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Frequent *FLT3* and *IDH* co-mutations in acute myeloid leukemia with mutated *NPM1*, *NUP98* rearrangement, and *KMT2A* partial tandem duplication but not rearrangement: potential for combined targeted therapy

Rainer Ordemann[1]*, Sandra Huber[1]*, Alessandro Baldi[1], Anna Stengel[1], Irene Fuhrmann[1], Christian Pohlkamp[1], Manja Meggendorfer[1], Sabit Delic[1], Wolfgang Kern[1], Torsten Haferlach[1], Gregor Hoermann[1]

Affiliation:

[1]MLL Munich Leukemia Laboratory, Munich, Germany

Authors' contributions:

*RO and SH contributed equally as co-first authors. RO and GH designed the study. IF and SD supported data collection. AS was responsible for chromosome banding and FISH analyses, MM for molecular and bioinformatic analyses, WK for immunophenotyping, and CP and TH for cytomorphologic analyses. SH and AB analyzed the data; RO, SH and GH interpreted the data. RO, SH, AB, and GH wrote the manuscript. All authors read and contributed to the final version of the manuscript.

Running head: Targetable co-mutations in menin-dependent AML

Corresponding Author:

Gregor Hoermann

MLL Munich Leukemia Laboratory

Max-Lebsche-Platz 31, 81377 München, Germany

T: +49-89-990-17-315

Email: gregor.hoermann@mll.com

Competing Interests

WK and TH declare part ownership of MLL Munich Leukemia Laboratory. RO, SH, AB, AS, IF, CP, MM, SD and GH are employed by the MLL.

Data-sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Menin inhibitors have emerged as new therapeutics for acute myeloid leukemia (AML) with aberrant *HOX/MEIS* expression, particularly in *NPM1*-mutated (m), *KMT2A*-rearranged (r), and *NUP98*r cases. Menin inhibitors revumenib and ziftomenib achieved clinically meaningful complete remission (CR) rates with acceptable safety in heavily pre-treated *KMT2A*r or *NPM1*m patients.[1,2] FDA has approved both for relapsed or refractory (r/r) *NPM1*m AML in the absence of alternative treatment options and revumenib for r/r *KMT2A*r acute leukemias. However, single-agent menin inhibitor efficacy remains suboptimal, with CR rates of approximately 30% in heavily pretreated r/r patients.[1,2] Co-occurring targetable mutations – particularly in *FLT3* and *IDH1/2* – present immediate opportunities for rational combination therapy. *FLT3* internal tandem duplications (ITD) or tyrosine kinase domain (TKD) mutations cause ligand-independent activation of the FLT3 receptor.[3] FDA and EMA have approved midostaurin for *FLT3*m and quizartinib for *FLT3*-ITD-positive newly diagnosed AML in combination with standard intensive induction chemotherapy followed by consolidation, and gilteritinib as monotherapy for r/r *FLT3*m AML. *IDH1*/*2* mutations establish founding clones through epigenetic dysregulation via 2-hydroxyglutarate accumulation, which competitively inhibits α-ketoglutarate-dependent dioxygenases including TET2 and histone demethylases.[4] Ivosidenib is approved for adults with *IDH1*m AML, both as monotherapy in r/r disease and, in combination with azacitidine, for newly diagnosed patients unfit for intensive induction. FDA but not EMA approved olutasidenib for *IDH1*m and enasidenib for *IDH2*m r/r AML. As responses to menin inhibition are often transient, identifying co-occurring actionable genetic alterations may enable rational combination strategies to improve both the depth and durability of clinical responses. Herein, we report a comprehensive analysis of a large AML cohort demonstrating additional genetic targets in the majority of AML patients with *NPM1*,

KMT2A, or *NUP98* aberrations, with distinct co-mutation signatures that profoundly impact optimal combination strategies with menin inhibitors.

We retrospectively analyzed 13 458 newly diagnosed AML patients (median age: 70 years [18-100]; 45% female) sent to the MLL Munich Leukemia Laboratory between 2005 and 2025. Bone marrow and/or peripheral blood samples were analyzed by cytomorphology, immunophenotyping where necessary, cytogenetics (chromosome banding analysis and/or fluorescence in situ hybridization/FISH) and molecular genetics as previously described.[4] In brief, mutational data including *NPM1*, *FLT3*-TKD, *IDH1*, and *IDH2* were retrieved using next generation sequencing (NGS), *FLT3*-ITD was analyzed by fragment length analysis, and *KMT2A* partial tandem duplication (PTD) with Mentype AMLplex screening assay (BIOTYPE GmbH, Dresden, Germany). *NUP98*-r cases were identified by FISH and/or RT-PCR. The evolutionary trajectory of genetic events was inferred from clone size determined by interphase FISH (as percentage of aberrant cells) or calculated by doubling the variant allele frequency (VAF) of mutations determined by NGS and using a minimal clone size difference of ≥10% to distinguish ancestral from secondary events. In 769 patients, whole genome and transcriptome sequencing were performed. Hierarchical clustering based on 21 *HOX/MEIS* signature genes was used to identify potential menin inhibition sensitive cases. All patients gave their informed consent for laboratory and genetic analyses. The study complied with the Declaration of Helsinki and was approved by the institutional review board and the Ethics Committee of the Bavarian Medical Association.

We first analyzed *HOX/MEIS* gene expression in 769 AML patients (Figure 1). Two clusters showed high *HOX/MEIS* activity, as expected mainly containing *NPM1*m, *KMT2A*r, *NUP98*r, and *DEK::NUP214* cases – known *HOX*-dependent leukemias

(Figure 1A/B). Additional analysis revealed that *KMT2A*-PTD was also enriched in these *HOX/MEIS*-high groups (Figure 1C), suggesting that these cases might also respond to menin inhibition, although they should currently not be considered an established subtype with clinical menin inhibitor-sensitivity (ClinicalTrials.gov identifier: NCT04065399, NCT06229912). Thus, for the remainder of the study, we concentrated on cases with *KMT2A*r, *NPM1*m, *NUP98*r, *DEK*::*NUP214* and *KMT2A*-PTD.

Among 13 458 AML patients 3 891 (29%; median age: 65 [18-95] years; 54% female; Suppl. Table S1) had aberrations qualifying for menin inhibitor therapy: 367 *KMT2A*r (9%), 3 403 *NPM1*m (88%), 67 *NUP98*r (2%) and 54 *DEK*::*NUP214* (1%; Figure 2A). Of the remaining 9 567 patients, additional 544 presented *KMT2A*-PTD (10% of 5 190 cases specifically tested; Figure 2A). The most frequent rearrangement partners were *MLLT3* (41%) for *KMT2A* and *NSD1* (70%) for *NUP98* (Suppl. Figures S1A/B). Interphase FISH analysis showed a median clone size of 85% for *KMT2A*r and 84% for *NUP98*r (Suppl. Figures S1C/D). With respect to the *NPM1*m cohort, *NPM1* mutations had a median clone size of 62% (corresponding VAF: 31%; Suppl. Figure S2).

Complete co-mutation data for *FLT3* and *IDH1/2* were available in 3 196 of the 4 435 AML patients with *KMT2A*r, *NPM1*m, *NUP98*r, *DEK*::*NUP214* or *KMT2A*-PTD. Interestingly, among these patients 2 013 (63%) harbored at least one additional targetable alteration in *FLT3*, *IDH1*, or *IDH2* (Figure 2B). This high prevalence enables therapeutic strategies beyond menin inhibitor monotherapy as the majority of patients harbor molecular vulnerabilities amenable to dual- or even triple-target approaches. Menin inhibitors disrupt the menin-KMT2A complex at *HOX* loci, providing the biological rationale for combinatorial strategies.[5] Preclinical data indicate a dual vulnerability in menin/*FLT3* co-mutated cases demonstrating a synergistic anti-

leukemic effect.[3,6] Currently, two ongoing trials (NCT06222580, NCT06313437) are investigating the combination of menin and FLT3 inhibitors in AML patients. Likewise, the combination of menin inhibitors with IDH inhibitors provides complementary mechanisms, the preclinical evidence for a specific synergy between these inhibitors remains scarce.[7]

The co-mutation landscape in our dataset exhibited striking subtype-specific signatures with direct therapeutic implications (Figure 2C). In the *NPM1*m cohort, *FLT3*-ITD mutations occurred in 39%, *FLT3*-TKD in 13%, *IDH2* in 19%, and *IDH1* in 15% in line with recent studies.[8,9] The *KMT2A*r cohort displayed a lower overall co-mutation frequency with a distinct pattern of mainly *FLT3*-TKD (12%; *FLT3*-ITD, *IDH1*, and *IDH2* <3%). This relative paucity of targetable co-mutations may reflect the dominant driver role of the KMT2A fusion protein itself.[10] Most strikingly, the *NUP98*r cohort demonstrated *FLT3*-ITD in 55% and the *DEK::NUP214* cohort in 58%, representing the predominant co-mutation pattern (Figure 2C). Our findings are in line with published cohorts of pediatric patients demonstrating the frequent co-mutation of *NUP98::NSD1* and *FLT3*-ITD,[11] and recent data of a large adult cohort of *NUP98*r patients showing a frequency of *FLT3*-ITD co-mutations of 48%.[12] Given the high *FLT3*-ITD prevalence observed in our cohort, *NUP98*r and *DEK::NUP214* AML may be particularly interesting for dual menin/FLT3 targeting strategies.

Finally, the *KMT2A*-PTD co-mutation profile closely resembled *NPM1*m rather than *KMT2A*r AML, with frequent *FLT3*-ITD (27%), *FLT3*-TKD (7%), *IDH1* (18%), and *IDH2* (24%) mutations (Figure 2C). This is also in agreement with *HOX*/*MEIS* expression clustering, where the majority of *KMT2A*-PTD cases (58%; 18/31) clustered with *NPM1*m cases and not with *KMT2A*r cases (Figure 1). However, clinical data for *KMT2A*-PTD AML regarding menin inhibition remain limited. Preclinical data in

KMT2A-PTD AML demonstrated that this subtype, despite *HOX/MEIS* activation, is largely menin-independent at a functional level and therefore does not meaningfully benefit from menin inhibition.[13]

Interestingly, 40% (384/949) of all *IDH1/2*-mutant cases in our *KMT2A*r, *NPM1*m, *NUP98*r, *DEK*::*NUP214*, or *KMT2A*-PTD AML cohort also harbored *FLT3* alterations (Suppl. Figure S2C), indicating overlapping eligibilities that may benefit from combination targeted regimens. Menin inhibitors demonstrated manageable toxicity profiles that support combination approaches.[1] This tolerability profile, combined with well-established safety profiles of FLT3 inhibitors and IDH inhibitors, could support feasibility of combination targeted therapy without prohibitive cumulative toxicity. However, the concomitant use of menin and IDH inhibitors may increase the risk of differentiation syndrome owing to their shared differentiation-promoting activity and therefore warrants close clinical surveillance. Furthermore, multi-agent targeted combinations simultaneously targeting multi-mutated clones might potentially reduce treatment resistance through poly-pharmaceutical pressure. Analysis of clonal hierarchy in menin-eligible patients revealed *KMT2A*r and *NUP98*r as mainly ancestral compared to *FLT3* and *IDH* mutations (90% and 68% of cases, respectively), while *NPM1*m were often secondary (70% of cases; Figure 3). In the *NPM1*m cohort, *IDH1* and *IDH2* mainly showed larger clone size (median: 77% and 79%) than *NPM1* (62%) and *FLT3* (54%). The co-mutation pattern and the underlying clonal hierarchy might influence the long-term efficacy of mono-therapies targeting either the founder or the subclone.[4]

In summary, our analysis of 13 458 AML cases confirmed high *HOX*/*MEIS* expression in *KMT2A*r, *NPM1*m, *NUP98*r, *DEK*::*NUP214*, and *KMT2A*-PTD subtypes and established a biomarker-driven treatment framework. Additional targetable mutations

were identified in 63% of patients potentially eligible for menin inhibitor therapy. While combinations of menin inhibitors with chemotherapy, hypomethylating agents like azacitidine, and/or the BCL-2 inhibitor venetoclax have already shown clinical efficacy and are further tested in ongoing trials[14], our data focus on precision medicine approaches exploiting the individual profile of molecular targets. In *NPM1*m AML – the largest menin-eligible group – frequent *FLT3*-ITD, *FLT3*-TKD, and *IDH1/2* mutations theoretically support dual-targeted strategies, while concurrent *FLT3* and *IDH1/2* alterations even suggest potential for triple-target menin/FLT3/IDH inhibition. Of course, clinical trials on combinatorial targeted therapy are needed as there is clearly a lack of prospective data on optimal sequencing versus simultaneous inhibition and on additive toxicity. For combinatorial strategies in small subgroups as *NUP98*r AML novel trial concepts like in silico trials, inclusion of synthetic data or digital twins may be needed to overcome cohort size restrictions.[15] Clinical trials should integrate comprehensive *FLT3* and *IDH1/2* profiling to optimize menin-based combination therapies and advance precision treatment for *HOX*-dependent AML.

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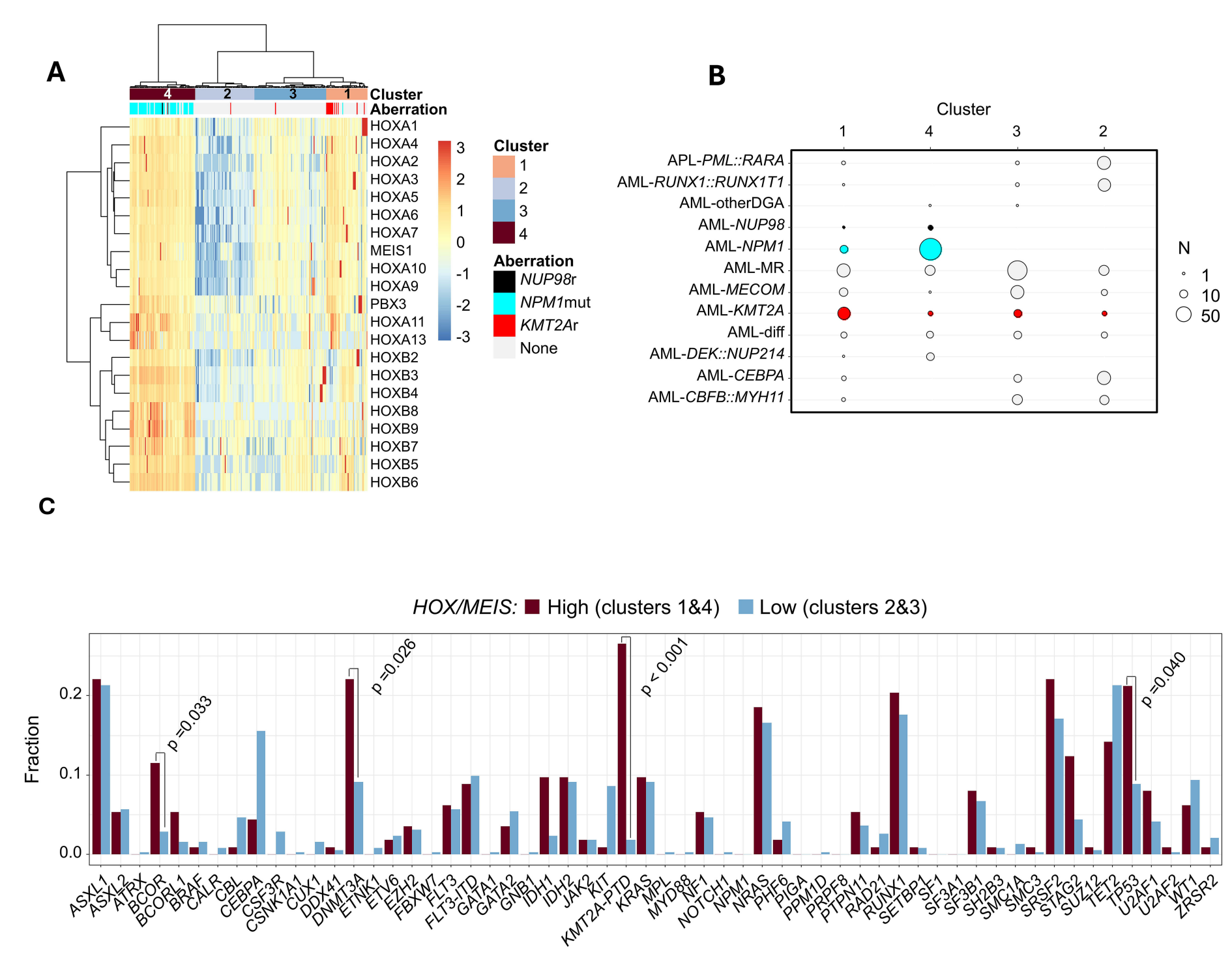
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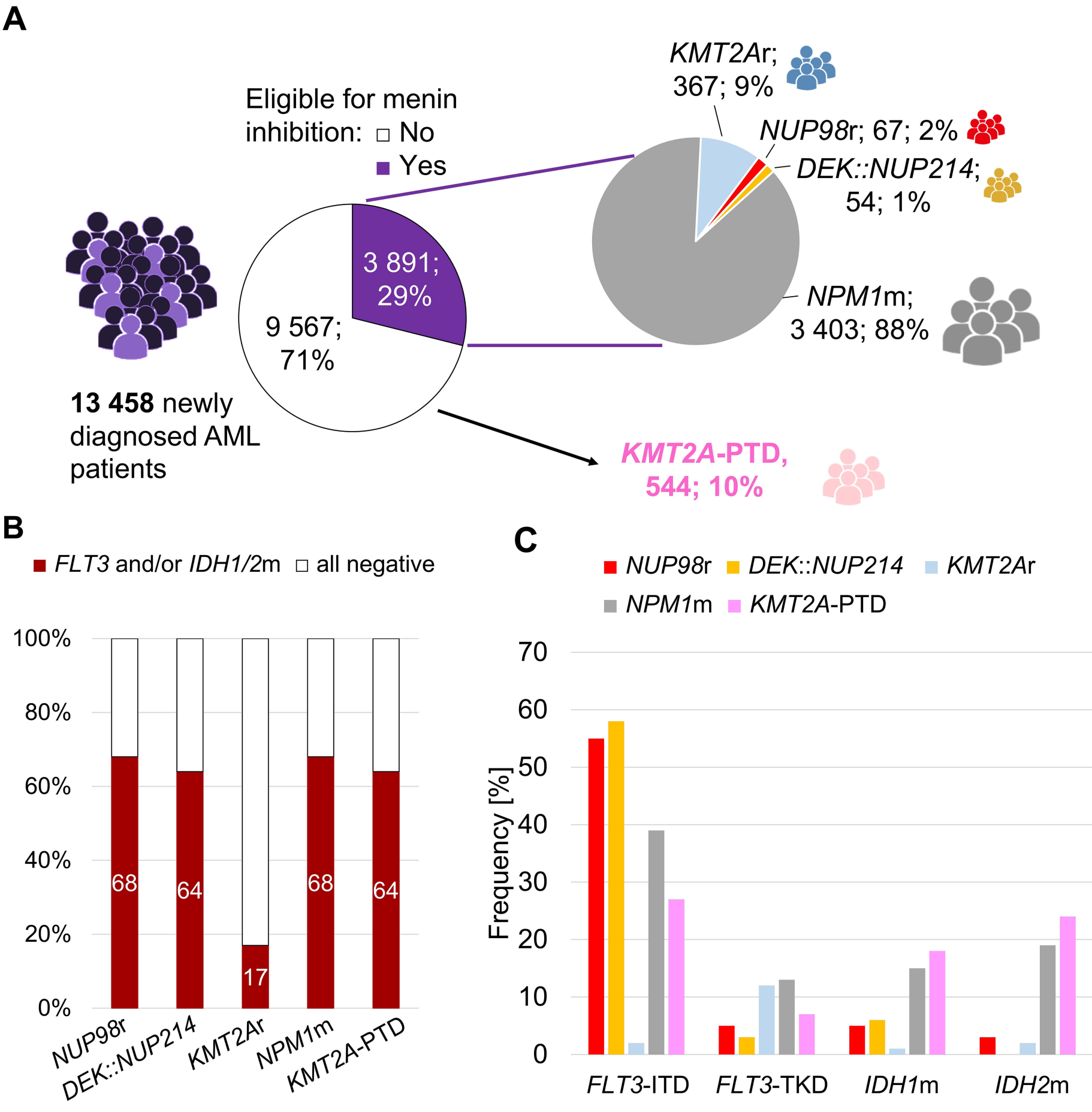
Figure 1: Clustering of AML cases by expression of *HOX/MEIS*-signature genes. (A) Hierarchical clustering of 769 AML cases by *HOX/MEIS* expression reveals four distinct expression clusters. Clusters 1 and 4 are characterized by elevated *HOX/MEIS* expression and contain all *NPM1*m and *NUP98*r and most (43/58) *KMT2A*r cases. (B) WHO2022 classification of cases clustered by *HOX/MEIS* expression. (C) Prevalence of mutations in *HOX/MEIS*-high (clusters 1 & 4) or *HOX/MEIS*-low cases (clusters 2 & 3) (p-values by Fisher's exact test and Bonferroni correction). Only cases without the known menin-dependent aberrations *NPM1*m, *KMT2A*r, *NUP98*r, and *DEK*::*NUP214* were analyzed.

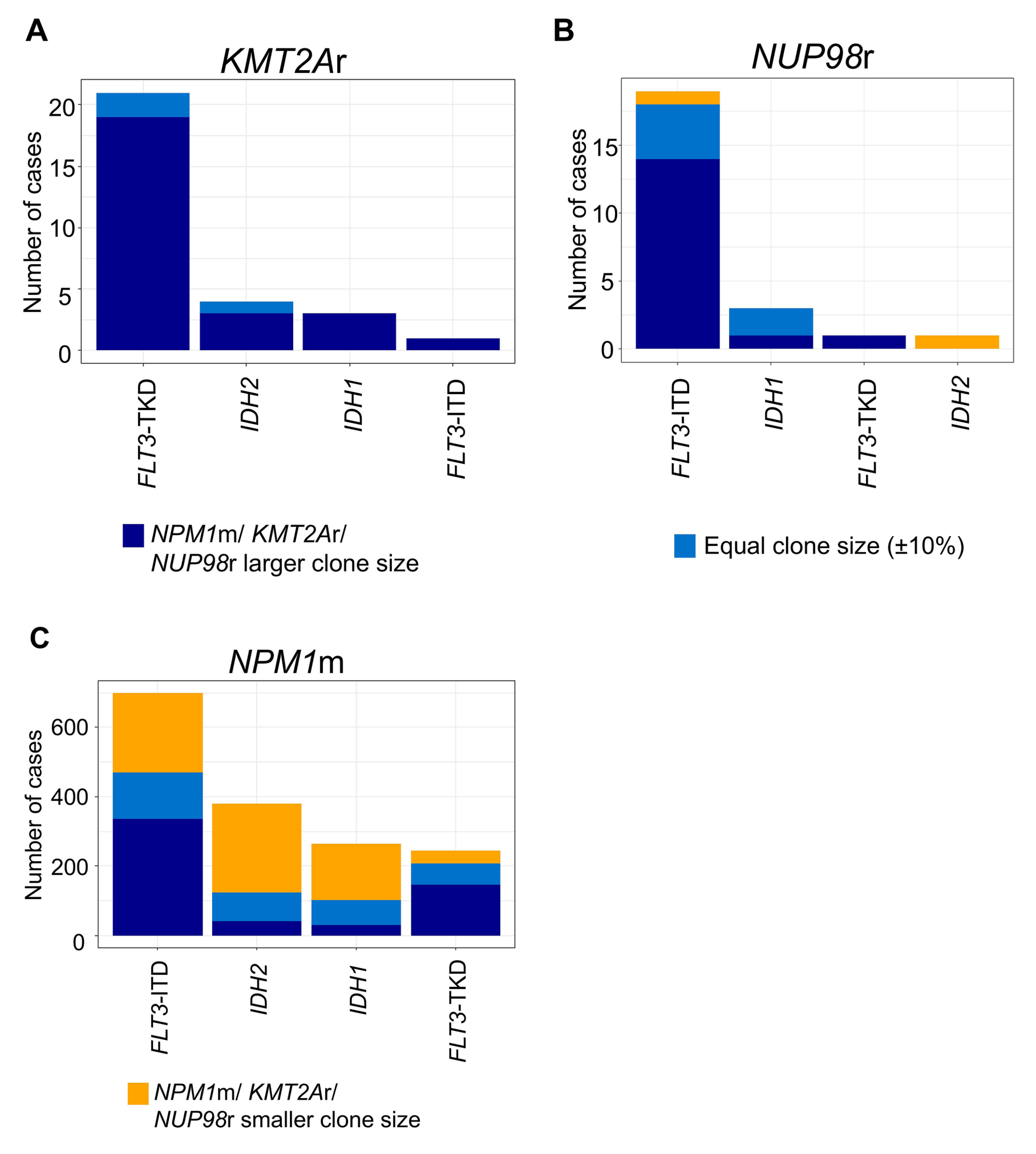
Figure 2: Cohort overview and co-mutation pattern. (A) Distribution and frequency of cases potentially eligible for menin inhibitor therapy within the entire AML cohort. All 13 458 AML cases were analyzed by cytomorphology, cytogenetics and molecular genetics. *KMT2A*r and *DEK*::*NUP214* cases were identified from cytogenetic analysis available in all cases. *NUP98*r cases were identified by FISH and/or PCR available in 1 973 cases (67 *NUP98*r: 3% of specifically tested). Of 9 567 patients negative for *KMT2A*r, *DEK*::*NUP214*, *NUP98*r, *NPM1*m 5 190 cases were specifically tested for *KMT2A*-PTD detecting additional 544 cases (10% of specifically tested) with *KMT2A*-PTD. **(B)** Frequency of cases with co-mutations in *FLT3* and/or *IDH1/2*. **(C)** Co-mutation pattern for *FLT3*-ITD, *FLT3*-TKD, *IDH1* and *IDH2* within the different cohorts.

Figure 3: Clonal hierarchy for cases potentially eligible for menin inhibitor therapy. Clonal hierarchy of *KMT2A*r **(A)**, *NUP98*r **(B)** and *NPM1*m **(C)** cases based on clone size of *KMT2A*r, *NUP98*r and *NPM1*m compared to co-mutations in *FLT3* and *IDH*. Clone size of mutations in *NPM1*, *FLT3*, and *IDH* was calculated by doubling the VAF and compared to that of *KMT2A*r and *NUP98*r (percentages of aberrant cells

determined by interphase FISH). A minimal clone size difference of ≥10% was used to distinguish ancestral (dark blue) from secondary (orange) events. VAF: variant allele frequency.


A
Cluster
Aberration
HOXA1
HOXA4
HOXA2
HOXA3
HOXA5
HOXA6
HOXA7
MEIS1
HOXA10
HOXA9
PBX3
HOXA11
HOXA13
HOXB2
HOXB3
HOXB4
HOXB8
HOXB9
HOXB7
HOXB5
HOXB6
Cluster
1
2
3
4
Aberration
NUP98r
NPM1mut
KMT2Ar
None
B
Cluster
APL-PML::RARA
AML-RUNX1::RUNX1T1
AML-otherDGA
AML-NUP98
AML-NPM1
AML-MR
AML-MECOM
AML-KMT2A
AML-diff
AML-DEK::NUP214
AML-CEBPA
AML-CBFB::MYH11
N
C
HOX/MEIS: High (clusters 1&4) Low (clusters 2&3)
Fraction
p =0.033
p =0.026
p < 0.001
p =0.040
ASXL1
ASXL2
ATRX
BCOR
BCORL1
BRAF
CALR
CBL
CEBPA
CSF3R
CSNK1A1
CUX1
DDX41
DNMT3A
ETNK1
ETV6
EZH2
FBXW7
FLT3
FLT3-ITD
GATA1
GATA2
GNB1
IDH1
IDH2
JAK2
KIT
KMT2A-PTD
KRAS
MPL
MYD88
NF1
NOTCH1
NPM1
NRAS
PHF6
PIGA
PPM1D
PRPF8
PTPN11
RAD21
RUNX1
SETBP1
SF1
SF3A1
SF3B1
SH2B3
SMC1A
SMC3
SRSF2
STAG2
SUZ12
TET2
TP53
U2AF1
U2AF2
WT1
ZRSR2


A
Eligible for menin inhibition: □ No ■ Yes
3 891; 29%
9 567; 71%
13 458 newly diagnosed AML patients
KMT2Ar; 367; 9%
NUP98r; 67; 2%
DEK::NUP214; 54; 1%
NPM1m; 3 403; 88%
KMT2A-PTD, 544; 10%
B
FLT3 and/or IDH1/2m □ all negative
100%
80%
60%
40%
20%
0%
68
64
17
68
64
NUP98r
DEK::NUP214
KMT2Ar
NPM1m
KMT2A-PTD
C
NUP98r DEK::NUP214 KMT2Ar
NPM1m KMT2A-PTD
Frequency [%]
70
60
50
40
30
20
10
0
FLT3-ITD
FLT3-TKD
IDH1m
IDH2m


A
KMT2Ar
Number of cases
0
5
10
15
20
FLT3-TKD
IDH2
IDH1
FLT3-ITD
NPM1m/ KMT2Ar/
NUP98r larger clone size
B
NUP98r
Number of cases
0
5
10
15
FLT3-ITD
IDH1
FLT3-TKD
IDH2
Equal clone size (±10%)
C
NPM1m
Number of cases
0
200
400
600
FLT3-ITD
IDH2
IDH1
FLT3-TKD
NPM1m/ KMT2Ar/
NUP98r smaller clone size

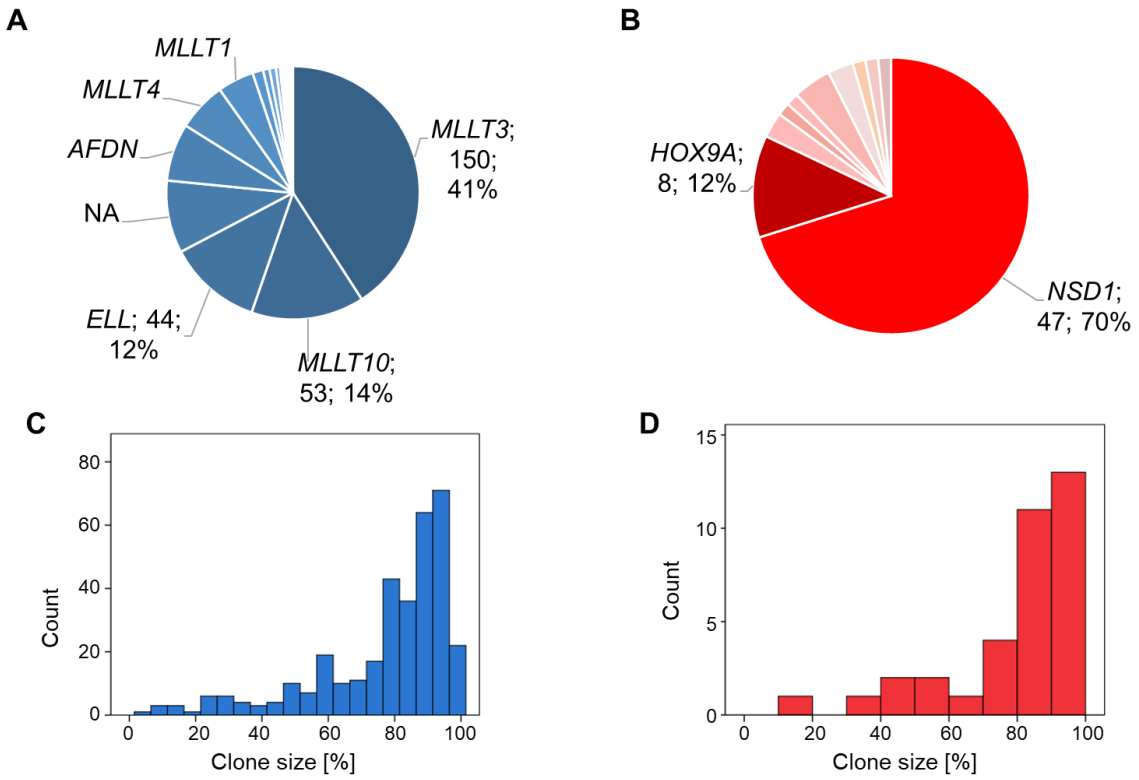
Supplementary Data

Supplementary Tables and Figures

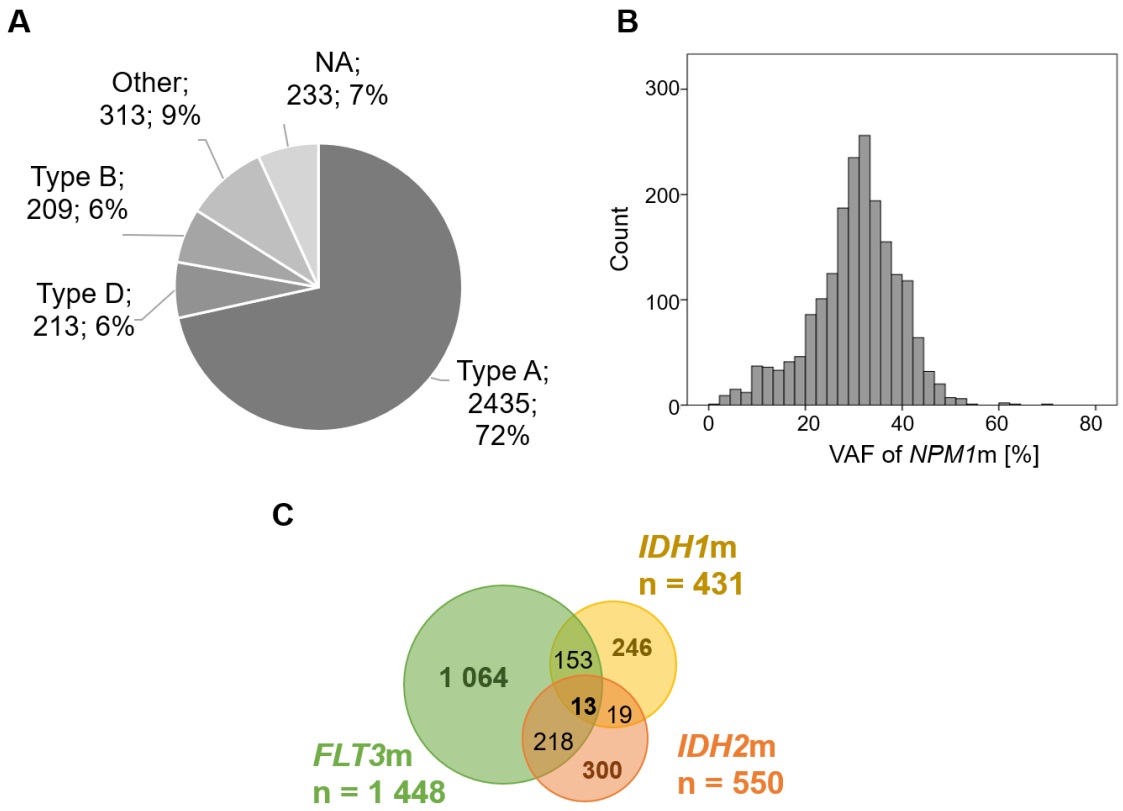
Table S1. Cohort overview

Subgroup	**Number of patients**	**Age** (years; median [range])	**Sex** (female/male)	**BM blasts** (median)
All AMLs	13 458	70 [18-100]	45% / 55%	50%
***KMT2A*r**	367	53 [18-88]	54% / 46%	80%
FLT3/IDH+	46	61 [23-81]	59% / 41%	82%
FLT3/IDH-	231	54 [18-88]	51% / 49%	80%
***NPM1*m**	3 403	66 [19-95]	54% / 46%	70%
FLT3/IDH+	1 736	67 [20-95]	55% / 45%	75%
FLT3/IDH-	825	67 [19-94]	52% / 48%	59%
***NUP98*r**	67	48 [18-85]	48% / 52%	67%
FLT3/IDH+	41	43 [18-85]	41% / 59%	63%
FLT3/IDH-	19	55 [21-77]	63% / 37%	72%
DEK*::*NUP214	54	56 [20-91]	57% / 43%	44%
FLT3/IDH+	23	55 [24-84]	49% / 51%	54%
FLT3/IDH-	13	57 [34-91]	54% /46%	34%
***KMT2A*-PTD**	544	70 [21-100]	42% / 58%	51%
FLT3/IDH+	167	69 [22-98]	50% / 50%	59%
FLT3/IDH-	95	72 [21-96]	26% / 74%	36%

BM: bone marrow.



Supplementary Figure S1: Rearranged partners and clone sizes of *KMT2A*r and *NUP98*r cases. Distribution of rearranged partner genes in the *KMT2A*r **(A)** and *NUP98*r **(B)** cohort. Histograms showing the distribution of clone sizes (aberrant interphase FISH nuclei per 100 cells) of *KMT2A*r **(C)** and *NUP98*r **(D)** cases. NA: not available.



Supplementary Figure S2: Type and VAF of *NPM1*m cases and overlapping *FLT3* and *IDH1/2* co-mutations. (A) Distribution of mutation types in the *NPM1*m cohort. NA: not available (as *NPM1*m was detected by fragment length analysis). **(B)** Histogram showing the distribution of VAF for *NPM1*m cases. VAF: variant allele frequency. **(C)** Overlap of *FLT3* and *IDH1/2* mutations in patients with *KMT2A*r, *NPM1*m, *NUP98*r, *DEK*::*NUP214*, or *KMT2A*-PTD (2 013 / 3 196 patients with available data on co-mutations).