MDS secondarie: a che punto siamo?

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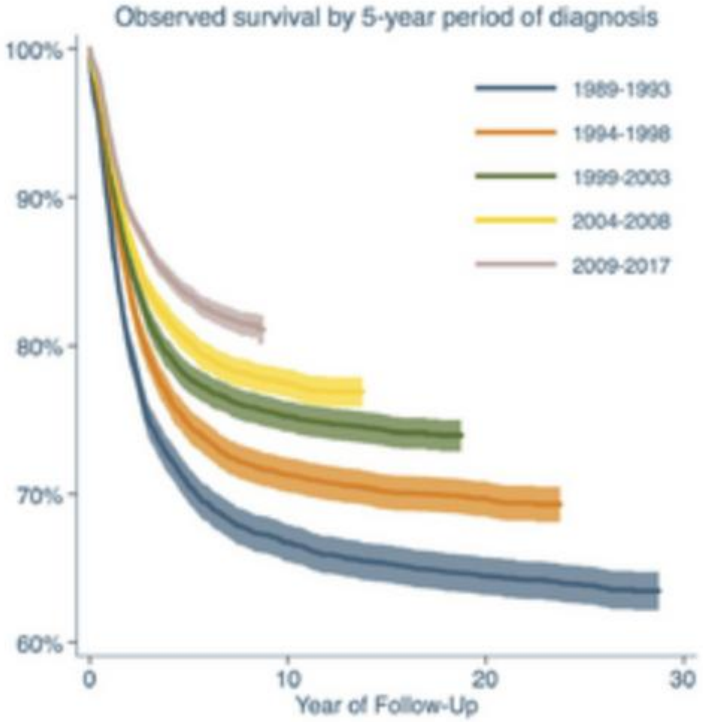


0.8%– 6.3% survivors

5-11% post solid tumor

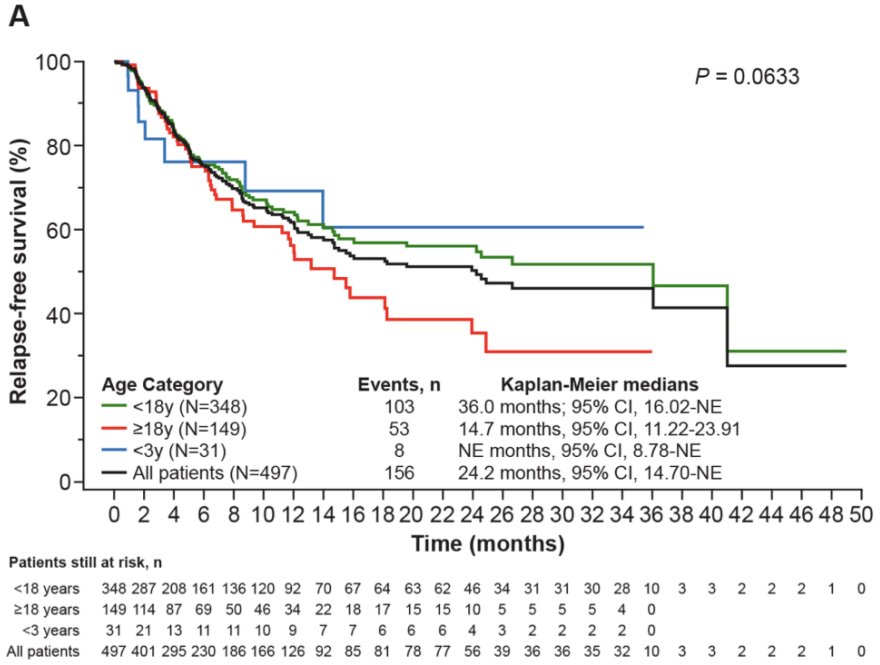
1-5% post leukemia

2400 new diagnosis paed/year in Italy

84% survivors

16-127 pz tMDS/AML 3-7 years post front line tx

Pession et al, Int J Cancer 2024, Sharma et al, BMT 2021, Locatelli and Strahm, Blood 2018



768 RR-ALL paed pts treated 2017- 2022

Median follow up: 32 months (range 12-55)

24 months RFS (censoring HSCT)= 50%

5 cases of lineage switch, 2 of secondary

MDS, no T cell related malignancies

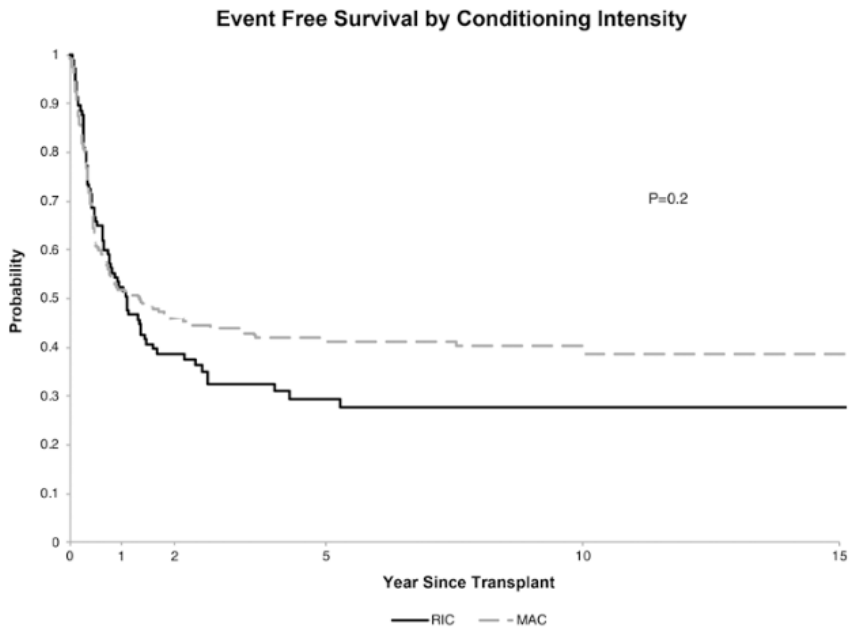
—> sec neoplasms at 1%

John et al, Blood advance 2025

- CIBMTR e EBMT adults and kids OS: 30%
- Paeds only OS 13-20%
- Short time between dx and HSCT improves outcome
- For induction chemo only if >20% blasts
- Frequent post HSCT chimerism monitoring to drive early IS tapering and potential DLI

Study	Design / Cohort	Patients (n)	Main Treatment(s)	Survival Outcomes	Key Findings
Gassas et al. 2018 (UK)	Multicenter retrospective 2000–2016	36	FLAG ± idarubicin +HSCT	5-yr OS 33%	HSCT feasible but high TRM main cause of death
Imamura et al. 2018 (Japan)	Multicenter retrospective 2000–2013	43 (33 AML)	Chemo; Allo-HCT in 32 pts	7-yr OS 39% ; allo-HCT 79% vs 12%	allo-HCT in CR key for survival
Sharma et al. 2021 (USA, Europe, Australia)	Multicenter retrospective 1995-2017	401 t-MNs (AML/MDS)	HSCT	5-yr OS 40%; DFS 33%	Large cohort; HSCT can cure subset; survival better in CR and with matched donors

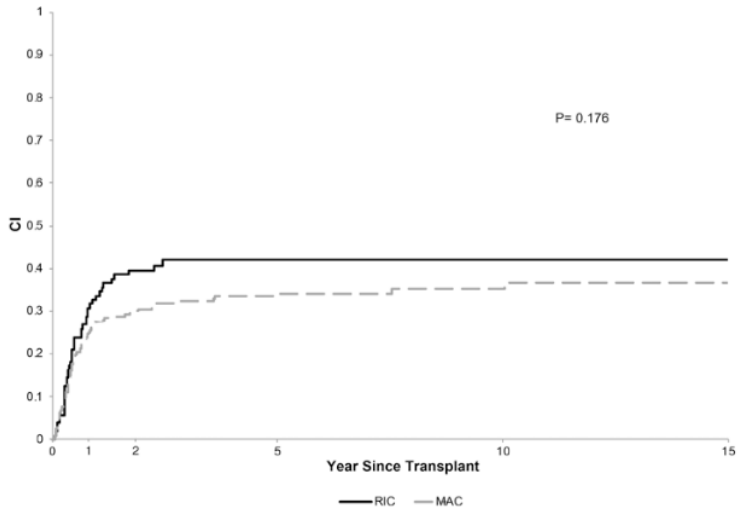
B



- No survival benefit RIC vs MAC
- Drop in EFS RIC post 1st year —> MVA severe aGvHD and TBI based MAC worse EFS
- MVA: Complex karyotype and MDS—> worse EFS (no pre HSCT chemo?)

Sharma et al. 2021 BMT

C



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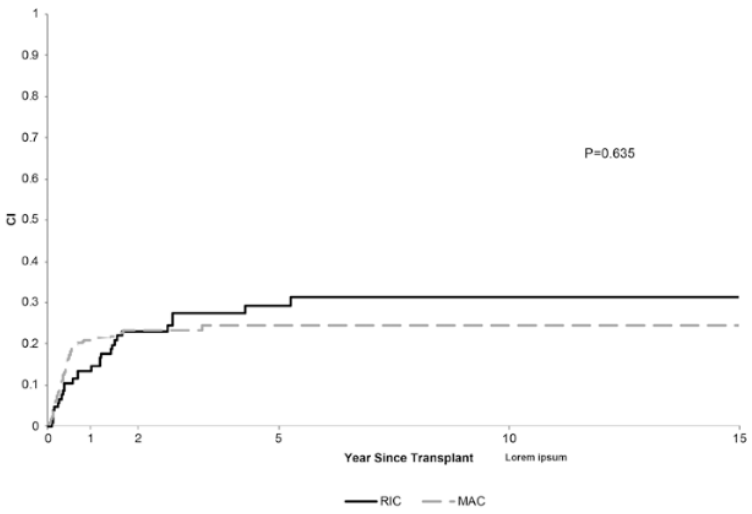


CIR 42% RIC vs 35% MAC (ns)

NRM 31% RIC vs 24% MAC (ns), MVA year HSCT <94 and severe GVHD

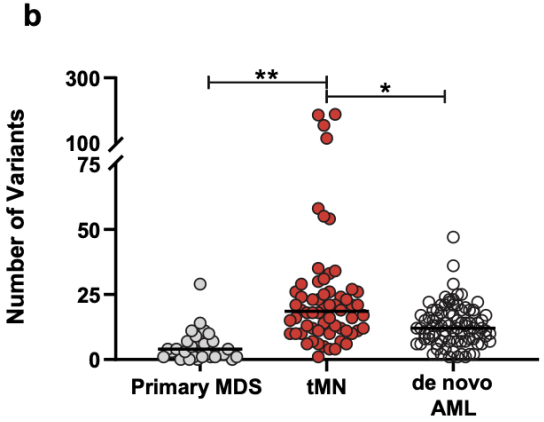
Sharma et al. 2021 BMT

Which HSCT?

- Probably reduced toxicity but not reduced intensity
- No TBI
- Be careful with inducing allo effect to enhance GvL as you might pay w
- Does this depend on genetics?
- What do we do with pre HSCT bridging?
- And post HSCT?

Granulocyte transfusion during cord blood transplant for relapsed, refractory AML is associated with massive CD8$^+$ T-cell expansion, significant cytokine release syndrome and induction of disease remission

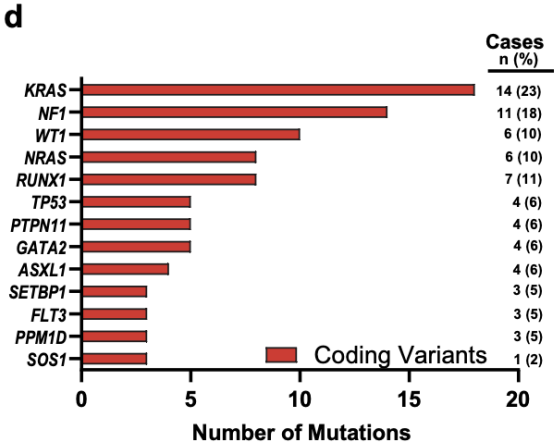
Roisin Borrill, Kay Poulton, Laura Kusyk, Amy Routledge, Denise Bonney, Ramya Hanasoge-Nataraj,



84 pediatric MDS 28/AML56

median age = 13 @tMN,

median time 1st tumor = 2.9 yrs



Median of 28 somatic mutation per pts, some hyper mutated cases (PMS2 or MSH6)

Most commonly altered pathways Ras/MAPK

Germline mutations in 15% (vs 8-10% in other groups of paeds with cancer).

TP53 mutated (somatic, germline or mosaic) in 18%.

No germline mutation in RUNX1/GATA2/SAMD9/9L

Mutational signature: cisplatin (4 cases) thiopurine (5); clock like(8 cases), MMR (2 pts)

Schwartz et al, Nat com 2021

Karyotype

Chromosomal rearrangement in 70% of pts.

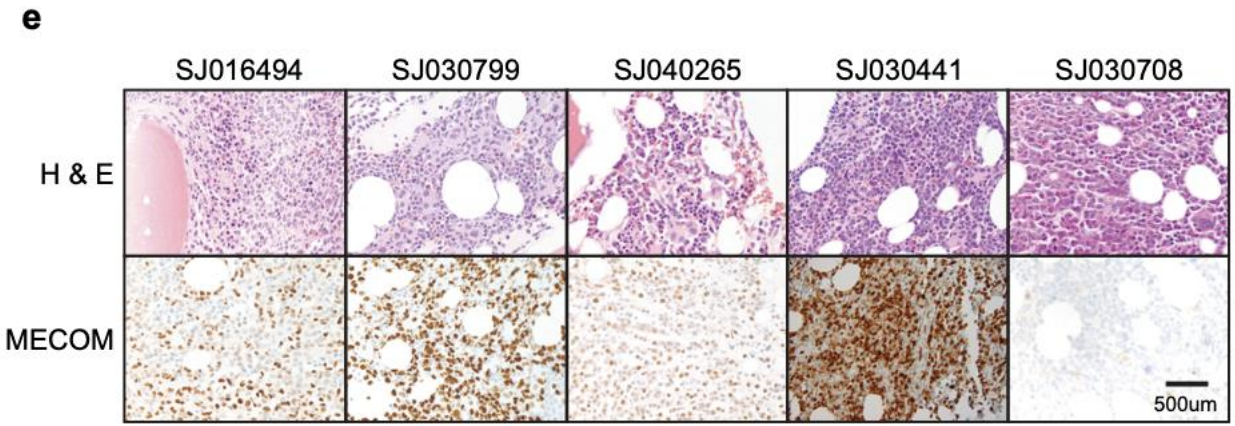
KMT2A most prevalent (60%)

Deletion or CN/LOH chr 7 (35%)

other in frame fusions involving NUP98 and ETV6 or RUNX1.

Complex karyotype associated to higher disease progression (MVA, HR 2.17)

43% of pts had MECOM high expression especially in KMT2A pts

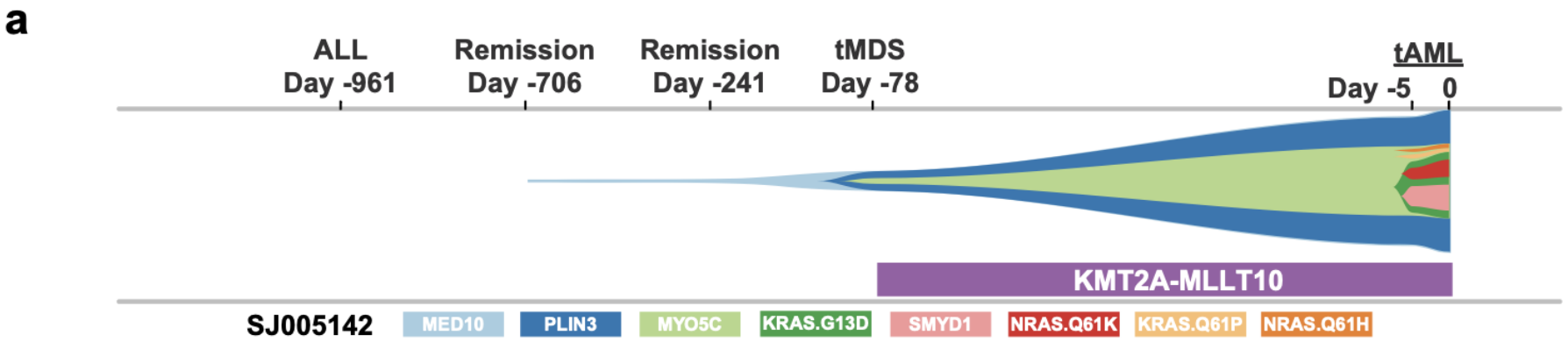


Schwartz et al, Nat com 2021

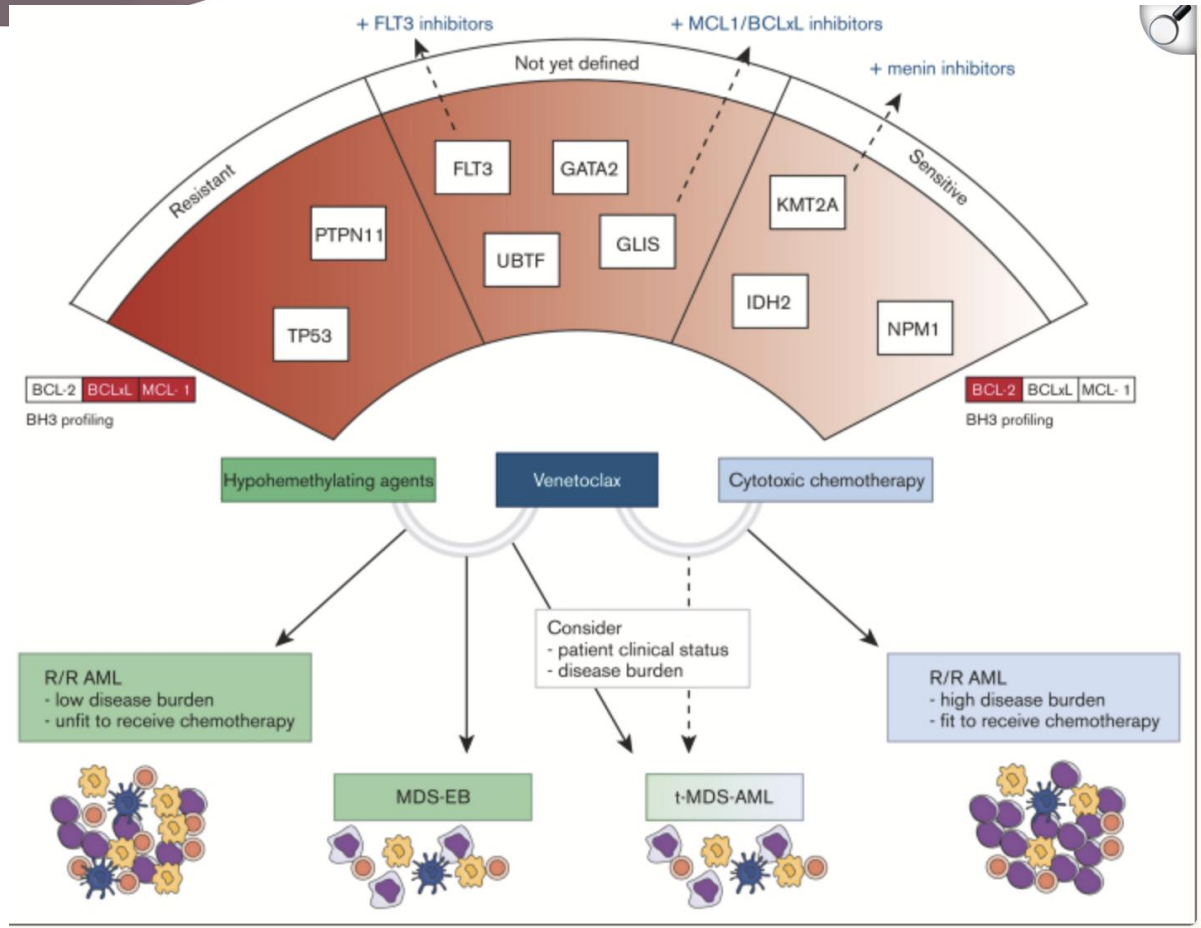
Clonal evolution evaluable in 37 cases (only 3 cases clonal related to primary disease)

Somatic variants mostly arose after cytotox therapy up to 748 days prior to morphologic tMN

No somatic p53 clone in the pre treatment samples (different from adults)

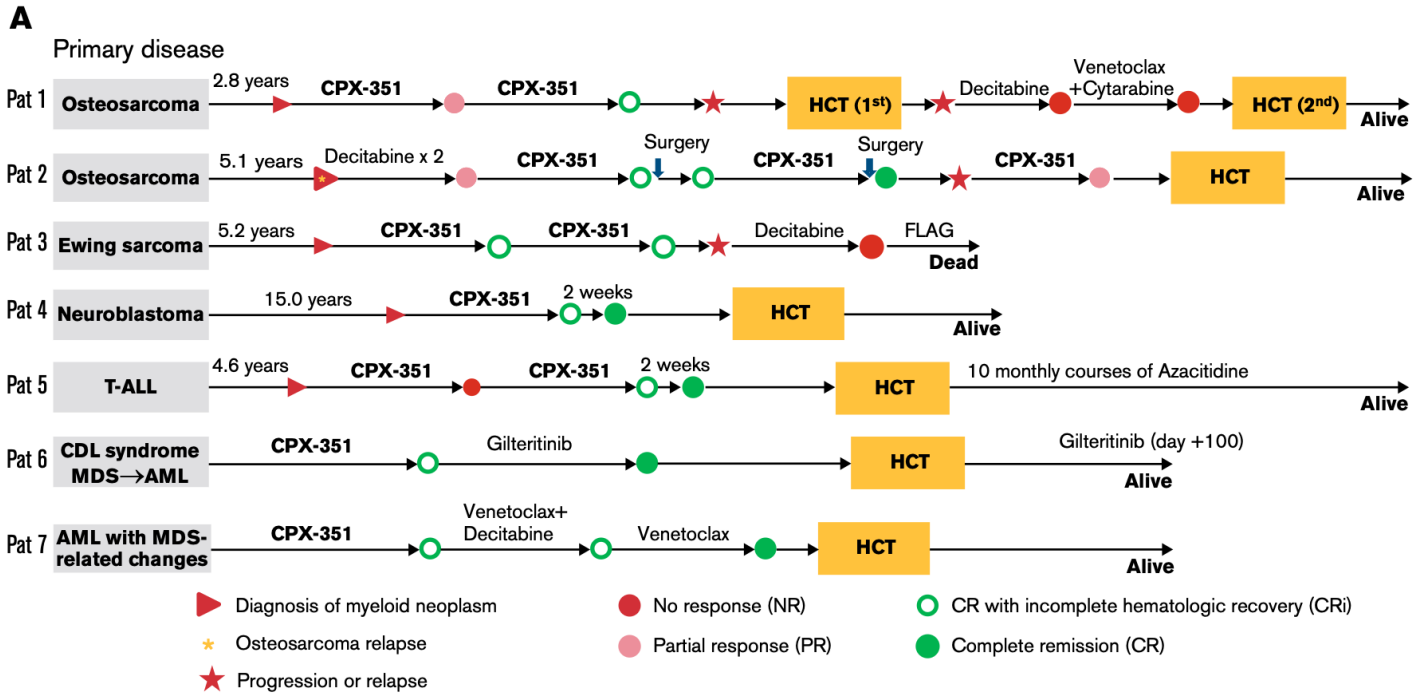


Schwartz et al, Nat com 2021



Masetti et al, Blood Advance 2024

Liposomal combination of cytarabin and daunomycin 5:1



7 pads
median time from
1st malignancy to MDS
17 years

Hu et al, Blood advance 202

Augment 101 study NCT04065399: Revumenib

2021 to 2023, N= 94 patients (1.3-75yrs)

Grade ≥3 AE

febrile neutropenia (37.2%),

differentiation syndrome (16.0%),

QTc prolongation (13.8%).

CR/CRh rate 22.8% (95% CI, 12.7 to 35.8)

OR rate 63.2% (95% CI, 49.3 to 75.6),

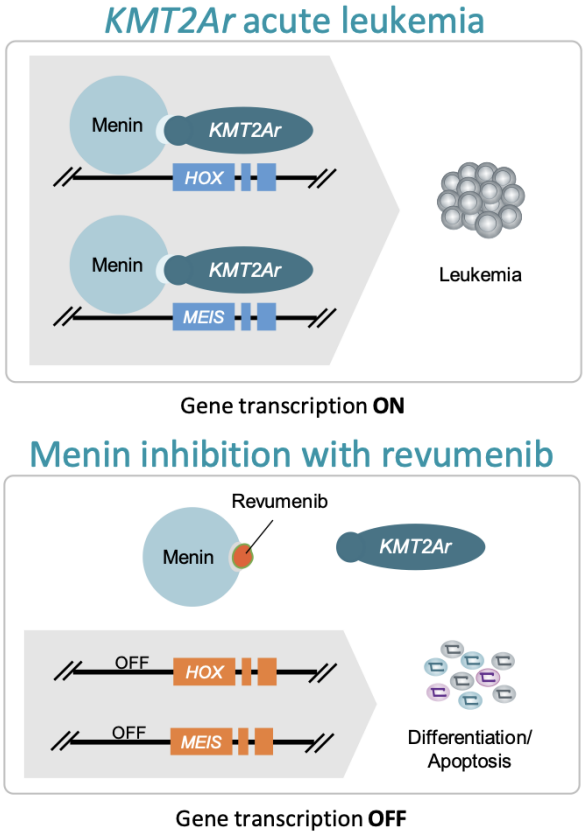
with 68% pts having no detectable residual disease.

6 pts post CART

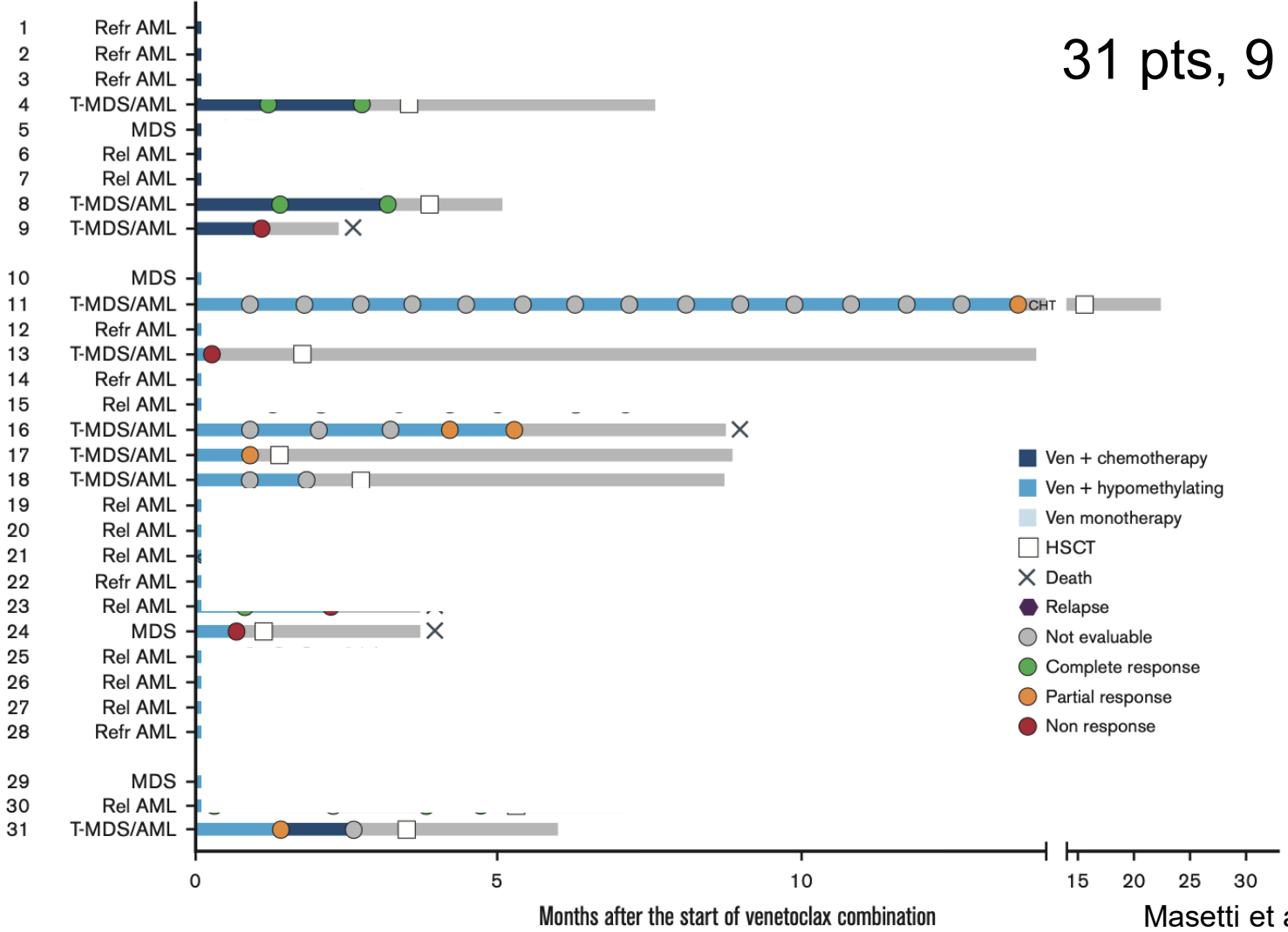
13 paediatrics

5 pts maintenance post HSCT

Issa, JCO 2024



31 pts, 9 sMDS/AML

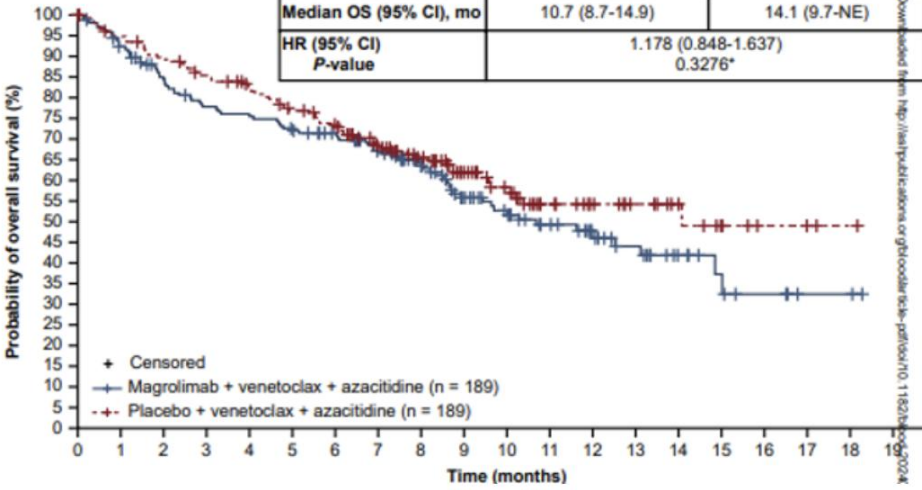


Masetti et al, Blood Advance

Magrolimab functions by inhibiting CD47, a transmembrane protein expressed on both normal and cancerous cells. CD47 interacts with signal regulatory protein alpha (SIRPα) on macrophages, transmitting a "don't eat me" signal that prevents phagocytosis.

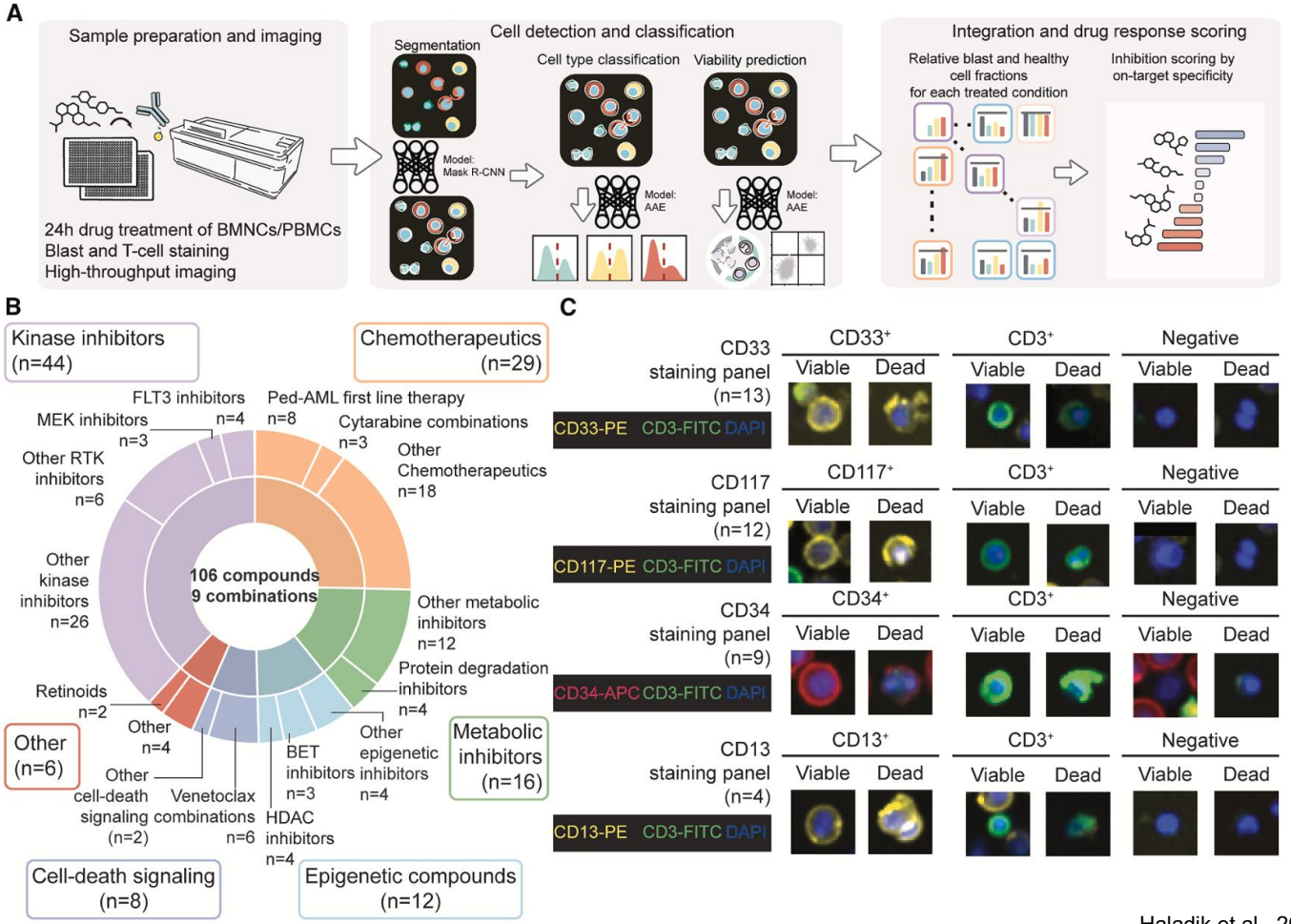
Figure 2. Overall survival (final analysis).

	Magrolimab + venetoclax + azacitidine (n = 189)	Placebo + venetoclax + azacitidine (n = 189)
Deaths, n (%)	84 (44.4)	70 (37.0)
Median OS (95% CI), mo	10.7 (8.7-14.9)	14.1 (9.7-NE)
HR (95% CI) *P*-value	1.178 (0.848-1.637) 0.3276*	

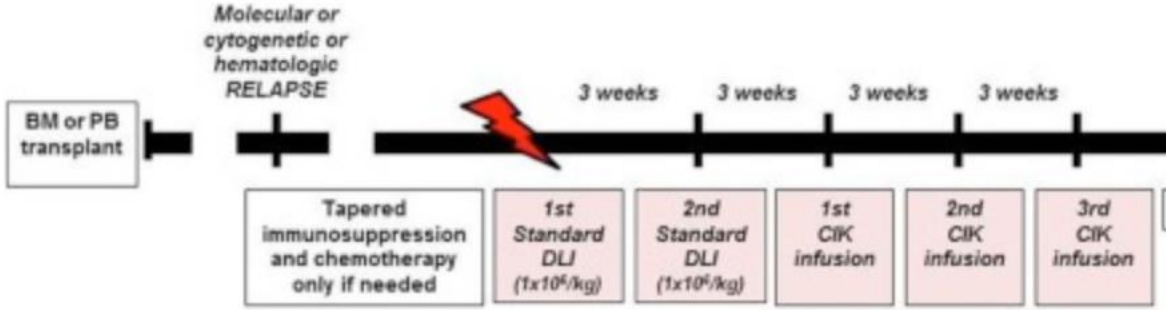


The ENHANCE-3 study's discontinuation follows an independent DTC assessment of topline overall survival (OS) results. Analysis indicated that magrolimab plus azacitidine and venetoclax resulted in futility and an increased risk of death (infections)

Daver, Blood 2025

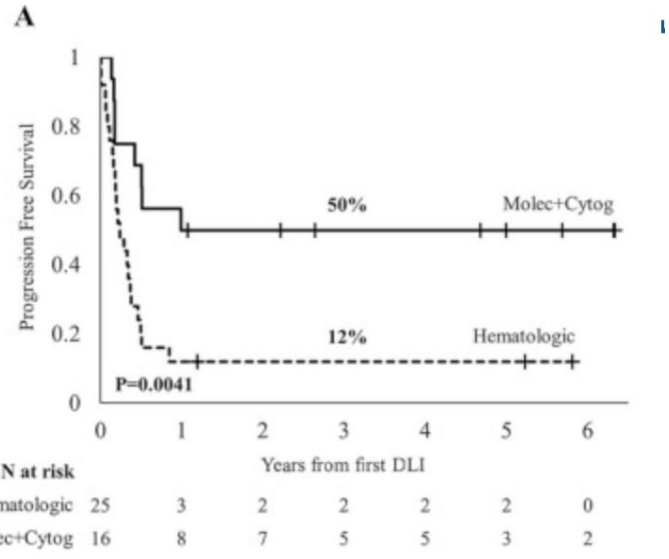


Haladik et al., 2025, Cell Reports Medicine



74 pts, 15 peads, 7% severe aGVHD ,
10% cGVHD mod/sev

More recently 2 pts with s-MDS/AML treated with CIK only prophylactic post HSCT
Maintained long term remission, but overall data on haplo CIK post T replete haplo still needs evaluation as of GVHD risk



Introna et al, BBMT 2017

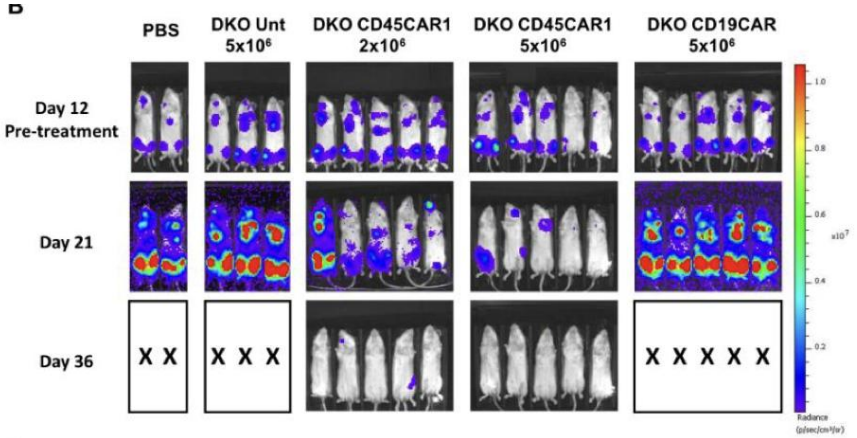
CAR per MDS/AML?

Base edited, allogeneic CD33 CART, London ongoing

Non viral, allogeneic Dual CD33-123 CARCIK, Monza 2026

Non viral, allogeneic CD123 CARNK, Rome 2026

Viral, allogeneic DKO CD45/TCR CART, London/Madrid/Monza 2027



GdL sindromi mielodisplastiche

1) At dx: collect pre dx and dx samples + germline for clonal reconstruction
2) At dx: drug screening for pre or post HSCT use
3) Attempt for pre HSCT chemo aiming for better disease control Ven or target or CPX
4) HSCT no TBI, reduced toxicity but not reduced intensity
5) rather than GVH/GvL push try post HSCT maintenance from drug screening or based
6) prospective guidelines implementation

ALWP 2414 pts with sAMLcontrollare