



ADVANCED MYELODYSPLASTIC NEOPLASMS OR AML FAILING HMA-BASED THERAPY - INTERIM ANALYSIS RESULTS OF THE IMPRESS STUDY

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INTRODUCTION

Hypomethylating agents (HMAs), alone or in combination with venetoclax (VEN), are the standard for patients with HR-MDS or AML not eligible for intensive chemo or allogeneic stem cell transplantation^{1,2}. However, many patients do not respond or subsequently relapse, resulting in dismal outcome with very limited further treatment options.

Imetelstat (GRN163L) inhibits telomerase, which is upregulated in various cancers. Its inhibition leads to loss of a cancer cell's ability to maintain telomere length, resulting in cell-cycle arrest, apoptosis or senescence. In June 2024, imetelstat was approved by the FDA for the treatment of transfusion-dependent LR-MDS in ESA ineligible /relapsed /refractory patients³.

AIM

Imetelstat's clinical activity in HR-MDS or AML is unknown so far.

This multicenter phase 2 trial led by the European Myelodysplastic Neoplasms Cooperative Group (EMSCO) evaluates the safety and efficacy of imetelstat in patients with HR-MDS or AML who are refractory, relapsing or intolerant after at least 6 or 4 cycles of either azacitidine (AZA) or decitabine (DAC), respectively, or 3 cycles of VEN plus AZA.

METHODS

This first part of the IMpress study was carried out with the following characteristics:

- Imetelstat sodium at a **dose of 7.5 mg/kg** i. v. once every 4 weeks for 4 cycles of 28 days
- Treatment until disease progression, unacceptable toxicity, withdrawal of consent or lack of response
- The **primary endpoint** (PE) was **ORR** (CR, CRi, PR, HI) assessed after 4 months
- **Responding** patients (at least **PR** or **HI**) were eligible to continue treatment until loss of response/disease progression
- Non-responding patients stopped treatment after 4 months

RESULTS

Table 1: Summary of SAEs (total n=30)

Type of SAE	#	Outcome
Infections	18	
Lung infections	8	
Pneumonia	3	1 fatal / 2 recovered
Fungal infection	2	2 fatal
Bacterial infection	1	recovered
Exacerbated COPD	1	recovering / resolving
Pulmonary abscess	1	fatal
Febrile neutropenia / sepsis	5	5 recovered
Dental infection / caries	2	2 recovered
Infected hematoma	1	recovered
Bone infection	1	recovered
Urinary tract infection	1	not recovered
Disease progression / transformation to AML	9	6 fatal / 2 not recovered / 1 unknown
Ileus	1	fatal
Hemorrhage	1	recovered
Pneumopathy	1	recovered

Safety results:

A total of 30 SAEs occurred in 18 patients of which 21 SAEs required hospitalizations. **The majority of SAEs (18/30) was of infectious nature with infections of the lung, febrile neutropenia and sepsis being the most common complications (see table 1).** Overall, 11 of the 30 SAEs resulted in death (n=6 due to disease progression/ transformation to AML, n=4 due to infectious complications and n=1 due to ileus) and one was assessed as being possibly related to imetelstat (pneumonia). 11 of the SAEs resolved without sequelae. Overall, no new safety signals occurred beyond those already known for imetelstat.

Efficacy results:

Between June and October 2023, 23 patients (MDS=6, AML=17) in Germany, France and Australia received at least one dose of imetelstat with an average of 2.8 doses administered per patient. In this first part of the trial, **none of the 23 treated subjects reached the PE visit**, which was scheduled after 4 cycles of treatment. 16 of the 23 patients reached the first (preliminary) disease assessment visit after two cycles of imetelstat. At this assessment, only 1 patient showed a response in form of both HI-E and HI-P. 7 patients had stable disease (SD) and 8 had progressive disease (PD). In addition, short-term transient improvement in hematological values was observed in individual cases.

CONCLUSIONS

Absence of responses according to the stringent primary efficacy endpoint was observed in this interim analysis. No unexpected safety findings were observed and most were attributed to the underlying HR-MDS and AML.

Based on the observations in this first cohort, the protocol was amended to a more frequent dosing schedule (imetelstat every 2 weeks for at least the first 4 cycles) for a second cohort of patients who have started to be enrolled and treated with this modified schedule starting in September 2024.

REFERENCES

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3. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-imetelstat-low-intermediate-1-risk-myelodysplastic-syndromes-transfusion-dependent>

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Table 2: Disposition of patients and primary analysis results

	MDS	AML	Overall
Enrolled			24
Withdrawn before treatment			1
Treated	6 (100 %)	17 (100 %)	23 (100 %)
1 dose		2 (11.8 %)	2 (8.7 %)
2 doses		6 (35.3 %)	6 (26.1 %)
3 doses	3 (50 %)	6 (35.3 %)	9 (39.1 %)
4 doses	3 (50 %)	3 (17.6 %)	6 (26.1 %)
Reached primary endpoint visit	0 (0 %)	0 (0 %)	0 (0 %)
Responder	0 (0 %)	0 (0 %)	0 (0 %)
Disease progression*	6 (100 %)	10 (58.8 %)	16 (69.6 %)
Death	1 (16.7 %)	14 (82.4 %)	15 (65.2 %)
* documented progression at visit 5 response assessment, study exit form or IMP discontinuation form in eCRF; MDS: myelodysplastic syndromes; AML: acute myeloid leukemia			

Table 3: Response analysis at visit 5

Subset	n	%
Response Assessment (Visit 5) performed?	16	69.6
Responder at visit 5	1	4.3
Disease response		
Stable disease (SD)	7	30.4
Progressive disease (PD)	8	34.8
Unknown	1	4.3
Reached primary endpoint visit		
Erythroid response (HI-E)	1	4.3
Platelet response (HI-P)	1	4.3
Neutrophil response (HI-N)	0	0
Progression or relapse after HI	6	26.1

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