Actinomycin D in Combination with Low-dose Cytarabine and Venetoclax in Relapsed or Refractory NPM1-mutated Acute Myeloid Leukemia

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INTRODUCTION

Actinomycin D has previously demonstrated antileukemic efficacy in R/R *NPM1*m AML. Herein, we present our real-world study of Actinomycin D, low-dose cytarabine, and venetoclax (ACTIVE) as salvage treatment in R/R *NPM1*m AML.

AIM

To evaluate the efficacy and toxicity of the ACTIVE regimen in R/R *NPM1*m AML.

METHODS

- This was a retrospective study. The ACTIVE regimen consisted of Actinomycin D 12.5 mcg/kg (days 1-3 or days 1-2 in patients ≥ 65 years), cytarabine 20 mg/m^2 (days 1-10), and Venetoclax 600 mg/d (days 1-14).
- Venetoclax was continued for 21 or 28 days if marrow on day 14 showed >5% blasts.
- Gilteritinib 80 or 120 mg/d was added to ACTIVE in *FLT3* co-mutated cases.
- After 1 or 2 ACTIVE cycles, responders proceeded to allogeneic HSCT or continued maintenance with low-dose cytarabine + venetoclax.
- We collected baseline characteristics, CRc (CR+CRh+CRi) rate, ORR (CR+CRh+CRi+MLFS), MRD-negativity rate, OS, RFS, 30-day and 60-day mortality rate.

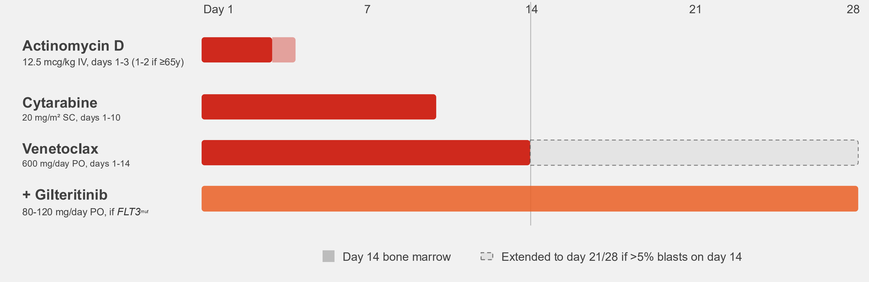


Figure 1. *ACTIVE treatment schedule*

RESULTS

- 28 R/R *NPM1*m AML patients were enrolled with a median age of 64 years (20-87) and a median ECOG of 1 (0-3).
- **75% (21/28) were previously exposed to intensive chemotherapy** ± Midostaurin, whereas 25% (7/28) were treated with HMA ± Venetoclax.
- *FLT3* co-mutations were identified in 64% (18/28), and additional Gilteritinib was used in 57% (16/28).
- Extramedullary involvement was confirmed in 21% of cases.
- **The CRc rate was 81% (21/26), and the ORR was 92% (24/26).** 2 patients died prior to the response evaluation.
- MRD negativity rate in CRc patients was 62% (13/21).
- **54% (15/28) of patients were bridged to allogeneic SCT**.
- The median **OS was 17.2 months (7.2 - NR**), and the median RFS was 13.9 months (4.5 - NR). The median OS and RFS were not reached in allotransplanted patients.
- The 30-day and 60-day mortality rates were 11% (3/28) and 18% (6/28), respectively.

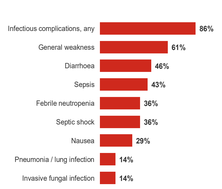


Figure 3. *Key adverse events*

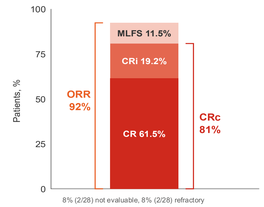


Figure 2. *Best response*

Characteristic	n	%
DEMOGRAPHICS		
Median age, years (range)	64	20-87
Age ≥ 65 years	11	39%
Median ECOG (range)	1	0-3
ECOG 2–3	8	29%
DISEASE		
De novo AML	25	89%
Secondary AML	3	11%
Extramedullary involvement	6	21%
ELN RISK CLASSIFICATION	**ELN 2022**	**ELN 2024**
Favorable	12 (43%)	11 (39%)
Intermediate	14 (50%)	17 (61%)
Adverse	2 (7%)	0 (0%)

Table 1. *Demographics and disease*

Characteristic	n	%
CO-MUTATIONS		
FLT3-ITD or *FLT3-TKD*	18	64%
DNMT3A	16	57%
TET2	7	25%
IDH1 or *IDH2*	11	39%
NRAS	2	7%
KARYOTYPE		
Normal/Non-adverse	27	96%
Adverse	1	4%
REGIMEN RECEIVED		
ACTIVE	11	39%
ACTIVE + Gilteritinib	16	57%
ACTIVE + Ivosidenib	1	4%

Table 2. *Genetics and regimen*

Characteristic	n	%
PRIOR LINES OF THERAPY		
Median lines (range)	1	1-5
2 prior lines	5	18%
PRIOR EXPOSURE		
Intensive chemotherapy ± Midostaurin	21	75%
HMA ± Venetoclax	7	25%
Prior allogeneic transplant	2	7%

Table 3. *Prior treatment history*

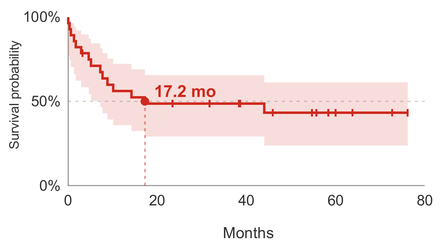
Characteristic	n	%
RESPONSE (N=26)		
CRc (CR + CRi)	21	81%
CR	16	62%
CRi	5	19%
MLFS	3	12%
ORR (CRc + MLFS)	24	92%
RD	2	8%
MRD-negativity in CRc	13	62%
Non-evaluable for response (early death)	2	7%

Table 4. *Response*

Characteristic	n	%
COUNT RECOVERY, MEDIAN DAY (RANGE)		
ANC > 0.5 × 10^9/L	27	6-57
ANC > 1.0 × 10^9/L	33	18-59
POST-REMISSION		
Bridged to allogeneic transplant	15	54%
Median time to response, days (range)	28.5	14-67
EARLY MORTALITY		
30-day mortality	3	11%
60-day mortality	5	18%

Table 5. *Haematologic recovery and early mortality*

Overall survival



Relapse-free survival

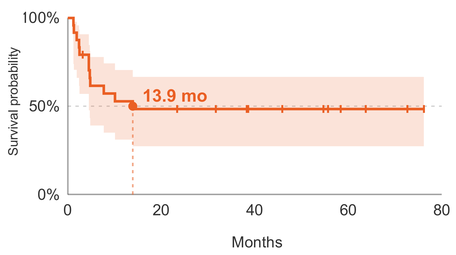


Figure 4. *Overall and relapse-free survival. Median follow-up 54.7 months (95% CI 38.3-60.0)*

CONCLUSIONS

ACTIVE regimen demonstrates **promising efficacy** and **tolerability** in R/R *NPM1*m AML. Further evaluation in clinical trials is warranted.

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CONTACT INFORMATION

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