LONG-TERM FOLLOW-UP OF ORAL DECITABINE/CEDAZURIDINE (ASTX727) PLUS VENETOCLAX IN NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA: A PHASE 2 STUDY

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INTRODUCTION

- Older or unfit patients with newly diagnosed AML (NDAML) have poor outcomes, particularly those with secondary AML (sAML).
- In our prior phase II study of the overall cohort, oral decitabine/cedazuridine plus venetoclax demonstrated clinical activity in older/unfit AML.[1]

AIM

- To report extended follow-up of a phase II study evaluating oral decitabine/cedazuridine plus venetoclax, with comparison of outcomes between de novo and sAML in frontline setting.

METHOD

Study design and patients

- Design: Single-center phase II study of older/unfit patients with NDAML
- Patients: 68 ND AML (32 de novo, 36 sAML)
- Study period: March 2021-July 2025

Treatment regimen

- Oral decitabine/cedazuridine (ASTX727): 35/100 mg PO, Days 1-5
- Venetoclax: 400 mg PO, Days 1-21/28
- 28-day cycles with dose adjustments per toxicity

Assessments

- Primary: Overall survival (OS), relapse-free survival (RFS)
- Secondary: Overall response rate (ORR), Minimal residual disease (MRD) negativity, safety
- Exploratory: ELN2024, Molecular risk stratification

Statistical analysis

- Survival: Kaplan-Meier (KM), compared by log-rank test
- Subgroup analyses: de novo vs sAML, ELN 2024[2], molecular prognostic risk signature profile[3]

RESULTS

Key baseline characteristics (high-risk ND AML cohort)

- TP53 mutations (18%)
- Complex karyotype (26%)
- Prior hypomethylating agent (HMA) exposure (31%/sAML)
- Median age (80)
- ECOG ≥ 2 (50%)

Response outcomes

Responses were rapid and deep in both cohorts

- **ORR**
  - De novo: 75% (24/32)
  - sAML: 58% (21/36)
- **CR/CRi rates**
  - De novo: CR 56%, CR/CRi 75%
  - sAML: CR 31%, CR/CRi 50%
- **MRD negativity (CR/CRi)**
  - De novo: 58%
  - sAML: 56%
- **Median time to response**: 41 days (29-56)

Survival outcomes

- Median follow-up**: 32 months**
- **Median OS:**
  - De novo: **12.7 months**
  - sAML: **7.2 months** (p=0.61)
- **1-year/2-year OS rates**
  - De novo: **51%/17%**
  - sAML: **42%/31%**
- **RFS (CR/CRi patients):**
  - De novo: 9.2 months
  - sAML: 11.7 months (p=0.56)

Prognostic stratification

- **ELN 2024** retained strong prognostic discrimination (p<0.01)
- **Molecular prognostic risk signature (mPRS):** further redlined OS across risk groups (p<0.01)

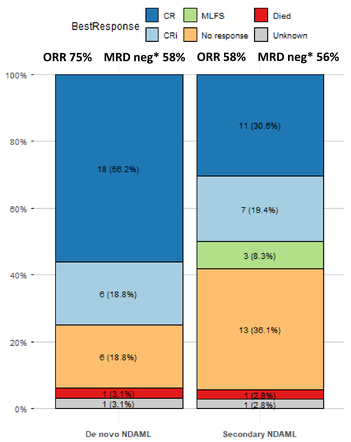
Safety and tolerability

- Grade ≥3 AEs: **66%**
  - Thrombocytopenia **15%**
  - Febrile neutropenia**: 12%**
- Venetoclax dose reductions by cycle 2**: 59%**
- **All-cause 4-/8-wk mortality:**
  - De novo: **6%**
  - sAML: **8/22%**

Table 1. Baseline characteristics

Characteristic		De novo AML (n=32)	sAML (n=36)
Age, years		81 (78-84)	78 (75-82)
ECOG PS ≥ 2		18 (56%)	16 (44%)
Complex karyotype		6 (19%)	12 (33%)
TP53 mutation		5 (16%)	7 (19%)
NPM1 mutation		7 (22%)	2 (6%)
FLT3-ITD		3 (9%)	1 (3%)
IDH ½		3 (9%)	0
ELN 2024 risk	• Favorable	19 (59%)	22 (61%)
	• Intermediate	8 (25%)	7 (19%)
	• Adverse	5 (16%)	7 (19%)
Prior untreated MDS/MPN			10 (28%)
Prior treated MDS/MPN			15 (42%)
Therapy-related AML			11 (31%)
Prior HMA exposure			11 (31%)
Prior venetoclax exposure			2 (6%)

Figure 1. Responses in evaluable patients



* Among CR/CRi

Figure 2. OS comparing de novo (DN) and sAML

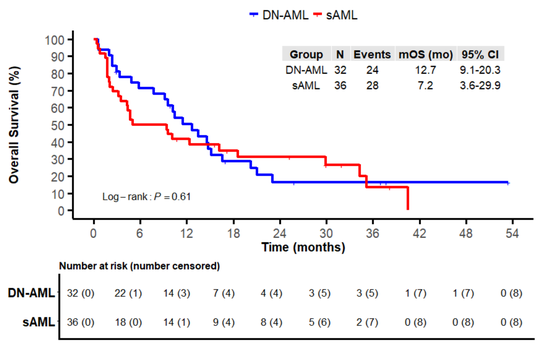


Figure 3. OS by mPRS risk

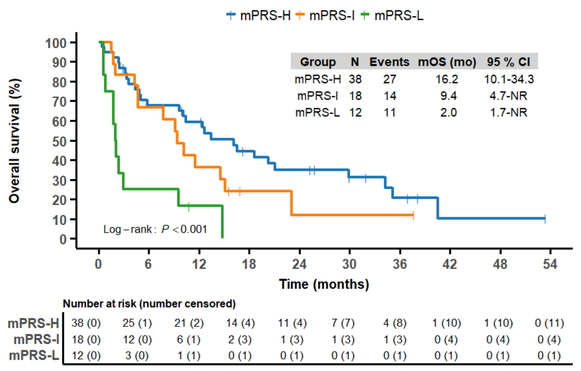
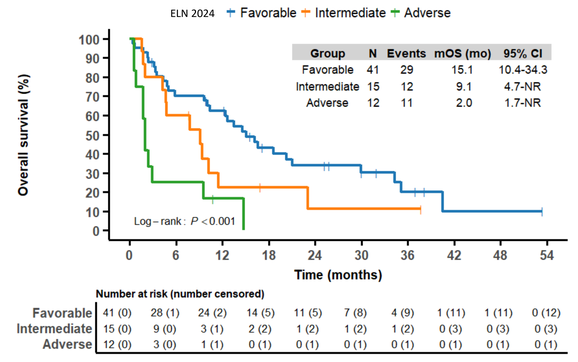


Figure 4. OS by ELN 2024 risk



CONCLUSIONS

- In this long –term follow up study, oral decitabine/cedazuridine plus venetoclax showed meaningful activity in older or unfit patients., with higher response rates and numerically longer survival in de novo AML.
- Early all-cause mortality was high in secondary AML, consistent with it's higher-risk clinical profile.

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REFERENCES

1. Bazinet et al. Lancent hematol2024
2. Döhner et al. ELN 2024 AML. Blood 2024
3. Döhner et al. Blood 2022.

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DISCLOSURES

Full disclosure available upon request for MK and FR.

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