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EHA-SWG Scientific Meeting on Recent Advances in the Pathogenesis and Treatment of Secondary Acute Myeloid Leukemias

Berlin, Germany
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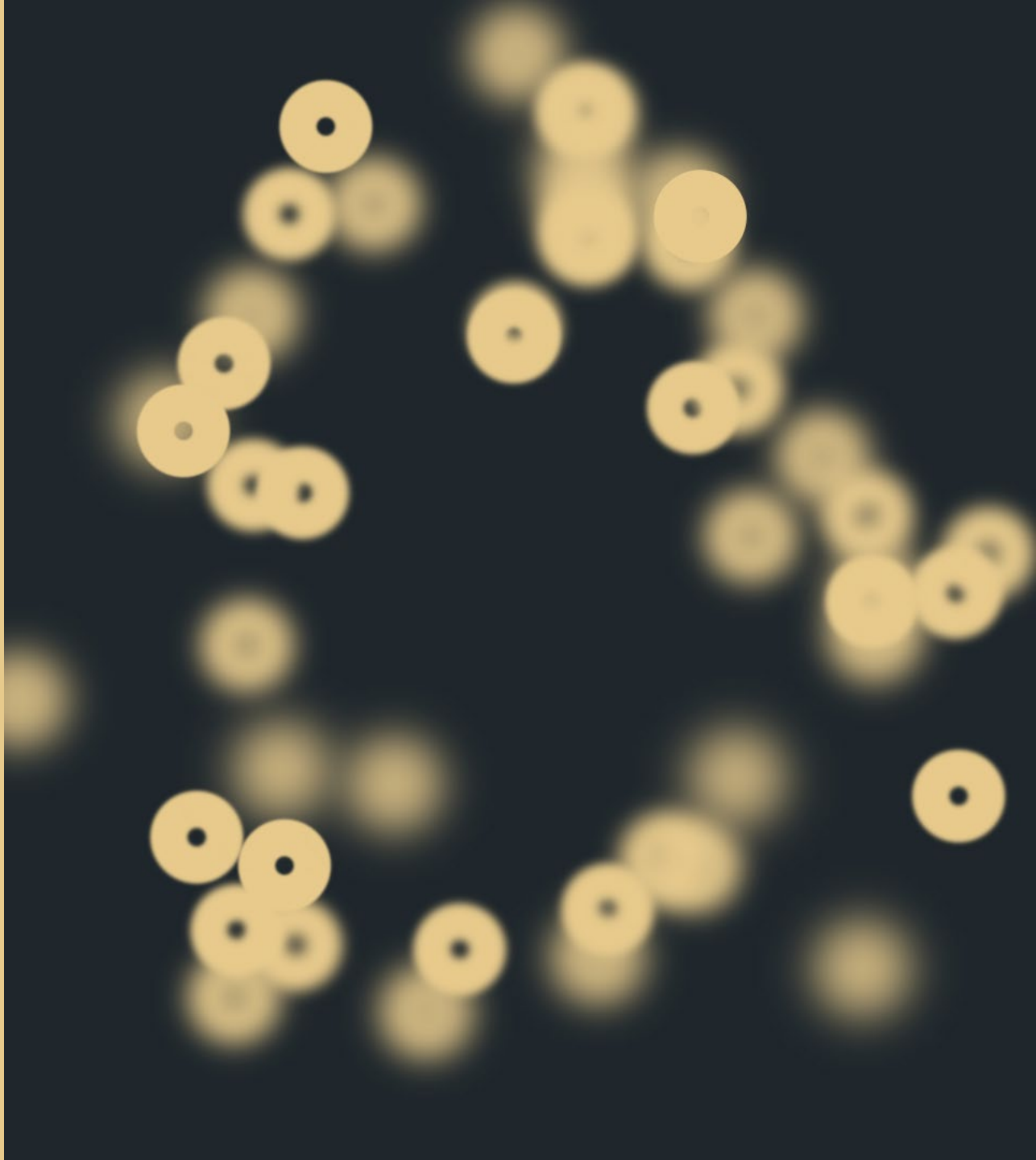
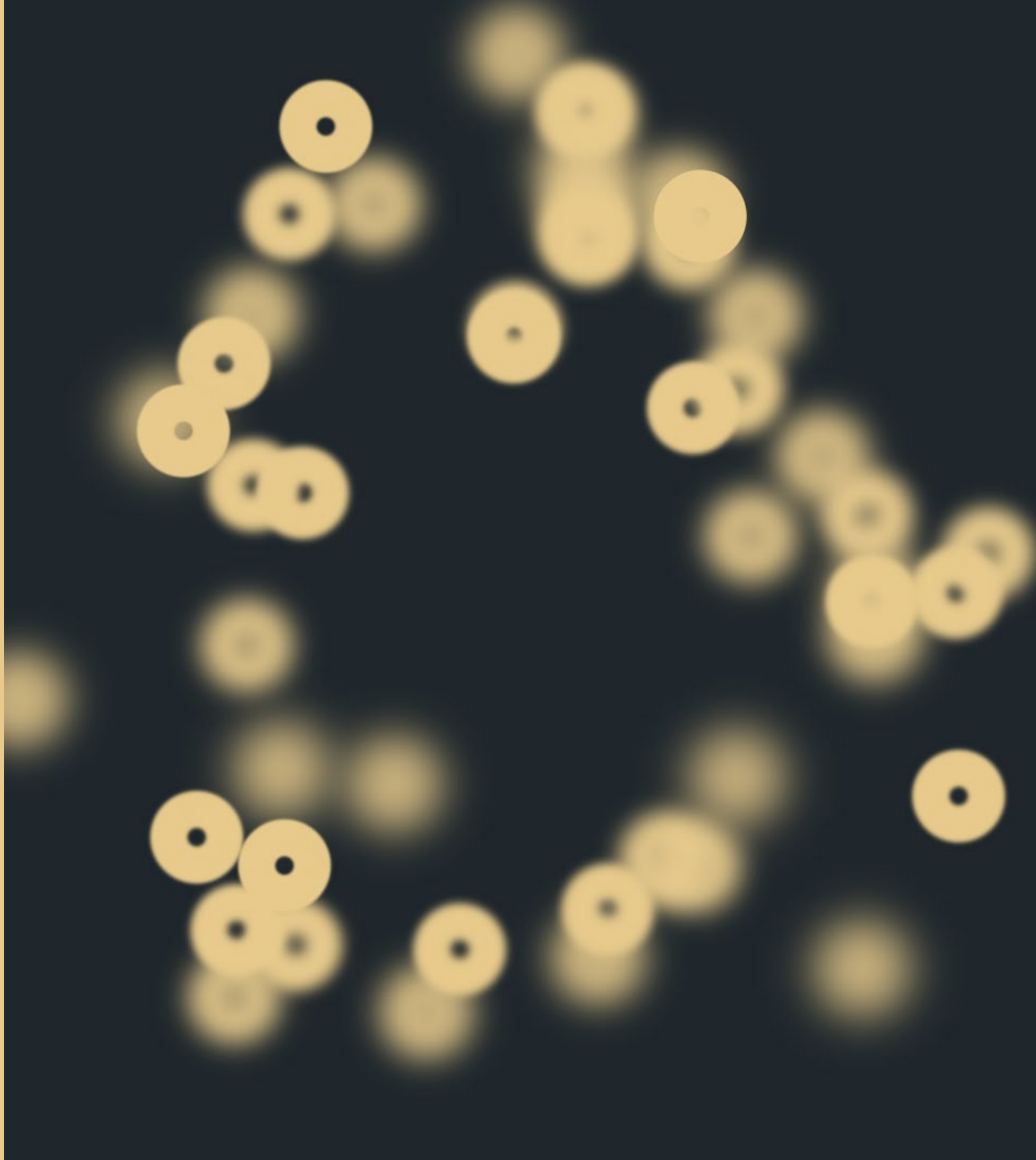


HIGH RISK MUTATIONS IN CRITICAL GENES DO NOT SIGNIFICANTLY AFFECT REMISSION RATES AND MRD CLEARANCE IN AML PATIENTS RECEIVING CPX-351 INDUCTION

Paola Minetto, MD, PhD



Background

Better understanding of the molecular basis of **Acute Myeloid Leukemia** (AML) allowed to **identify critical gene** mutations related to a higher risk of treatment **failure** in patients receiving **conventional 3+7 chemotherapy**

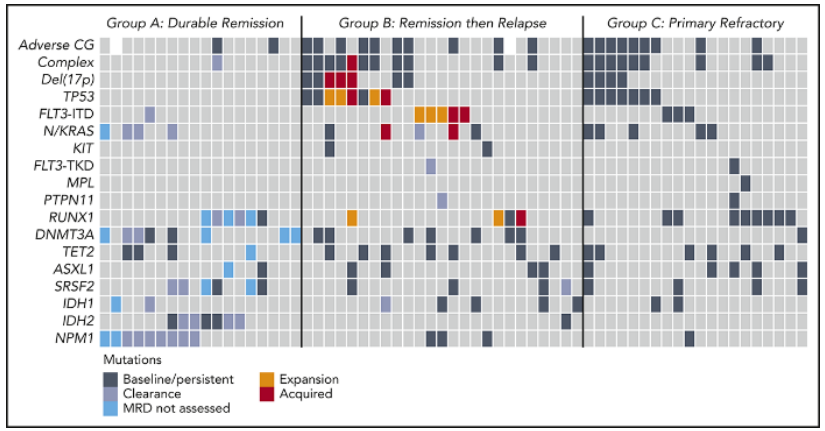
Consequently, the presence of at least one mutation among ***TP53, ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*** confers adverse risk according to the recent European LeukemiaNet (ELN) 2022 classification

In patients receiving **less intensive** treatment with **hypomethylating agents plus Venetoclax (HMA+VEN)**, ***TP53***, ***RUNX1, FLT3-ITD, N/KRAS, CBL***, **and *KIT*** mutations have been reported to predict treatment failure

ADVERSE RISK ACCORDING TO ELN 2022

t(6;9)(p23;q34.1); *DEK-NUP214*
t(v;11q23.3); *KMT2A* rearranged
t(9;22)(q34.1;q11.2); *BCR-ABL1*
t(8;16)(p11;p13)/*KAT6A-CREBBP*
inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
t(3q26.2;v)/*MECOM(EVI1)*-rearranged
-5 or del(5q); -7; -17/abn(17p)
Complex karyotype, monosomal karyotype
Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*
Mutated *TP53*

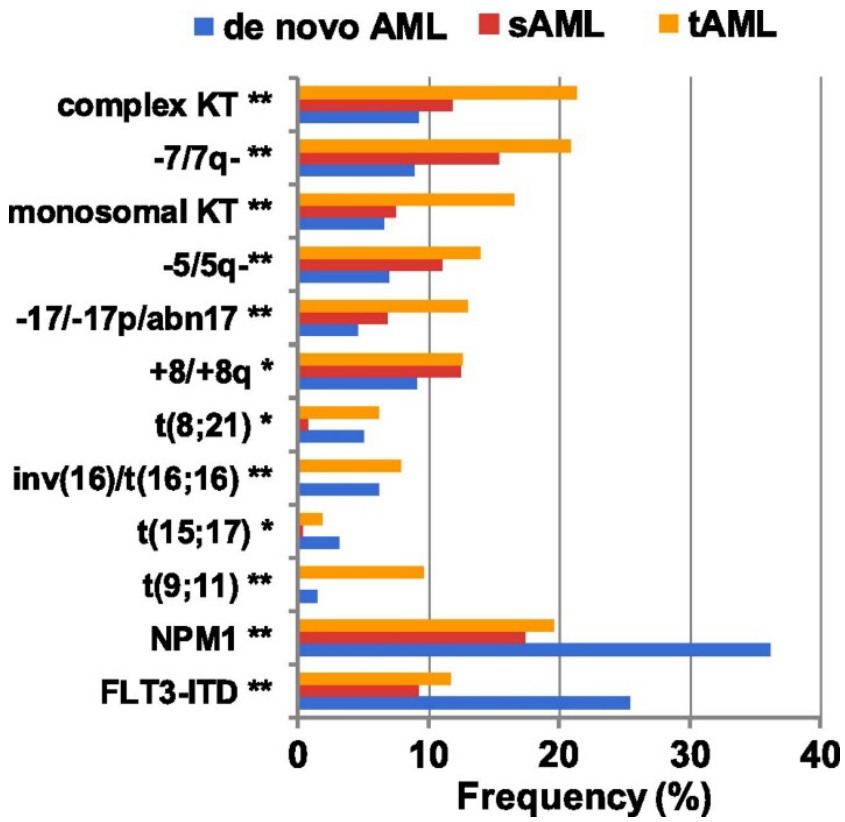
Mutational profiles related to resistance to HMA + VEN



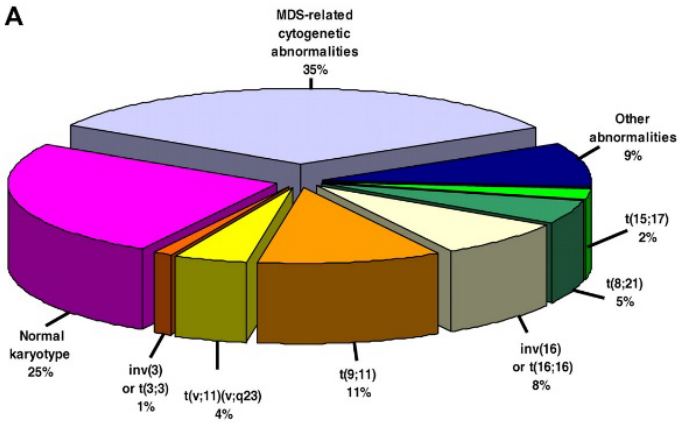
Döhner H, et al. Blood. 2022
DiNardo CD, et al. Blood. 2020

High risk features are **particularly frequent** among AML arising after a previous MDS **(s-AML)** or after a previous chemo or radiotherapy **(t-AML)**

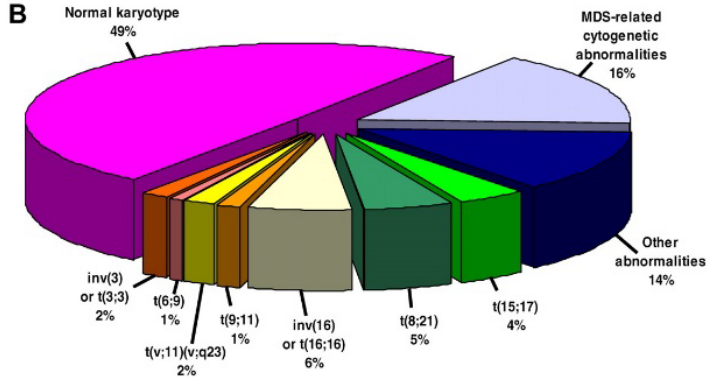
As a result, s-AML and t-AML have a **dismal outcome with conventional chemotherapy** and allogeneic stem cell transplantation **(allo-SCT)** is the **only curative option** in this setting



t-AML

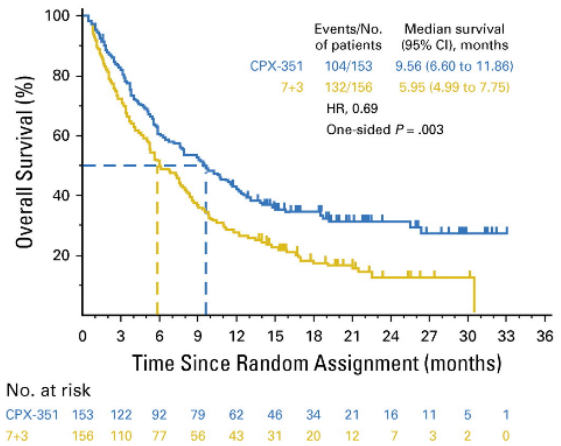


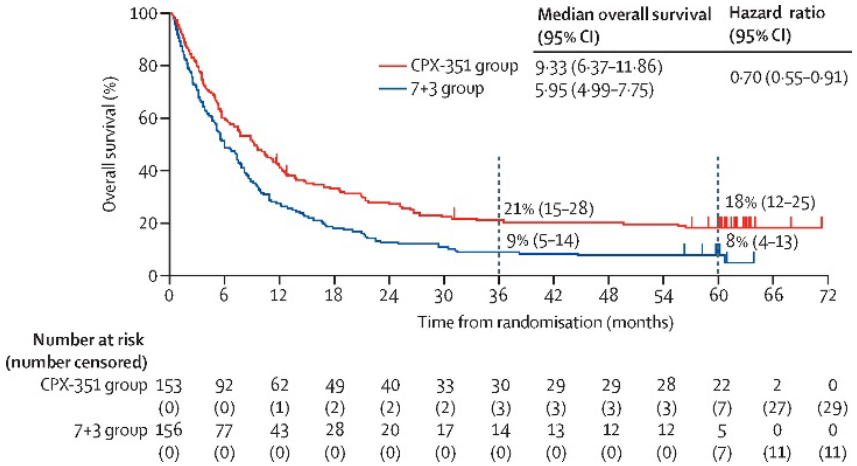
s-AML



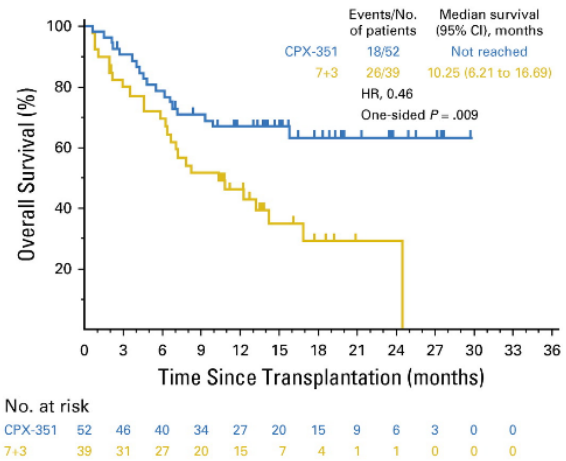
Heuser M. Am Soc Hematol Educ Program 2016
Strickland SA, et al. Critical reviews in Oncology / Hematology 2022

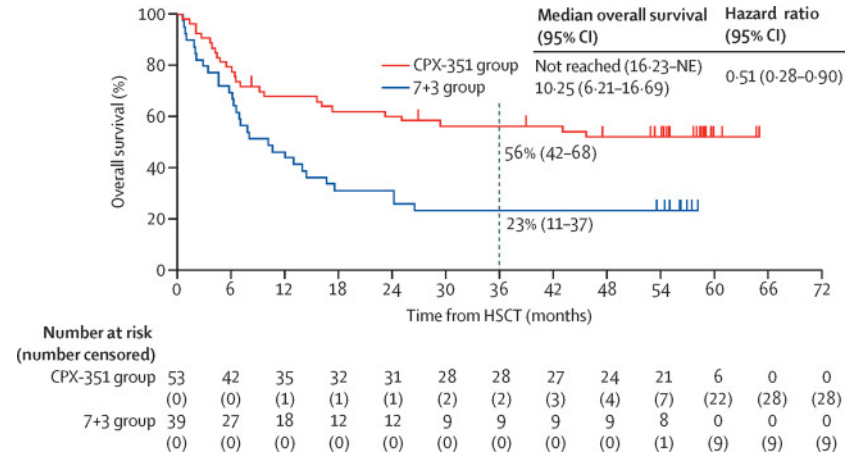
CPX-351 in s-AML and t-AML





All patients





Allo-SCT patients

CPX-351 proved in a phase III trial to be **superior** to **conventional «3+7»** chemotherapy in terms of CR rate and survival, in a cohort of **t-AML and s-AML** patients aged 60 or more

The survival **advantage** was **evident** both in patients receiving **allo-SCT** and in **non-transplanted** patients

Long term follow up of the Phase III trial confirmed those results

CPX-351 is generally accepted as the therapy of **choice** for **fit s-AML** and **t-AML** patients

Lancet JE, et al. Journal of Clinical Oncology 2018
Lancet JE, et al. Lancet Hematology 2021

Aim of the Study

- Data concerning the prognostic **relevance of adverse risk mutations** in **CPX-351 treated** patients are still **incomplete**
- **A fraction of s-AML patients** may be considered **eligible both to CPX-351** and **HMA-VEN induction**
- **No available data** about the efficacy of **CPX-351 in s-AML patients** harboring **gene mutations predictive of HMA-VEN failure**

Our study aims to explore the **prognostic** relevance of **adverse risk mutations** or **co-mutation patterns** in a cohort of **elderly patients** with **s-AML** treated with **CPX-351**

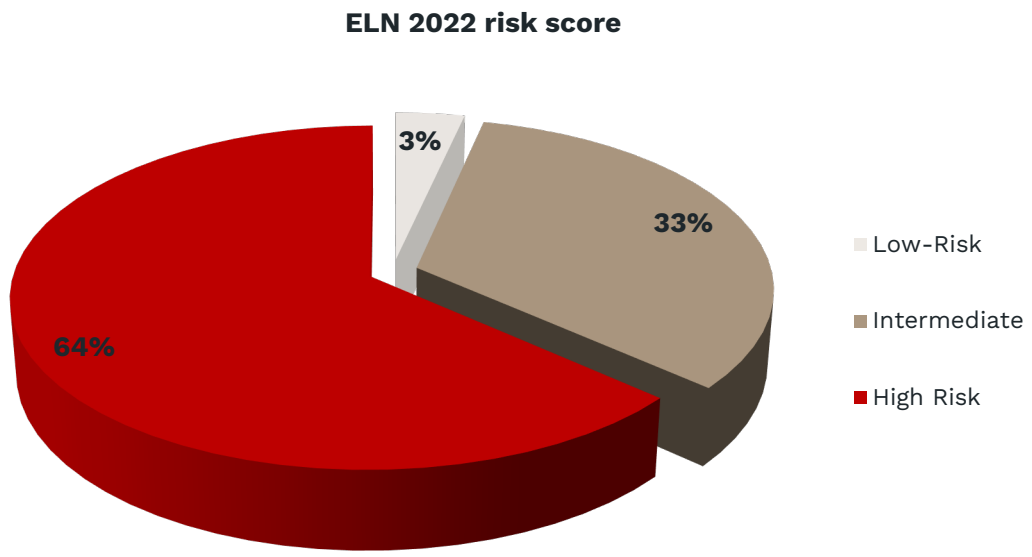
Patients and Methods

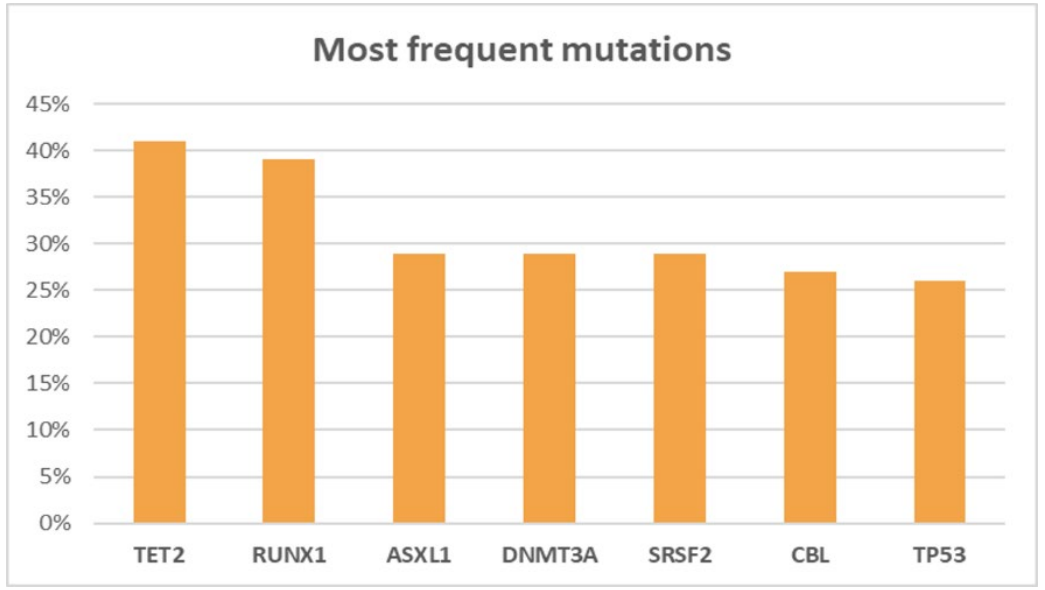
- **80 s-AML or t-AML** patients who received CPX-351 as induction therapy in our Institution (Jan 2019 – June 2023) were enrolled
- All had **s-AML defined according to WHO 2016** classification (required for commercial use of CPX-351)
- **Median age 69 years** (range 37-77)

- NGS was performed using the **Myeloid Solution panel by SOPHiA Genetics**, encompassing **34 critical genes**. Samples were processed on an **Illumina MiSeq platform** and analysis was performed with **SOPHiA DDM® Software**
- **Minimal Residual Disease (MRD)** was analyzed in all patients achieving complete remission (CR) with **multicolour flow-cytometry (MFC),** with a threshold of **0.1%**

Results

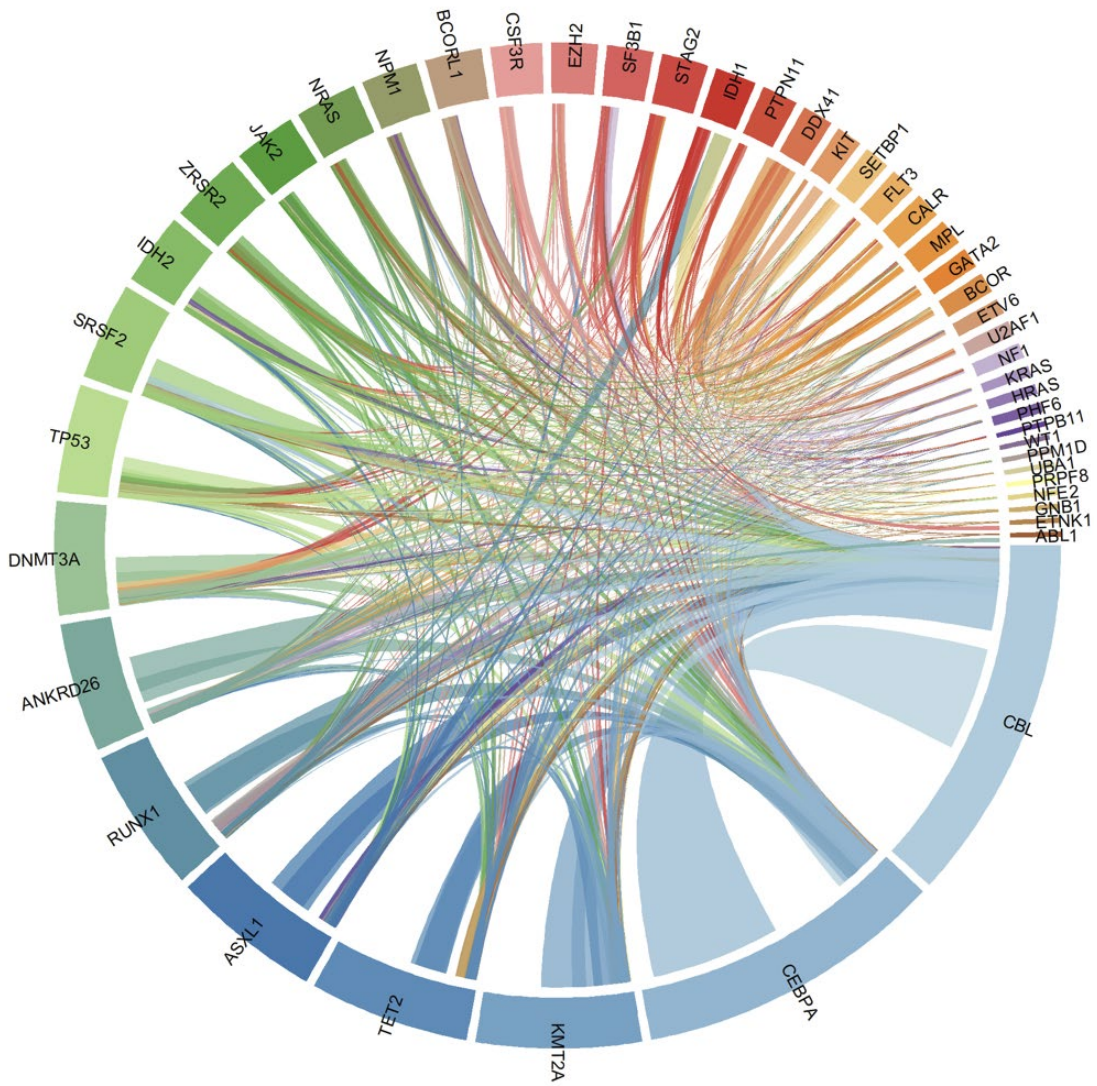
- Cytogenetic analysis showed **high risk karyotype in 48 (60%) and intermediate in 32 patients (40%)**
- **Fifty-three patients (62%)** showed **high risk gene mutations,** as defined by ELN 2022 risk score
- **50 patients (62.5%)** had **molecular aberrations** predictive of **HMA-VEN failure**
- **Most frequent mutations** involved **TET2 (41%), RUNX1 (39%), ASXL1 (29%), DNMT3A (29%), SRSF2 (29%), CBL (27%) and TP53 (26%)**





Median number of gene mutations for single patient **was 5 (range 2-10)**

42 (53%) patients had **high mutational burden (≥ 4 mutations)**



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Response to CPX-351

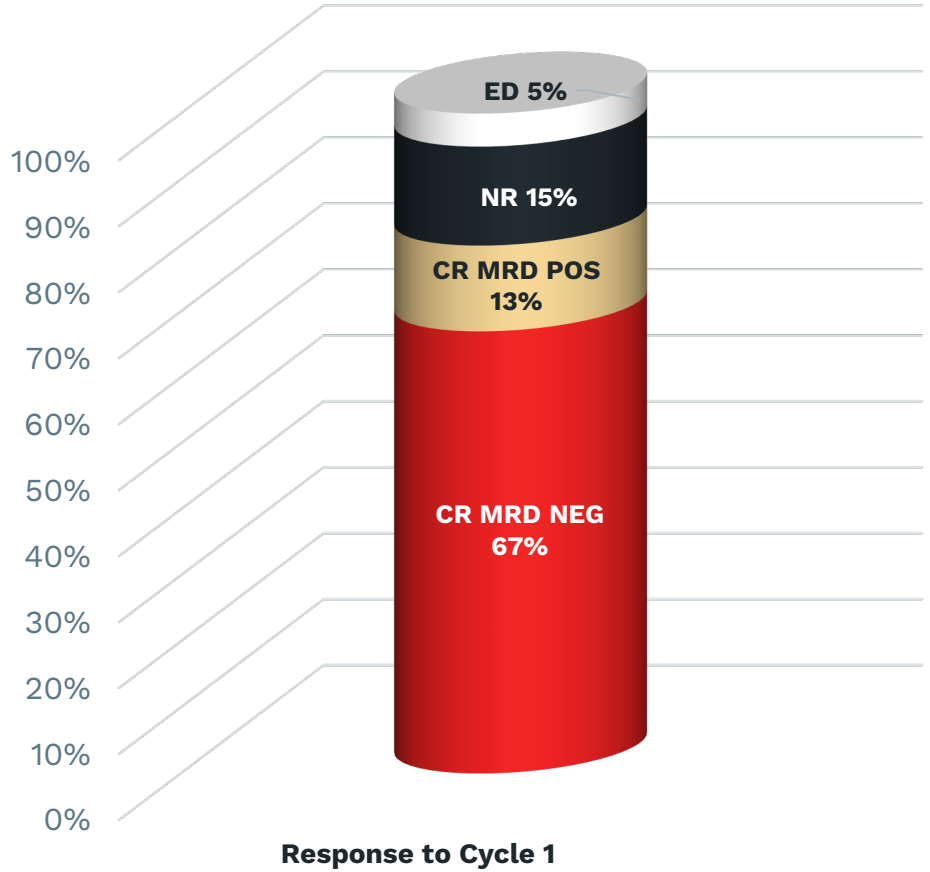
- After cycle 1, 64 patients (**80**%) **achieved CR**
- **MFC-MRD negativity 67%**

- **Four patients** (**5%**) **died** before response assessment, mainly due to **infections**

- **CR and MRD** negativity rate were **not affected** by **adverse cytogenetics** or by the presence of ELN 2022 **high-risk mutations** or by **any other single gene** mutation (p=n.s.)

- **CR and MRD** negativity were also **unaffected** by the presence of **high mutational burden** or mutations predictive of **HMA-VEN failure** profile (p=n.s.)

- **In multivariate analysis none** of the variables impacted **CR** or **MRD negativity** rate

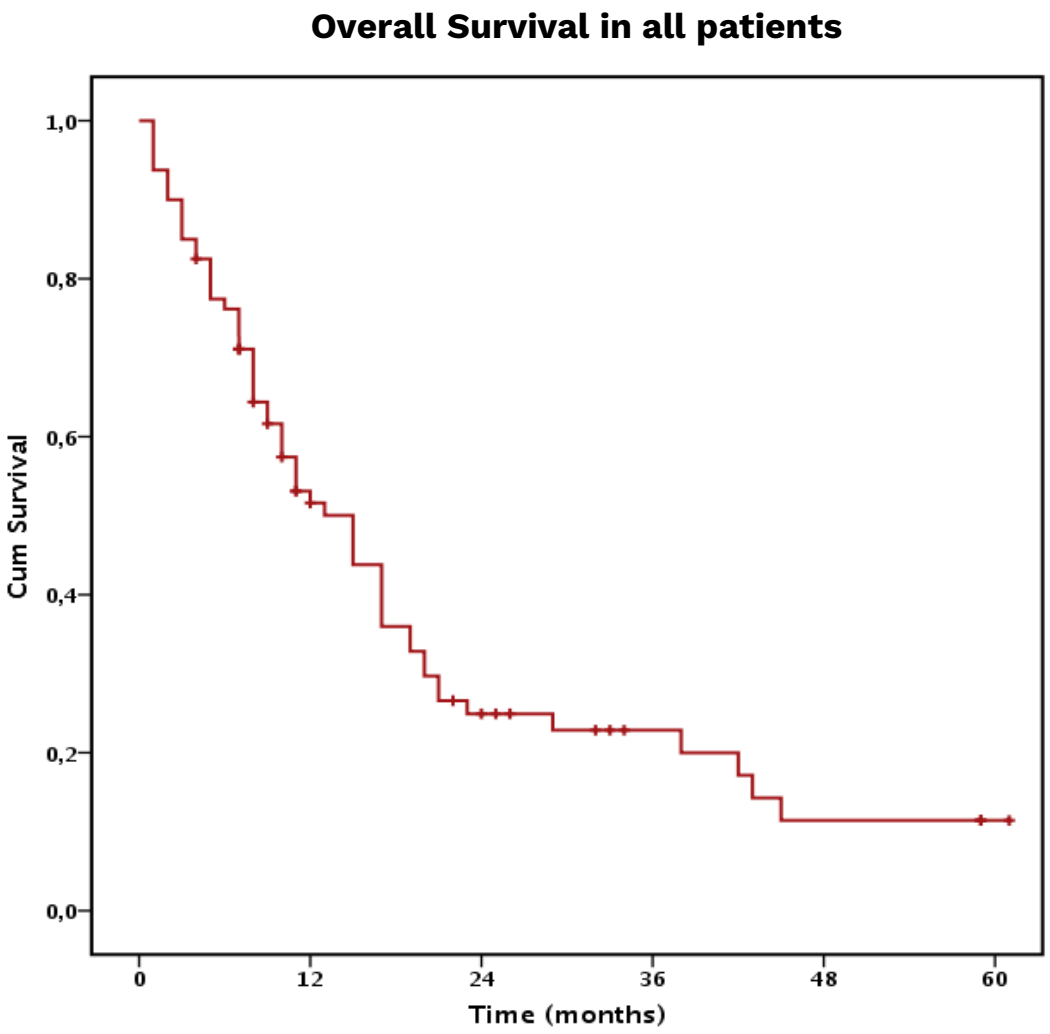


Survival

- **Median Follow-up** was **39.3 months**
  (CI 95%; 41-60 months)

- Median **OS** was **18 months** (CI 95% 15.66-19.89)
- **2-year OS was 26.2%**

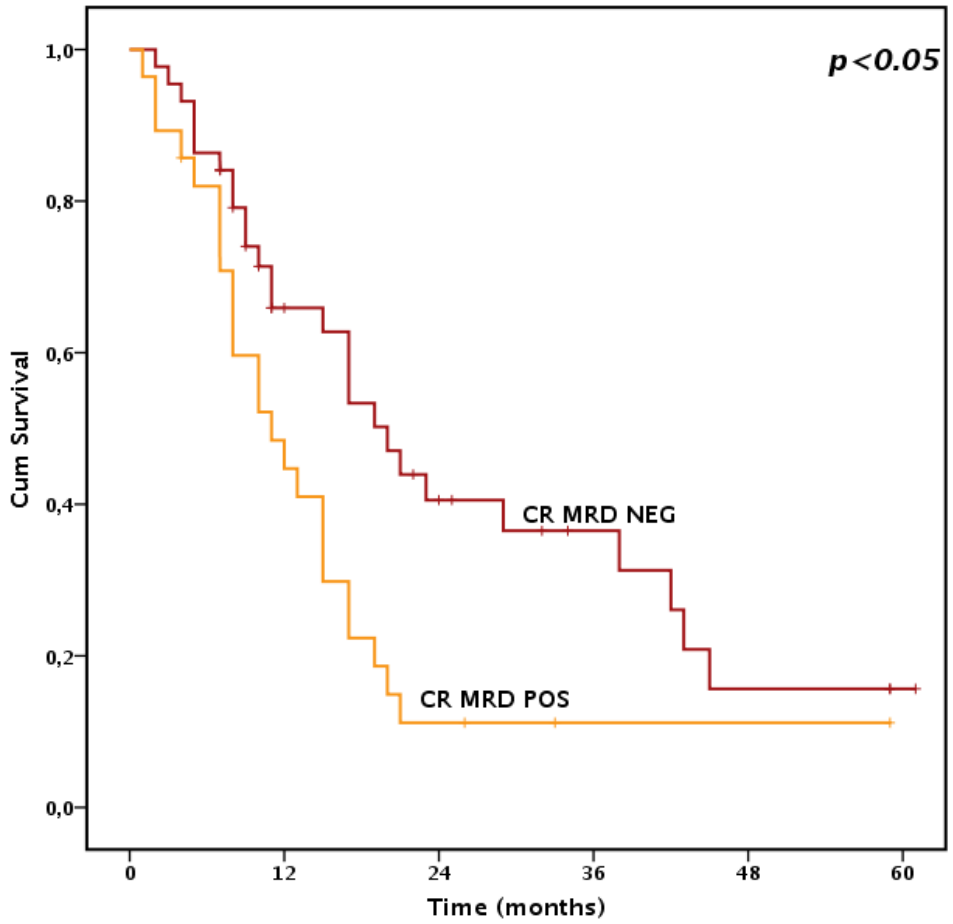
- Median **EFS** was **9.3 months**
- 2-year EFS was 28.6%



- **Median survival** was **20 months** in **MRD negative** CR patients, compared to 11 months to in MRD positive CR patients (p<0.05)

- Multivariate OS analysis showed that **negative MRD** was the **strongest** independent prognostic factor (p<0.05)

Overall Survival in CR patients according to MFC MRD status



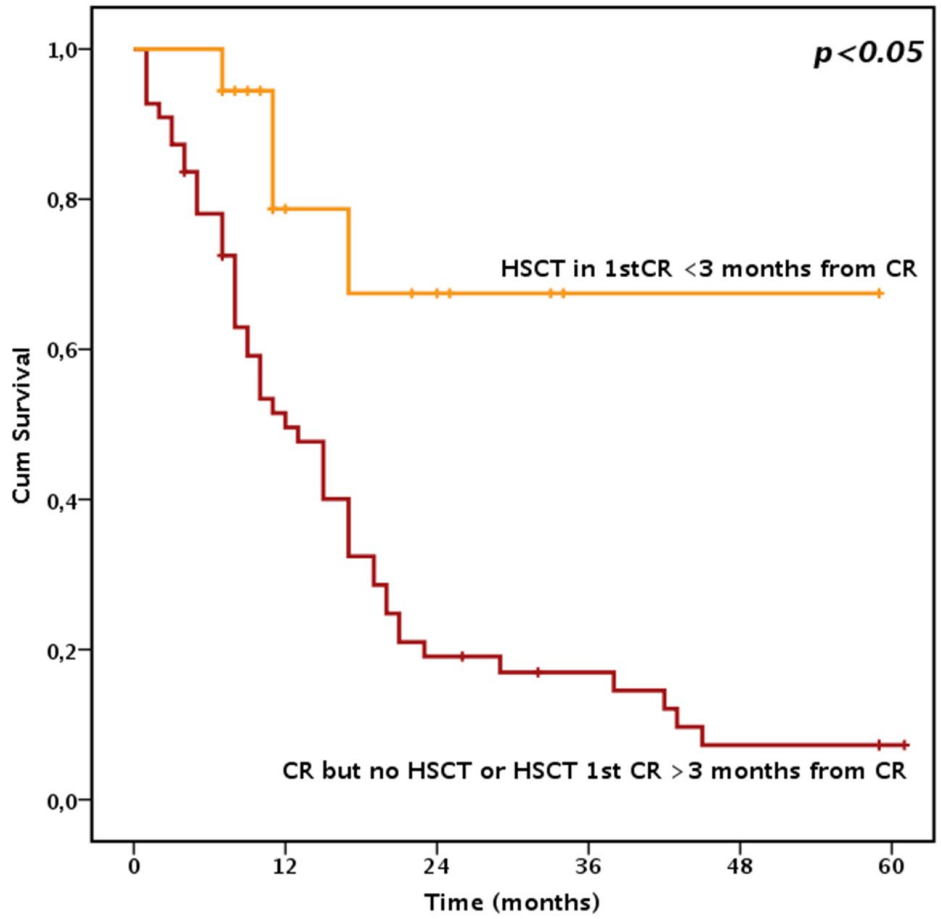
Allogeneic Stem Cell Transplantation

- A **landmark model** was built in order to assess the **impact** of **HSCT consolidation** including **patients alive** and in **CR at day 60**

- **Patients achieving CR** and **proceeding to HSCT** (n=23) **within 3 months** from CR (n=8) had a **significantly better outcome** (median OS not reached) if compared to CR patients who did not receive HSCT (n=41, median OS 11 months) or proceeded to transplant later (n=15, median OS 13 months)

- Multivariate analysis in the landmark model confirmed that **early HSCT consolidation** was the **strongest**, independent, predictor of **longer survival**

Overall Survival in CR patients according to HSCT timing (landmark analysis)



Conclusions

With the limitation of our retrospective cohort, **common risk stratifications appears to be less relevant** for patients receiving CPX-351

High mutational burden does not affect probability of achieving CR and MRD negativity

Early HSCT consolidation is **strongly advised** in order to achieve long term survival

Further analysis are necessary in order to disclose **co-mutation patterns** possibly predictive of response or treatment failure in patients receiving CPX-351

Acknowledgements

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