(S174) OFIRNOFLAST, A FIRST-IN-CLASS NEK7 INHIBITOR, INDUCES ROBUST TRANSFUSION INDEPENDENCE AND MULTILINEAGE HEMATOLOGICAL IMPROVEMENT IN LOWER-RISK MYELODYSPLASTIC SYNDROME(LR-MDS): PHASE 2 RESULTS

Topic: 10. Myelodysplastic syndromes - Clinical

Varun Bafna*[1], Uttam Kumar Nath[2], Sandip Shah[3], Arijit Nag[4], Chandran Nair[5], Ramesh Uppada[6], Devan Bursey[7], Ajisa Muthayil Ali[7], Jeremiah Bearss[7], Alan List[7], David Bearss[7]

[1]Star Superspeciality Clinic and Hospital, Kolhapur, India;[2]All India Institute of Medical Sciences, Rishikesh, India;[3]Hemato Oncology Clinic Vedanta Institute of Medical Sciences, Admedabad, India;[4]Tata Medical Center, Kolkata, India;[5]Malabar Cancer Centre, Kerala, India;[6]HCG Cancer Centre, Vishakhapatnam, India;[7]Halia Therapeutics, Lehi, United States of America;

Background

NLRP3 inflammasome hyperactivation is a central driver of ineffective hematopoiesis in MDS through caspase-1 activation, pyroptotic cell death of hematopoietic progenitor cells, and GATA-1 degradation. Ofirnoflast (HT-6184) is the first-in-class, oral, allosteric inhibitor of NEK7, a scaffold protein essential for NLRP3 inflammasome assembly. NEK7 inhibition prevents inflammasome assembly and downstream inflammatory signaling, thereby restoring multilineage hematopoiesis.

Aims

Evaluate the safety and efficacy of ofirnoflast in ESA-refractory, lower-risk MDS.

Methods

This open-label, single-arm, phase 2 trial enrolled ESA-refractory, intolerant, or ineligible adults with IPSS-R lower-risk MDS (score ≤4.5) and symptomatic anemia (hgb < 9 g/dL) or RBC transfusion-dependence (TD). Ofirnoflast was administered orally at 2 mg QD for up to 32 weeks, 5 days on/2 days off. The primary endpoint was hematological improvement (HI) per the IWG 2018 criteria.

Copyright Information: (Online) ISSN: 2572-9241
©2026 The Author(s). HemaSphere is published by John Wiley & Sons Ltd on behalf of European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND), which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.
Abstract Book Citations: Authors, Title, HemaSphere, 2026;10:(S1):pages. The abstract book DOIs can be found on the "Author Information" page.
Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.

Results

37 patients were treated [ages 31-86, 62% male]. 18/37 (49%) had a high transfusion burden (HTB), 5/37 (14%) had a low TB (LTB), and 14/37 (43%) were non-TD (NTD) per IWG 2018. Disease subtypes included MDS with low blasts (25/37), SF3B1 (2/37), MDS/MPN (4/37), del(5q) (3/37), and increased blasts (3/37) with a median IPSS-R score of 3.5. Median treatment duration was 32 weeks.
Ofirnoflast demonstrated a highly favorable safety profile. Treatment-related adverse events (TRAEs) occurred in 27% of patients; with only two grade ≥3 TRAEs [hypertension (n=1), leukopenia, (n=1)]. Zero treatment-related serious adverse events were reported. One patient with an initial diagnosis of MDS/MPN discontinued due to TRAE (leukocytosis).

Among the 30 evaluable patients (7 subjects were found to be ineligible or did not complete the treatment period), Ofirnoflast achieved a 67% overall HI response rate comprising 63% erythroid (HI-E), 60% platelet (HI-P), and 50% neutrophil (HI-N) responses. 55% of TD patients achieved transfusion independence (TI) for ≥8 weeks and 39% for ≥16 weeks, with a median TI duration of 28.5 weeks. Among NTD patients, 75% achieved HI-E. The median maximum hemoglobin rise in HI-E among responders was 4.2 g/dL from a baseline of 7.5 g/dL. Morphologic responses included complete remission (CR) in 9/30 (30%) and marrow CR in 1/30 (3%) patients. HI was observed across all WHO MDS subtypes and mutation backgrounds, including *SF3B1* and Del5q.

Pharmacodynamic data confirmed on-target activity, with significant reductions in TNF-alpha (mean change –5.5 pg/mL; q=0.048) and large reductions in oxidized DNA (mean change –105 pg/mL, q=0.052) after 16 weeks of treatment. Quality of life metrics notably improved, with the greatest gains in HI responders being in overall QOL-E score, fatigue and social/family well-being domains.

Outcome	Efficacy Population
TI	55% (10/18)
Median TI Duration	28.5 weeks
Overall HI Rate	67% (20/30)
HI-E	63% (19/30)
HI-P	60% (3/5)
HI-N	50% (2/4)

Summary/Conclusion

Ofirnoflast demonstrated clinically meaningful, multilineage efficacy in ESA-refractory LR-MDS, with a 67% overall HI rate and 55% transfusion independence in TD patients. It also had an exceptional safety profile with no treatment-related serious adverse events. These results represent the first clinical validation that NEK7 blockade can durably suppress the NLRP3 inflammasome and restore hematopoiesis across all MDS subtypes, supporting Ofirnoflast as a transformative treatment for this high-unmet-need population.

Copyright Information: (Online) ISSN: 2572-9241
©2026 The Author(s). HemaSphere is published by John Wiley & Sons Ltd on behalf of European Hematology Association. This is an open access Abstract Book distributed under the Attribution-NonCommercial-NoDerivs (CC BY-NC-ND), which allows third parties to download the articles and share them with others as long as they credit the author and the Abstract Book, but they cannot change the content in any way or use them commercially.
Abstract Book Citations: Authors, Title, HemaSphere, 2026;10:(S1):pages. The abstract book DOIs can be found on the "Author Information" page.
Disclaimer: Articles published in the journal HemaSphere exclusively reflect the opinions of the authors. The authors are responsible for all content in their abstracts including accuracy of the facts, statements, citing resources, etc.