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

Ashkan Emadi,1,2,3 Noa G. Holtzman,1,2 Mohammad Imran,1 Firas El Chaer,1,2 Madhurima Koka,1 Zeba Singh,1 Amir Shahlaee,4 Edward A. Sausville,1,2 Jennie Law,1,2 Seung Tae Lee,1,2 Arnob Banerjee,1 Aaron Rapaport,1 Huidong Shi,1 Ravi Kolte,1 Maria R. Baer,1 Yu H. Duong,1,2 David H. Munn,6 Michael Loken,7 Eugene Kennedy,1,8 Nicholas Vahanian,8 Charles Link8

1University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD; Departments of 2Medicine, 3Pathology, 4Radiology, 5University of Maryland School of Medicine, Baltimore, MD; 6Institute for Allergy and Asthma, Chevy Chase, MD; 7Georgia Cancer Center and Department of Pediatrics, Medical College of Georgia, Augusta, GA; 8Hematology Inc., Seattle, WA; 9NewLink Genetics Corp., Ames, IA.

BACKGROUND
- Acute myeloid leukemia (AML) is the highest incidence among all types of leukemias in adults and accounts for the greatest number of leukemia-related deaths in the United States.
- The median survival for patients with AML is the lowest of any type of leukemia.
- For the best 40% of patients there has been combination chemotherapy with a platinum and an anthracycline, resulting in complete remission rates of approximately 65% to 70%, but 3-year survival rates are 30% to 40%.
- Although the underpinnings are not clear, too many patients progress to secondary therapies.
- AML cells can acquire immune evasion and tolerance through overexpression of indoleamine 2-3-dioxygenase (IDO), which leads to immunosuppressive effects through depletion of tryptophan (Trp) and its catabolite kynurenine.
- Indoximod (4-hydroxyindole-3-acetic acid), a pro-drug for indoximod, is a small-molecule inhibitor of the IDO pathway that acts directly on immune cells to reverse IDO pathway-mediated expression by inhibiting tryptophan metabolism (see Figure 1).

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

Efficacy Criteria
- ≥18 years of age with 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 syndrome (MDS), MDS-related acute leukemia (ARL), non-AVL MDS, or AML from therapy-related myelodysplasia.
- AML must be at least 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 syndrome (MDS), MDS-related acute leukemia (ARL), non-AVL MDS, or AML from therapy-related myelodysplasia.
- A phase 1/2 dose escalation of the indoximod (IP) plus idarubicin and cytarabine starting dose of 0.1 mg/m2 daily throughout induction courses I and II, patients received IP 1,200 mg/m2 daily. In patients who received ≥80% of their scheduled induction doses, 1 due to primary refractory AML arising from the underlying AML, cytarabine, or idarubicin.

RESULTS

Characteristics
- A total of 18 central AML (DAE) have been reported, of which were considered unrelated or unlikely to be related to indoximod.
- Grade 3: Febrile neutropenia (n = 2); due to primary refractory AML arising from the underlying AML, cytarabine, or idarubicin.
- Grade 1: Hypersensitivity (n = 1); Grade 1: Hypersensitivity (n = 1).
- 2 patients had a dose cutback of IP as part of the treatment of AML.
- The dose escalation or de-escalation will follow a modified Fibonacci sequence.
- No RLTs have been observed to date.
- Indoximod does not appear to add significant toxicity to standard remission induction and consolidation therapy for patients with newly diagnosed AML.

ACKNOWLEDGMENTS
- Supported by NewLink Genetics Co. The authors thank their colleagues and their families, patients, and caregivers who participated in the studies. They thank the members of the study teams and the clinical research organizations and data management and statistical analysis organizations who provided support. They thank the patients and families for their contributions to the studies.

REFERENCES