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Acute leukemias

December 13, 2025

BHS course

Pediatric aggressive hemopathies

Barbara De Moerloose

UZ Gent – UGent

BHS course Acute leukemias: 13-12-2025

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Pediatric aggressive hemopathies

PART 1

- Introduction
- Aggressive lymphomas
- Acute lymphoblastic leukemia (ALL)

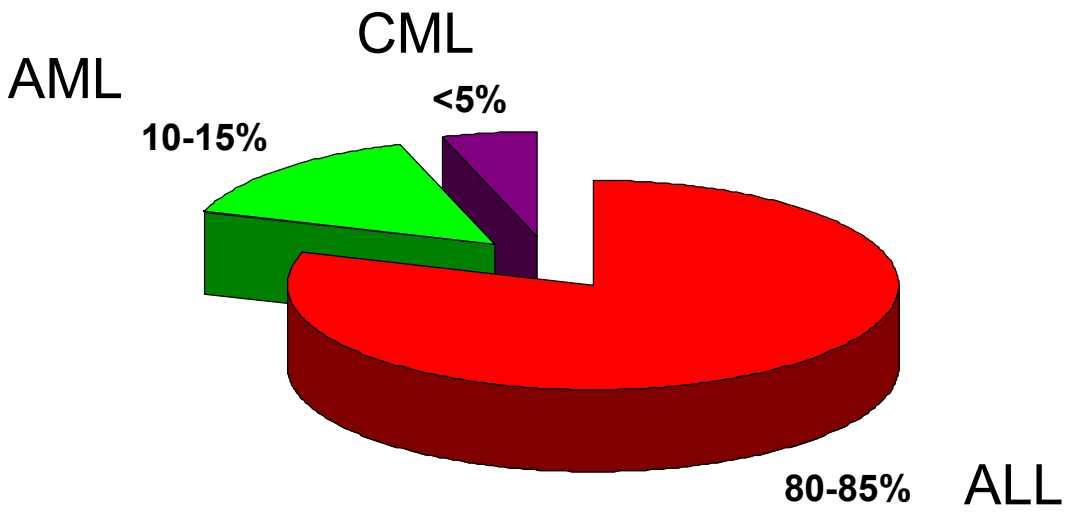
PART 2

- Myeloid malignancies in children:
  - Acute myeloid leukemia (AML)
  - Myelodysplasia (MDS)
  - Juvenile myelomonocytic leukemia (JMML)
  - Myeloid disorders associated with Down syndrome (TAM/TMD, ML-DS)

Myeloid malignancies in children

- Acute myeloid leukemia (AML)
- Myelodysplasia (MDS)
- Juvenile myelomonocytic leukemia (JMML)
- Myeloid disorders associated with Down syndrome (TAM, ML-DS)

Leukemia in children (<15y)



ALL = acute lymphoblastic leukemia → 70 children/year in Belgium
AML = acute myeloïd leukemia → 10 children/year in Belgium
CML = chronic myeloïd leukemia → 1-2 children/year in Belgium

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Acute myeloid leukemia in children

- Rare disease in children
- Mostly primary/de novo AML
- Very few secondary AML, very few APL
- Genetically different than AML at older age; > fusion-transcript driven

- Collaborative study groups, academic clinical trials for frontline AML treatment
- As good as no “unfit” patients → intensive treatment schedules
- Risk grouping according to genetic aberrations and response to treatment (flow MRD)
- alloHSCT only for HR patients (20%-35%)
- Targeted treatment in frontline? Currently only Flt3 inhibitors and venetoclax in study

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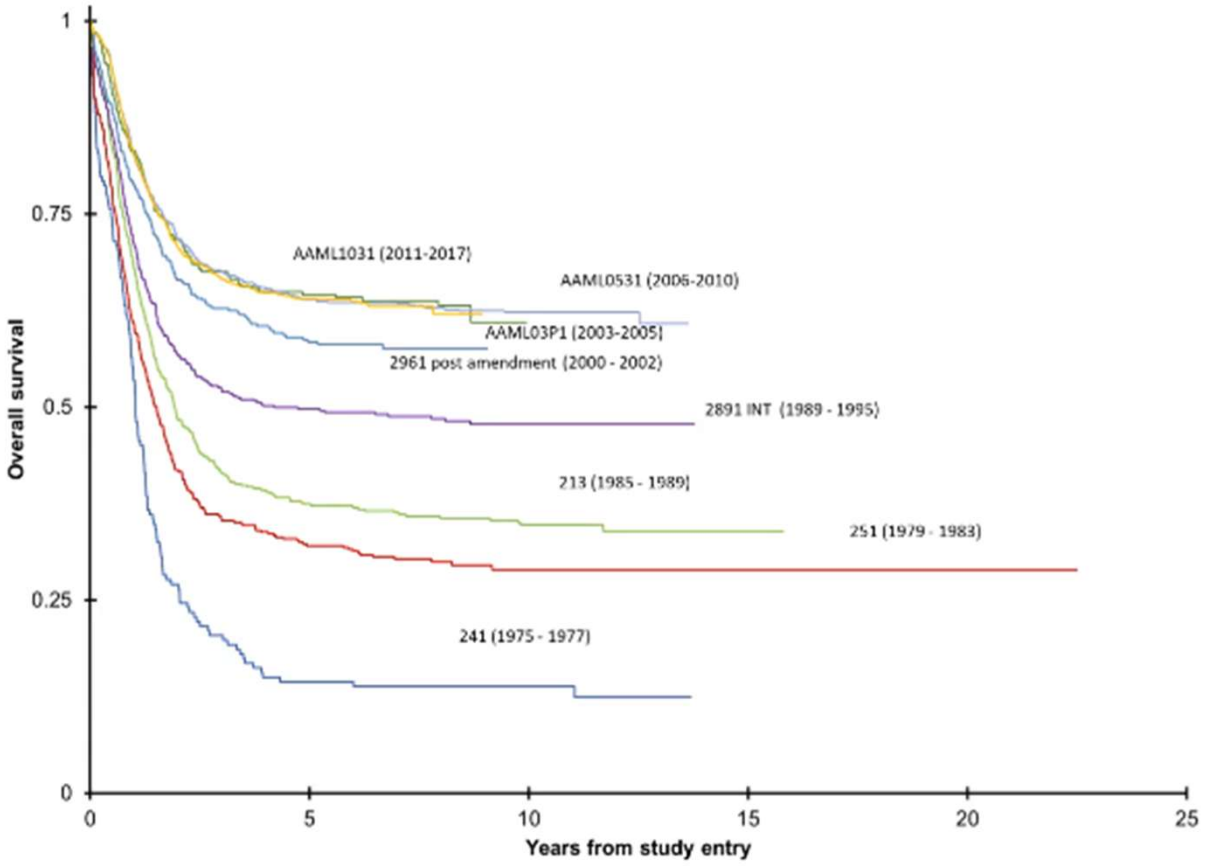
Pediatric AML Trials in North America



Courtesy of Todd Alonzo; Rob Gerbing

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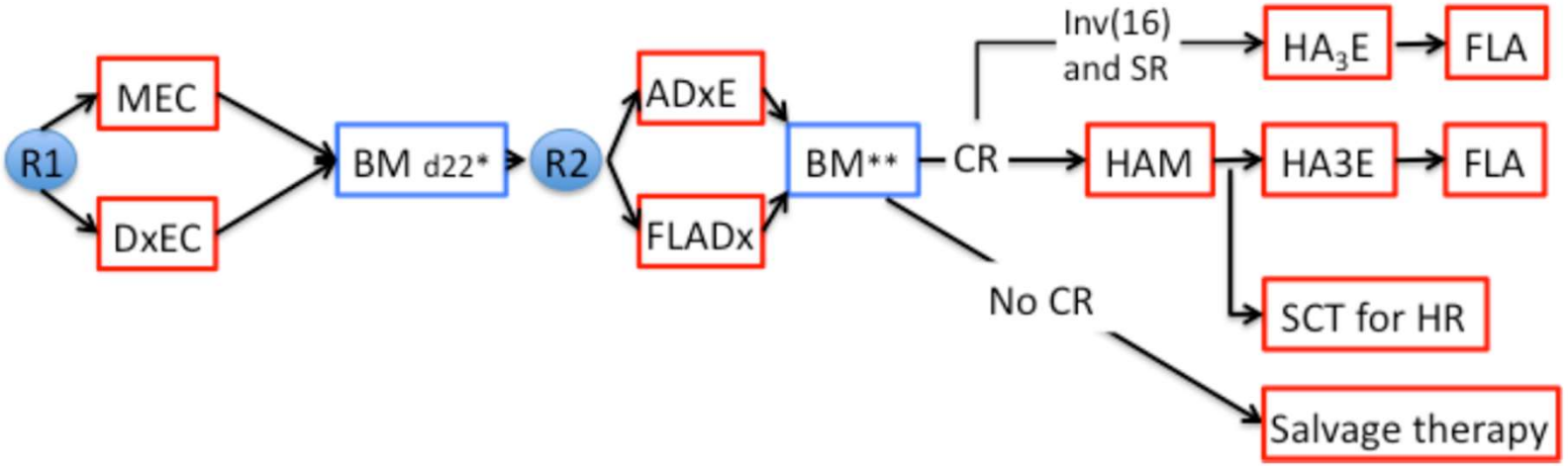
AML treatment by the NOPHO-DB SHIP consortium

NOPHO-DBH AML 2012



High risk definition: (<20%)
MRD ≥15% at any time after course 1
MRD ≥0.1% before consolidation
FLT3-ITD without NPM1

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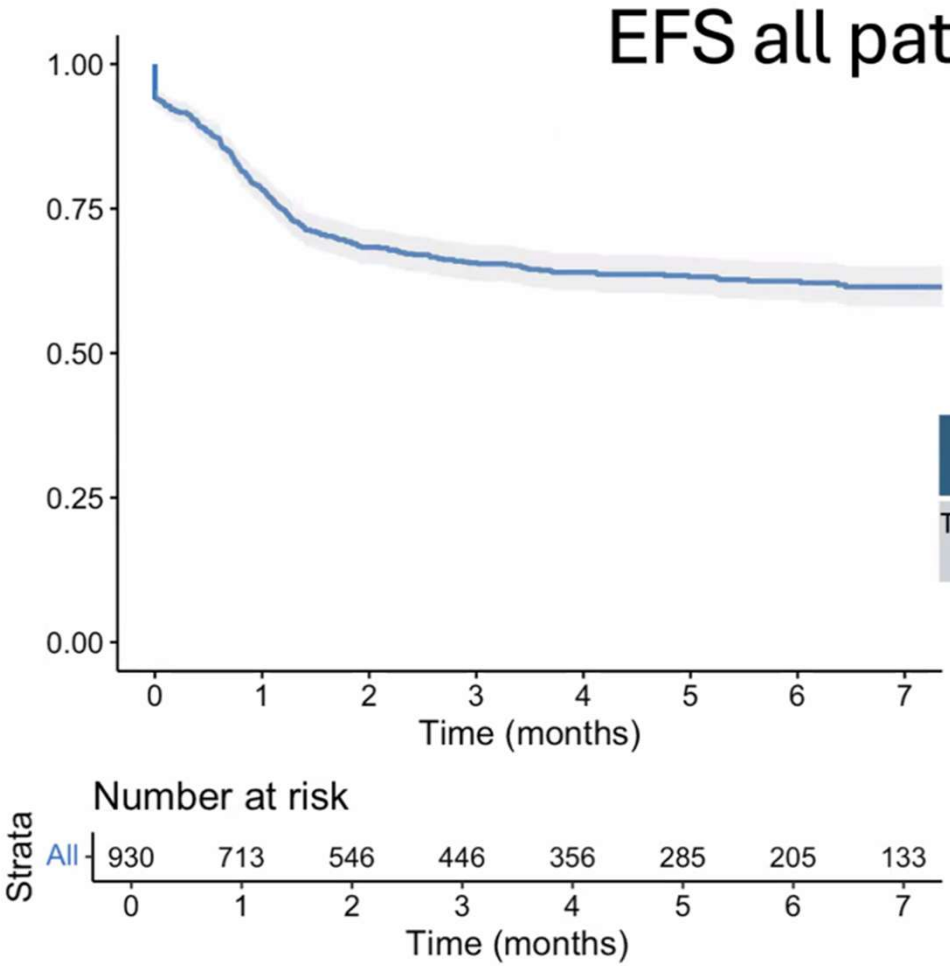
NOPHO DBH AML 2012: EFS



	N (E)	EFS_{2y} (%)	EFS_{3y} (%)	EFS_{5y} (%)	EFS_{7y} (%)
Total	930 (329)	68.3 (65.4-71.4)	65.6 (62.5-68.8)	63.2 (60.0-66.5)	61.4 (58.1-65.0)

Tierens A, J Clin Oncol 2024

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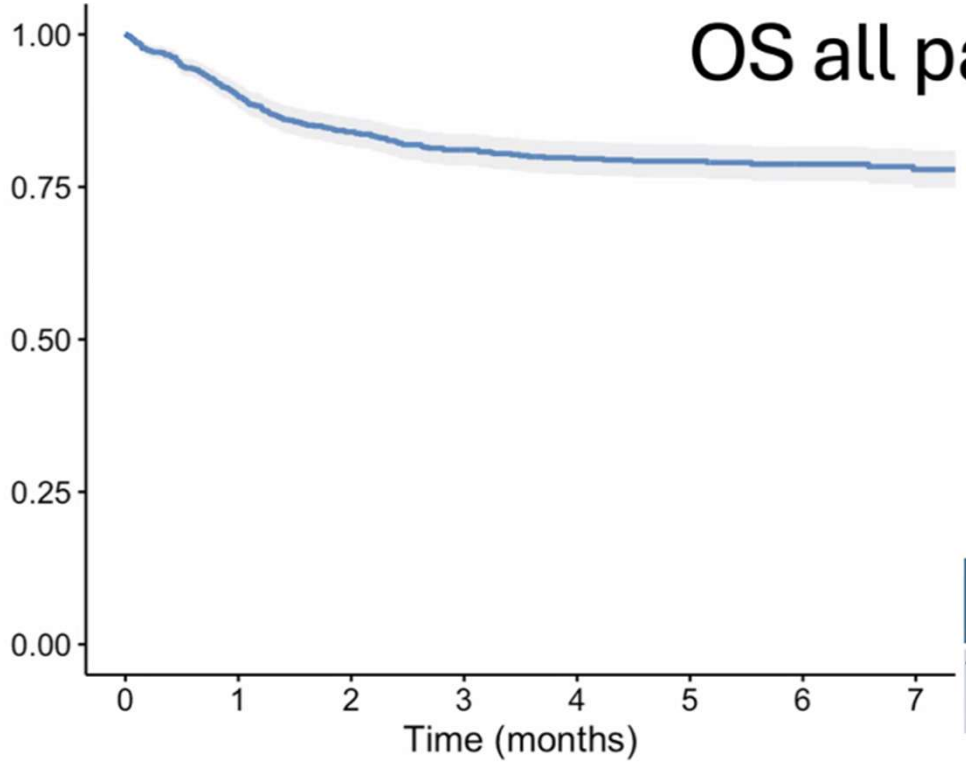
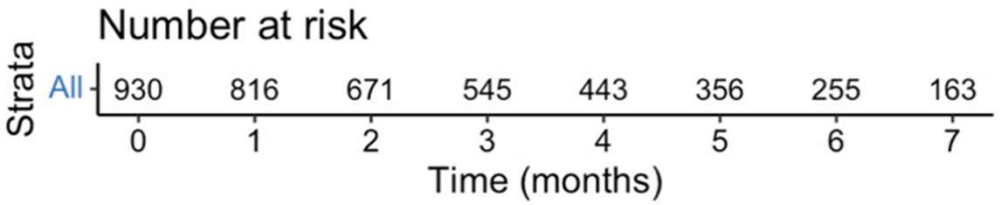
NOPHO DBH AML 2012: OS



	N (E)	OS_{2y} (%)	OS_{3y} (%)	OS_{5y} (%)	OS_{7y} (%)
Total	930 (182)	84.0 (81.7-86.4)	81.1 (78.5-83.7)	79.2 (76.5-82.0)	77.9 (74.9-81.0)



Tierens A, J Clin Oncol 2024

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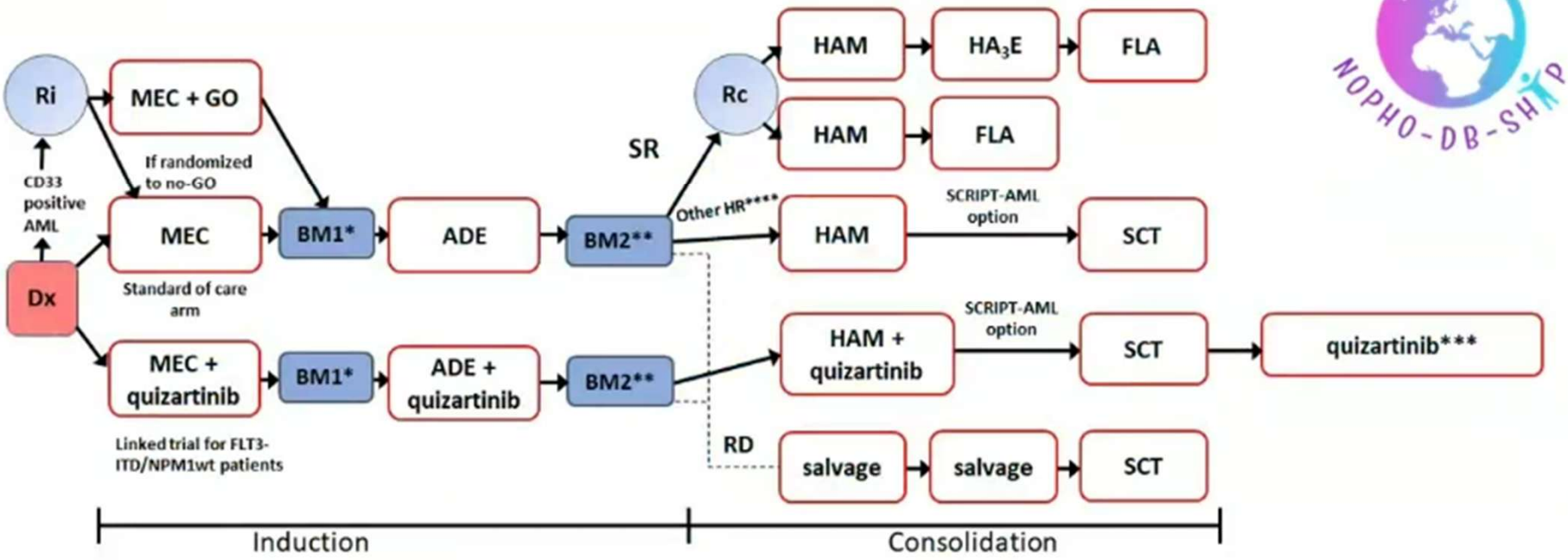
Current frontline AML protocol: CHIP-AML22



- Standard induction treatment is MEC and ADE. Standard consolidation treatment is 3 courses if SR, or the indicated treatment for HR and RD patients.
- *BM1 is done shortly before start of ADE, **BM2 shortly before HAM (salvage chemotherapy if RD)
- A day 22 BM (day 27 for patients in quizartinib trial) from start of course 1 will be done 1) to identify patients with ≥5% leukemic cells, who are eligible for intensified induction (not awaiting bone marrow regeneration), and 2) to identify patients with ≥15% leukemic cells, who will be high-risk. If BM day 22 contains <0.1% LC, repeated BM aspirations are not indicated, unless in case of delayed regeneration >42 days.
- A day 22 BM (day 27 for patients in quizartinib trial) from start of course 2 will be done in case of ≥5% leukemic cells in BM day 22 (or 27) after course 1 or in BM1 and is used 1) to identify patients with ≥5% leukemic cells, which is considered as RD, which should start salvage therapy immediately, and 2) to identify patients with <5% LC that can proceed to BM2 upon regeneration.
- Rc indicates the randomization during consolidation for SR patients.
- HAM (or salvage if RD) can only start once the MRD result of BM2 is known, in those with MRD ≥0.1% in BM1.
- FLT3-ITD/NPM1wt patients in the linked trial willget quizartinib added to all chemo courses, and as continuation treatment post-SCT in selected cases***.
- All other HR patients (see box) will get HAM followed by allo-SCT****.
- Salvage therapy is further explained in chapter 13.

SR (standard-risk):
- No HR/RD characteristics

HR (high-risk)
- ≥15% LC in day 22 BM after course 1
- KMT2A (excl. KMT2A/MLLT3) with ≥0.1% LC after course 1 in BM1
- ≥0.1-5% LC after course 2 in BM2 (EOI)
- All FLT3-ITD/NPM1wt patients
- All patients with RAM-phenotype and/or CBFA2T3-GLIS2

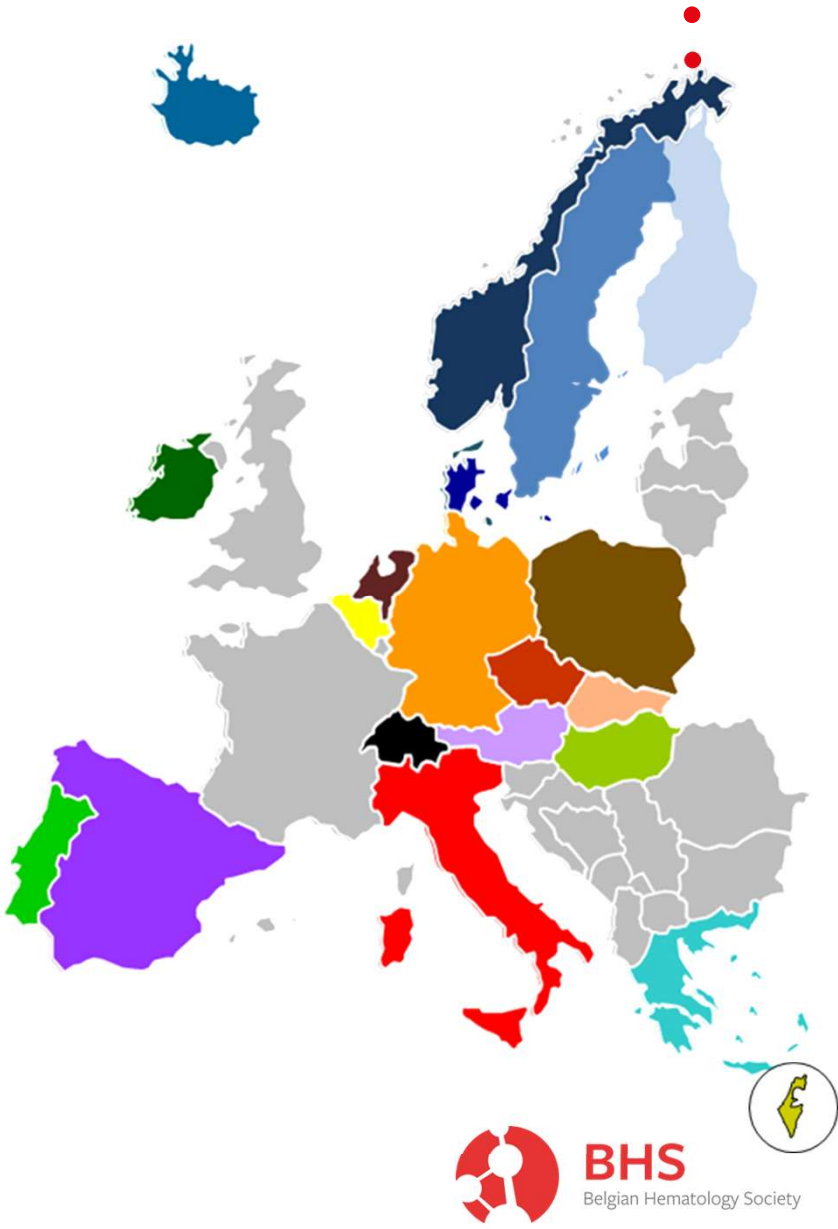
RD (refractory disease):
- ≥5% LC after course 2 in BM2 (EOI)

Future subtrials: + menin inhibitor (Revumenib); + venetoclax

MDS and JMML in children

EWOG-MDS

- National coordinators in 20 countries
  Barbara De Moerloose, UZ Gent
- Reference diagnostic laboratories
  in 20 EU countries
  Pathology lab: St Jan Brugge (Pascale De Paepe)
  Cytology lab: UZ Gent (Mattias Hofmans)
  Cytogenetics lab: UZ Gent (Nadine Van Roy)
- Coordinating study center Freiburg/Ulm, Germany



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Pediatric MDS: a unique disease

	Children (0-18 y)	Adults (older than age 40 y)
Incidence per million	1-4	>40
Refractory anemia with ringed sideroblasts (%)	<1	25
Associated IBMFSs and predisposition syndromes (%)	>30	<5
Familial aggregation	Present in a proportion of patients	Uncommon
General aim of treatment	Curative	Often palliative

Primary > secondary

Secondary > primary

Locatelli F and Strahm B, Blood, 2018

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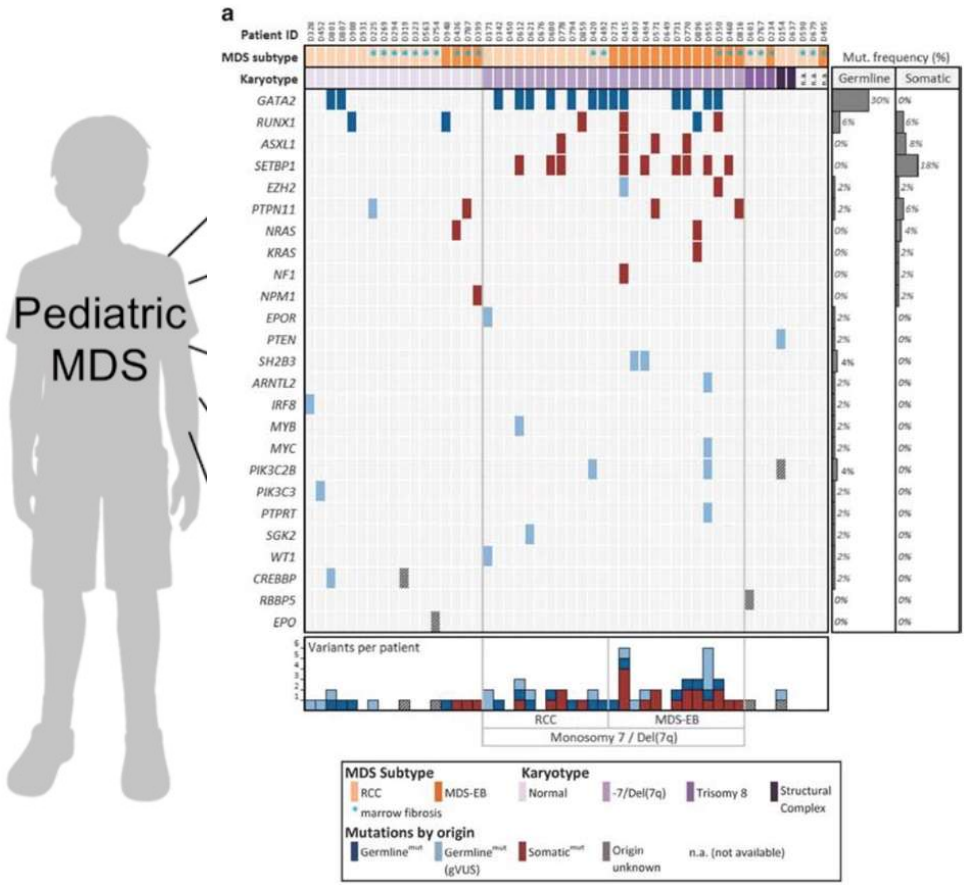
Pediatric MDS: specific genetics



- Genes known to be **commonly mutated in adult** MDS, such as TET2, DNMT3A, TP53 and the spliceosome complex, **are not involved in disease pathogenesis in children**.
- Instead, somatic driver mutations in **SETBP1, ASXL1, RUNX1** and the **RAS oncogenes** define the genomic landscape of the pediatric counterpart.
- This reinforces the notion that **primary pediatric MDS**, as an early onset disease, **requires direct leukemogenic hits.**

Kotmayer L. et al., *Haematologica,* 2025; Pastor V. et al., Haematologica, 2025

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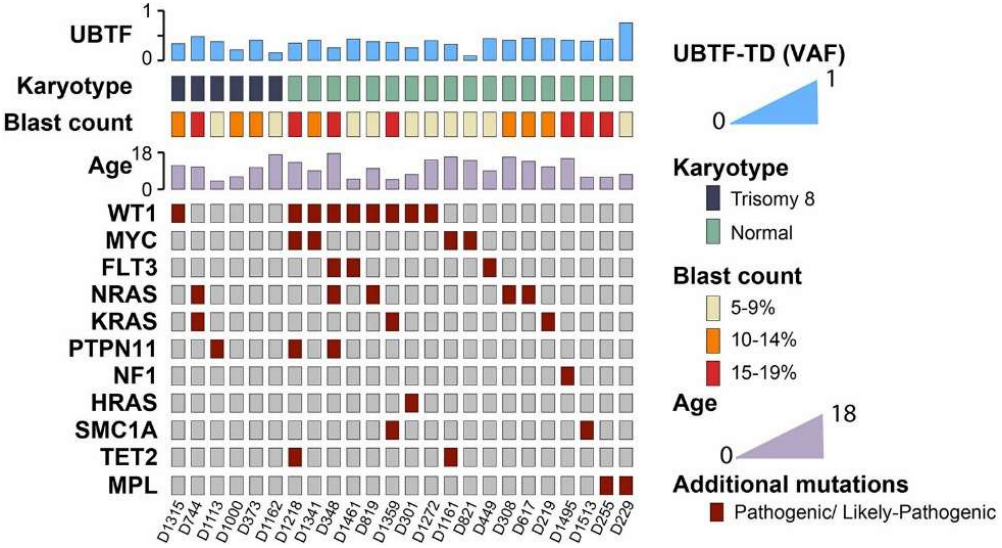
Pediatric MDS: specific genetics

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

UBTF tandem Duplications Account for a Third of Advanced Pediatric MDS without Genetic Predisposition to Myeloid Neoplasia

Miriam Erlacher, Sebastian Stasik, Ayami Yoshimi, Julia-Annabell Georgi, Gudrun Göhring, Martina Rudelius, Irith Baumann, Stephan Schwarz-Furlan, Barbara De Moerloose, Henrik Hasle, Riccardo Masetti, Shlomit Barzilai-Birenboim, Jan Stary, Marcin W. Wlodarski, Natalia Rotari, Senthilkumar Ramamoorthy, Dirk Lebrecht, Peter Noellke, Brigitte Strahm, Charlotte M. Niemeyer, Christian Thiede

- UBTF-TDs were detected in 25 of the 104 pts (24%; 16 males/9 females)
- None of the pts with predisposition harbored a UBTF-TD



NPM1

P6 - NPM1 MUTATIONS IN CHILDREN WITH MYELODYSPLASTIC SYNDROME WITH EXCESS BLASTS

Ayami Yoshimi [1] · Miriam Erlacher [1] · Peter Noellke [1] · Senthilkumar Ramamoorthy [1] · Gudrun Göhring [2] · Shlomit Barzilai – Birenboim [3] · Ivana Bodova [4] · Jochen Buechner [5] · Albert Catala [6] · Valérie De Haas [7] · Barbara De Moerloose [8] · Michael Dworzak [9] · Henrik Hasle [10] · Kirsi Jahnukainen [11] · Krisztian Kallay [12] · Marko Kavcic [13] · Paula Kjollerstrom [14] · Franco Locatelli [15] · Riccardo Masetti [16] · Sophia Polychronopoulou [17] · Markus Schmugge [18] · Owen Smith [19] · Jan Stary [20] · Dominik Turkiewicz [21] · Marek Ussowicz [22] · Natalia Rotari [1] · Marcin Wlodarski [23] · Brigitte Strahm [1] · Charlotte Niemeyer [1] Show less

- NPM1 mutation was identified in 14 of 235 patients with material for genetic testing available (6%, M/F=7/7, median age 12.7 years).
- All but one patient (45, X,-Y) had a normal karyotype.
- All patients had 1-3 additional somatic mutations including PTPN11 (36%), NRAS (43%) and WT1 (21%), but no UBTF-TD or FLT3-ITD.

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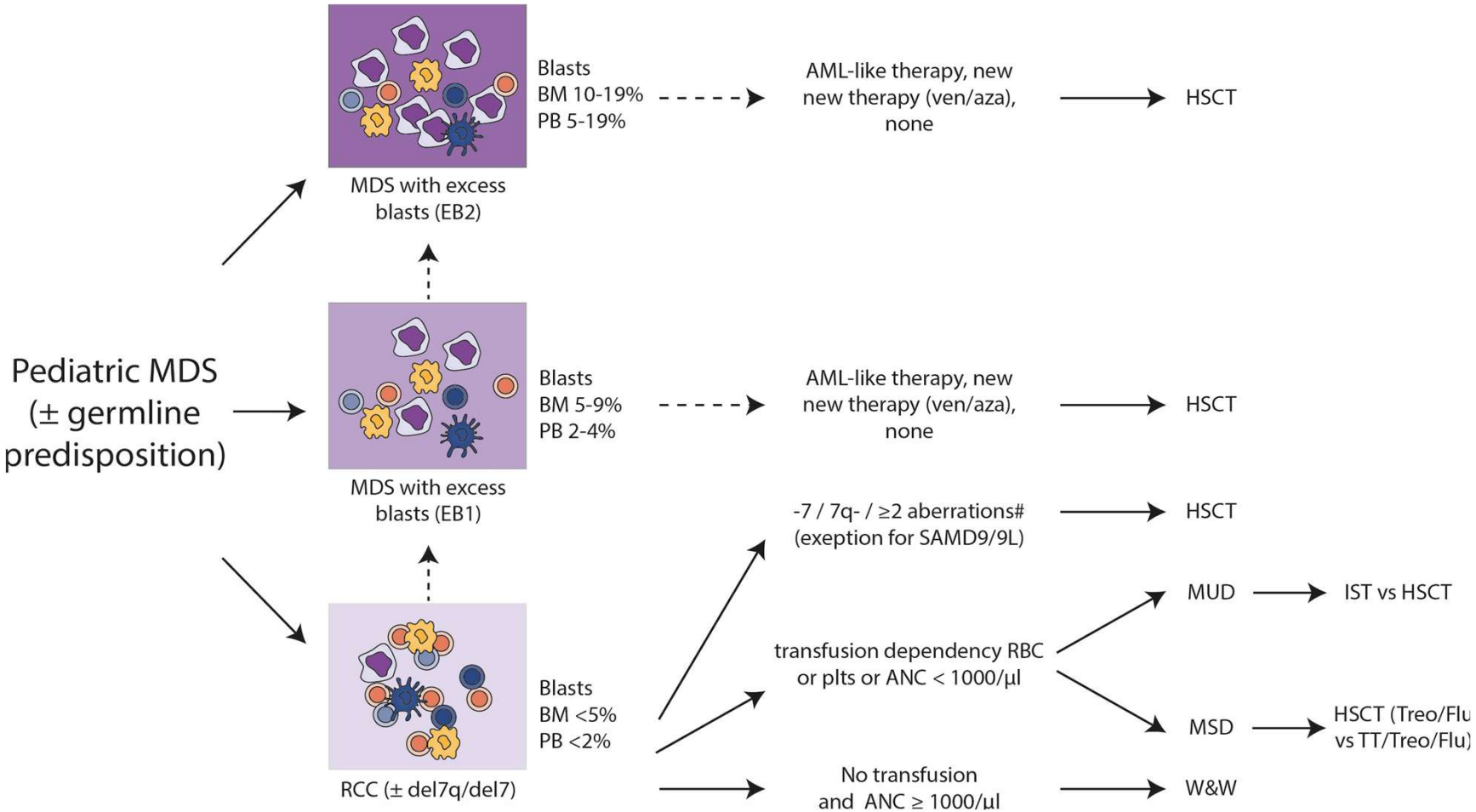
Pediatric MDS types: RCC and MDS-EB (MDS-IB)



Locatelli F, Strahm B. Blood. 2018 Mar 29;131(13):1406-1414.

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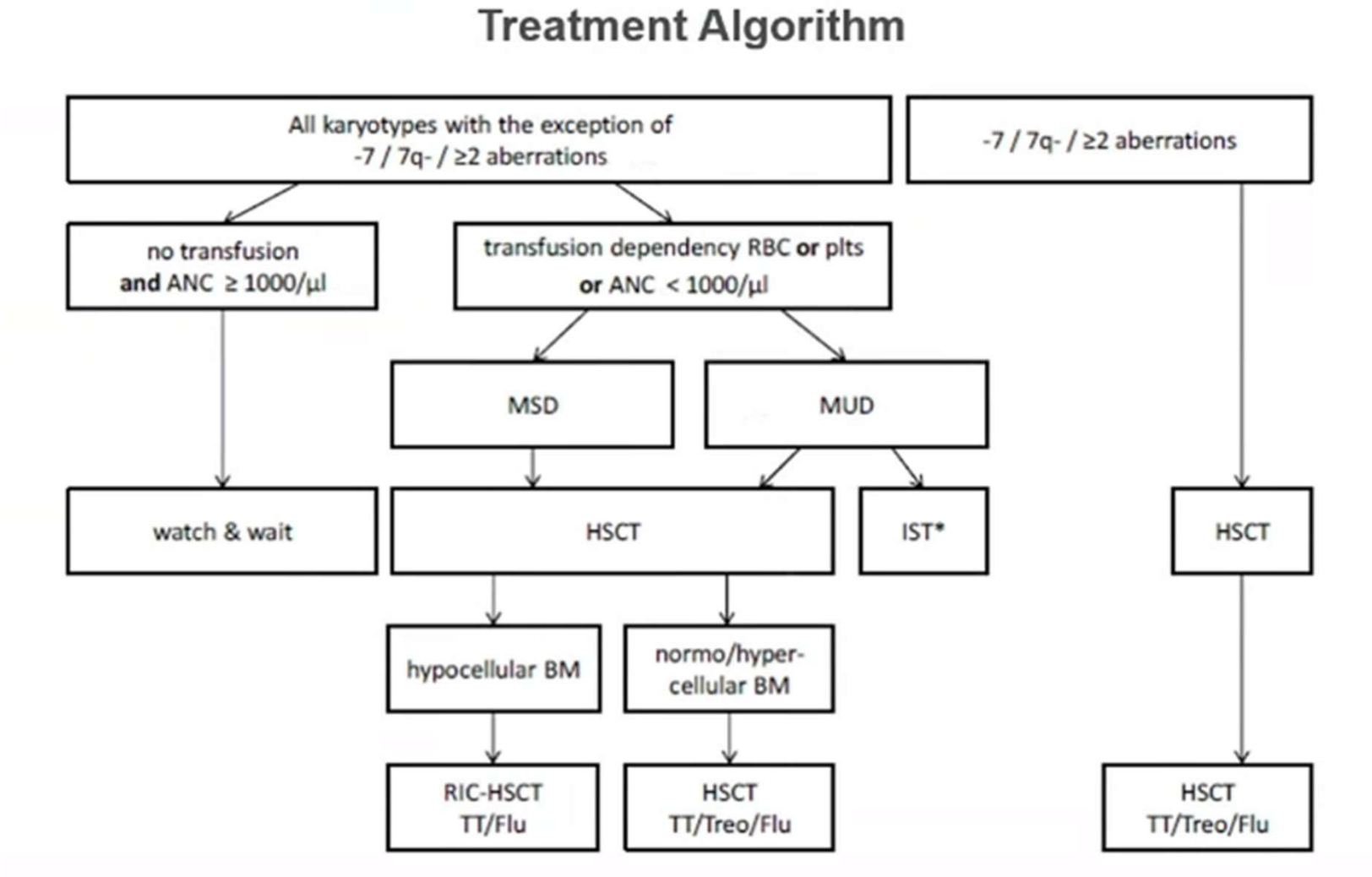
Refractory cytopenia of childhood (RCC)



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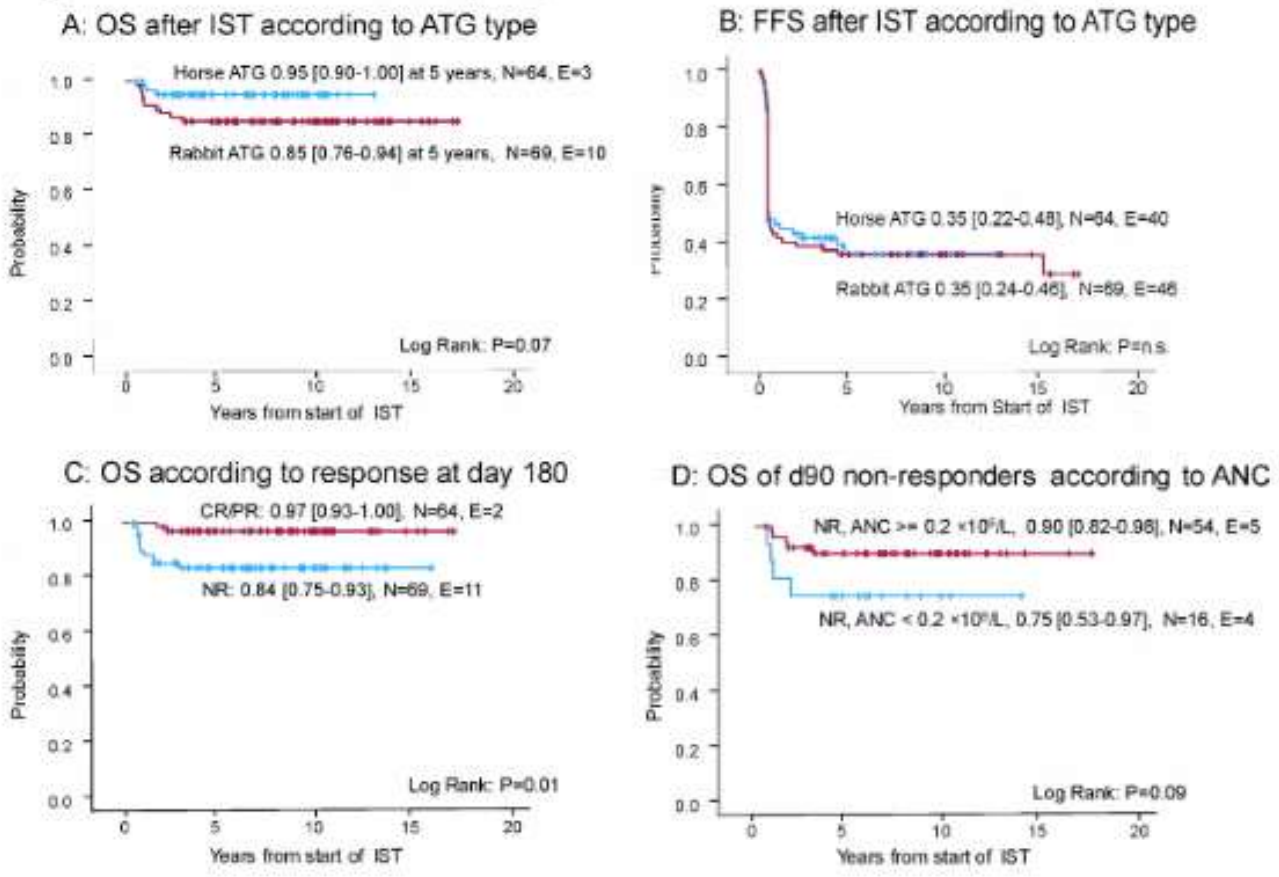
Refractory cytopenia of childhood (RCC)

Figure 2 Overall survival (OS) and failure-free survival (FFS)



C: NR include patients who received HSCT and second IST before day 180. D: Among 70 non-responders at day 90, patients with ANC of < 0.2 ×10^9/L had a worse survival compared to those with an ANC of >= 0.2 ×10^9/L

IST =

Cyclosporin A

hATG versus rATG

Methylprednisolone

(+ G-CSF in case of neutropenia)

Yousef M, EWOG symposium 2025

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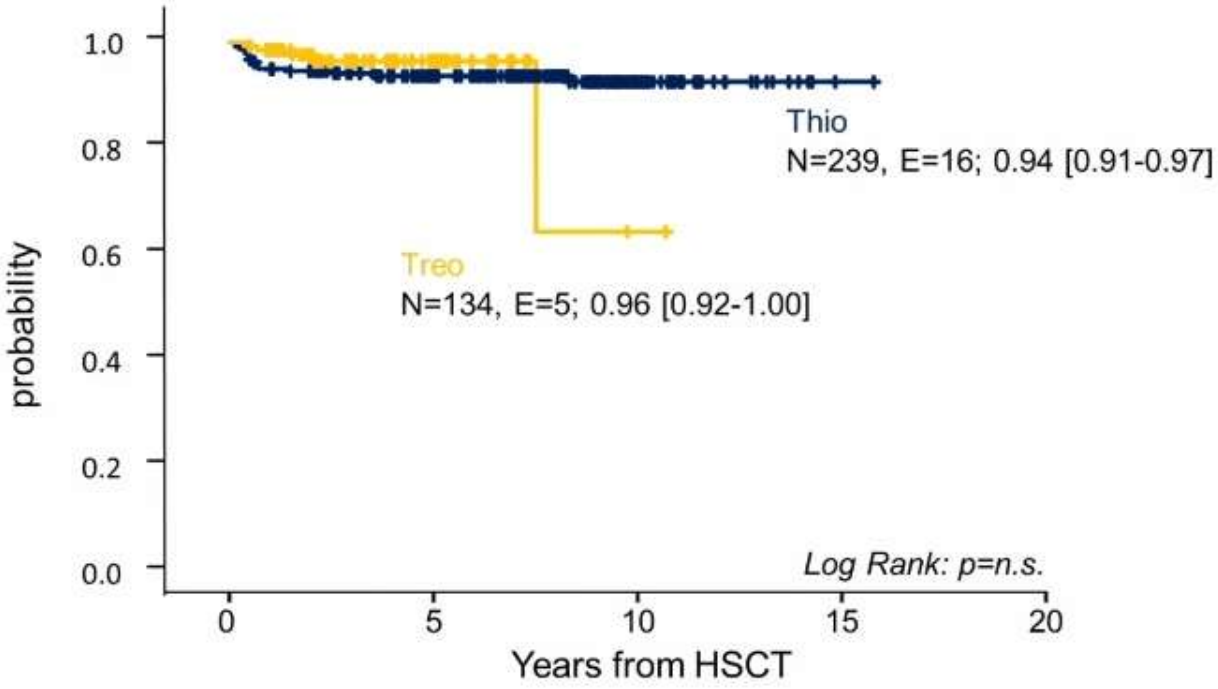
HSCT in RCC results in an excellent Overall Survival



HSCT:

TT Flu versus Treo TT Flu

Follow Up 5.7 (0.5-15.9) yrs

Strahm B et al, EWOG symp 2025, submitted

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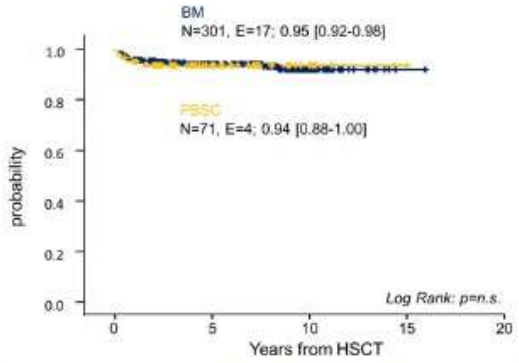
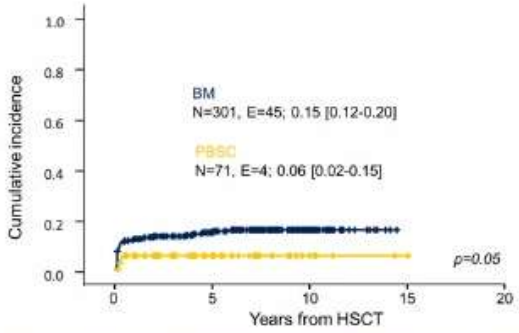
Refractory cytopenia of childhood (RCC)

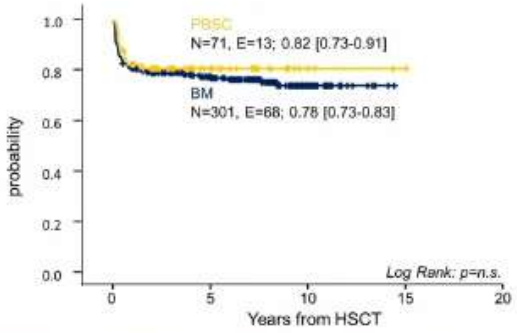
5-yrs OS according to stem cell source



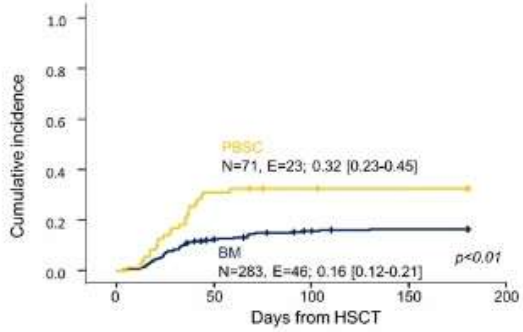
5-yrs GF according to stem cell source



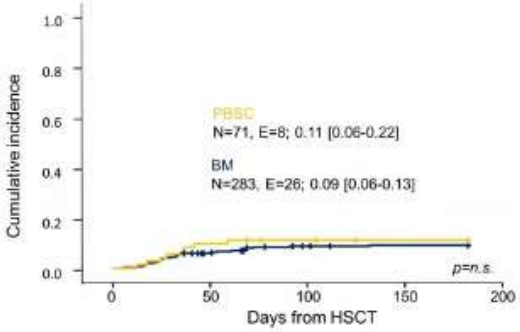
5-yrs cGRFS according to stem cell source



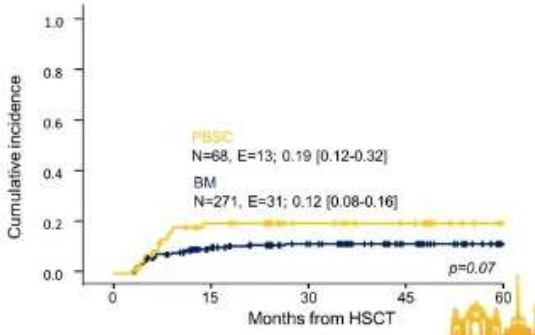
Acute GvHD II-IV according to stem cell source



Acute GvHD III-IV according to stem cell source



Chronic GvHD according to stem cell source



Treo TT Flu

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Summary and Conclusions

- ✓ In patients with RCC HSCT following reduced intensity/toxicity regimens result in excellent overall survival
- ✓ Conditioning with Thiotepa/Fludarabine resulted in a higher incidence of GF, acute and chronic GvHD and inferior cGRFS
- ✓ Conditioning with Treo/Flu was associated with a higher rate of viral infections (ADV/EBV)
- ✓ The addition of serotherapy had no impact on the outcome of MSD-HSCT
- ✓ High dose ATG (60 mg/kg Grafalon) was associated with a higher incidence of GF and chronic GvHD resulting in a lower OS and cGRFS
- ✓ The increasing use of letermovir and the pTCy platform for MM donors will have an impact on the results
- ✓ This is a unique cohort to study the late effects of conditioning regimens

MDS-EB

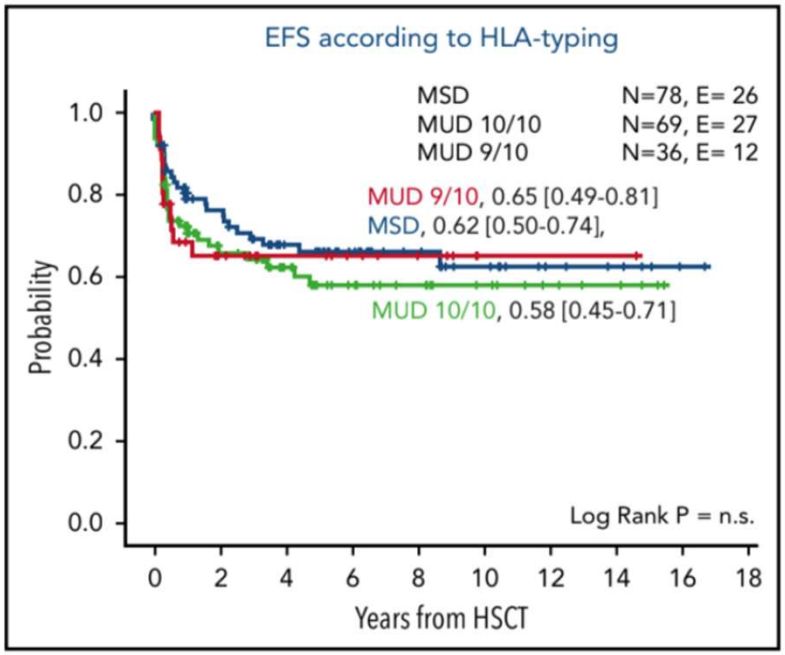

Figure 3. Outcome of patients with advanced MDS given allogeneic HSCT. Probability of EFS according to the type of donor (HLA-identical sibling, 10/10 allelic matched and 9/10 allelic matched unrelated volunteer) used in patients with MDS-EB given an allograft after a myeloablative conditioning regimen that included busulfan, cyclophosphamide, and melphalan. Data from the EWOG-MDS registry. E, events observed; N, number of patients at risk; n.s., not significant.

Pediatric advanced MDS remains a challenging disease with a 5-year OS probability of nearly 65% and with:

- TRM and disease recurrence contributing equally to treatment failure
- Intensive chemotherapy in MDS-EB (not tested in a systematic way) cannot be routinely recommended
- No innovation in cytoreductive regimens
- Inadequate first-line therapies (pre and post HSCT)

- Venetoclax-Azacytidine ?
- Menin inhibitors?
- Other targeted treatment?

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Locatelli F, Strahm B. Blood. 2018 Mar 29;131(13):1406-1414.

Lack of efficacy of AZA in pre-SCT

Patient	Sex, M/F	Age, years[a]	At C1 D1 Karyotype	Germline mutation	WBC, ×G/L	PB blast (smear), %[b]	Platelets, ×G/L	BM blast (smear), %[b]	Clinical response to azacitidine at C3 D28	HSCT, yes/no	Status, alive/dead from HSCT, years
1	M	13.2	Normal[c]	None	4.5	16	26 Tx	23	PD	Yes	Alive, +5.5 years
2	M	14.1	Complex[d]	None	3.4	6[e]	90 Tx	10[e]	–[f]	Yes	Dead (relapse), 0.9 years
3	F	15.3	Normal	None	7.9	6	55 Tx	19	PD	Yes	Dead (relapse), 0.3 years
4	F	13.1	Normal	*GATA2*	1.7	0	69	9	mCR[g]	Yes	Alive, +7.0 years
5	F	6.6	–7		2.9	0	112	11	PD	Yes	Dead (relapse), 2.3 years
6	F	15.9	Normal	*GATA2*	0.8	0	144	5	–[f]	Yes	Alive, +5.5 years
7	M	13.4	Normal	None	9.2	0	8 Tx	6	PD	Yes	Alive, +6.0 years
8	M	1.9	Other[h]	None	5.4	2	36 Tx	18	PD	Yes	Alive, +5.5 years
9	M	13.3	Normal[c]	None	2.1	1	18 Tx	20	SD	Yes	Alive, +2.9 years
10	M	4.8	–7	*SAMD9L*	5.7	0	24 Tx	5[e]	–[f]	Yes	Alive, +7.0 years

At Cycle 3 Day 28, no response was confirmed in any patient based on central review (95% CI: 0.0–30.8); one patient achieved an unconfirmed marrow CR (Table 1). As less than two patients achieved confirmed CR, PR, or marrow CR at Cycle 3 Day 28, the study was closed after completion of stage 1.

The **lack of efficacy of azacitidine in pediatric patients with advanced MDS** in this study suggests that there remains an unmet need for new treatments in this patient population.

Locatelli F, et al Pediatr Blood Cancer. 2024

Venetoclax in pre-SCT

- Study from centers in Italy and Germany

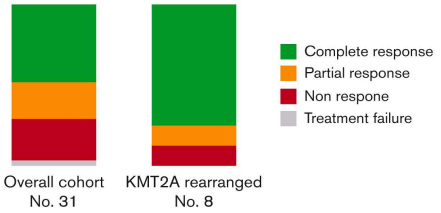
Table 1. Patient characteristics

Patients (n = 31)	n (% or range)
Sex	
Male	18 (58.1)
Female	13 (41.9)
Diagnosis	
Advanced MDS	4 (23.5)
Relapsed AML	11 (35.5)
Refractory AML	7 (22.6)
Postcytotoxic therapy MDS/AML	9 (29.0)
Age, y, median (range)	10.2 (1.3-17.4)
Best response achieved	
CR*	16 (51.6)
PR	6 (19.4)
ORR	22 (71.0)
NR	8 (25.8)
TF	1 (3.2)
No. of cycles to best response (in 22 responders), median, range	1 (1-7)

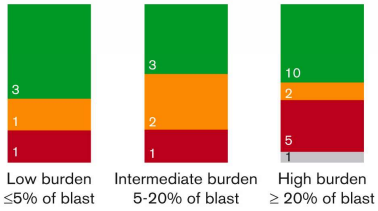
Masetti et al, Blood Advances 2024

- Mixed cohorts of children with various diagnoses
  - MDS-EB/Advanced MDS (24%)
  - VEN/HMA (n=19; 61%)

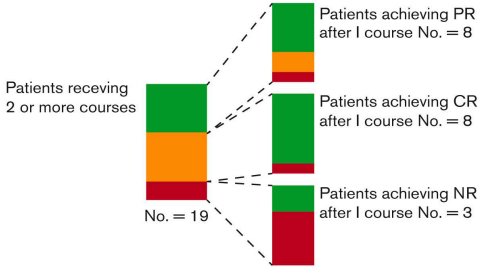
Best response to venetoclax combination



Best response to venetoclax combination by disease burden

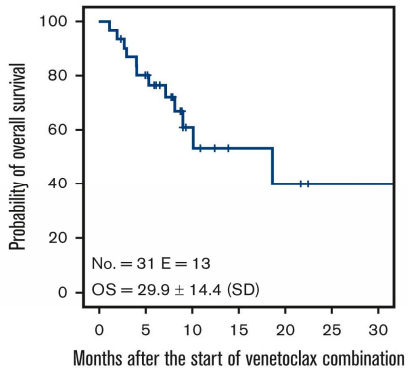


Response after II courses of venetoclax

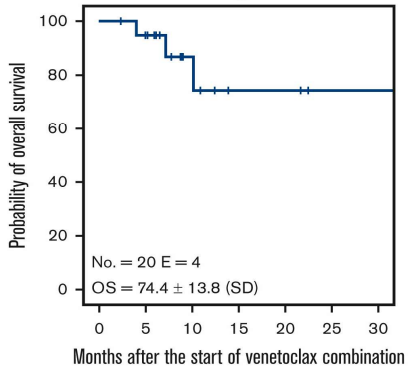


Overall survival after venetoclax combination

Overall cohort

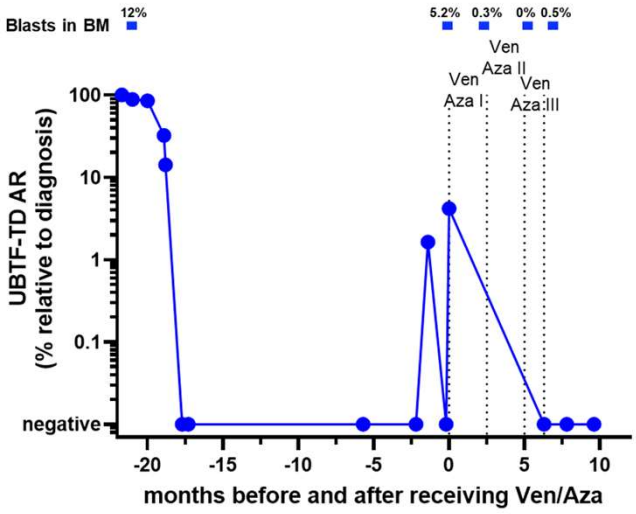


Patients bridged to HSCT

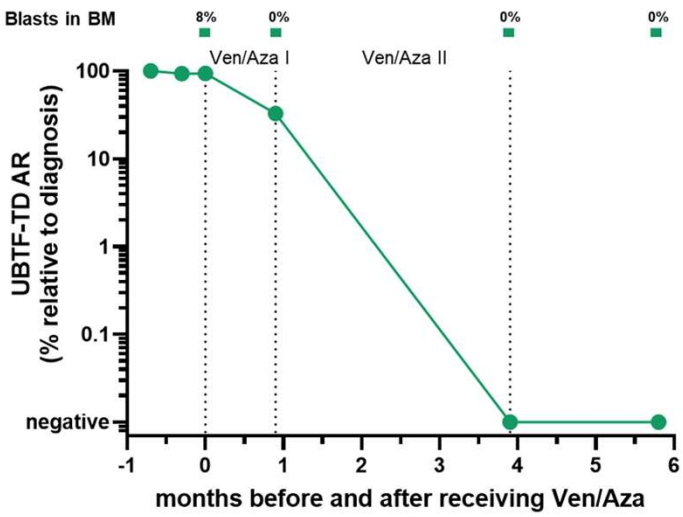


UBTF-TD AdvMDS response to VEN-AZA

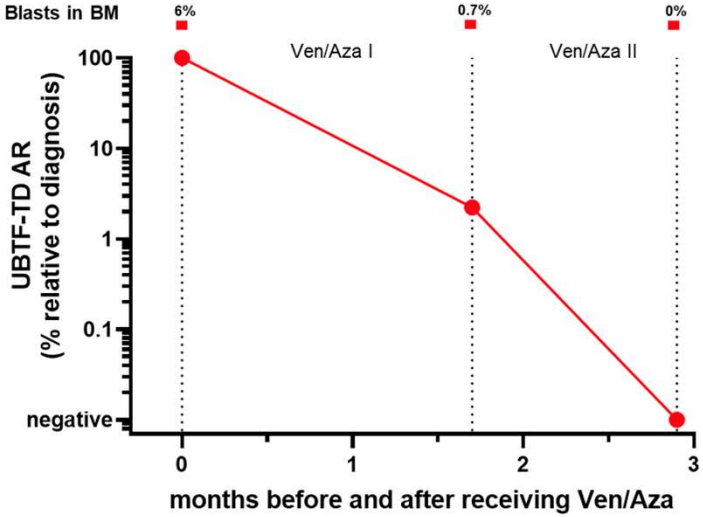
Case 1



Case 2



Case 3



UBTF-TD allelic ratio (AR) reduction (as percentage relative to diagnosis) is represented over time. The reduction is consistent with bone marrow (BM) flow cytometry evaluation reported onvtop of every graph.

Merli P, Masetti R, Baccelli F et al Am J Hematol. 2025

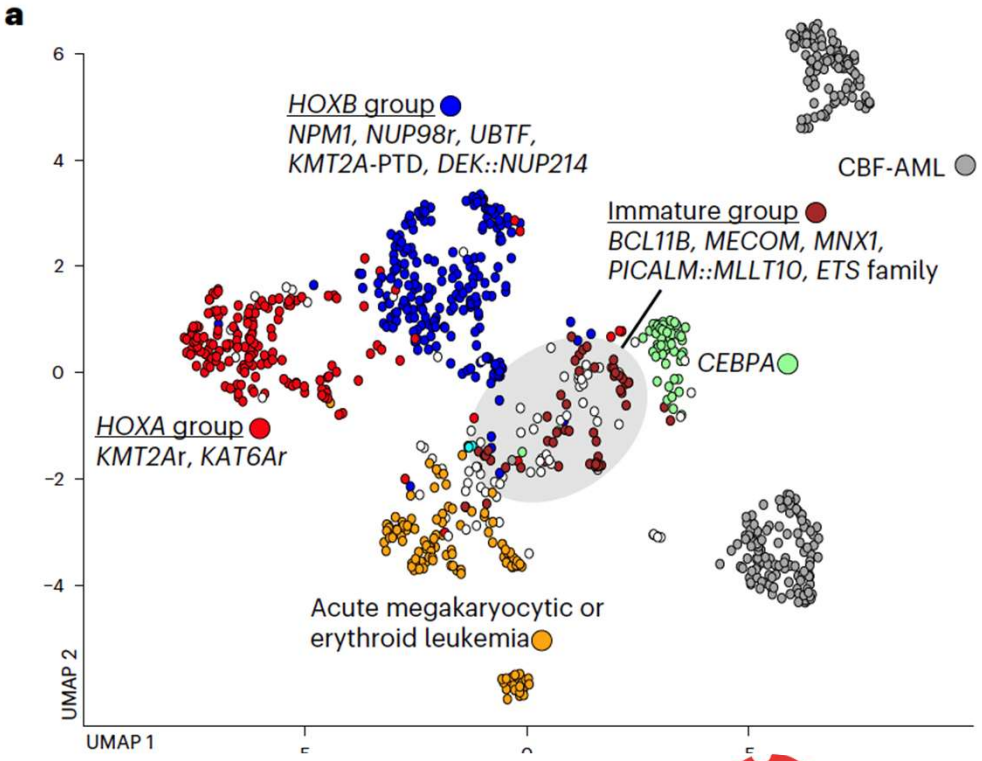
Venetoclax/menin susceptibility by specific subgroups

The cluster **characterized by high expression HOXB genes** included NPM1, NUP98r, UBTF, KMT2A-PTD and DEK::NUP214 (HOXB group), which are generally associated with poor prognosis except for NPM1 and could be susceptible to both VEN and Menin-based regimen

Table 2 Genetic alterations with overexpression of *HOXA* genes predicted to potentially respond to menin inhibitors.

Alteration/mutation	Cytogenetics	Phenotype				References
KMT2Ar	11q23 rearrangements	AML, ALL, MPAL	✓	✓	✓	[26, 132, 133]
KMT2A-PTD	Normal karyotype	AML	✓	✓		[26, 134]
NPM1c	Normal karyotype	AML	✓	✓	✓	[26, 135]
NPM1-MLF1	t(3;5)(q25;q34)	MDS, AML	✓			[136, 137]
NUP98r	11p15 rearrangements	AML, T-ALL, MDS	✓	✓	✓	[122–124]
SET-NUP214	t(9;9)(q34;q34)	AML, T-ALL, AUL	✓		✓	[138]
RUNX1-EVI1	t(3;21)(q26;q22)	AML	✓		✓	[139]
MYST3-CREBBP	t(8;16)(p11;p13)	AML	✓			[140]
CDX2-ETV6	t(12;13)(p13;q12)	AML		✓		[141]
CALM-AF10	t(10;11)(p13;q14-21)	T-ALL, AML, MPAL	✓	✓	✓	[142–144]
MN1-ETV6	t(12;22)(p13;q12)	AML, MDS		✓	✓	[145]
EZH2	–	MDS, AML	✓			[146]
IDH1/IDH2	–	MNs			✓	[147, 148]
ASXL1	–	MNs		✓		[149]
CEBPA	–	AML			✓	[150]
	Trisomy 8	MNs	✓			[151]

Denotes direct examination of patient samples with the corresponding genotype showing upregulation of *HOXA* genes.
Denotes mouse models of the corresponding genotype leading to upregulation of *Hox* genes.
Denotes examination of cells lines or other in vitro investigations demonstration a role of *HOX* genes or menin inhibition in the corresponding genotype.



Huls et al, Blood 2024

Humeda Nat.Genetics 2024

BHS Belgian Hematology Society

Treatment beyond classification

One possible option could be to move beyond the nosological categories of current classifications based on blast percentage and instead **start grouping patients who may be potentially sensitive to targeted therapy according to their biological profile.**

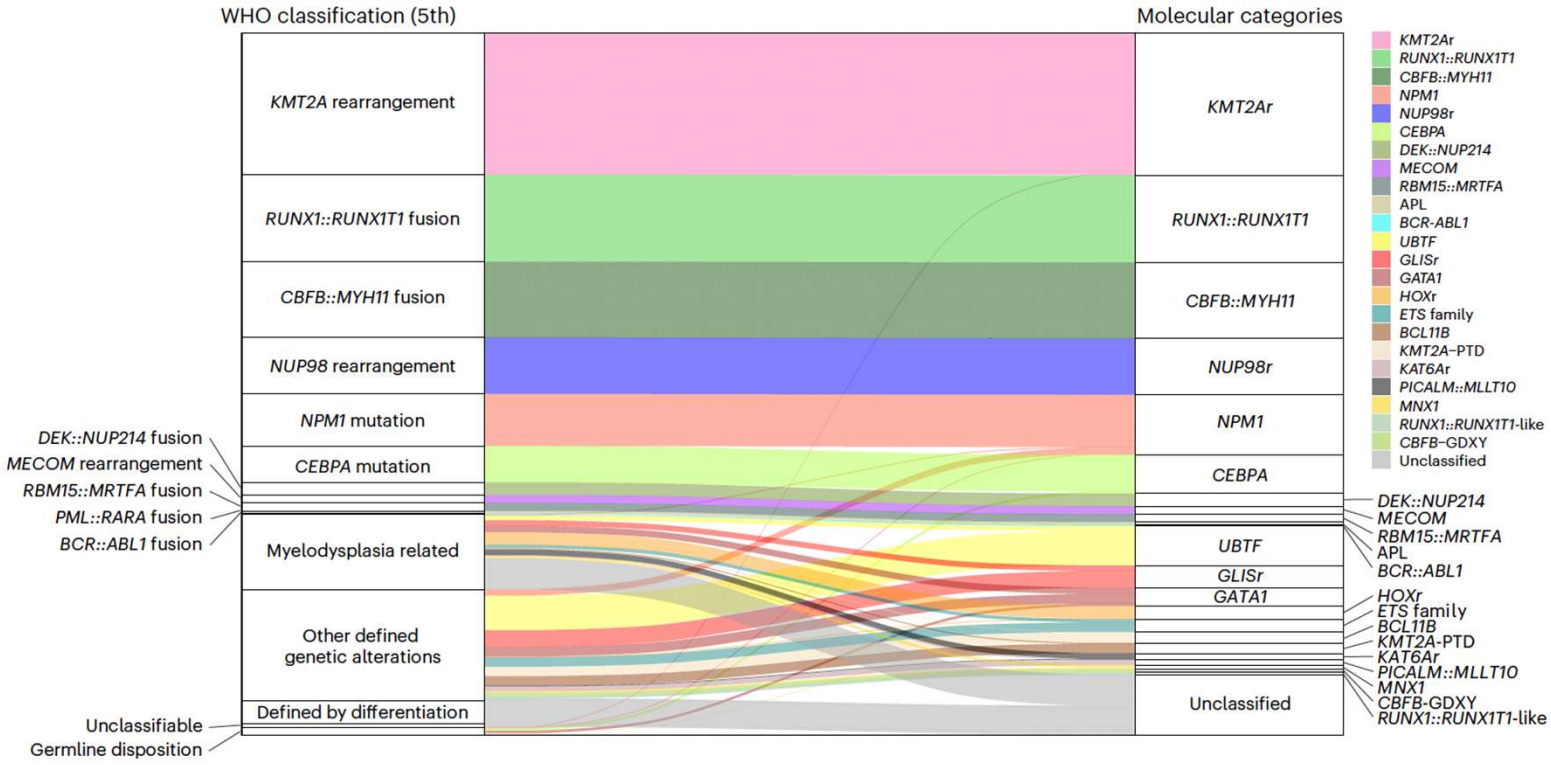
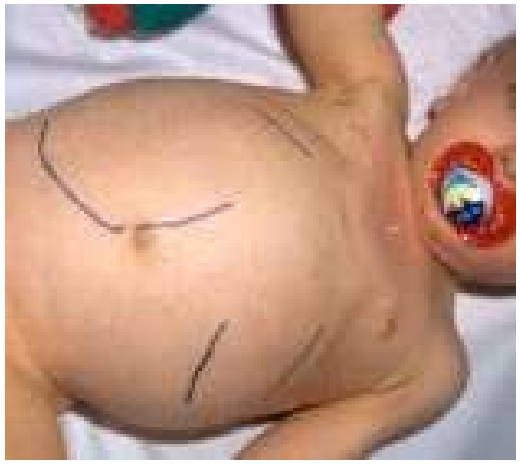


Fig. 3 | Comparison between molecular categories and the WHO classification. The colors of the ribbon plot represent molecular categories of samples in the pAML cohort ($n = 887$).

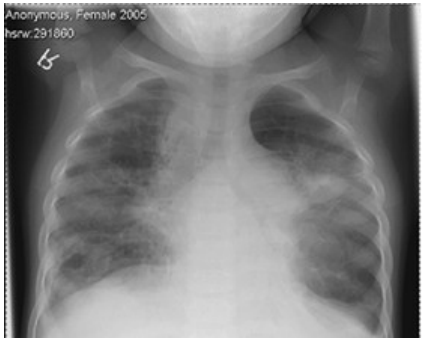
Humeda Nat.Genetics 2024

JMML: The clinical and hematological presentation of JMML

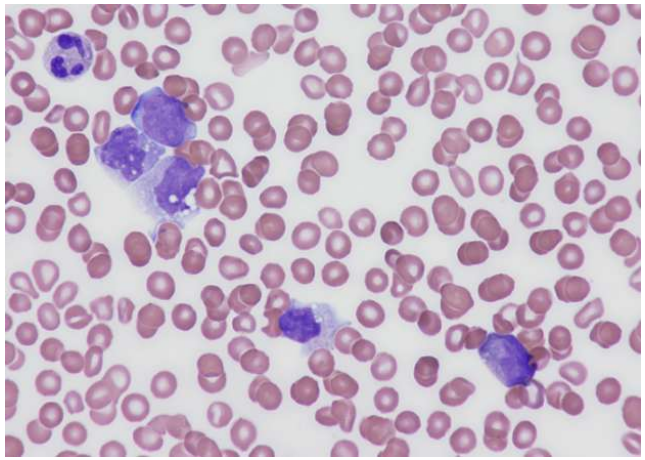
Clinical picture



Median age	1.9 years
Splenomegaly	97%
Cough	40%



PB indicative / BM compatible with Dx



WBC (median)	33 x 10^9/L
Monocytes > 1 G/L	93% of patients
Platelets (median)	54 x 10^9/L
Precursors in PB	90 % of patients

Karyotype	Patients (%)
Normal	65
Monosomy 7	25
Other Abnormalities	10

Autoimmunity

Autoimmunity	Patients (%)
IgG, IgM or IgA	65
Antinucl. antibodies	22
Antiglobin test pos.	14

Niemeyer et al. Blood 89: 3534, 1997

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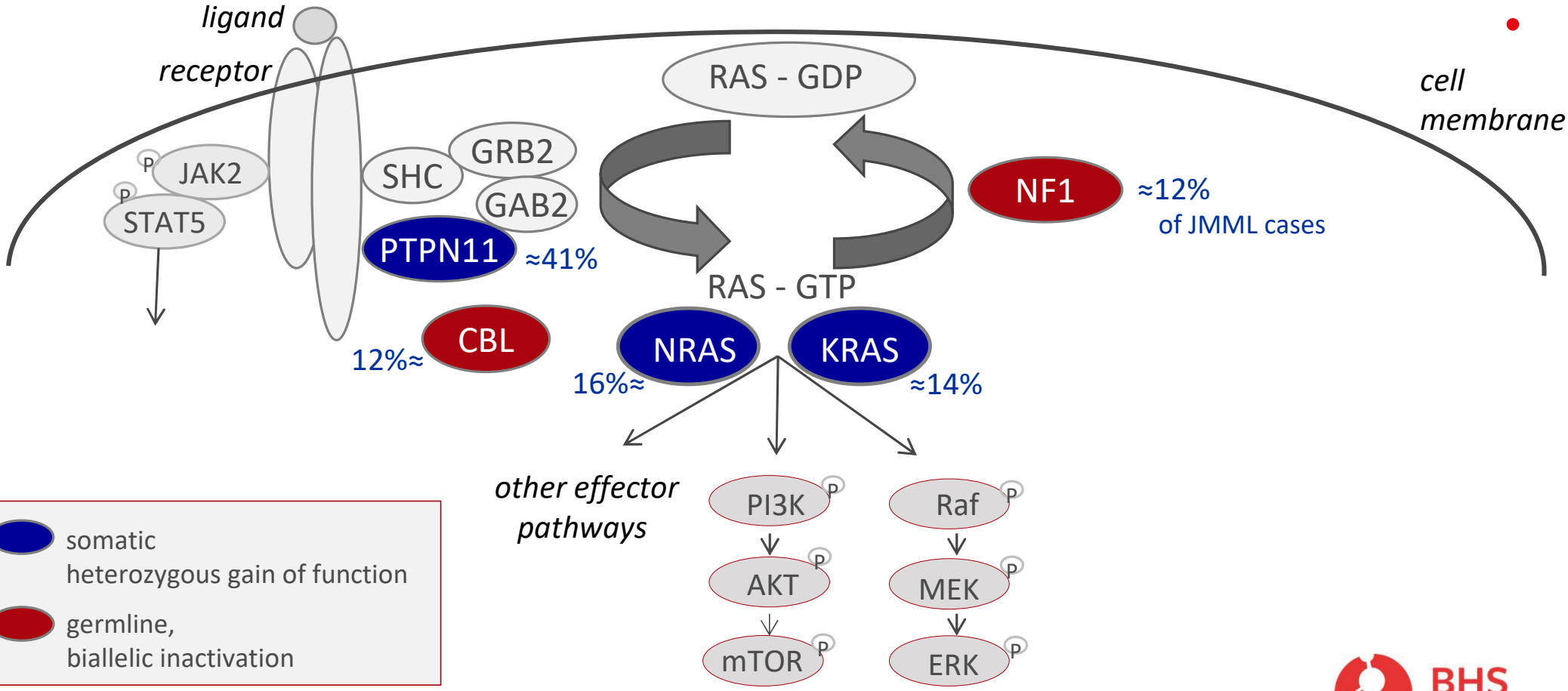
The dogma: JMML is a RAS driven neoplasia with 5 major genetic subtypes



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The International Consensus Classification (ICC) of JMML

Juvenile myelomonocytic leukemia (JMML), JMML-like neoplasms and Noonan syndrome-associated myeloproliferative disorder

	PB/BM blasts	Mutation	Secondary mutations	Karyotype
JMML	<20% PB <20% BM	*PTPN11*, *NRAS*, *KRAS*, *RRAS*, *NF1**, *CBL***	Any	Any (monosomy 7 in 25%)
JMML-like neoplasms	<20% PB <20% BM	Absence of RAS-pathway mutation	Any	Any
Noonan syndrome–associated myeloproliferative disorder	<20% PB <20% BM	*PTPN11****, *NRAS****, *KRAS**** *RIT1****	None	Normal#

*Germline mutation with additional aberration resulting in biallelic inactivation of the *NF1* gene

**Germline mutation with additional aberration resulting in biallelic inactivation of the *CBL* gene; some cases with heterozygous germ line mutation only

***Germline mutation, patients generally display syndromic features of Noonan syndrome

#In rare instances monosomy 7 can develop[122, 123]

Rudelius et al. Virchows Archiv (2023)

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The International Consensus Classification (ICC) of JMML

Diagnostic criteria for juvenile myelomonocytic leukemia

I. Clinical and hematologic criteria (the first 2 criteria are present in most cases; the last 2 are required)

- Peripheral blood monocyte count ≥ 1 × 10^9/L*
- Splenomegaly†
- Blast percentage in peripheral blood and bone marrow < 20%
- No BCR::ABL1 fusion

II. Genetic criteria (1 criterion required)

- Somatic mutation in PTPN11‡ or KRAS‡ or NRAS‡ or RRAS‡
- Clinical diagnosis of neurofibromatosis type 1 or germline NF1 mutation and biallelic inactivation of NF1°
- Germline CBL mutation and loss of heterozygosity of CBL§
- Germline or somatic mutations in RRAS2

* In 7% of cases monocyte count is less than 1 × 10^9/L.

† Splenomegaly is absent in 3% of cases at initial diagnosis.

‡ Germline mutations need to be excluded.

° Rare cases of somatic biallelic NF1 mutations cannot be excluded.

§ Occasional heterozygous splice site mutations are observed.

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Risk factors for survival / relapse after HSCT in JMML are highly dependent parameters

		Higher risk
Clinical	Age	≥ 2 years
	HbF	≥ 15% (age < 6 months: low risk patients)
Genetic	Subclonal mutations	≥ 1 subclone (*SETBP1*, *JAK3*, double *RAS,* others)
Epigenetic	DNA methylation profile	high methylation class (candidate genes, whole genome)

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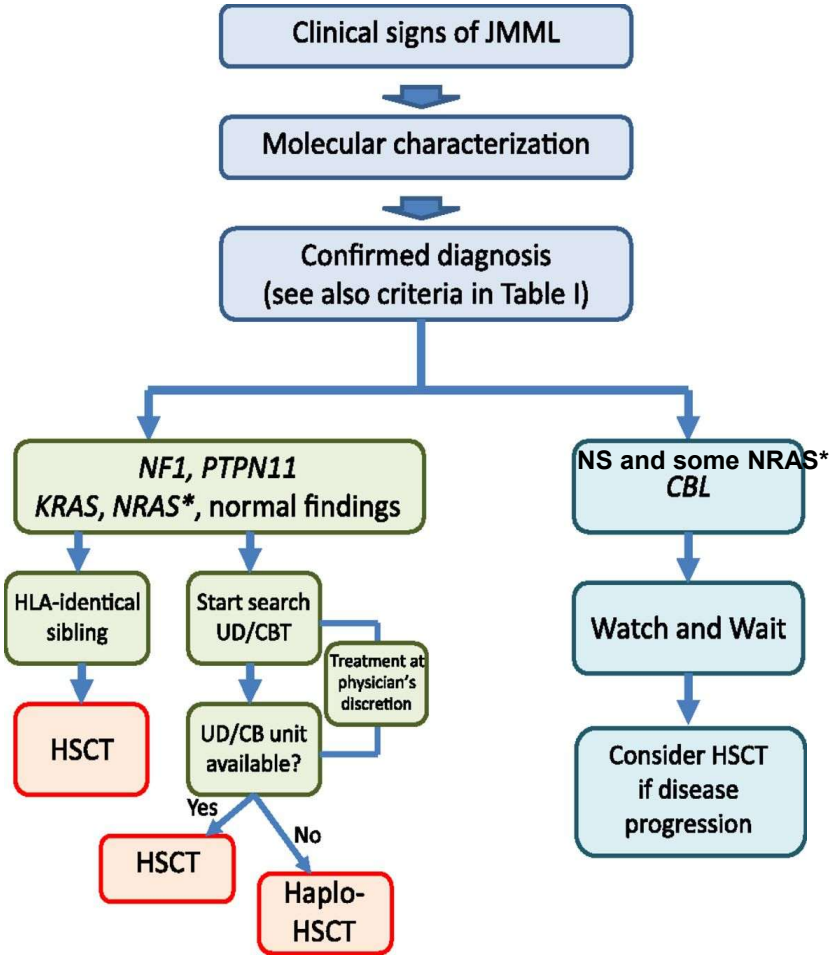
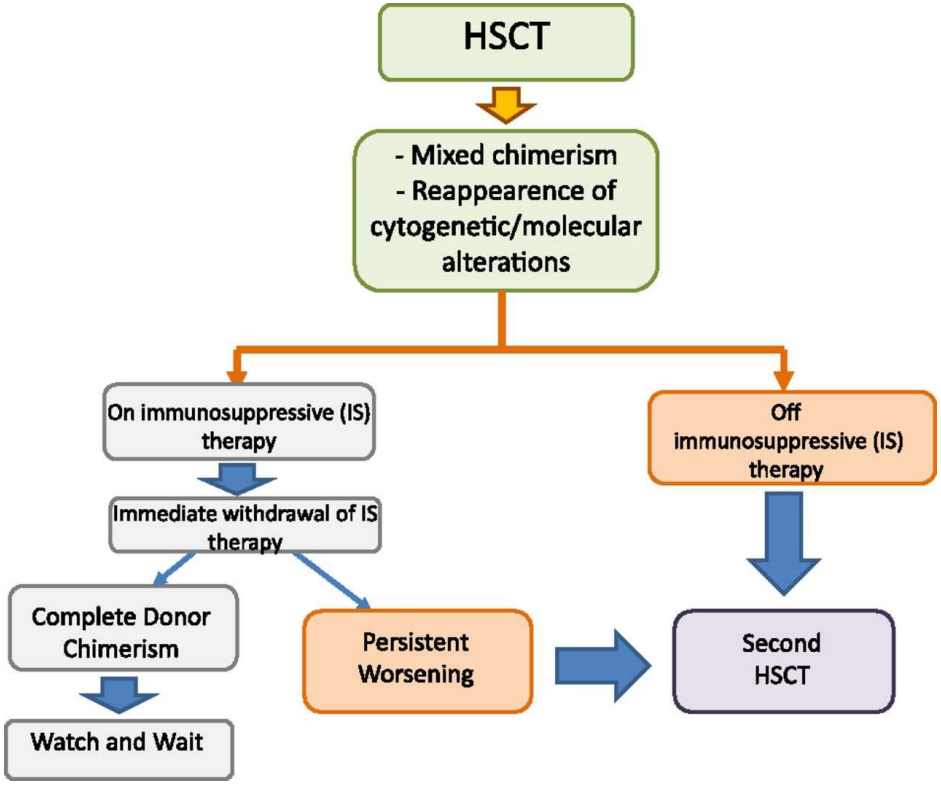
JMML treatment in EWOG-MDS

First line treatment



PreSCT : 6MP or Azacytidine

Relapse after HSCT



Franco Locatelli, and Charlotte M. Niemeyer Blood 2015;125:1083-1090

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JMML outcome

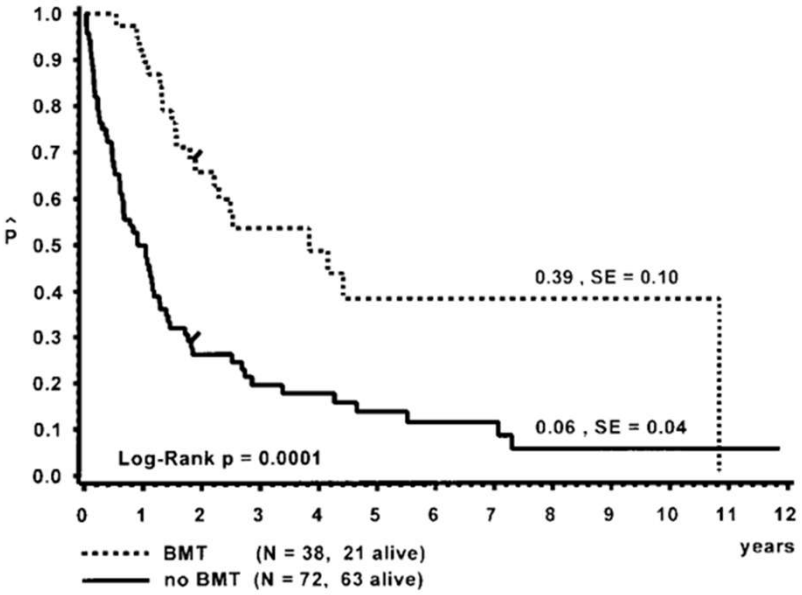
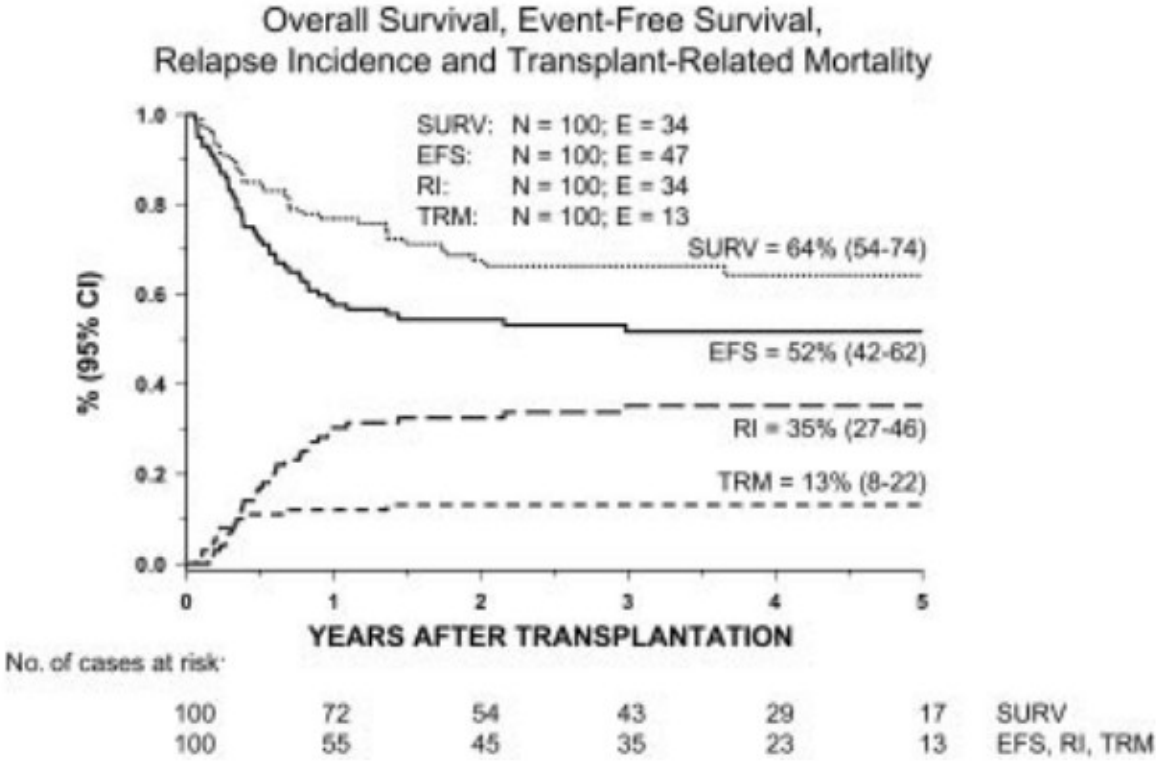


Fig 3. Survival of patients with and without BMT. Data are given from the time of diagnosis. The last event in the BMT group is in a child transplanted 9.4 years after diagnosis.

Niemeyer, 1997



Locatelli, Blood, 2005

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Myeloid disorders associated with Down syndrome

- Down syndrome
  - Predisposition for leukemia (AML x150 (4y) – ALL x20 fold higher than non-DS)
  - Lower risk to develop a solid tumor
  - In vitro and in vivo very sensitive to chemotherapy (esp AraC)

- Myeloid disorders associated with Down syndrome:
  - TAM (transient abnormal myelopoiesis,
    transient leukemia, transient myeloproliferative disorder (TMD))
  - Myeloid leukemia in Down syndrome (ML-DS)

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Transient abnormal myelopoiesis (TAM)

- Only in newborns with Down syndrome
- Incidence (postnatal): 10%
- Incidence (pre + postnataal): 20%
- Prenatal: > foetal hydrops and death in utero

- Diagnosis in 1st week of life, median 2 days
- Coincidental finding in most cases
- Hepatosplenomegaly 69%-85%
- Sometimes very severe clinical picture (hepatomegaly, cardio-respiratory problems, hyperleukocytosis, liver fibrosis …)

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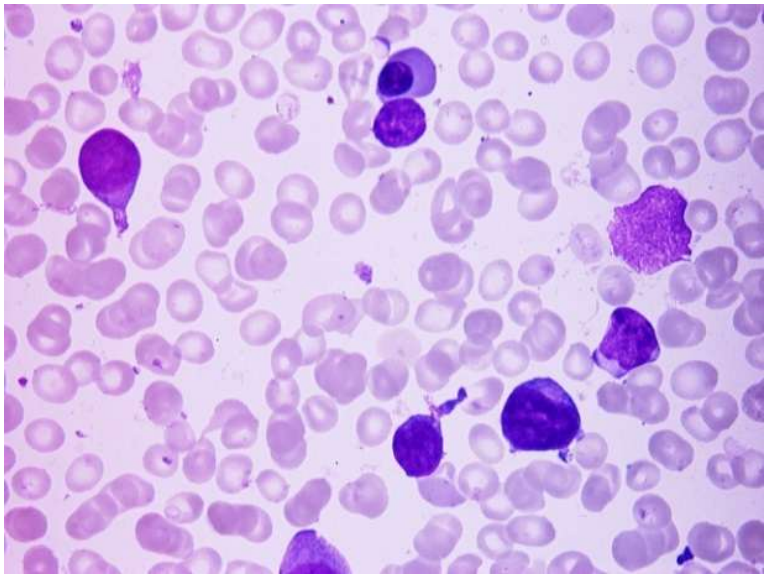
Transient abnormal myelopoiesis (TAM)

- Leukocytosis 5.0-384.0 x 10^9/L
  9.1-1300.0 x 10^9/L
- Hemoglobin usually normal (4.0-23.3 g/dL)
- Thrombocytes 5.0-1,800 x 10^9/L

- Increased blast percentage in PB and less blasts in BM
- Morpho: mostly FAB M7
- GATA1 mutation in blasts



Transient abnormal myelopoiesis (TAM)

- In most cases (70-90%) spontaneous recovery in 2-3 months (median 54 d)
- Sometimes severe course
  - **EFS 63%, OS 85%** (Klusmann, *Blood 2008*)
- Treatment if clinically necessary: low dose cytarabine

EVOLUTION:

In 20-30% of DS-TAM: evolution to ML-DS in the first 4 years of life !

- PB and WBC differentiation every 3 months until the age of 3y and every 6 months until the age of 6 years

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Myeloid leukemia of Down syndrome

- Onset often as myelodysplasia (20-69%)
- Starts with progressive thrombocytopenia; anemia
- >> AML FAB M7, sometimes FAB M6 of M0
- Molecular: GATA1 mutation
- NO spontaneous recovery!

➢ Screening of all newborns with DS for GATA1 mutation?

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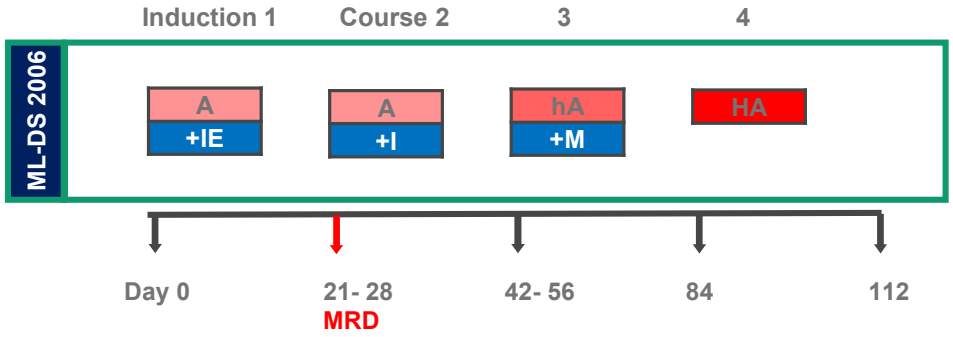
ML-DS 2006



- **AIE**:
  cytarabine 100 mg/m²/d [days 1-2] and 100 mg/m²/12h [days 3-8]
  idarubicin 8 mg/m²/d [days 3, 5 and 7]
  etoposide 150 mg/m²/d [days 6, 7 and 8])
- **AI**:
  cytarabine 500 mg/m²/d [days 1-4]
  idarubicin 5 mg/m²/d [days 3 and 5])
- **haM**:
  cytarabine 1 g/m²/12h [days 1-3]
  mitoxantrone 7 mg/m²/d [days 3-4]
- **HA**:
  high-dose cytarabine 3 g/m²/12h [days 1-3]

Cumulative doses

- 27,400 mg/m² cytarabine
- 450 mg/m² etoposide
- 34 mg/m² idarubicin
- 14 mg/m² mitoxantrone

Uffmann et al.,
Blood 2017

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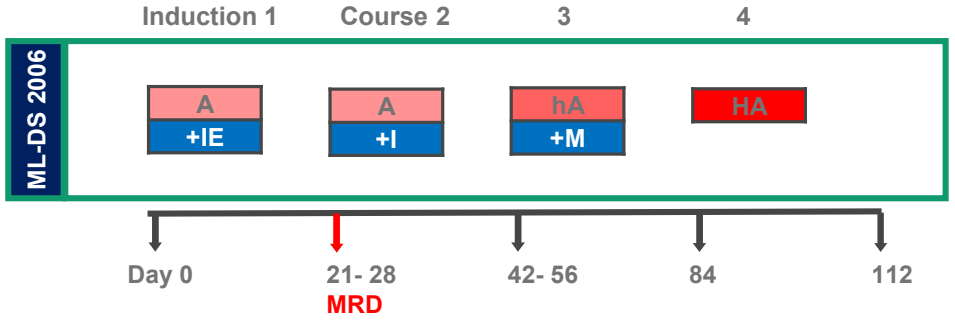
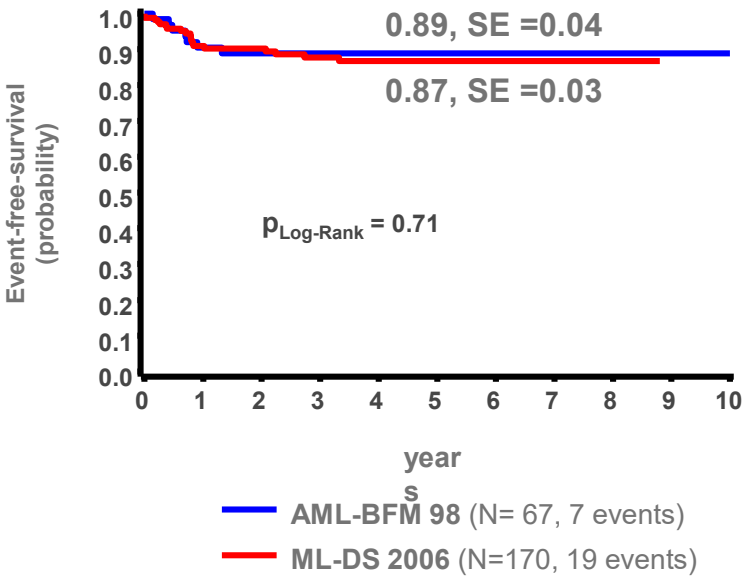
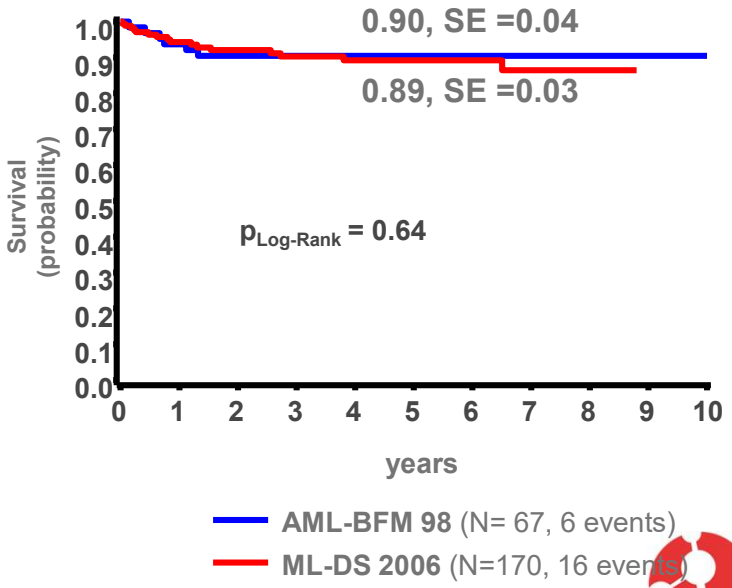
-Good outcome
-Poor rescue after relapse (2/9 relapses alive)
-2,9% TRM
-Response in BM after Ind 1 is prognostic.
-Most toxicity after Ind 1 and course 4

ML-DS 2006







Uffmann et al., Blood

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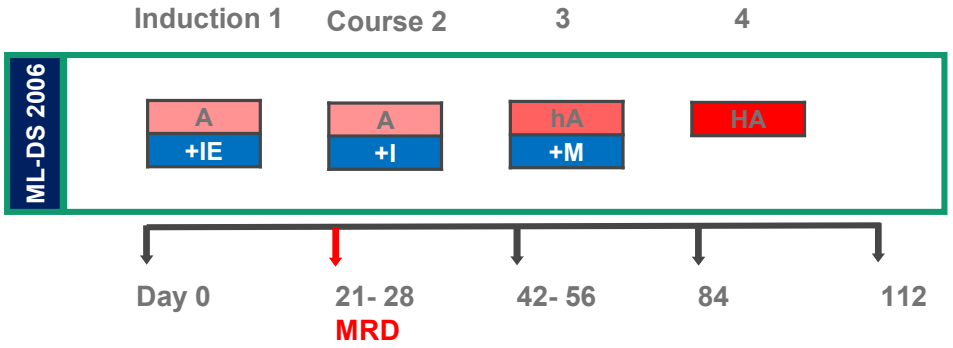
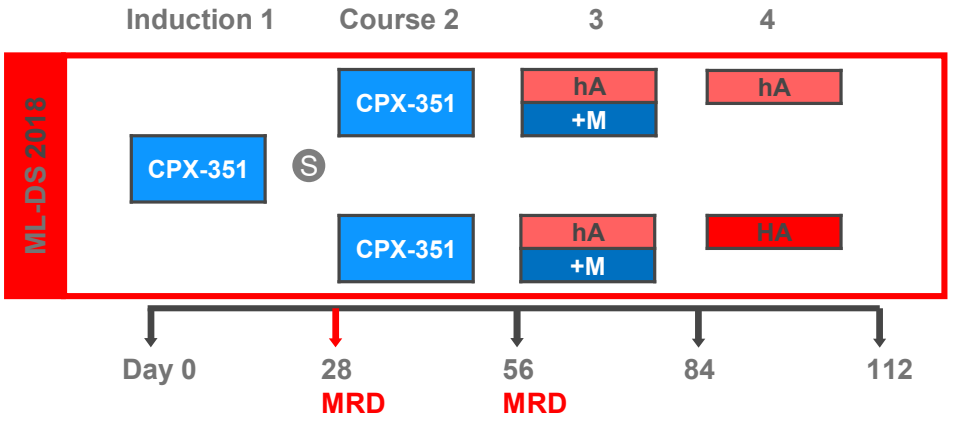
ML-DS 2018: Trial overview

- ML-DS 2006



- ML-DS 2018



S Stratification based on MRD level

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ML-DS 2018: Inclusion Criteria

- Myeloid Leukemia (ML) or Myelodysplastic Syndrome (MDS), according to WHO
- Trisomy 21: Down syndrome or mosaic
- Age: > 6 months and ≤ 4 years of age with/without GATA1 mutation OR
  > 4 years of age < 6 years of age with GATA1 mutation
- Morphology/Immunophenotyping: FAB M0, M6 or M7
- Lansky performance score at least equal to 50; or Karnofsky performance status at least equal to 50, whichever is applicable
- Understand and voluntarily provide written permission of parental/legal representative(s) to the ICF prior to conducting any study related assessments/procedures, also concerning data and tumor material transfer according to ICH/GCP and national/local regulations
- Able to adhere to the study visit schedule and other protocol requirements

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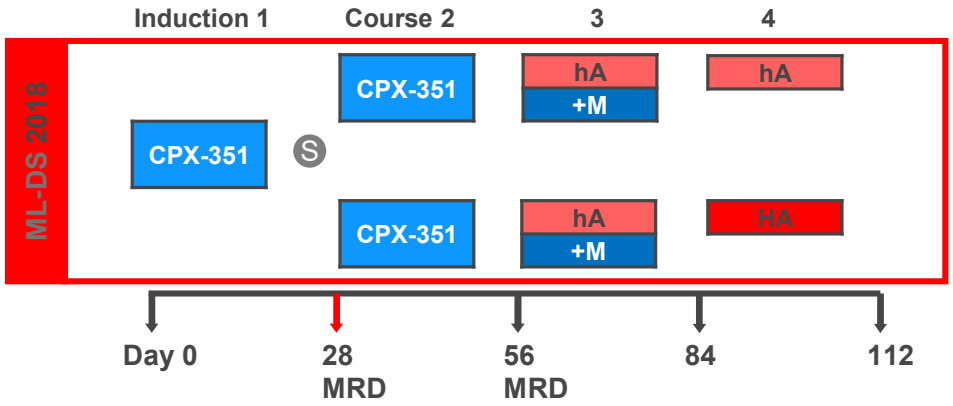
ML-DS 2018: Trial overview

CPX351 dose amended in 2025 (100/44)



Risk Stratification based on MRD level : patients with MRD <0,1% after induction have a good prognosis, cytarabine dose will be reduced from 3g/m2 to 1g/m2 in course 4 of therapyRPatientRD D

≥0.1% blasts in the bone marrow (MRD+; poor early responders)

- **CPX-351**:
  CPX-351 66 U/m²/d [days 1, 3 and 5] in course 1 and [day 1,3] in course 2, IV 90 min infusion
  = 66 mg/m² cytarabine
  + **30** mg/m² daunorubicine (29?)
- **haM**:
  cytarabine 1 g/m²/12h [days 1-3]
  mitoxantrone 7 mg/m²/d [days 3-4]
- **hA**:
  cytarabine 1 g/m²/12h [days 1-3]
- **HA:**
  high-dose cytarabine 3 g/m²/12h [days 1-3]

Cumulative doses

- 12,000 (low risk) or 24,000 (high risk) mg/m² cytarabine
- 396 U/m² CPX-351 (= 400 mg/m² cytarabine + 176 mg/m² daunorubicine)
- 14 mg/m² mitoxantrone

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Myeloid malignancies in children

- Acute myeloid leukemia (AML)
- Myelodysplasia (MDS)

- Juvenile myelomonocytic leukemia (JMML)
- Myeloid disorders associated with Down syndrome (TAM, ML-DS)

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