ADVANCED MYELODYSPLASTIC NEOPLASMS OR AML FAILING HMA-BASED THERAPY – PRELIMINARY RESULTS OF THE IMPRESS STUDY

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INTRODUCTION

Hypomethylating agents (HMAs), as monotherapy or combined with venetoclax (VEN), are standard of care for patients with higher-risk MDS (HR-MDS) or AML ineligible for intensive chemotherapy[1,2]. However, most patients fail to respond or relapse and outcomes after HMA-based therapy remain poor, with limited effective options.

Imetelstat is a potent selective telomerase inhibitor recently approved by FDA[3] and EMA[4] for transfusion-dependent lower-risk (LR) MDS patients ineligible for or refractory to ESA. Its clinical efficacy in HR-MDS or AML has not yet been established.

AIM

The multicenter phase 2 IMpress trial (NCT05583552), led by EMSCO, evaluates safety and efficacy of imetelstat sodium in HR-MDS or AML patients refractory, relapsing or intolerant following at least 6 or 4 cycles of either azacitidine (AZA) or decitabine (DAC), respectively, or 3 cycles of VEN/AZA.

METHOD

In cohort 1 (ASH 2024), patients received 7.5 mg/kg i.v. once every 4 weeks for 4 cycles. **Due to a lack of response and no new safety signals, the protocol was amended to biweekly dosing for the first 4 cycles (cohort 2).** The primary endpoint (PE) was overall response rate after 4 months (CR, CRi, PR, HI).

All patients achieving CR, CRi, PR or HI after 4 months of imetelstat were considered responders and allowed to continue treatment until loss of response/disease progression. Non-responding patients stopped treatment after 4 months.

RESULTS

Table 1: Disposition of patients and baseline characteristics

Baseline characteristics	1st cohort 7.5 mg/kg i.v. once every 4 weeks	2nd cohort 7.5 mg/kg i.v. once every 2 weeks
Patients treated	23	23
MDS / AML distribution	6 MDS / 17 AML	6 MDS / 17 AML
Median number of doses per patient	3	5
Median age (range)	77 (68–87)	77 (66–88)
Male / Female	15 / 8	14 / 9
Median ECOG performance status	1 (0–2)	1 (0–2)
Complex karyotype	6/23	6/23
Median BM blasts at screening	30% (8–91)	27% (5.5–86)
Prior VEN treatment	47.8% (11/23)	39.1% (9/23)

Safety results:
In the second cohort, 24 SAEs occurred in 19 patients from August 2024 until 8th May 2025, of which none were deemed related to imetelstat. The most common SAEs were febrile neutropenia (n=6), disease progression/transformation to AML (n=4), sepsis (n=2) and fever (n=2). Overall, 11/24 SAEs resulted in death (n=4 disease progression or AML, n=2 cardiac/cardiorespiratory arrest, n=1 febrile neutropenia, n=1 sepsis, general health alteration and death of unknown reason). 8 of the SAEs resolved without sequelae and 2 remained unresolved.

In the first cohort, 30 SAEs occurred in 18 patients, with 3 deemed possibly related to imetelstat (pneumonia [n=2], febrile neutropenia [n=1]). The most common SAEs were disease progression/transformation to AML (n=9), pneumonia (n=3), febrile neutropenia (n=3), and sepsis (n=2). 10/30 SAEs resulted in death.

Despite higher drug exposure in the second cohort, no increase in toxicity was observed.

Efficacy results:
In the second cohort, 6/23 reached the primary endpoint visit, scheduled after 4 cycles of treatment, compared to none in the first cohort: 3 had stable disease (SD) and 3 showed progressive disease (PD). One patient with SD achieved neutrophil response (HI-N) and received 3 additional doses in the extension phase. 13 of the 23 patients reached the first (preliminary) disease assessment after 2 cycles. At this point, only 1 patient showed a response (SD with HI-N), 9 patients had SD and 2 had PD.
As of 17th June 2025, the median OS of the first and second cohort was 119 (95% CI: 83-144) and 102 days (95% CI: 67-TBD), respectively. The median PFS of the first and second cohort was 69 (95% CI: 57-113) and 92 days (95% CI: 57-TBD), respectively.

Table 2: Summary of safety analysis

Preliminary safety data (cut-off 05/2025)	1st cohort	2nd cohort
SAEs	30 in 18/23 patients	24 in 19/23 patients
IP related SAEs	3/30 possibly related • pneumonia (n=2) • febrile neutropenia (n=1)	0/24
Most common SAEs	• progression/ transformation (n=9) • febrile neutropenia (n=3) • sepsis (n=2) • pneumonia (n=3)	• progression/ transformation (n=4) • febrile neutropenia (n=6) • sepsis (n=2) • fever (n=2)
Fatal SAEs	10/30 SAEs • disease progression or AML (n=5) • infectious complications (n=4) • Ileus (n=1)	11/24 SAEs • disease progression or AML (n=4) • cardiac/cardiorespiratory arrest (n=2) • febrile neutropenia, sepsis, general health alteration, death of unknown reason (n=1)
SAE resolution	11 resolved without sequelae	8 resolved without sequelae, 2 unresolved

Table 3: Efficacy analysis

Preliminary data (cut-off 06/2025)	1st cohort	2nd cohort
Primary endpoint V9	0/23 (0%)	6/23 (26%) 3 SD [1/3 with HI-N] 3 PD
OS median	119 (95% CI: 83-144)	102 days (95% CI: 67-TBD)
PFS median	69 (95% CI: 57-113)	92 days (95% CI: 57-TBD)
Follow-up time median	107	97 days

CONCLUSIONS

Increased exposure to imetelstat in refractory, relapsing or intolerant AML/HR-MDS patients did not appear to be associated with additional toxicity. PE visit completion rose from 0/23 patients to 6/23 (26%) in the second cohort, despite only one achieving HI, and no marrow responses were observed.

One patient remains on treatment as of 16th October 2025. **Imetelstat has limited single agent activity in this very adverse prognosis group.**

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