Indoximod in Combination With Idarubicin and Cytarabine for Upfront Treatment of Patients With Newly Diagnosed Acute Myeloid Leukemia (AML): Phase 1 Report

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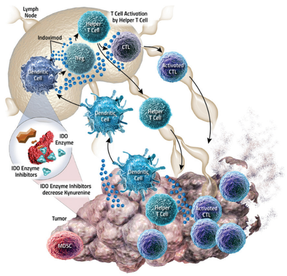
BACKGROUND

- Acute myeloid leukemia (AML) has the highest incidence among all types of leukemias in adults and accounts for the greatest number of leukemia-related deaths in the United States[1]
- The mainstay of induction therapy for AML for the last 40 years has been combination chemotherapy with cytarabine and an anthracycline, resulting in complete remission rates of approximately 60% to 70%; however, 5-year survival rates are 30% to 40%,[2] which underscores the urgent need for new therapeutic agents and strategies
- AML cells can acquire immune evasion and tolerance through overexpression of indoleamine 2,3-dioxygenase (IDO), which exerts immunomodulatory effects through tryptophan (Trp) catabolism and kynurenine production[3]
- Increased expression of IDO in AML has been demonstrated and is associated with poor outcomes,[3-5] thus providing a rationale for targeting IDO as part of the treatment of AML
- Indoximod is a small-molecule inhibitor of the IDO pathway that acts directly on immune cells to reverse IDO pathway–mediated suppression by interfering with Trp signaling (**Figure 1**)



IDO, indoleamine 2,3-dioxygenase; Treg, regulatory T cell; CTL, cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cell; Trp, tryptophan. Increased IDO expression by antigen-presenting cells leads to Trp depletion, which results in antigen-specific T-cell anergy and Treg recruitment. Indoximod interferes with the signaling by Trp degradation in effector T cells and Tregs. Tregs are transformed into helper-like T cells, suppressive dendritic cells are transformed into immunostimulatory dendritic cells, and MDSCs become inactive.

Figure 1. Targeting the IDO pathway with indoximod.

OBJECTIVE

- To assess the safety and tolerability of indoximod in combination with cytarabine and idarubicin in an ongoing phase 1b/2a study in patients with newly diagnosed AML

METHODS

Eligibility Criteria

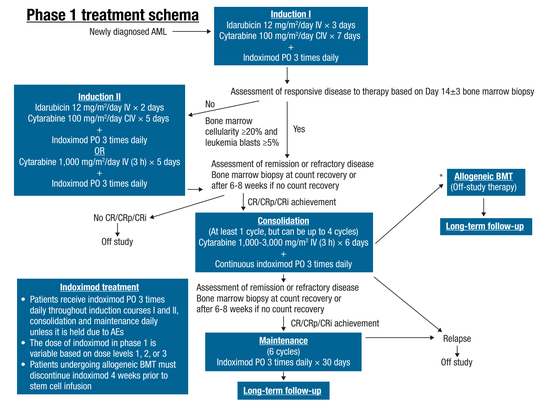
- ≥18 years of age with a confirmed diagnosis of AML based on World Health Organization classification with or without extramedullary disease (except for central nervous system disease), including patients with myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN) evolving into AML who are candidates for AML induction therapy
- No prior chemotherapy for AML, with the exception of hydroxyurea or leukapheresis for symptomatic hyperleukocytosis (prior hypomethylating or immunomodulatory agents for MDS are allowed)
- No previous allogeneic hematopoietic stem cell transplantation or prior treatment with anti-cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) blocking antibody or anti-programmed cell death protein 1 (PD-1) checkpoint antibodies
- Eastern Cooperative Oncology Group performance status ≤2
- Protocol-specified normal organ function
- Left ventricular ejection fraction ≥50%
- No active autoimmune disease or chronic inflammatory conditions that require concurrent use of systemic immunosuppressants, including steroids

Study Design

- This is a phase 1b/randomized phase 2a trial of indoximod in combination with standard of care (SOC) chemotherapy for frontline AML treatment
- During the phase 1 portion of the study, indoximod is administered at 4 potential dose levels (**Table 1**) using a 3+3 design in combination with 7+3 cytarabine and idarubicin remission induction and high-dose cytarabine (HiDAC) consolidation (**Figure 2**)
- Indoximod is administered orally 3 times daily starting on the day after completion of induction and is withheld on days that patients receive HiDAC chemotherapy
- Indoximod dose escalation or de-escalation will follow a modified Fibonacci sequence
- The phase 1 portion of the study assesses the regimen-limiting toxicities (RLTs) and defines the recommended phase 2 dose (RP2D) of indoximod in combination with cytarabine and idarubicin

Table 1. Indoximod Dose Escalation Schedule During the Phase 1 Portion of the Study

Dose level	Indoximod (mg) 3 times daily, administered orally
–1	400
0	600
1	1,000
2	1,200



AML, acute myeloid leukemia; IV, intravenous; CIV, continuous infusion; PO, orally; CR, complete remission; CRp, complete remission with incomplete platelet recovery; CRi, complete remission with incomplete blood count recovery; BMT, bone marrow transplant; AE, adverse event. *At the discretion of the treating physician.

Figure 2. Treatment schema for the phase 1b portion of the study.

- The phase 1b study will be followed by a randomized trial of fixed-dose indoximod (at the RP2D) or placebo combined with SOC chemotherapy
- Patients enrolled in the study are hospitalized as inpatients and continuously monitored during induction(s) and consolidation treatments. Patients do not remain hospitalized after HiDAC administration

Outcome Measures

- Safety assessment will follow guidelines provided in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03
- The phase 1 portion of the study will assess the RLTs and determine the RP2D of indoximod in combination with cytarabine and idarubicin
- RLTs include any Grade ≥3 nonhematologic adverse events (AEs) that are not clearly and incontrovertibly related to the underlying AML, cytarabine, or idarubicin
- Grade 3 elevation in bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or creatinine levels will be considered an RLT only if resolution to Grade ≤2 requires >21 days
- The period for determination of an RLT is from the first day of indoximod treatment until 21 days after starting indoximod
- The RP2D is the largest dose level at which ≤1 of 6 patients experience an RLT; if an RLT is not observed at the highest dose level (1,200 mg 3 times daily), this dose will be declared the RP2D
- Bone marrow aspirate and/or biopsies are performed to evaluate response to treatment
- A key secondary outcome is to determine the minimal (or measurable) residual disease (MRD) status, as measured by multidimensional flow cytometry, at the end of induction, after completion of the first cycle of HiDAC consolidation, and before maintenance or proceeding to allogeneic stem cell transplantation

RESULTS

Patient Characteristics

- As of June 1, 2017, 15 patients have been enrolled in the study and 4 patients currently remain on study
  - 4 patients at Dose Level 0 (indoximod 600 mg 3 times daily); 2 off study (1 due to relapse while on maintenance therapy, 1 did not complete scheduled indoximod doses due to inability to swallow)
  - 5 patients at Dose Level 1 (indoximod 1,000 mg 3 times daily); 5 off study (1 never received indoximod due to an insurance problem, 1 withdrew consent after only 2 doses of indoximod, 1 relapsed after the second HiDAC consolidation, 1 proceeded to allogeneic hematopoietic stem cell transplantation, 1 due to primary refractory AML)
  - 6 patients at Dose Level 2 (indoximod 1,200 mg 3 times daily); 4 off study (2 withdrew consent and did not complete scheduled indoximod doses, 1 due to primary refractory AML arising from MPN, 1 due to diagnosis of acute promyelocytic leukemia [APL; this patient never received indoximod])
  - Withdrawal of consent was not attributed to any indoximod-related AE
- Baseline characteristics for the 9 patients included in the per-protocol efficacy analysis are presented in **Table 2**

Table 2. Patient Characteristics*

Case	Sex/age	Prior treatment	Cytogenetics	Mutation panel	CBC: ANC (K/μL); Hgb (g/dL); platelet (K/μL)	ELN-2017 risk stratification
1	M/56	Hydroxyurea	47,XY,+8	*DNMT3A, IDH1, RUNX1, SRSF2*	0.72; 10.1; 43	Adverse
3	F/30	None	46,XX,inv(16) (p13.1q22)	Negative	0.46; 10.7; 116	Favorable
4	F/43	None	46,XX	*DNMT3A, FLT3-TKD, NPM1, NRAS*	0.71; 8.1; 42	Favorable
6	F/61	None	46,XX	*DNMT3A, NPM1, NRAS*	1.38; 11.5; 78	Favorable
9	M/69	None	45,X,-Y,t(11;17) (q23;q21)	*KRAS*	1.41; 9.3; 31	Adverse
11	M/18	None	46,XY	*FLT3-ITD, NPM1, WT1*	1.98; 10.4; 59	Favorable
14	M/51	None	46,XY	*DNMT3A, KRAS, NPM1, PTPN11, WT1*	0.69; 9.1; 22	Favorable
18	M/67	Decitabine, azacitidine (for MDS/MPN)	48,XY,+8,+8	*NRAS, CBL*	14.73; 6.8; 22	Adverse
19	M/43	None	46, XY, t(8;21) (q22;q22), del(9)	*NRAS*	2.75; 7.4; 160	Favorable

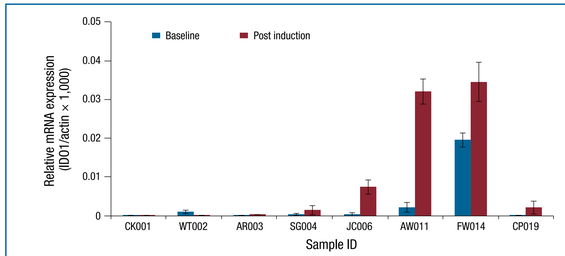
CBC, complete blood count; ANC, absolute neutrophil count; Hgb, hemoglobin; ELN, European LeukemiaNet; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; N/A, not available.
*Patients included in the per-protocol efficacy analysis (n = 9).

Safety

- No RLTs have been observed to date
- AEs have been reported for 13 of the 15 patients enrolled in the study
- The most frequently reported AEs, regardless of attribution, occurring in ≥20% of patients were febrile neutropenia, sinus tachycardia, abdominal pain, constipation, diarrhea, nausea, vomiting, asthenia, chest pain, fatigue, fever, contusion, decreased appetite, arthralgia, myalgia, dizziness, headache, delirium, cough, dyspnea, hypoxia, oropharyngeal pain, pruritus, maculopapular rash, and hypotension
  - Many of these events are known to be associated with chemotherapy and/or AML disease processes
- A total of 15 serious AEs (SAEs) have been reported, all of which were considered unrelated or unlikely to be related to indoximod
  - Grade 3 febrile neutropenia (n = 5; 2 of these patients also had Grade 4 febrile neutropenia), Grade 3 hypoxia (n = 2), Grade 4 hypocalcemia (n = 1), Grade 4 anemia (n = 1), Grade 3 atrial fibrillation (n = 1), Grade 3 fever (n = 1), Grade 4 hypotension (n = 1), and Grade 1 hematoma (n = 1)
- The most frequently reported possibly, probably, or definitely indoximod-related AEs (all grades) occurring in ≥5% of patients were abdominal pain, hyperhidrosis, diarrhea, fatigue, headache, nausea, vomiting, and asthenia
- 1 patient discontinued the study due to an AE (febrile neutropenia), which was attributed to cytarabine and line infection
- No patients have died as a result of an AE

Efficacy

- Patients who received ≥1 dose of indoximod have been included in the intention-to-treat (ITT) analysis
  - 2 patients never received any dose of indoximod due to being diagnosed with APL and an insurance problem; hence, the ITT population includes 13 patients
  - 11 of 13 patients (85%) in the ITT analysis achieved morphologic complete remission (CR)
- Patients (n = 9; **Table 2**) who received ≥80% of their scheduled indoximod doses have been included in the per-protocol analysis
  - 7 of 9 patients (78%) in the per-protocol analysis achieved morphologic CR
- All 7 patients (per-protocol analysis) who achieved CR had MRD negativity (<0.025%) after 1 cycle of induction therapy; MRD remained negative in all of these patients after the first cycle of HiDAC consolidation
- 2 of 9 patients (22%) had primary refractory AML and did not achieve CR
- AML relapsed in 2 patients: 1 patient died shortly after relapse and 1 patient received salvage cladribine, cytarabine, filgrastim, and mitoxantrone (CLAG-M) and still has residual disease 6 weeks after chemotherapy
- Overall, post-induction marrows were less cellular, but showed equal or even increased IDO1 mRNA (**Figure 3**)
  - This confirmed the presence (and perhaps attempted up-regulation) of the target IDO pathway during therapy



Bone marrow aspirates from paired baseline (pre-induction) and post-induction (Days 34-42) time points were compared for IDO1 mRNA by quantitative real-time RT-PCR (normalized to b-actin housekeeping gene). It should be noted that indoximod inhibits the functional activity of the IDO pathway, and thus blocks its immunologic effect, but this does not inhibit IDO1 transcription in response to inflammatory signals.

Figure 3. Confirmation of IDO1 target expression.

CONCLUSIONS

- **Indoximod does not appear to add significant toxicity to standard remission induction and consolidation therapy for patients with newly diagnosed AML**
- **No RLTs have been observed to date**
- **Initial data suggest a high CR rate (85% in the ITT cohort, 78% in the per-protocol cohort) with MRD negativity after 1 cycle of induction chemotherapy, and MRD negativity was maintained after the first cycle of HiDAC consolidation**
- **Based on the promising results observed to date with the combination of indoximod plus idarubicin and cytarabine chemotherapy for AML, the multisite phase 2 portion of the trial is eagerly anticipated**

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