	F	Yes	1	15	No	3.7	1.67	8.2	158	2	+1, der(1;7)	*DNMT3A*	Low	Moderate Low
3	77	M	No	1	6	Yes	1.2	0.64	7.5	9	12	Complex including del(5q) and del(20q)	*TET2, TP53*	Very High	Very High
4	61	F	Yes	8	8	Yes	1.4	0.76	6.9	35	5	t(1;3)	*DDX41, DNMT3A, IDH1, NRAS, PTPN11, SF3B1*	Very High	Very High
5	83	F	No	6	24	No	1.6	0.79	7.2	112	1	Normal	*SF3B1, TET2*	Low	Low
6	72	M	No	5	2	No	1.7	0.36	7.4	88	4	+1, der(1;7)	*RUNX1, SF3B1*	High	High
7	80	M	No	3	10	No	0.6	0.43	6.8	7	NA	Complex including del(5q), del(7q)	*DNMT3A, HRAS, RUNX1, SF3B1, SRSF2*	Very High	Very High

t-MDS: therapy-related MDS; Tx: treatment; HMA: hypomethylating agent; WBC: white blood cell; ANC: absolute neutrophil count; Hgb: hemoglobin; Plt: platelets; BM: bone marrow; CG: cytogenetics; M: male; F: female; NA: not available (due to unsatisfactory sample)

- Median age at study entry: 77 years (range: 61-83)
- 4 male patients (57%)
- High risk patient cohort:
  - 3 (43%) with t-MDS
  - 2 (29%) with complex cytogenetics
  - 2 (29%) with *TP53* mutations
  - 5 (71%) with high- or very high-risk MDS by IPSS-M or IPSS-M
- Heavily pre-treated
  - Median lines of prior therapy: 4 (range: 1-8)
  - Median previous cycles of HMA: 10 (range: 2-24)
  - 2 (29%) responded to prior HMA
  - 1 (14%) received venetoclax prior to enrollment

SAFETY AND TOLERABILITY

- Median number of tapotoclax cycles received: 3 (range: 2-4)
- No DLTs observed

TABLE 2. TREATMENT-RELATED ADVERSE EVENTS

Adverse Event	Number of Patients (%)	
	Grade 1-2	Grade 3
Nausea/Vomiting	5 (71)	1 (14)
Fatigue	4 (57)	-
Diarrhea	2 (29)	-
Palpitations/Ventricular Arrhythmias	1 (14)	-

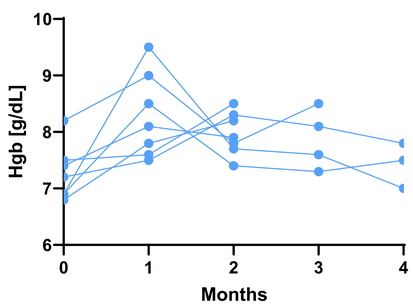
- 1 patient died of an infection during cycle 2 that was deemed unrelated to treatment
- Cardiac toxicities:
  - 1 patient experienced arrhythmias with premature atrial and ventricular contractions that were possibly related to tapotoclax but resolved without dose interruptions or reductions
  - 1 patient had prolonged QTc intervals but had similar prolongation prior to tapotoclax exposure
  - No clinically-significant cardiac enzyme elevations

RESPONSE

- No patients responded by IWG 2006 criteria
- Reasons for treatment discontinuation:
  - 4 (57%): progressive disease or lack of response
  - 1 (14%): allogeneic stem cell transplantation
  - 1 (14%): recurrent peritoneal cancer with need for therapy
  - 1 (14%): patient request for hospice and subsequent unrelated death

- 2 of 3 patients (67%) who started with BM blasts ≥ 5% underwent unsustained blast reduction after at least 1 cycle of tapotoclax
- All patients transfusion-dependent with packed red blood cells (pRBCs) at time of clinical trial enrollment
  - 5 (71%) decreased pRBC transfusion by 2 or more units between cycle 1 and 2
  - 1 (14%) attained transfusion independence for approximately 7 weeks

FIGURE 2. INDIVIDUAL HEMOGLOBIN LEVELS WHILE ON STUDY



CONCLUSIONS

- Tapotoclax safe and tolerated in a high-risk cohort of patients with MDS after HMA failure
- No DLTs observed
- Cardiac AEs self-resolved without dose interruptions or reductions
- No patients responded but 67% of patients with elevated BM blasts underwent transient blast reduction, indicating potential anti-leukemic effect
- All patients transfusion-dependent at study start but 71% decreased pRBC transfusion burden and 1 attained transfusion independence for 7 weeks
- Given manageable toxicity profile and transitory anti-leukemic and transfusion-independent effect, the use of tapotoclax in combination with HMA or other therapies may warrant further consideration

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