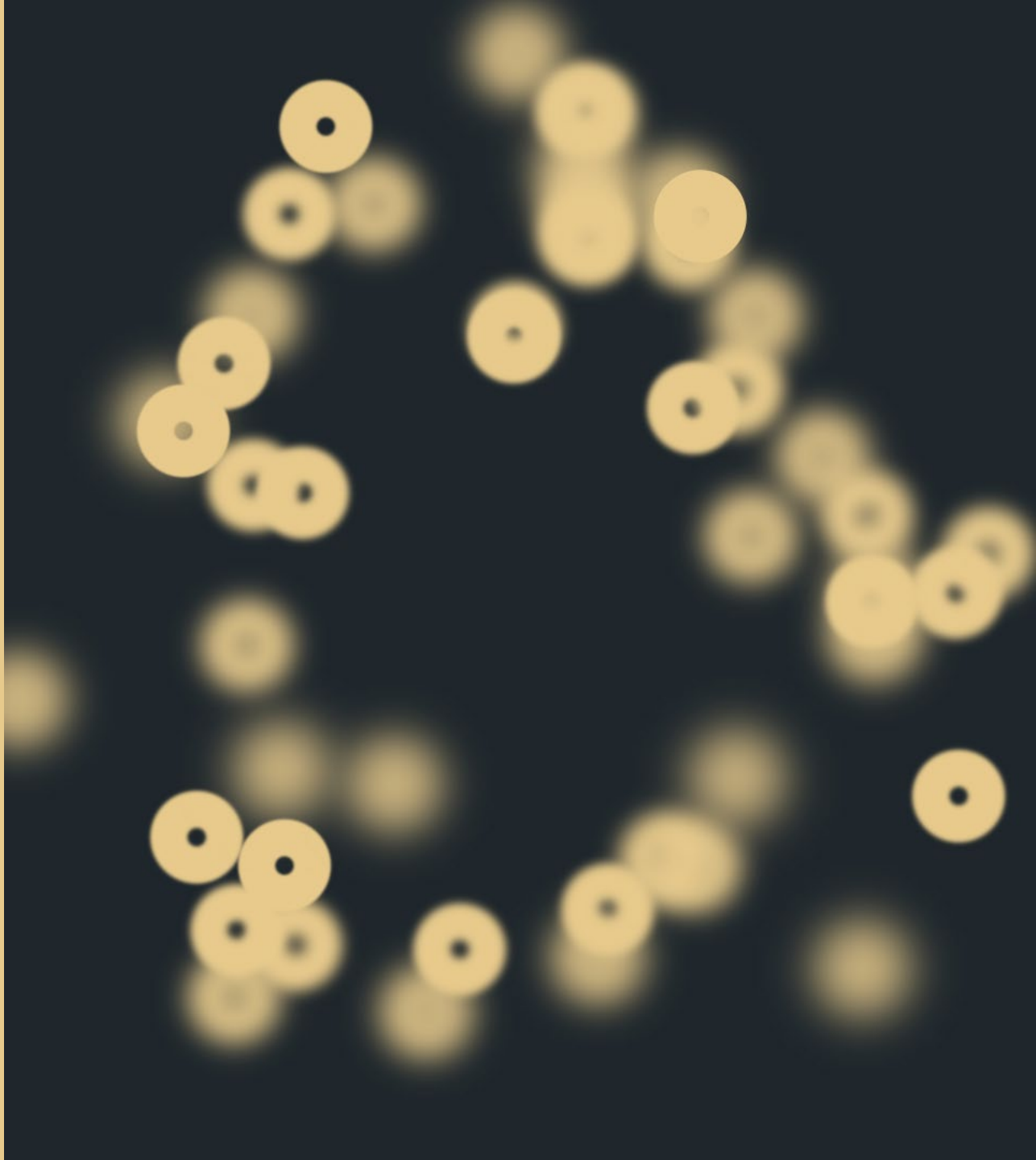
eha

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

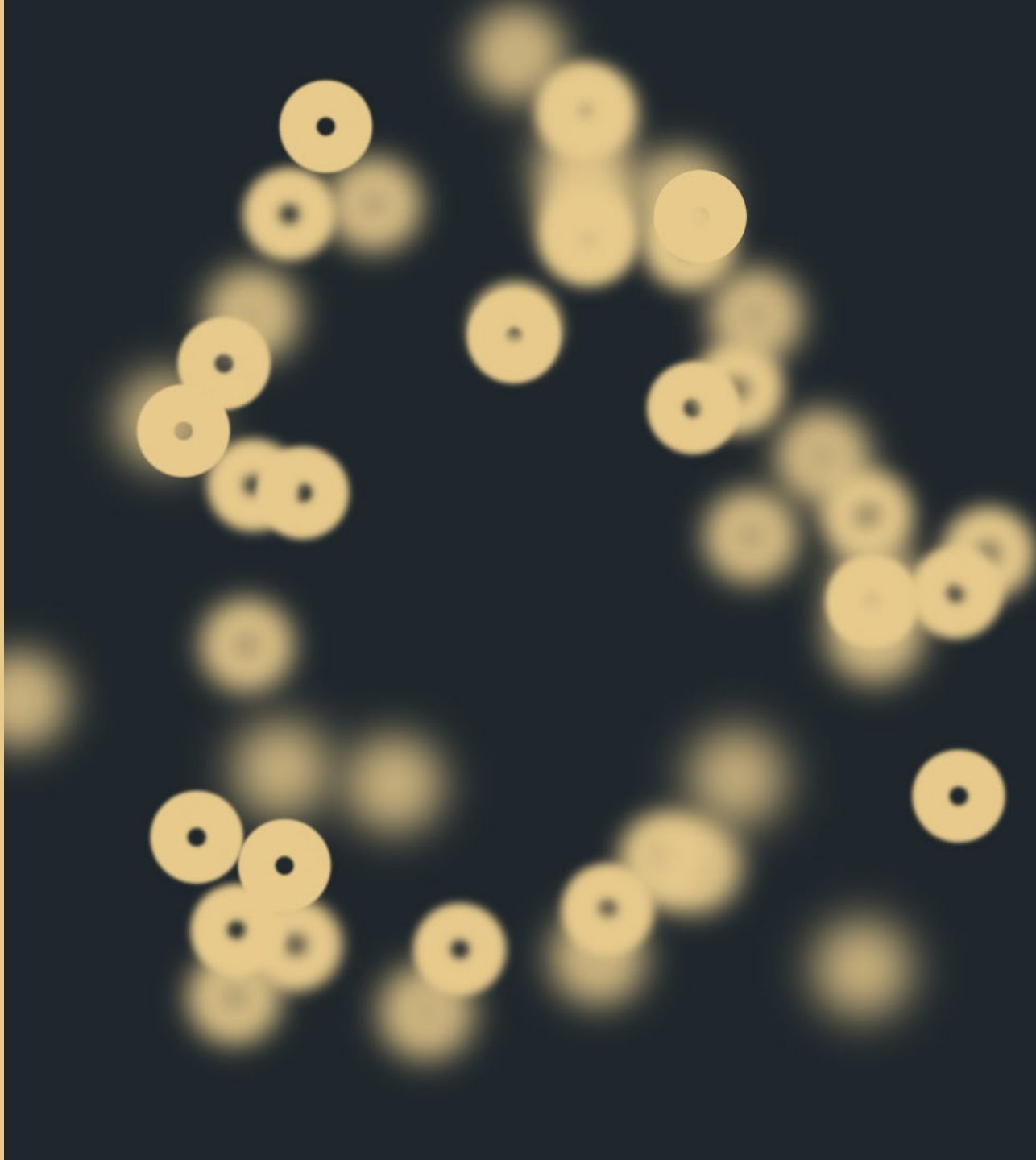
Berlin, Germany
April 25-26, 2025



Treatment of sAML Conventional chemotherapy

Prof. Christian Récher
Toulouse University

EHA-SWG
Berlin, April 26, 2025



Disclosure

Consulting or advisory role

Abbvie, Amgen, Astellas, BMS, Boehringer, Daiichi-Sankyo, Jazz Pharmaceuticals, J&J and Servier

Research funding

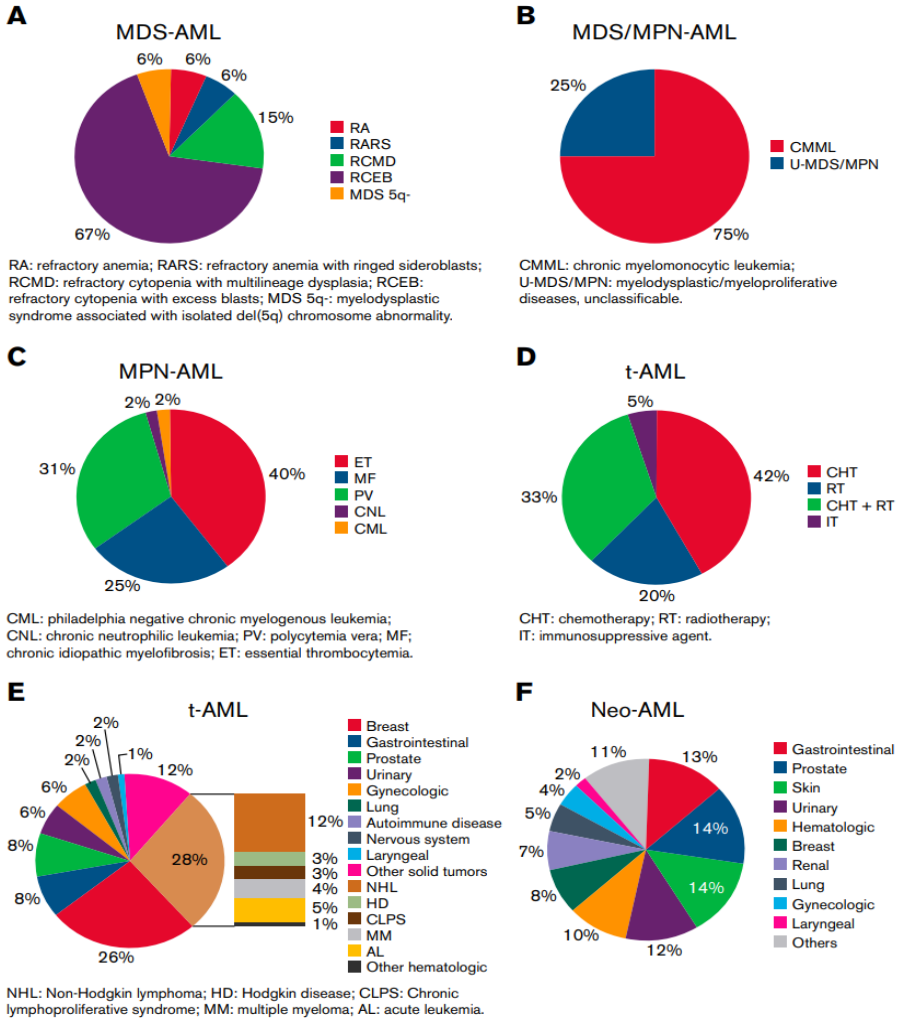
Abbvie, Amgen, Astellas, BMS, Daiichi-Sankyo, Iqvia and Jazz Pharmaceuticals

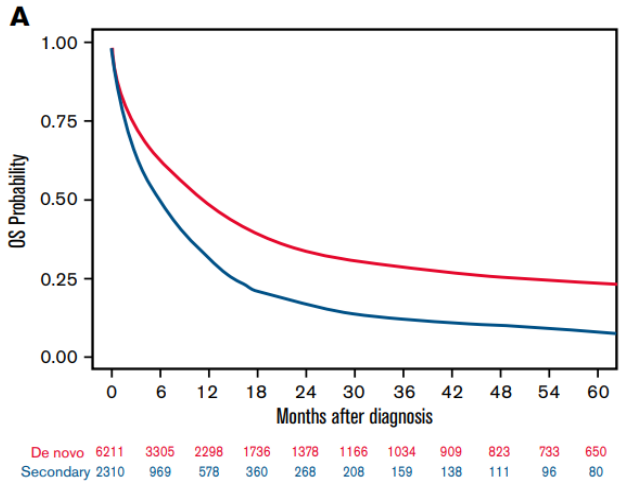
Support for attending meetings and/or travel

Abbvie, Daiichi-Sankyo, Novartis and Servier

sAML as a synonym for heterogeneity and poor prognosis

- **High-risk disease**
  - Poor-risk cytogenetics
  - Poor-risk mutations
  - Higher expression of MDR phenotype
- **High-risk patient characteristics**
  - Altered bone marrow reserves
  - Sequelae from previous cytotoxic therapy (heart, lung, GI, immune system)
  - Sequelae from previous cancer (surgery, iron overload, thrombosis, depression)
- **Exclusion from RCT**
- **Scarcity of prospective data (subgroups)**





Martinez-Cuadron D, Blood Advances 2022

Precision diagnostic and timeline of information required for decision making

Patient characteristics

Age
PS
Comorbidities
Sequelae from previous Tx

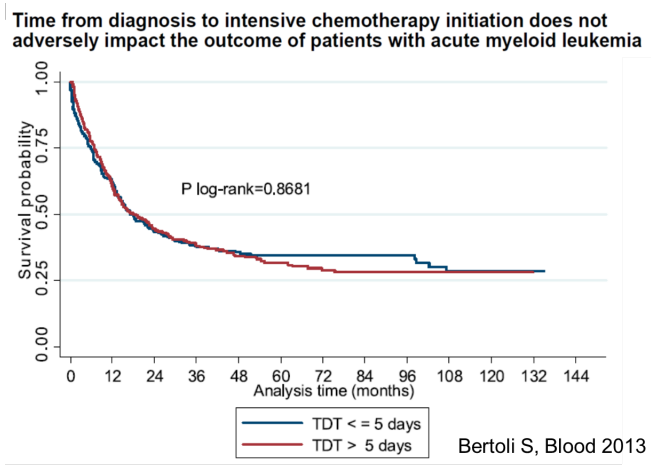
Previous solid tumor
Cancer type
Stage (M-/M+)
Nb of Tx lines
Latency
Cumulative doses of anthracyclines
RTx
Surgery
PARPi/checkpoint i

Previous lymphoid malignancy
Nb of Tx lines
Latency
Cumulative doses of anthracyclines
RTx
ASCT
Immunotherapy
CART-cells
Lenalidomide

Previous MDS-MDS/MPN-MPN
HMA-sAML
Nb of HMA cycles
Bone marrow reserve
Iron overload
Alloimmunizations
Previous infections
Splenomegaly
EMD

Cytoreduction
Pretreatment workup
Geriatric assessment

Patient's choice

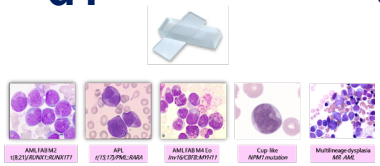


Bertoli S, Blood 2013

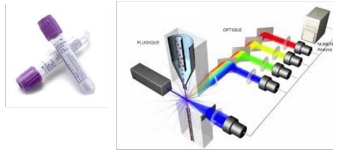
Diagnosis

d1 **d3** **d5** **d7** **d10-d21**

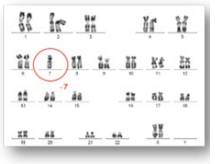
Disease characteristics



Morphology
(APL, CBF, NPM1, MR-AML)
Flow cytometry
(stage of leukemia arrest, MRD)



Cytogenetics
PML::RARA, CBFB::MYH11, RUNX1::RUNX1T1, KMT2A::R, BCR::ABL1
Complex/monosomal karyotype



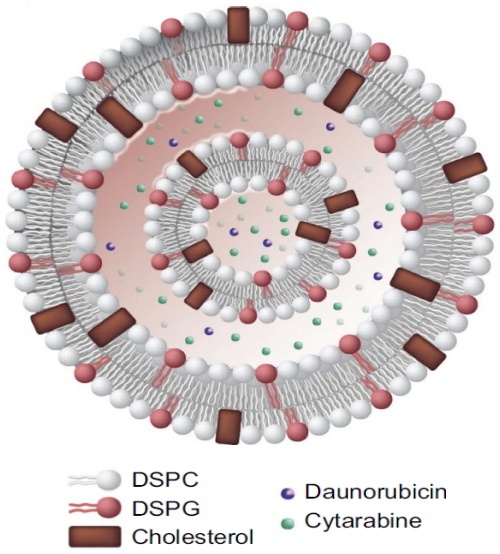
Mutations
Actionable therapeutic targets
NPM1
FLT3-ITD, *FLT3*-TKD
IDH1, IDH2
KMT2A::R

NGS
Myeloid gene panel
CEBPA, DDX41, TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2

Intensive chemotherapy remains an option in fit patients with sAML

- A few patients remain favorable
  - CBF-AML, AML with *NPM1* mutations
- May induce complete remission (> 50%)
- Bridge to transplant as a major goal (look for a donor as soon as Dx is made)
- Recent progress:
  - Induction
    - CPX-351
    - Third cytotoxic drug added to « 7+3 »
    - Intensified purine analogue-based regimen
  - Maintenance
    - Oral azacitidine
  - Transplantation strategies

CPX-351, a new standard for sAML



- Dual-drug liposomal encapsulation of cytarabine and daunorubicin
- Maximally synergistic and minimally antagonistic 5:1 molar ratio of cytarabine to daunorubicin
- Enhanced stability, circulating half-life, and tumor accumulation
- Prolonged drug exposure
- Accumulates in BM with preferential uptake by leukemia cells
- Improved drug therapeutic index by reducing toxicities and/or increasing efficacy.

Phase 3 Study of CPX-351 vs Standard Induction in Older Patients with Newly Diagnosed High-Risk AML

Key Eligibility
s-AML
Previously untreated
Ages 60-75 yrs
Fit for chemo
PS 0-2

Stratifications:
*t-AML
*History of MDS w/ and w/out prior HMA Rx
*History of CMML
*de novo AML with MDS karyotype
*60-69 yrs
*70-75 yrs

Induction 1
CPX-351*
100 units/m^2
Days 1, 3 and 5

Induction 2**
CPX-351
100 units/m^2
Days 1 and 3

n=153

Consolidation 1
CPX-351
65 units/m^2
Days 1 and 3

Consolidation 2
CPX-351
65 units/m^2
Days 1 and 3

CR/CRi

Induction 1
Dauno 60 mg/m^{2}x3
Ara-C 100 mg/m^{2}x7

Induction 2**
Dauno 60 mg/m^{2}x2
Ara-C 100 mg/m^{2}x5

n=156

Consolidation 1
Dauno 60 mg/m^{2}x2
Ara-C 100 mg/m^{2}x5

Consolidation 2
Dauno 60 mg/m^{2}x2
Ara-C 100 mg/m^{2}x5

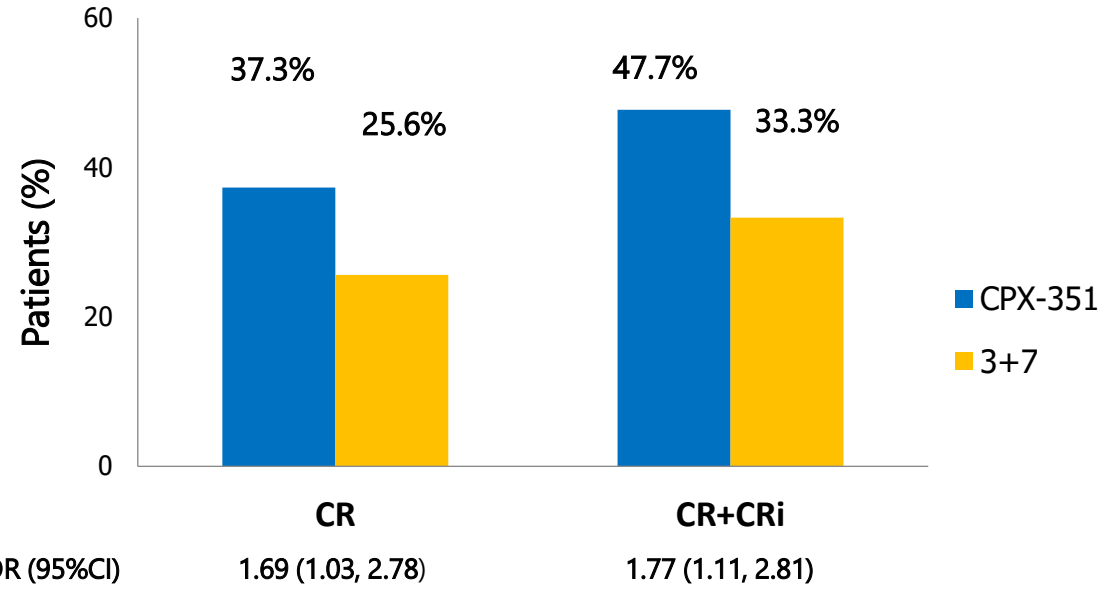
*1 unit = 1 mg cytarabine + 0.44 mg daunorubicin
** if residual BM blasts at d14
Allogeneic-HCT was performed at the discretion of the treating physician.

Lim, W. S., Leuk Res, 2010
Mayer L, International Journal of Nanomedicine 2019

Lancet JE, JCO 2018

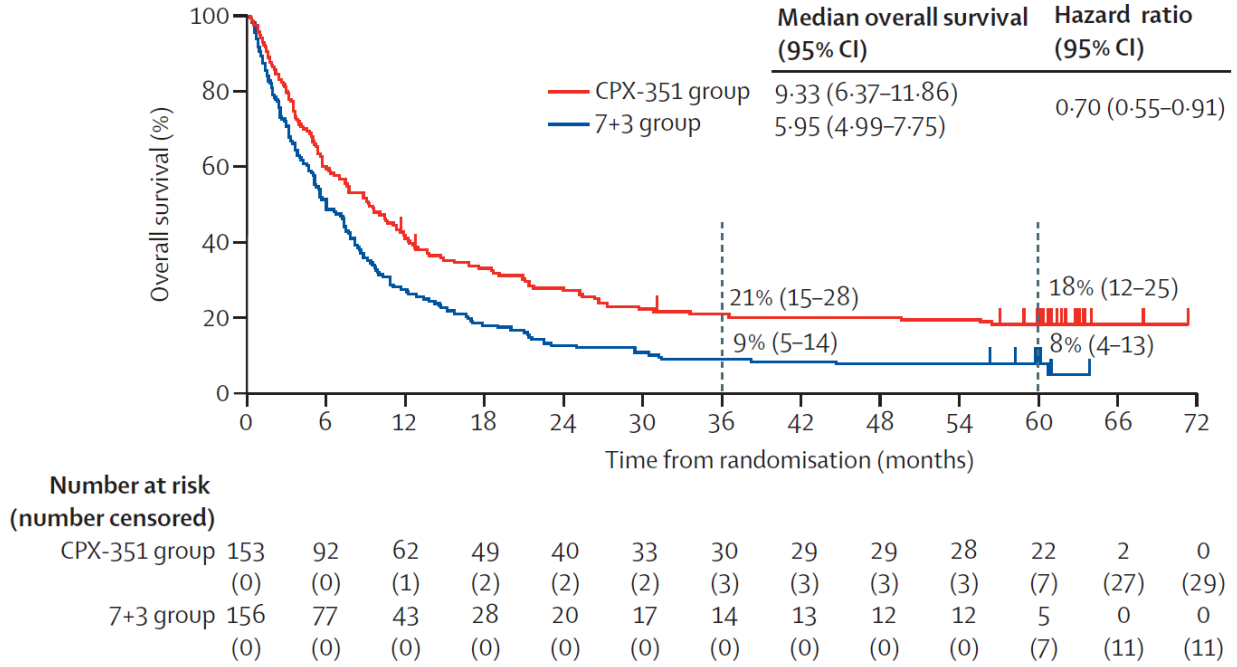
CPX-351 improves response rate and OS in sAML patients selected for intensive chemotherapy

Response



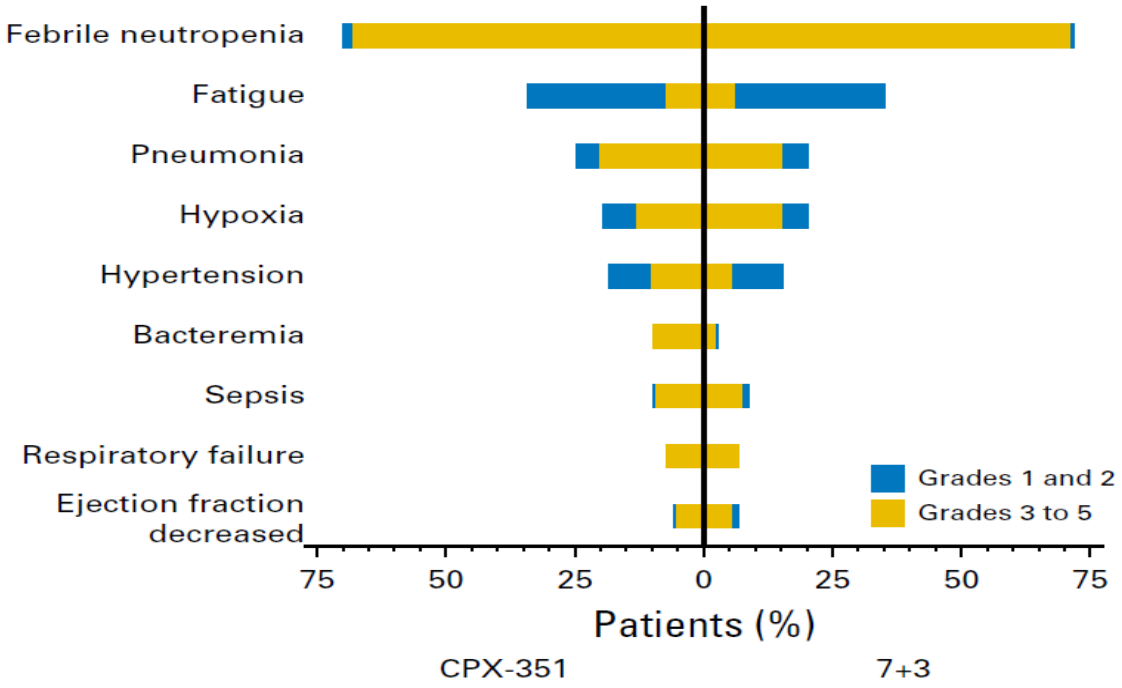
Lancet JE, JCO 2018

5y-Overall survival



Lancet JE, Lancet Haematol 2021

Safety of CPX-351: a more favorable toxicity profile



Lancet JE, JCO 2018

	CPX-351	3+7
ANC> 0.5 Median (days)	35	29
Platelets>50 Median (days)	36.5	29
Day-30 death	5.9%	10.6%
Day-60 death	13.7%	21.2%

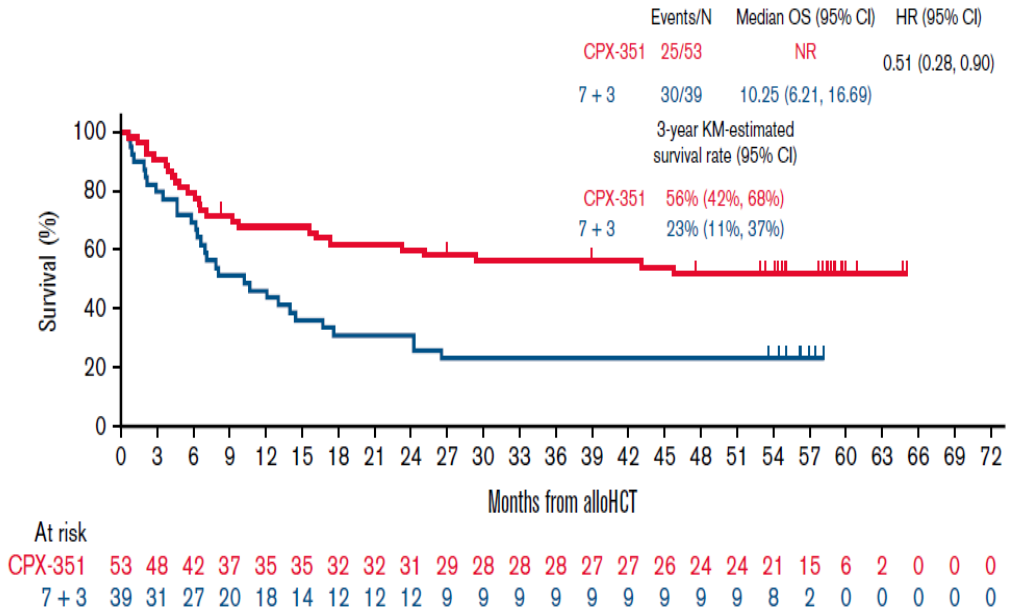
Lower rate of adverse events per patient-year with CPX-351

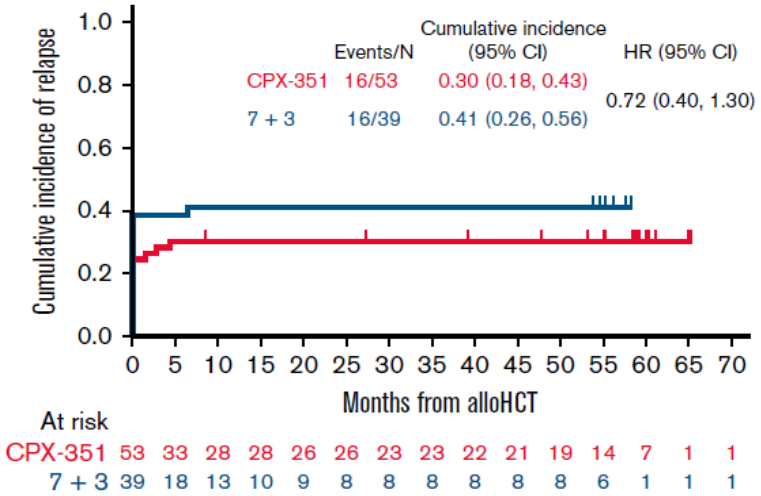
Also seen in phase II trials (1L and relapse)

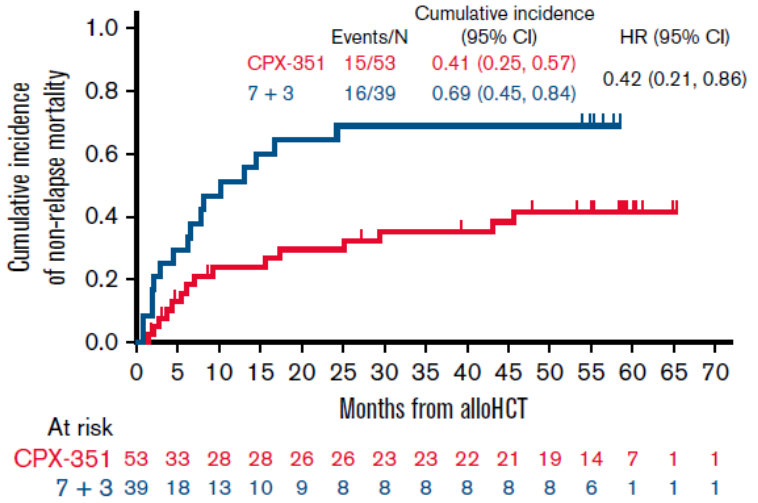
Lancet JE Blood 2014; Cortes J, Cancer 2015

Impact of CPX-351 in allografted patients

OS landmarked from the alloHCT date





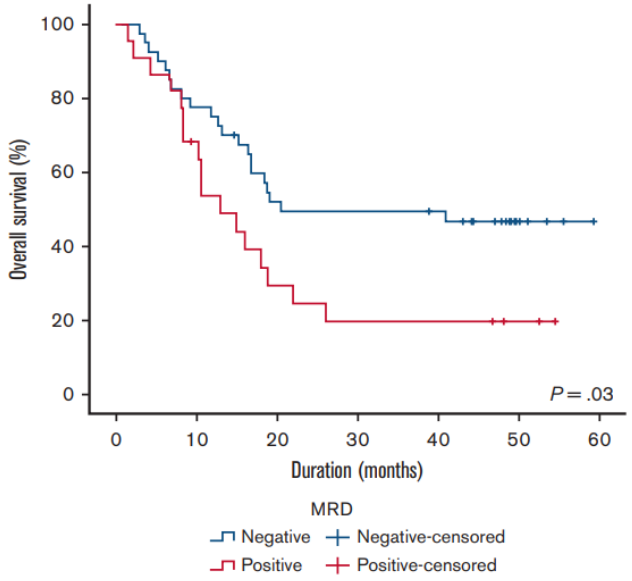


Lancet JE, Blood Advances 2022

Real-world experience with CPX-351

	RW studies (n=21)	Phase 3 (Lancet JE, JCO 2018)
CR/CRi	44-80%	48%
CR/CRi without MRD (MFC, WT1, NGS)	38-64%	No data
Early deaths **Day-30** **Day-60**	 0-14% 1-17%	 6% 14%
Allo-HSCT	28-80%	
Median OS (months) **HMA-sAML** **Allo-HSCT**	 5.2-NR 5.2-7.1 23-NR	 9.3 5.7 NR

Prognostic value of negative MRD



Lemoli R, Critical Reviews in Oncology / Hematology 2023; Cluzeau T, Blood Adv 2024

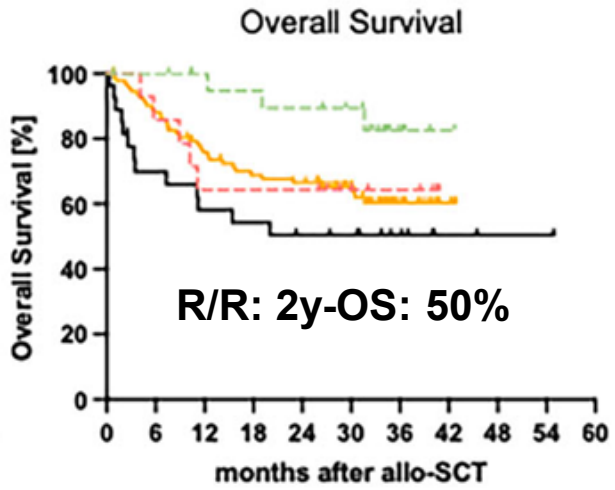
Real-world experience with CPX-351
Post-transplantation outcome

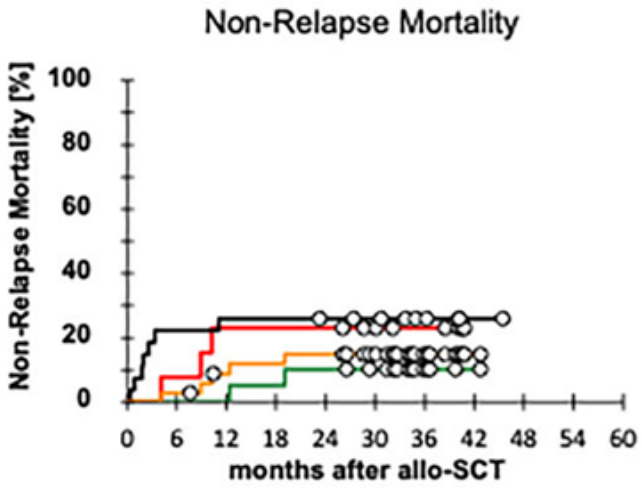
MRDneg

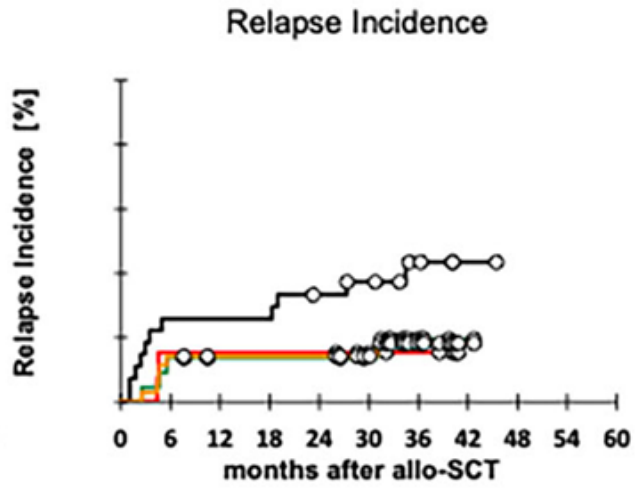
CR

MRDpos

R/R

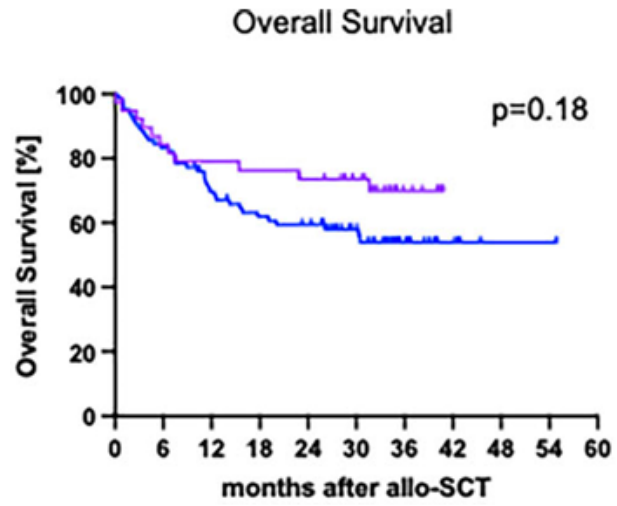


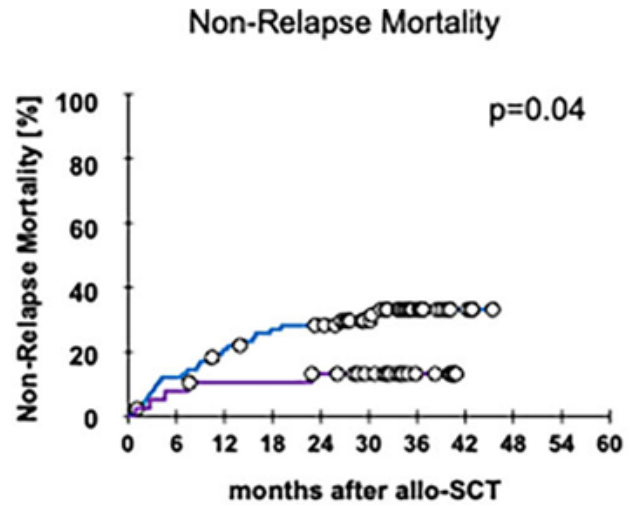


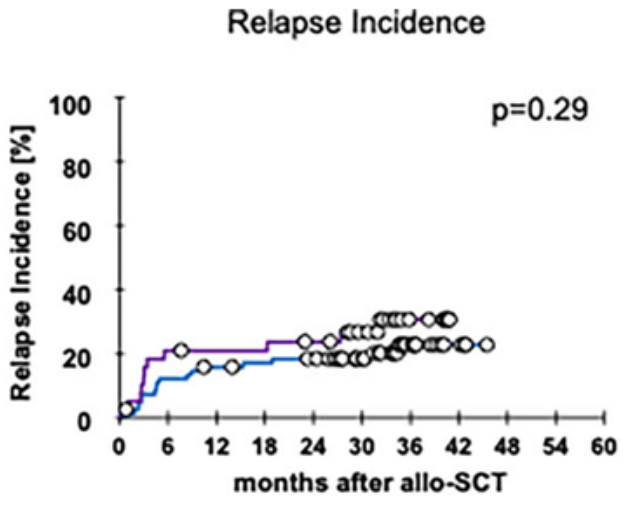


<60 years

≥60 years







Rautenberg C, Blood Cancer J, 2025

Can we extrapolate CPX-351 results to de novo AML with secondary type mutations?

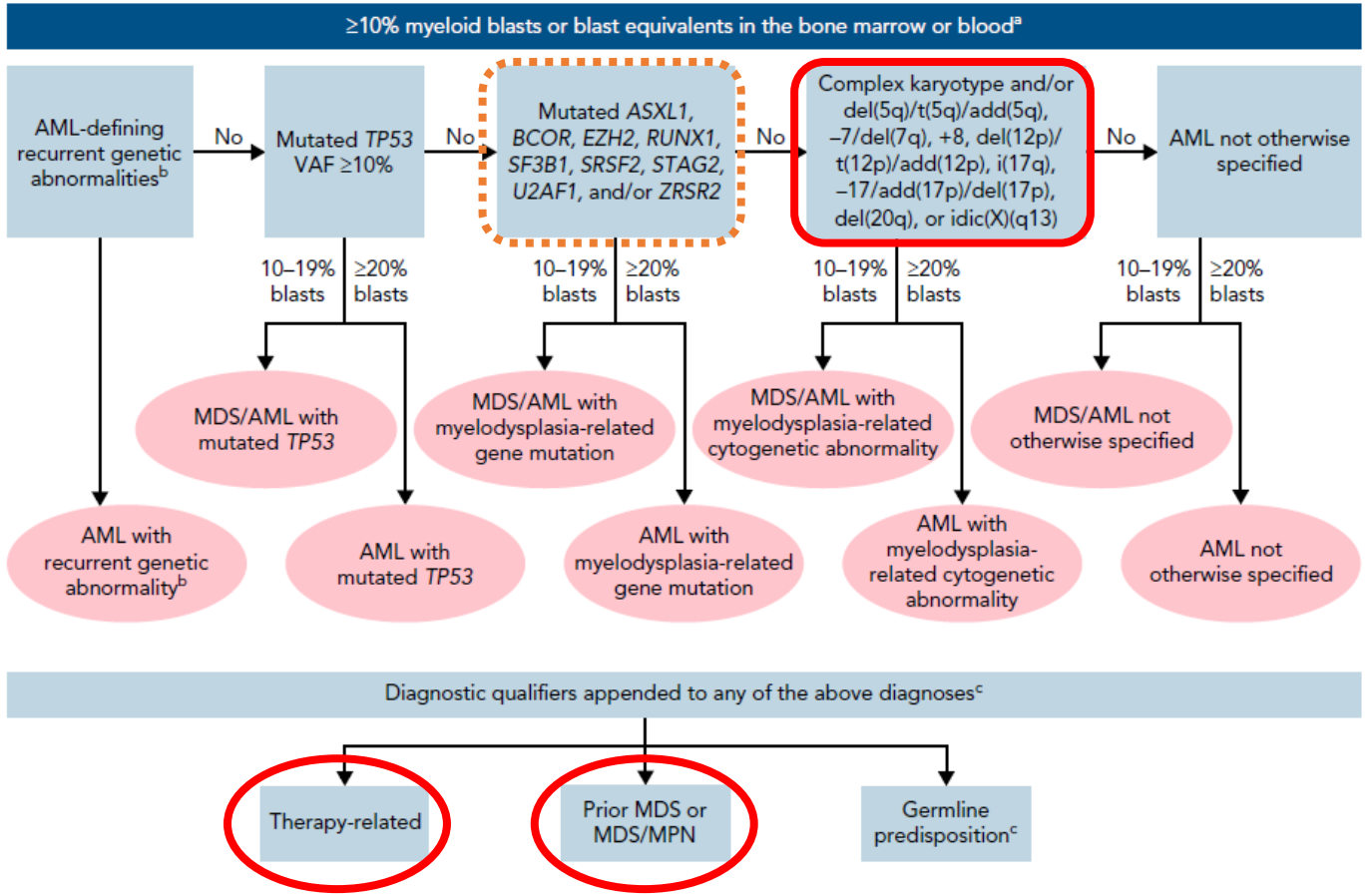
Vyxeos label

Newly diagnosed (ND) therapy-related AML

or

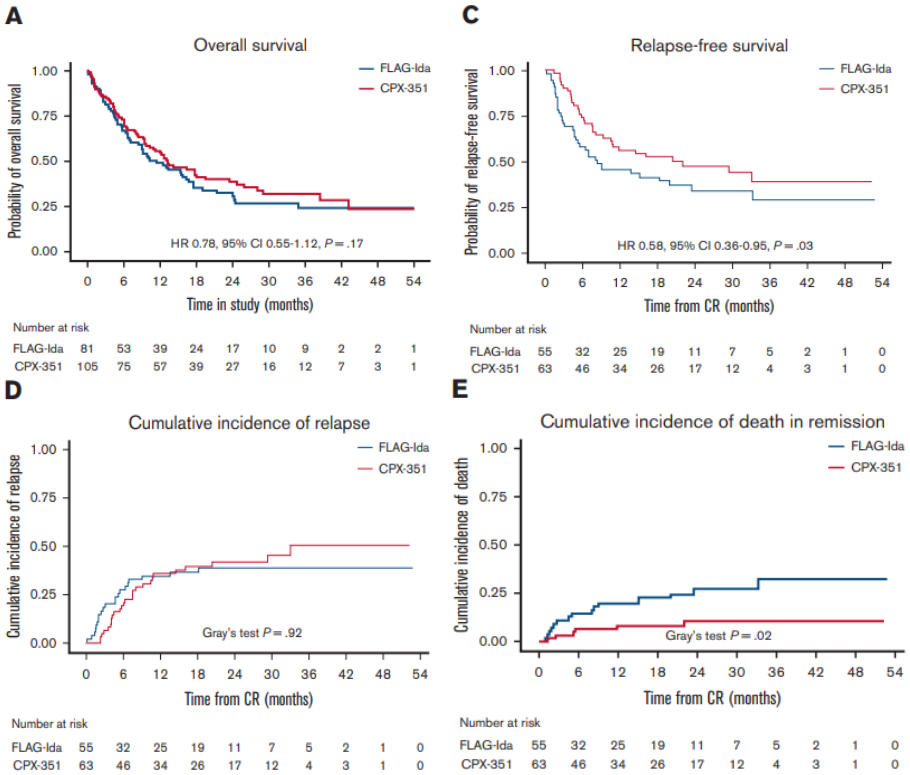
ND AML with myelodysplasia related changes (AML-MRC, WHO 2016):

* Multilineage dysplasia : ≥ 50% dysplastic cells in at least 2 cell lines (unless *NPM1* or *CEBPA*^{dm} mutations)
* Previous history of MDS or MDS/MPN
* MDS-related cytogenetic abnormalities (unless del9q)



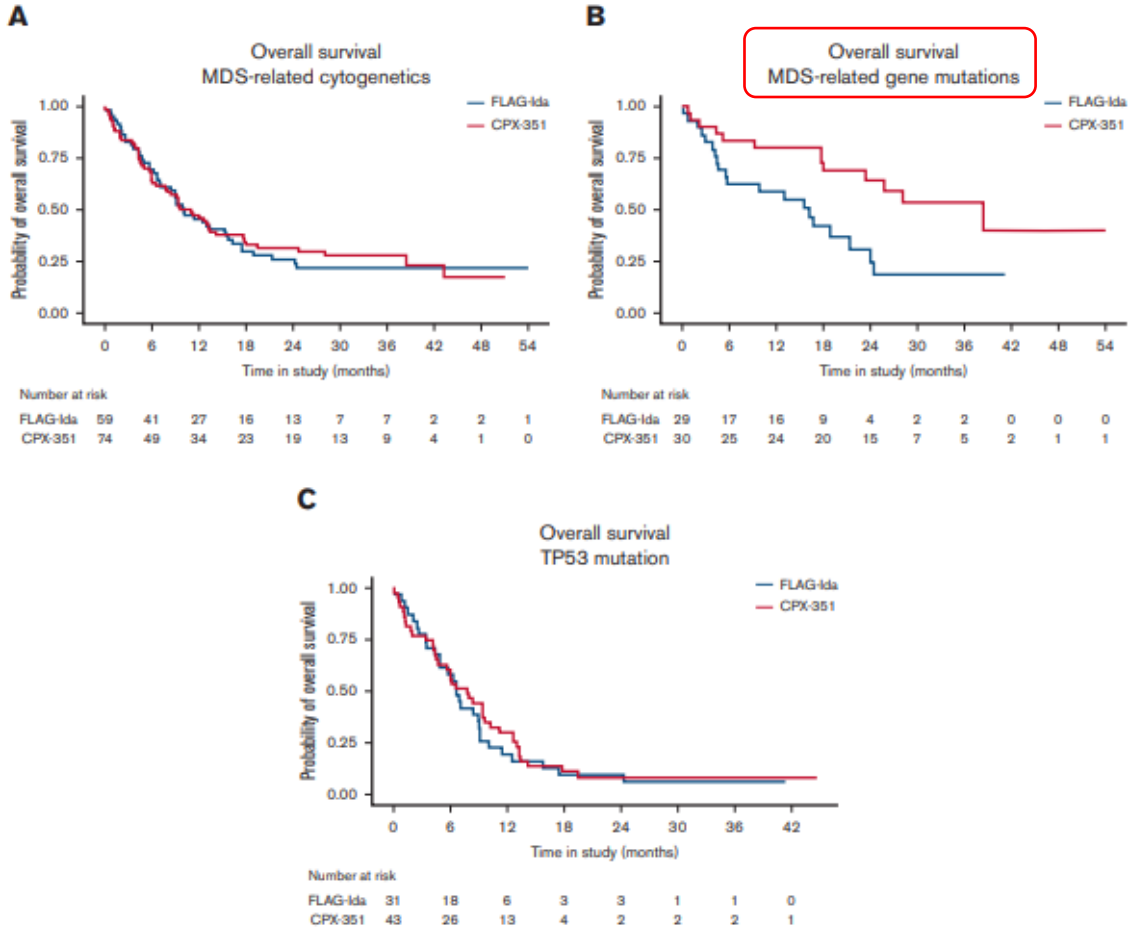
CPX-351 vs FLAG-Ida in adverse karyotype AML and high-risk MDS (UK NCRI AML19 trial)

	FLAG-IDA	CPX-351	P
CR/CRi (cycle 1)	65%	51%	.15
CR/CRi (cycle 2)	77%	64%	.06
Early mortality **Day 30** **Day 60**	 7% 11%	 5% 12%	 .46 .77

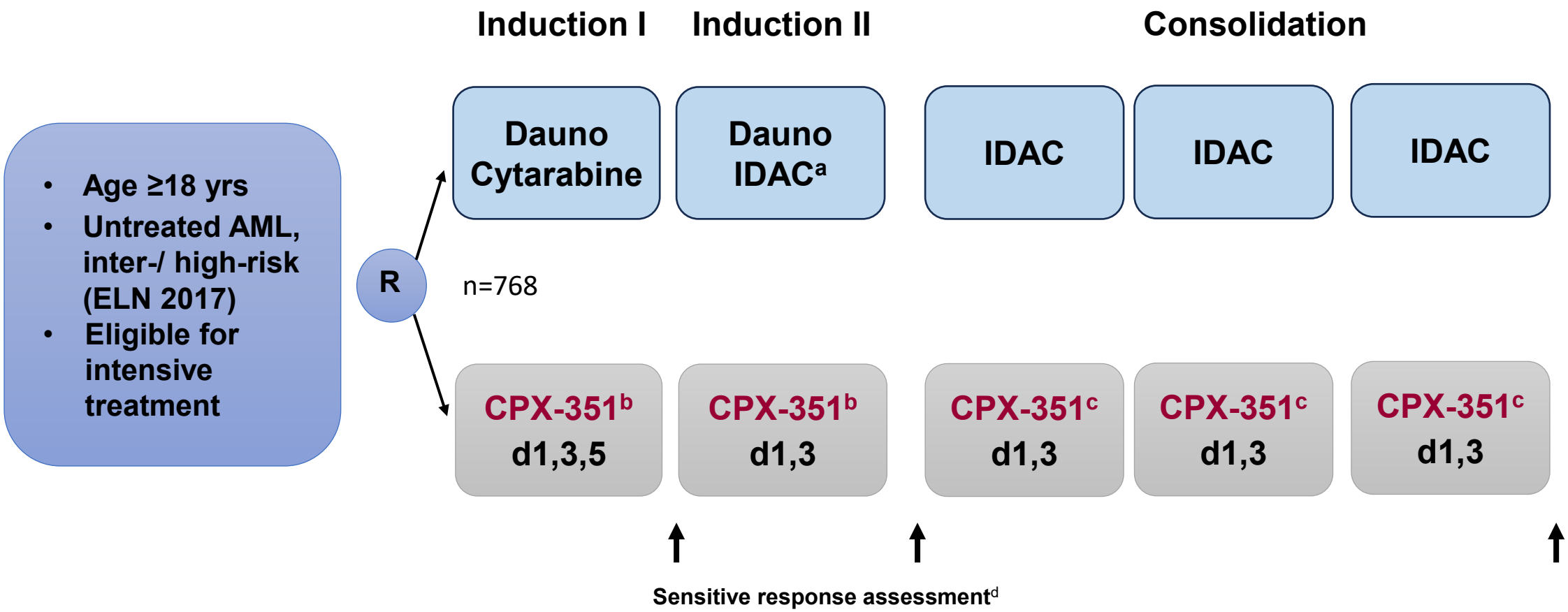


Impact of CPX-351 in MR gene mutations

(ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2)



AMLSG 30-18: CPX-351 *vs* "3+7" for patients with intermediate-/high-risk AML (ELN 2017)



Assignment to allogeneic hematopoietic cell transplantation (HCT) according to the local institutional or cooperative group prognostic algorithm; HCT can be performed at any time point following one induction cycle

[a] IDAC, intermediate-dose cytarabine; age-adapted dosing

[b] Patients 18-60 yrs: CPX-351 55/125 mg/m^2 (125 U/m^2); >60 yrs: CPX-351 44/100 mg/m^2 (100 U/m^2)

[c] CPX-351 29/65 mg/m^2 (65 U/m^2)

[d] Assessment by multi-parameter flow cytometry; and next-generation sequencing based analysis.

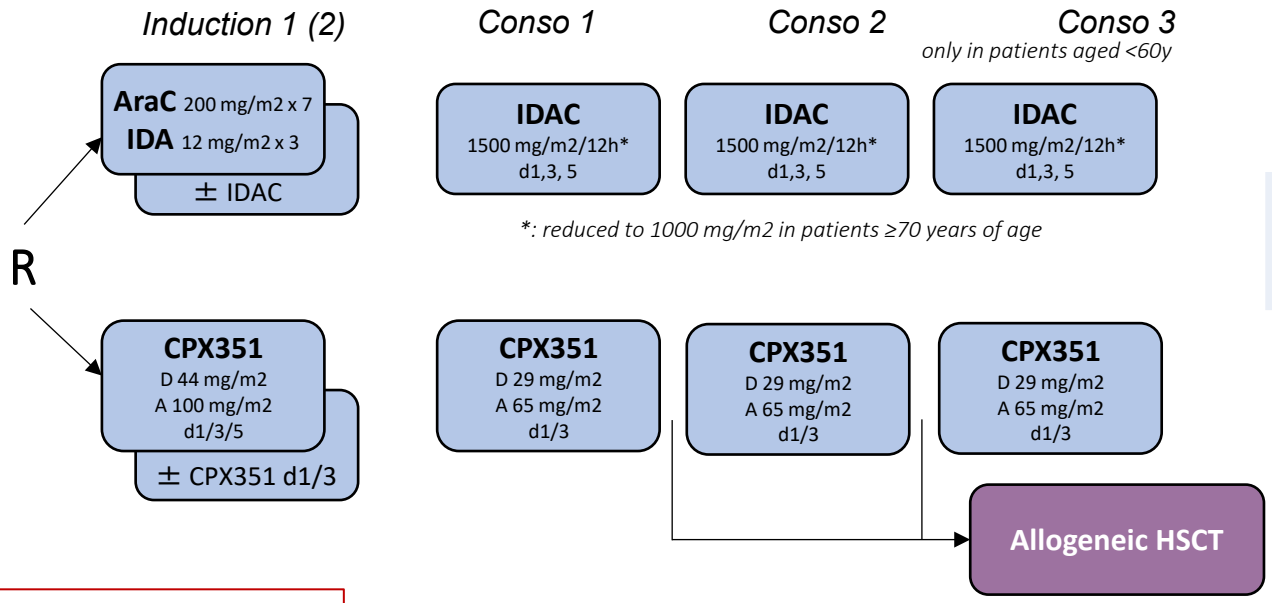
STUDY AML GROUP

ALFA-2101 – CPX-351 *vs* intensive CTx

A randomized Phase 2 study of CPX-351 *vs* intensive chemotherapy in adults (≥50y) with *de novo* intermediate-risk AML

Key eligibility criteria

- Age ≥ 50 years
- **Newly diagnosed *de novo* AML**
- **No MDS-related cytogenetics**
- **APL and CBF-AML excluded**
- ***FLT3- and/or NPM1*-mutated AML excluded**
- No CNS involvement
- ECOG-PS ≤2
- Informed consent



N= 210 patients needed
To demonstrate a 20% increase in the rate of LAIP/DfN MRD $<10^{-3}$ after induction (from 48 to 68%)

On February 17th, 2025:
71 patients included

Challenges:

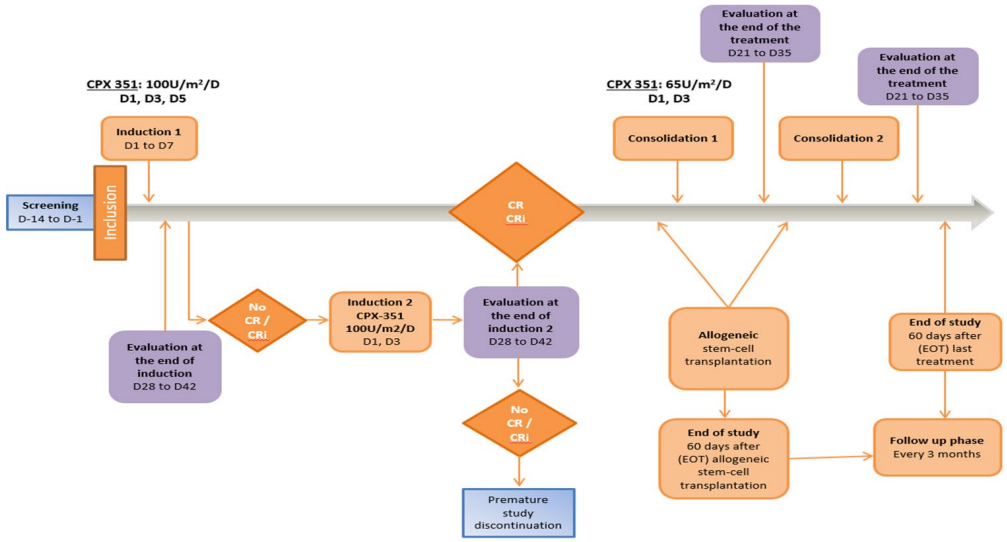
- *Randomization stratified by genomics: secondary AML-like gene mutations, Y/N (9 genes)*
- *Flow MRD response as primary endpoint*

- **Primary endpoint: rate of flow LAIP/DfN-based MRD $<10^{-3}$ after the first induction course**
- **Secondary endpoints:** subsequent MRD response, Flow LSC-MRD, NGS-MRD, OS, RFS, safety, QoL
- **Exploratory endpoint:**
  - interaction with the sAML-like mutational status
  - interaction with the PgP activity

Multicenter phase II non-randomized study assessing CPX-351 in post-MPN AML (FILO)

Key eligibility criteria

- Age ≥ 18 years
- Newly diagnosed post MPN-AML (ET, PV, PMF or post-ET/PV MF)
- Eligible for intensive chemotherapy



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	N=41 participants
Age	68 y (45-78)
Prior MPN	
ET	39%
PV	10%
PMF	29%
Post-ET/PV MF	22%
ECOG PS	
0-1	80%
2	20%
ELN 2022	
Favorable	2
Intermediate	8
Adverse	90
Mutations	
JAK2	49%
TP53	39%
ASXL1	37%
EZH2	27%
TET2	27%
CALR	17%
MPL	2%

	N=41 participants
CR/CRi	44%
CR/CRi without MRD (MFC)	27%
Day-30 death	12%
Allo-HSCT	10
mOS	6 months (4.5-12)
mEFS	5.5 months (3.3-6.5)

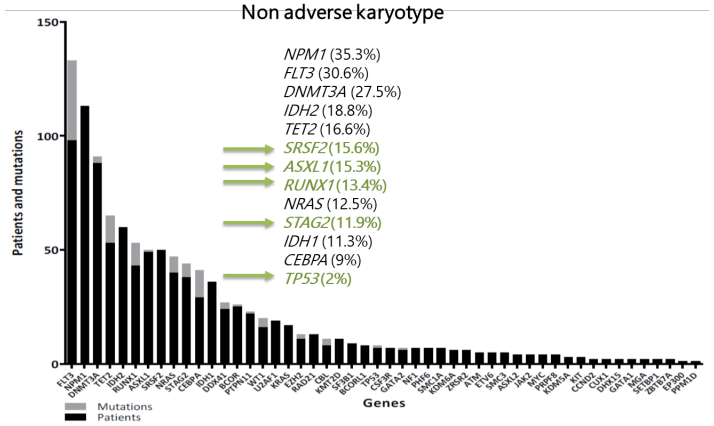
Median follow-up of 11.5 months (range 8.0-13.6)

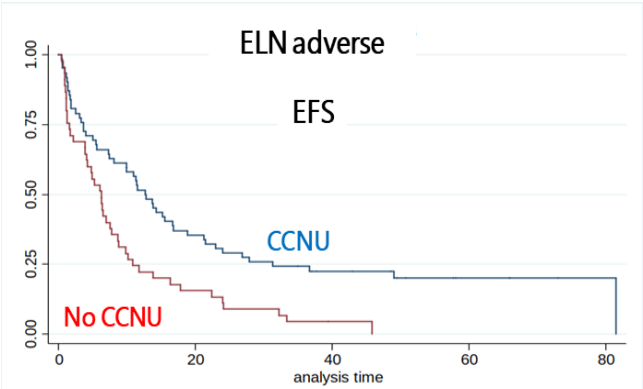
Molecular factors impacting OS
***TET2*-mut (OS, 3.6 months vs 8.2, *TET2*-WT)**
***TP53*-mut (OS, 4.6 months vs 9.7, *TP53*-WT)**

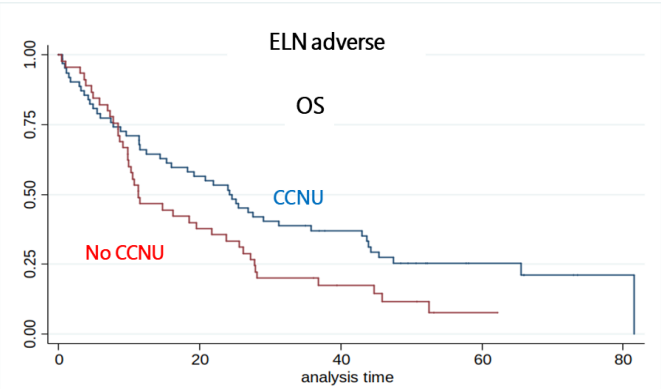
Garciaz S, ASH 2023

Adding a third drug to 7+3 may improve response rate and outcome Lomustine (CCNU) in older AML (>60y)

LAM-SA 2007 trial: IDA-ARAC-CCNU

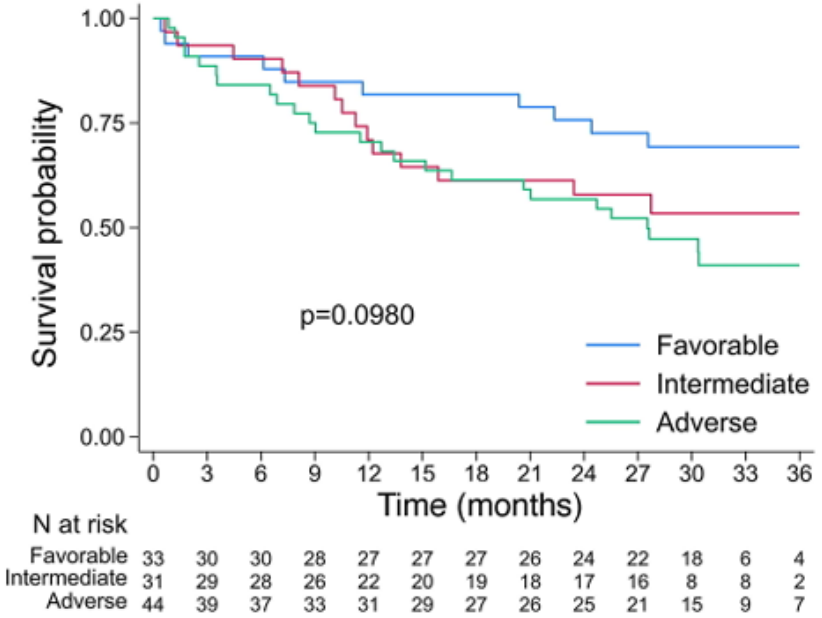






DEXAML-02 trial (>60y) IDA-ARAC-CCNU + DEXAMETHASONE

RUNX1: 23 (21%), ASXL1: 23 (21%), BCOR 6: (5%), EZH2: 5 (5%)
SF3B1: 3 (3%), SRSF2: 27 (24%), STAG2: 18 (16%), U2AF1: 7 (6%),
ZRSR2: 3 (3%) TP53: 2 (2%) (with intermediate-risk cytogenetics)



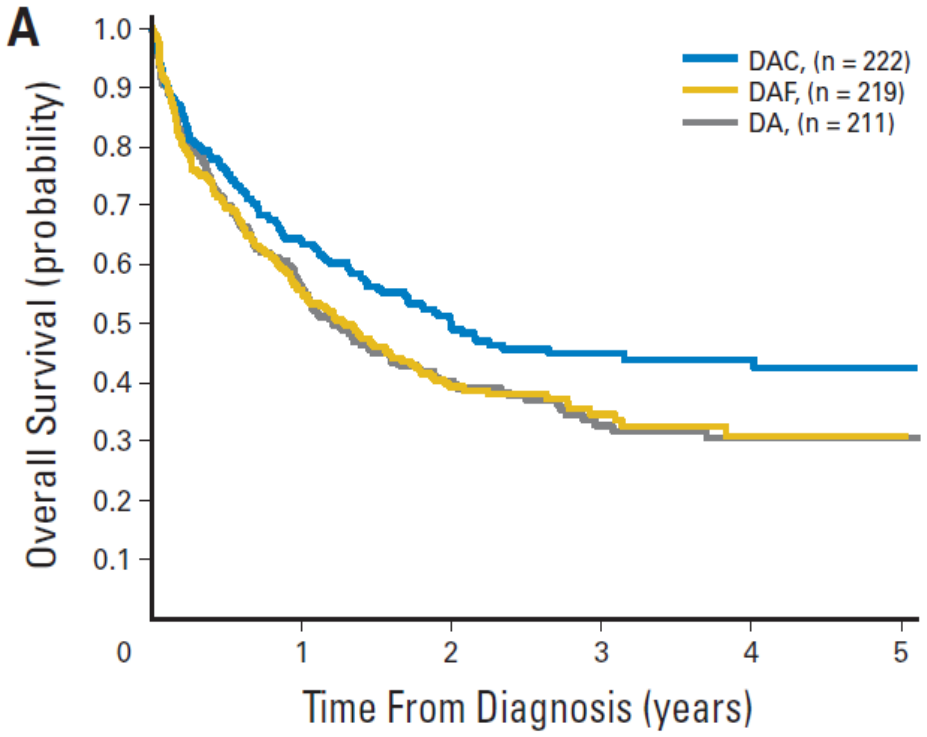
Median OS in adverse AML: 27·5 (9-NR)

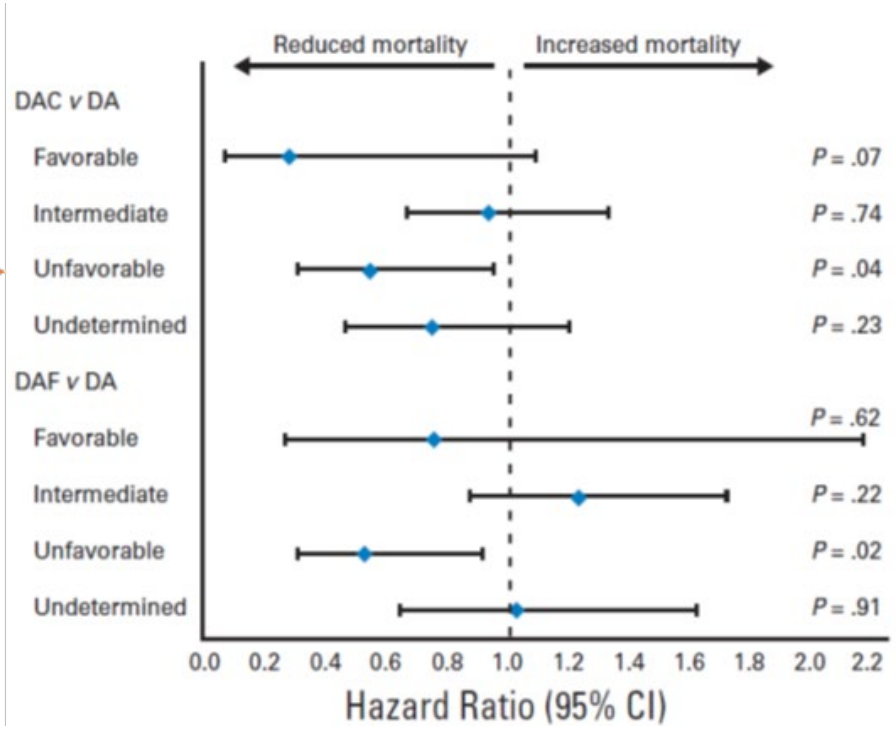
FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

Pigneux A, JCO 2018; Largeaud L, Leukemia 2020

Bertoli S, Haematologica 2025

Adding a third drug to 7+3 may improve response rate and outcome
Cladribine in younger HR-AML (18-60y)





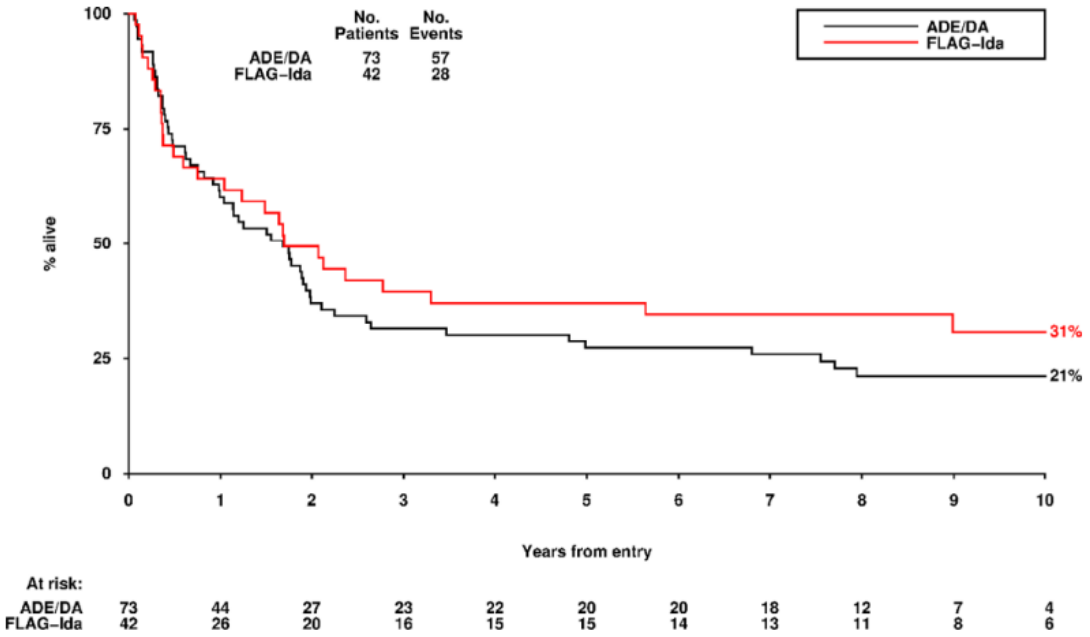
Holowiecki J, JCO 2012

Intensified purine analogue-based induction may improve response rate and outcome

FLAG-Ida vs DA/ADE

Long-term follow up of the MRC AML15 trial (16-59y)

	FLAG-Ida, %	DA/ADE, %	Unadjusted OR/HR (95% CI)	Stratified OR/HR (95% CI)
CR/CRi	81	79	0·91 (0·35–2·34); *P* = 0·8	0·54 (0·19–1·55); *P* = 0·3
5-year cumulative incidence of relapse	3	64	0·56 (0·32–1·00); *P* = 0·05	0·47 (0·24–0·93); *P* = 0·03
5-year cumulative incidence of death in remission	24	14	1·32 (0·50–3·50); *P* = 0·6	0·79 (0·26–2·34); *P* = 0·7
5-year relapse-free survival	41	22	0·70 (0·43–1·15); *P* = 0·16	0·54 (0·31–0·96); *P* = 0·04
2-year survival from relapse	8	19	1·43 (0·71–2·89); *P* = 0·3	0·67 (0·29–1·55); *P* = 0·3
5-year overall survival	37	27	0·81 (0·52–1·26); *P* = 0·4	0·45 (0·33–0·90); *P* = 0·02
5-year survival censored at SCT	54	39	0·77 (0·45–1·33); *P* = 0·3	0·49 (0·26–0·90); *P* = 0·02
Median survival	20.6 months	20.2 months		

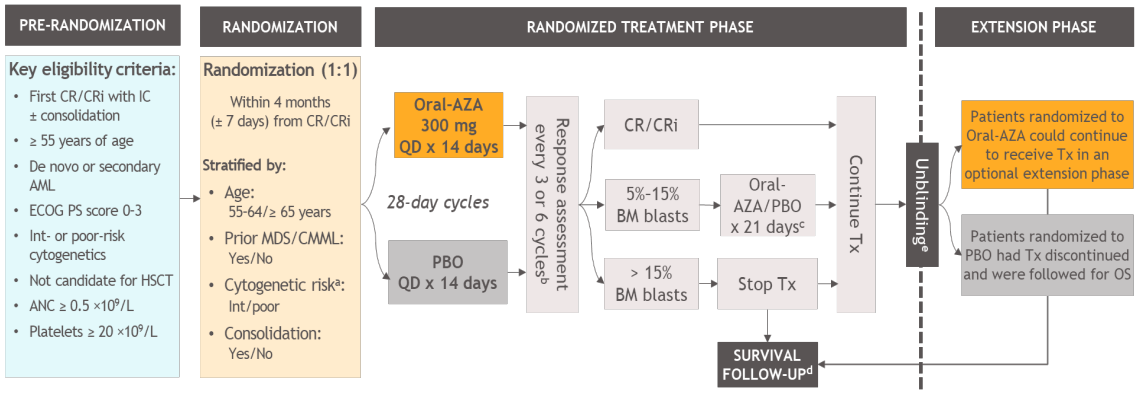


Russell N, BJH 2022

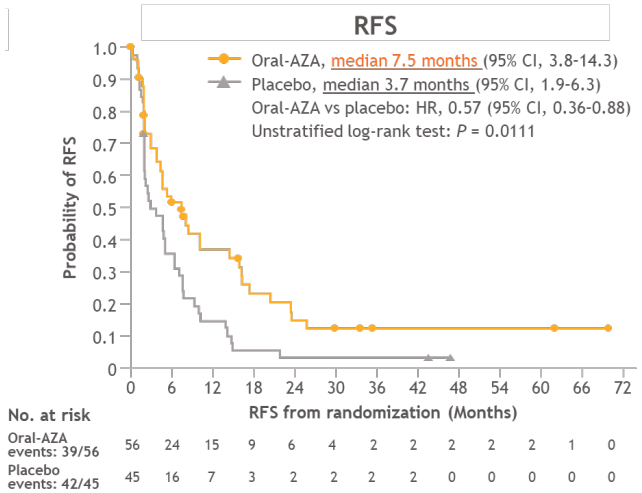
Oral azacitidine maintenance in MRC-AML

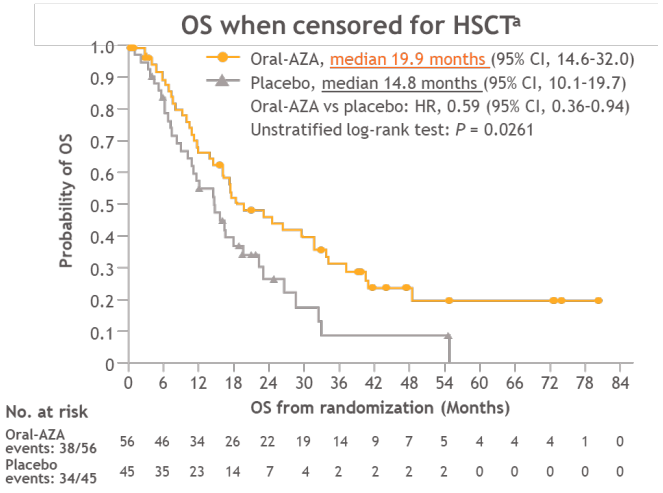
Oral-AZA maintenance in AML: QUAZAR AML-001 study design and eligibility criteria (Wei A, NEJM 2020)

International, multicenter, placebo-controlled, double-blind, randomized, phase 3 trial



A post-hoc analysis of outcomes of patients with AML with myelodysplasia-related changes who received oral azacitidine maintenance therapy in the QUAZAR AML-001 study



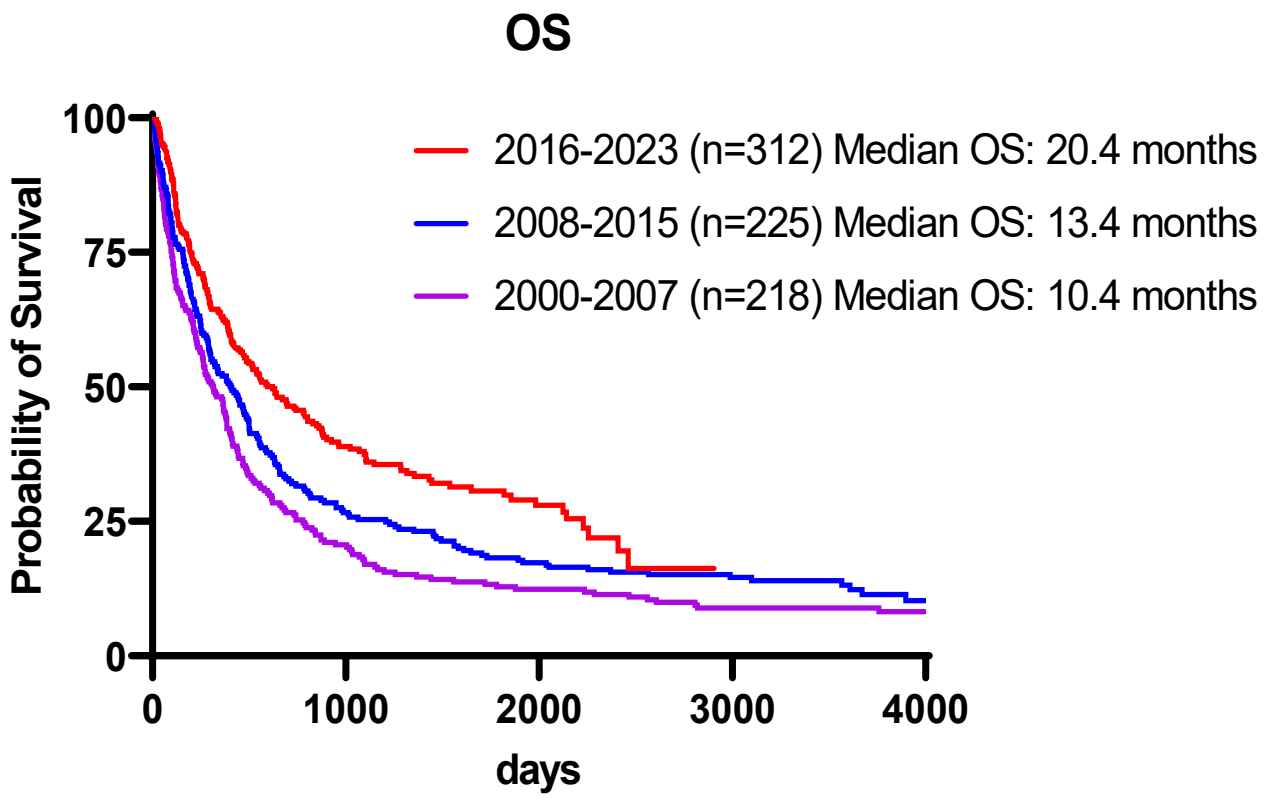


Voso MT, ASCO 2024

Recent progress in sAML

DATAML registry
Newly diagnosed s-AML
2000-2023
Intensive chemotherapy
N=772
Median age: 63y

	2000-2007	2008-2015	2016-2023
Median age	62y	63y	**64y**
CR/CRi	62%	68%	**79%**
Induction deaths	16%	12%	**5%**
Allo-HSCT	14%	27%	**35%**
3y-OS	17%	25%	**37%**

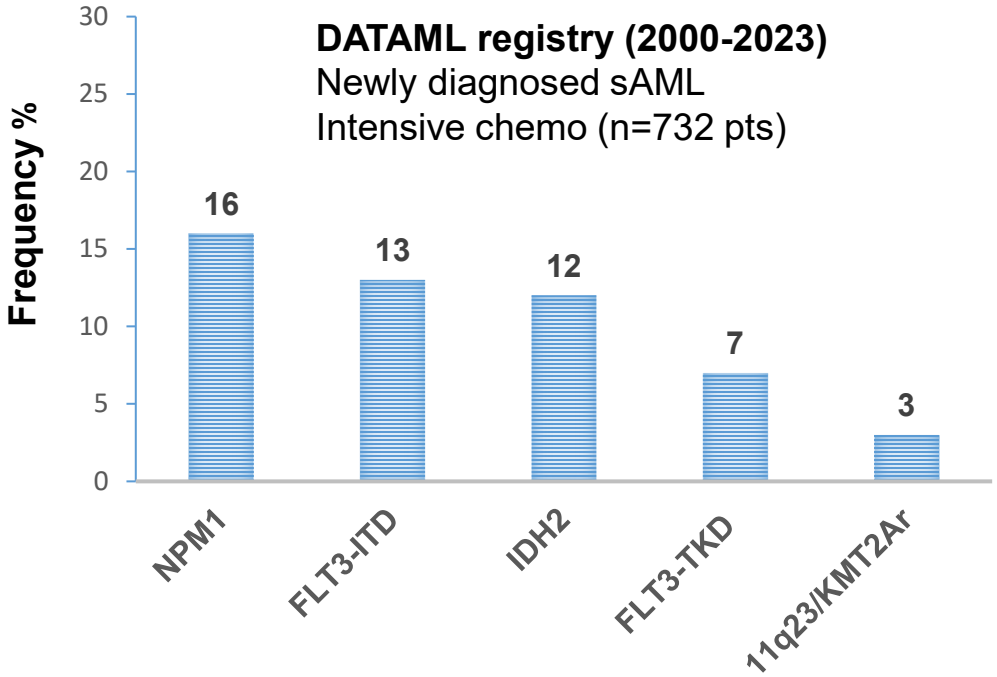


Unpublished data

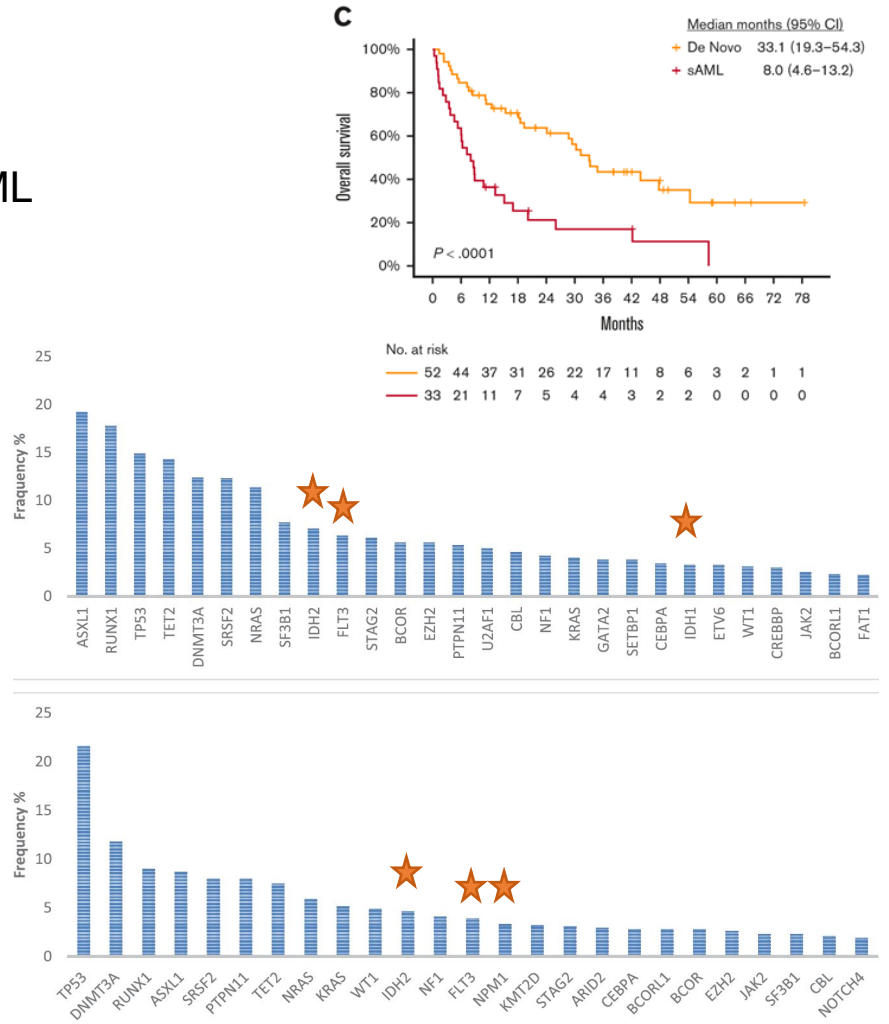
How to improve intensive chemotherapy in sAML?

- Adding venetoclax ?
  - CAVEAT study (DA, 2+5 + VEN) : mOS, 8 months (4.6–13.2) in sAML
  - Chua CC, Blood Adv 2025

- Targeted agents despite lower frequency in sAML?



Unpublished data



Incidence of mutations in genes relevant for hematopoiesis and in 1,154 myelodysplasia-related AML (A) patients and in 389 therapy-related AML patients (B). Query on the Genie 15.0 dataset of 7,156 leukemia patients

Marconi G, Frontiers Oncol 2024

V-FAST (Vyxeos - First Phase Assessment with Targeted Agents)

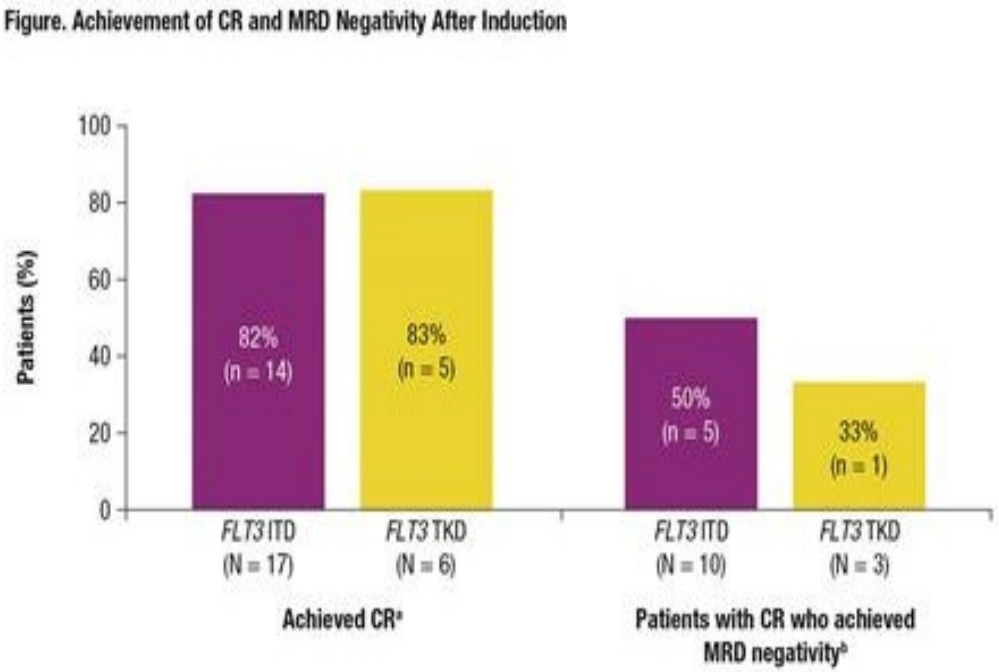
- **Open-label, multicenter, multi-arm, nonrandomized, phase 1b master trial (NCT04075747) to evaluate the safety and preliminary efficacy of CPX-351 combined with targeted agents (midostaurin, venetoclax, enasidenib).**

- CPX-351 (Daunorubicin 44 mg/m2 + cytarabine 100 mg/m2) on Days 1, 3, and 5 + MIDOSTAURIN 50 mg twice daily on Days 8 to 21.

Table. Baseline Characteristics of Patients Who Received CPX-351 + MID by *FLT3* Mutation Status

	FLT3 ITD (n = 18)	*FLT3* TKD (n = 6)
Age		
Median (range), years	68 (40, 74)	62 (40, 71)
18 to 59 years, n (%)	4 (22)	2 (33)
60 to 75 years, n (%)	14 (78)	4 (67)
Sex, n (%)		
Female	10 (56)	2 (33)
Male	8 (44)	4 (67)
Disease risk classification, n (%)		
Favorable	0	1 (17)
Intermediate	12 (67)	4 (67)
Poor	6 (33)	1 (17)
AML subtype, n (%)		
de novo AML	14 (78)	6 (100)
AML-AHD	3 (17)	0
Therapy-related AML	1 (6)	0
Prior HMA for MDS, n (%)	2 (11)	0
ECOG PS, n (%)		
0	4 (22)	3 (50)
1	12 (67)	3 (50)
2	2 (11)	0

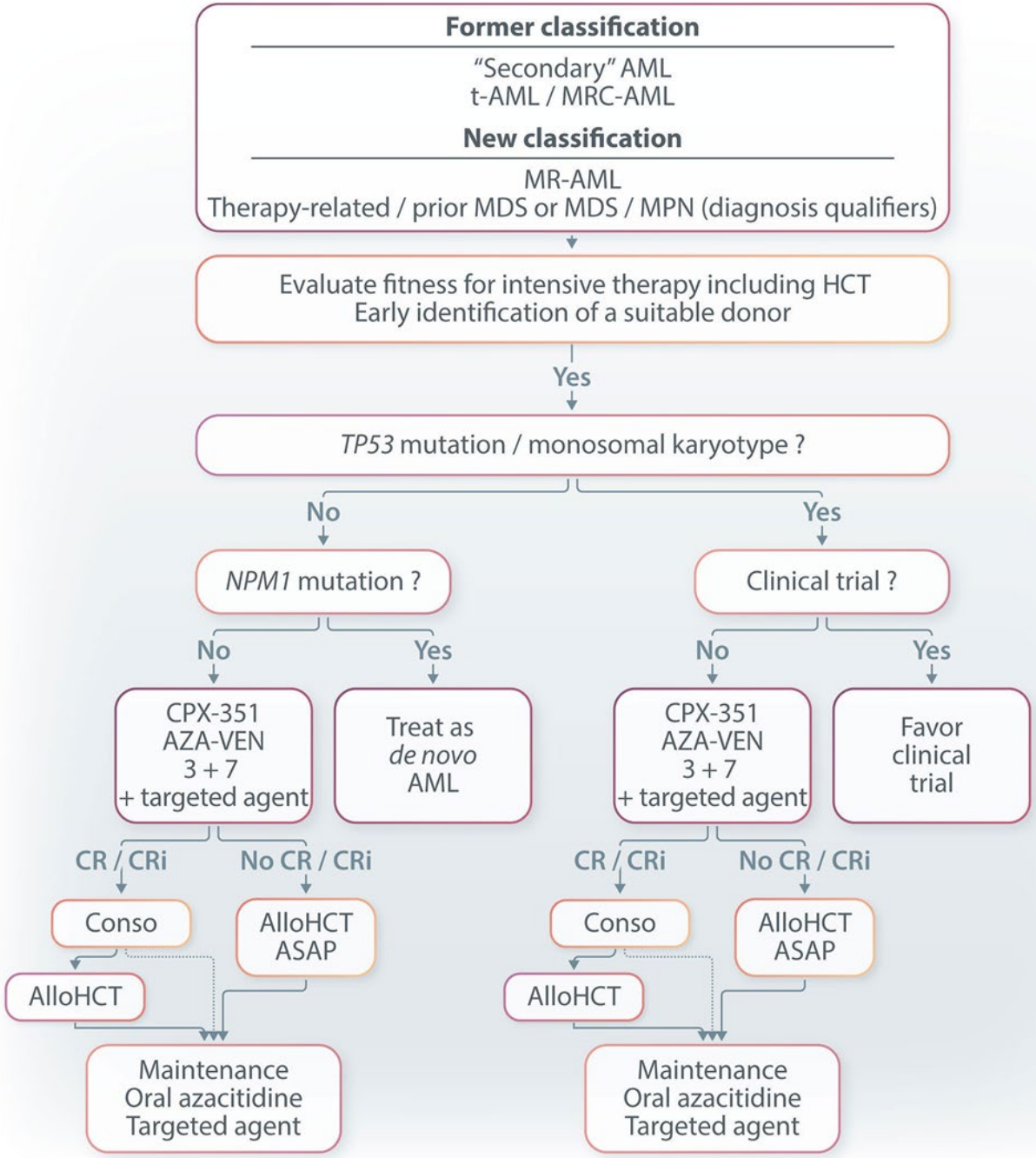
MID, midostaurin; ITD, internal tandem duplication; TKD, tyrosine kinase domain; AML, acute myeloid leukemia; AML-AHD, acute myeloid leukemia transformed from an antecedent hematologic disorder; HMA, hypomethylating agent; MDS, myelodysplastic syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status.
n = number of patients who received ≥1 dose of study drug and had sufficient data to be included in the analysis.



McCloskey J, ASH 2022

Future challenge

- Improve response rate to CPX-351 (and CR without MRD before alloHSCT)
- Schedule transplantation as soon as induction decision is made
- Post-alloHSCT intervention
- Improve maintenance in non transplanted patients
- Deal with new comers: post-immune intervention, post-PARPi
- Specific prospective clinical trials



Récher C, Haematologica 2024

Thank you!

Prof. Christian Récher

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