WBMT 2017

Session: HCT in Hematological Malignancies

HCT in Acute Myeloid Leukemia

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Day 3 (17 January 2017), 1:15-1:35 PM

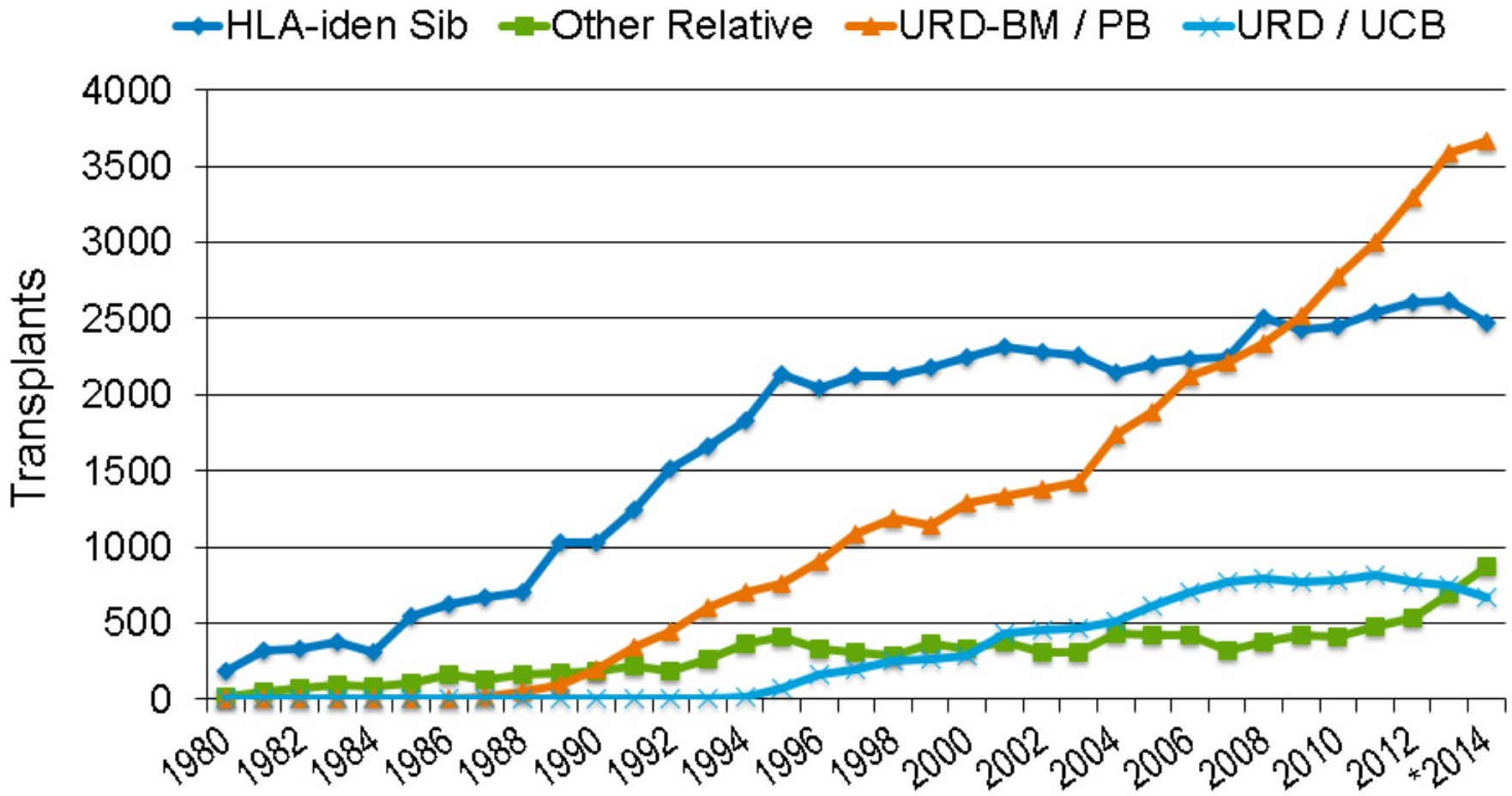

STAR TRIBUNE CagleCartoons.com
SACK
"After Jan 20th, 2017"
PATH TO CITIZEN-SHIP
PATH TO THE PATH TO CITIZEN-SHIP
QUICK SAND
MINE FIELD
POLITICS

Outline

- Historical perspectives
- Case based approach
- Improving outcomes in HCT for AML
- Alternate donor options
- MRD and relapse following HCT
- Take home message

Disclosures: None

Allogeneic Transplant Recipients in the US, by Donor Type



CIBMTR
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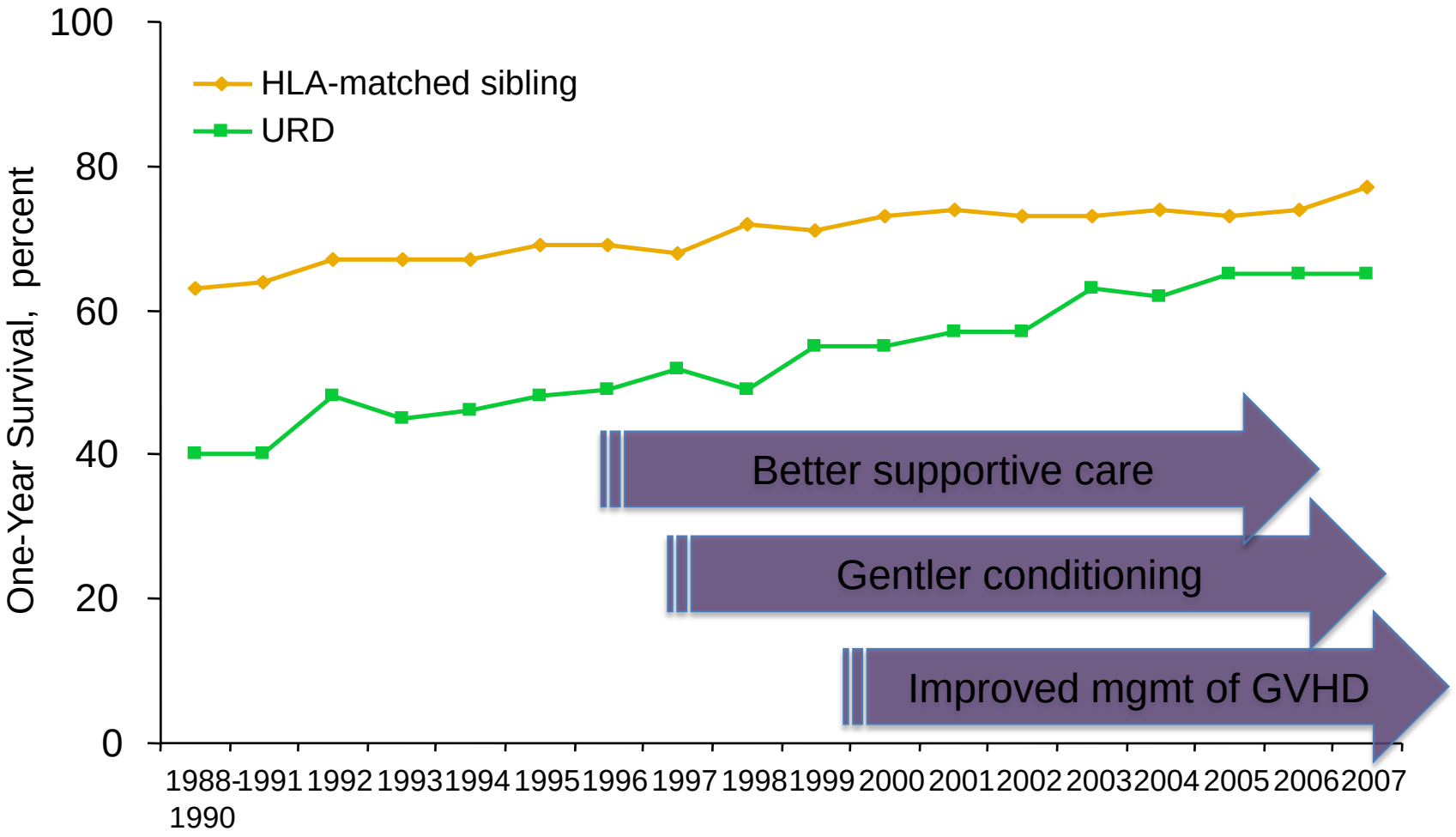
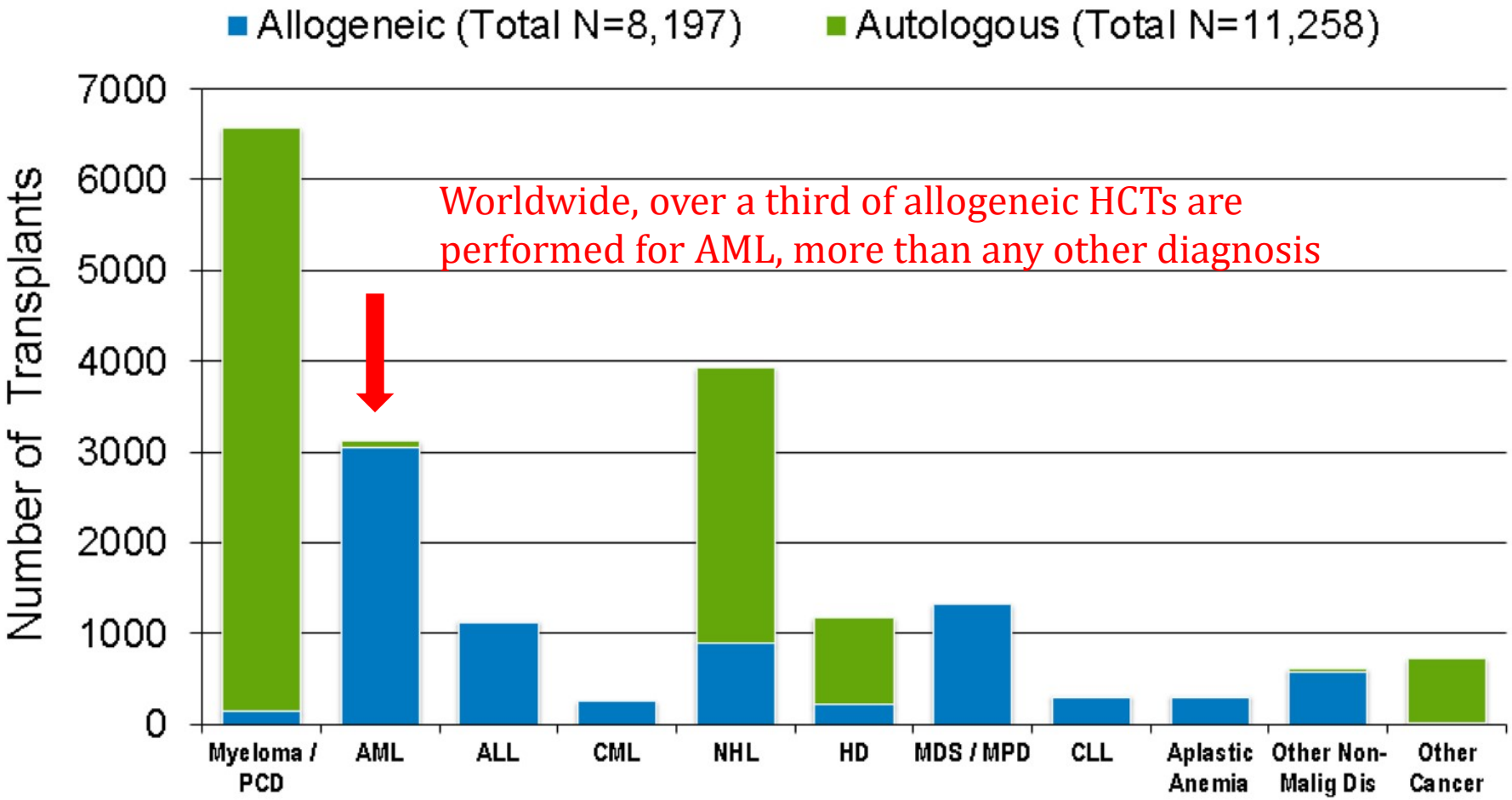
*2014 Data incomplete

Improving transplant outcome



Pasquini MC, Wang Z. CIBMTR

Indications for Hematopoietic Stem Cell Transplants in the US, 2013



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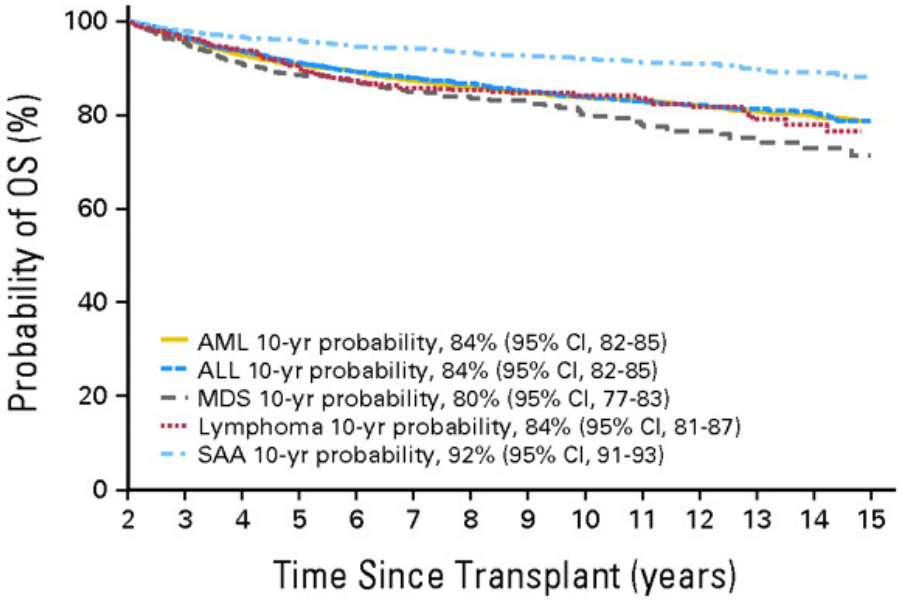
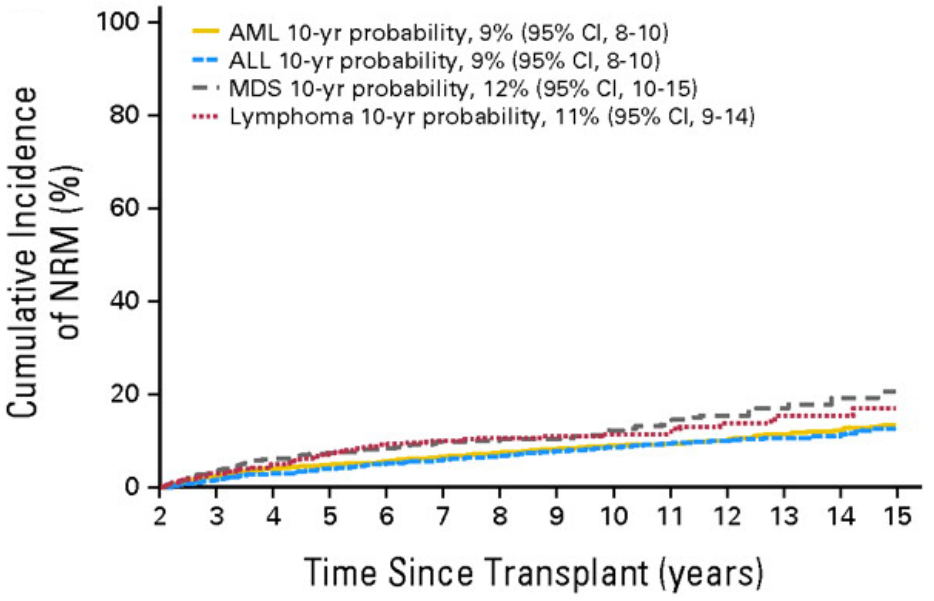
Long-term Survival after HCT

- CIBMTR study of 10,632 allogeneic HCT recipients surviving ≥ 2 years in remission (median follow-up 9 years)

Overall survival



Non-relapse mortality



J Wingard et al, J Clin Oncol. 2011 Jun 1;29(16):2230-9

Case history

- 66 year old male diagnosed with precursor AML in July 2012, WBC 52K on presentation
- Normal cytogenetic and FISH
- Molecular markers: FLT3 (wt); NPM1-mutated
- Normal organ function tests
- Medical conditions- DM-II, HTN, hyperlipidemia, H/O MI 1999- all controlled on medications
- Standard elderly AML induction chemotherapy regimen, achieved remission CR1, MRD+

Question

What next?

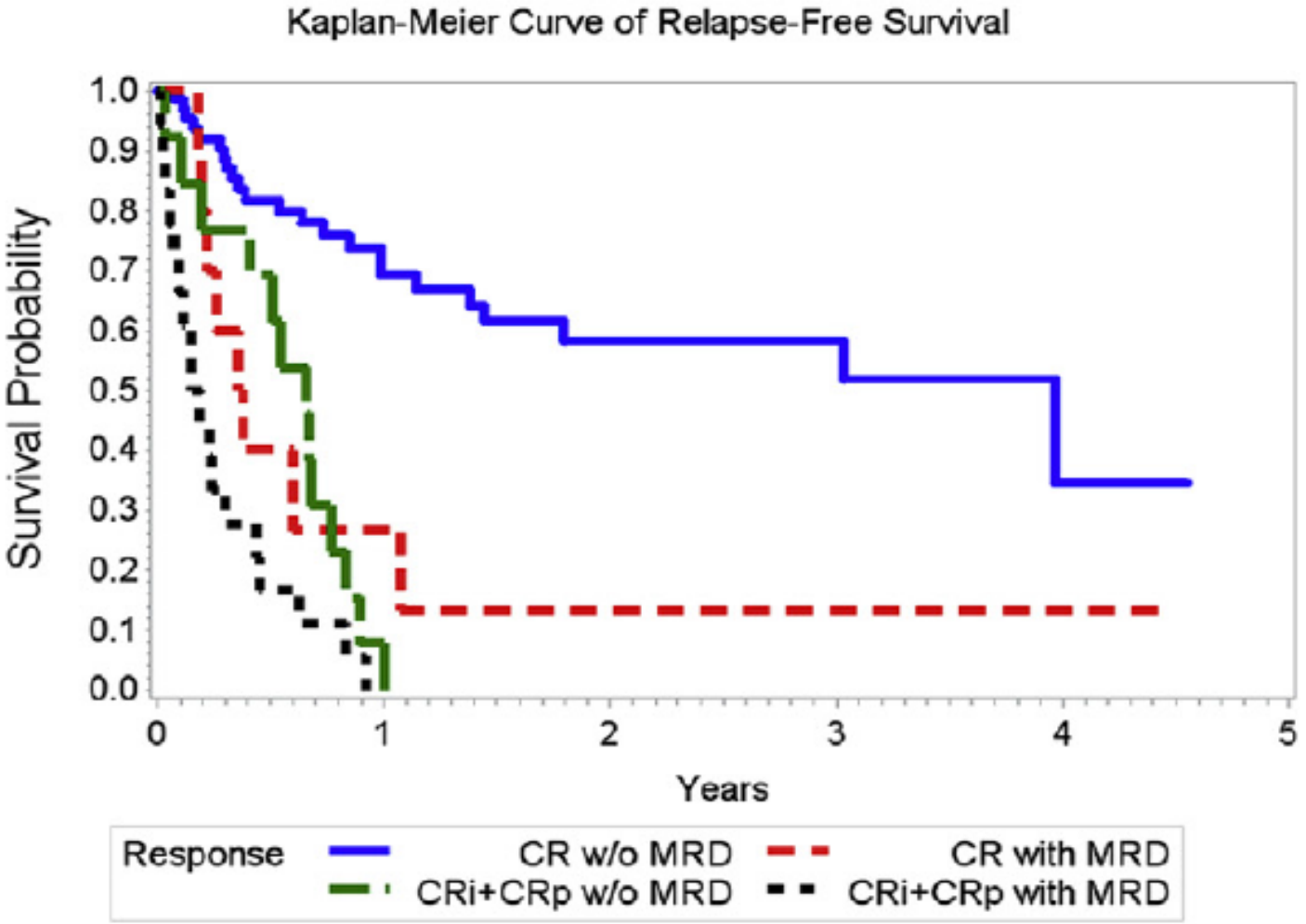
Q1. To remit, to cure, or to palliate?

Q2. Transplant or no transplant?

Characteristics of the most frequent mutations in AML with normal cytogenetics.

Features	NPM1	FLT3-ITD	DNMT3A	IDH1/2
Frequency in CN-AML	50-60%	20-25%	30-35%	15-20%
Specificity	AML	AML,MDS, ETP-ALL	AML, MDS, MPN, PTCL, T-ALL	AML, MDS, MPN, gliomas
GEP signature	Distinct	No	No	No
Micro-RNA profile	Distinct	No	No	No
Time of occurrence	Early	Late	Early	Early (IDH2)
Clonal hemopoiesis	No	No	Yes	Yes
Stability at relapse	Yes	No	Yes	Yes (IDH2)

Outcomes based on MRD status in a non-transplant cohort: FHCRC

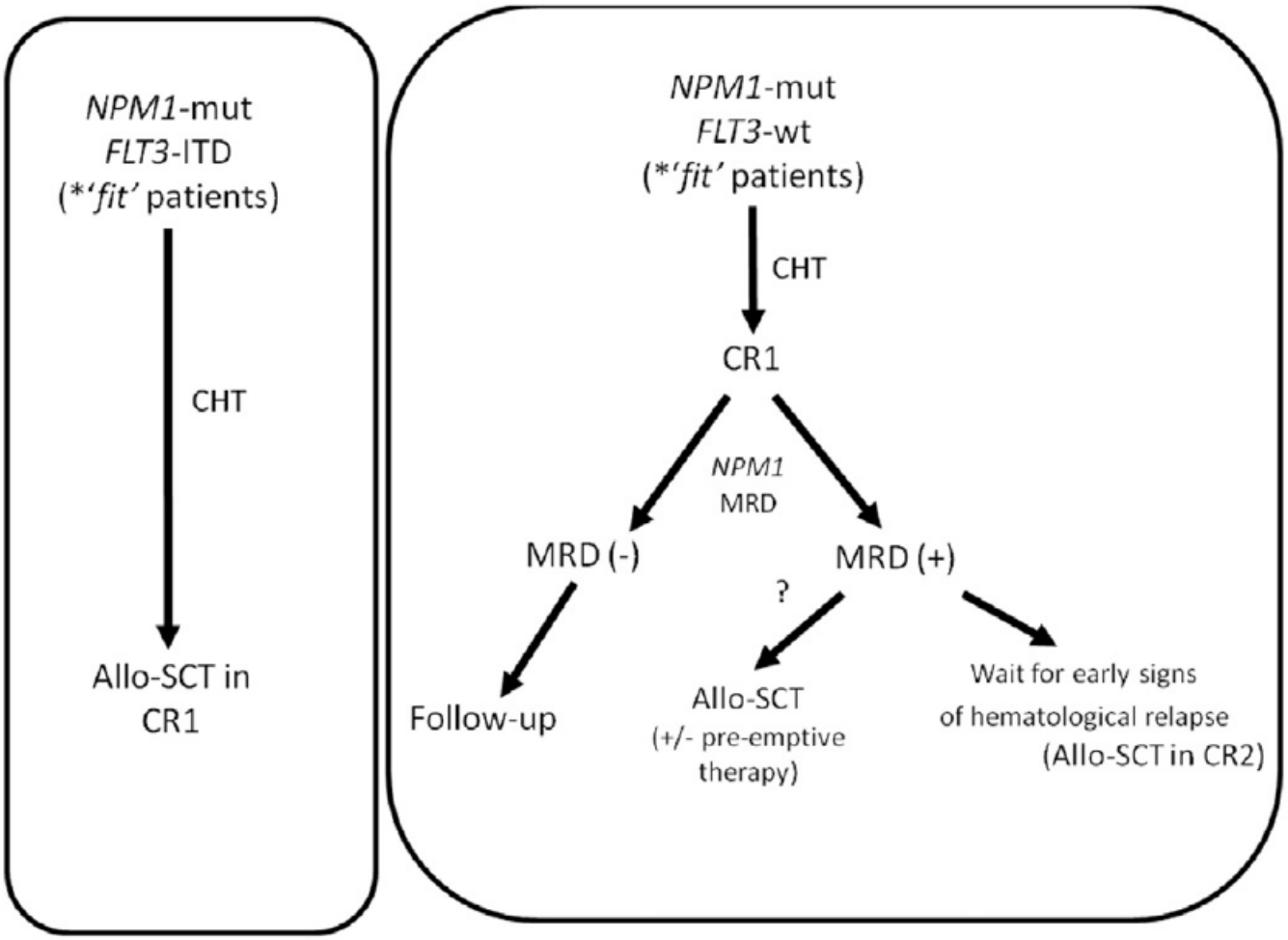


Frederick R. Appelbaum, BCP 2015

Management options

- Continue chemotherapy- elderly AML protocol and no transplant needed in CR1
- Change therapy to pediatric AML protocol and no transplant needed in CR1
- Haploidentical allo-SCT- daughter as a donor
- Double cord blood transplantation
- Continue chemotherapy while awaiting matched unrelated donor- continue donor search

Suggested Treatment strategy based on MRD status

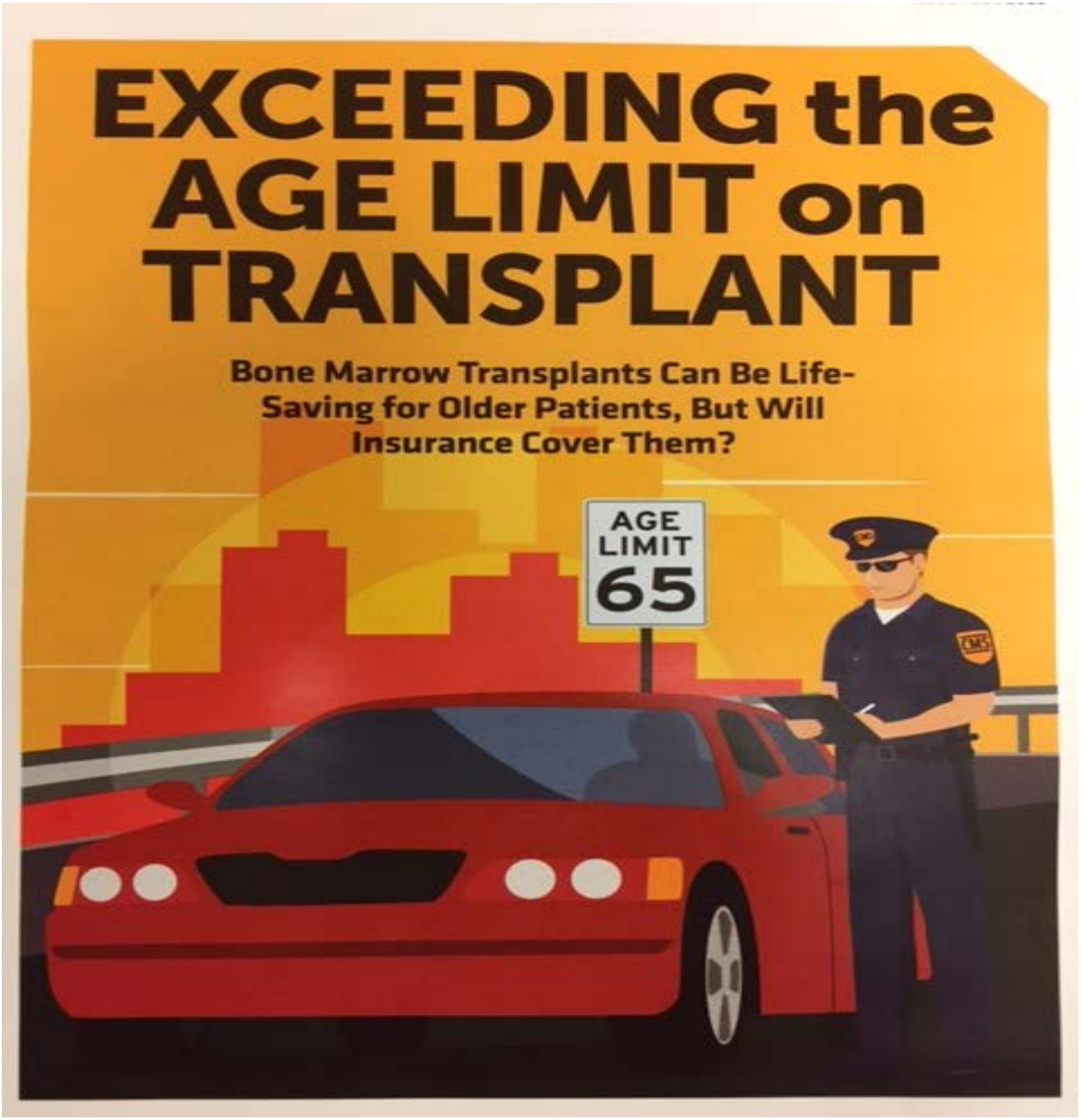


* Based on age, co-morbidities and clinical conditions, and related to transplant procedure toxicity.

B. Falini, M.P. Martelli; Best Practice & Research Clinical Haematology, 2015

After extensive discussion with patient and family, he opted for allogeneic stem cell transplant to optimize his chances

First challenge….



What is the preferred transplant approach?

Case history

- Donor search was initiated
- Two siblings (alive)- sister 72 year old on tamoxifen for h/o breast cancer (s/p chemotherapy); brother 68 year old not a match (multiple co-morbidities)
- NMDP- no matched unrelated donor, poor search
- Children- daughter 42 year (healthy) haplo-matched (7/10- A, B, C MM)
- Donor-recipient pairs were considered HLA-haploidentical if they were genotypically identical for at least one allele of each of these loci
- Several cord blood units available

HCT in AML- First remission

- Important role of molecular markers in the management of AML
- More patients receiving HCT in CR1
- Challenges remain
  - Improving patient selection for HCT
  - Excluding patients not needing HCT
  - The impact of measurable/minimal residual disease (MRD)
- Best outcome, but relapse remains major obstacle.

HCT in AML- Refractory disease

- Primary refractory vs. relapse refractory
- Transplant vs. no transplant
- Clinical trials
- Intensity of conditioning matters
- Achieving remission? early vs late
- Munich experience- FLAMSA sequential chemotherapy RIC HCT
- Ablative regimens- CyTBI, BuCy

HCT in AML- Refractory disease

- About 30–40% of patients do not achieve remission with standard induction therapy
- Relapse also suggests an increasing likelihood for chemotherapy resistance
- Retrospective analyses suggest allo-HCT with MAC produces long-term survival in ~10–20% of patients
- High risks of TRM and relapse with HCT

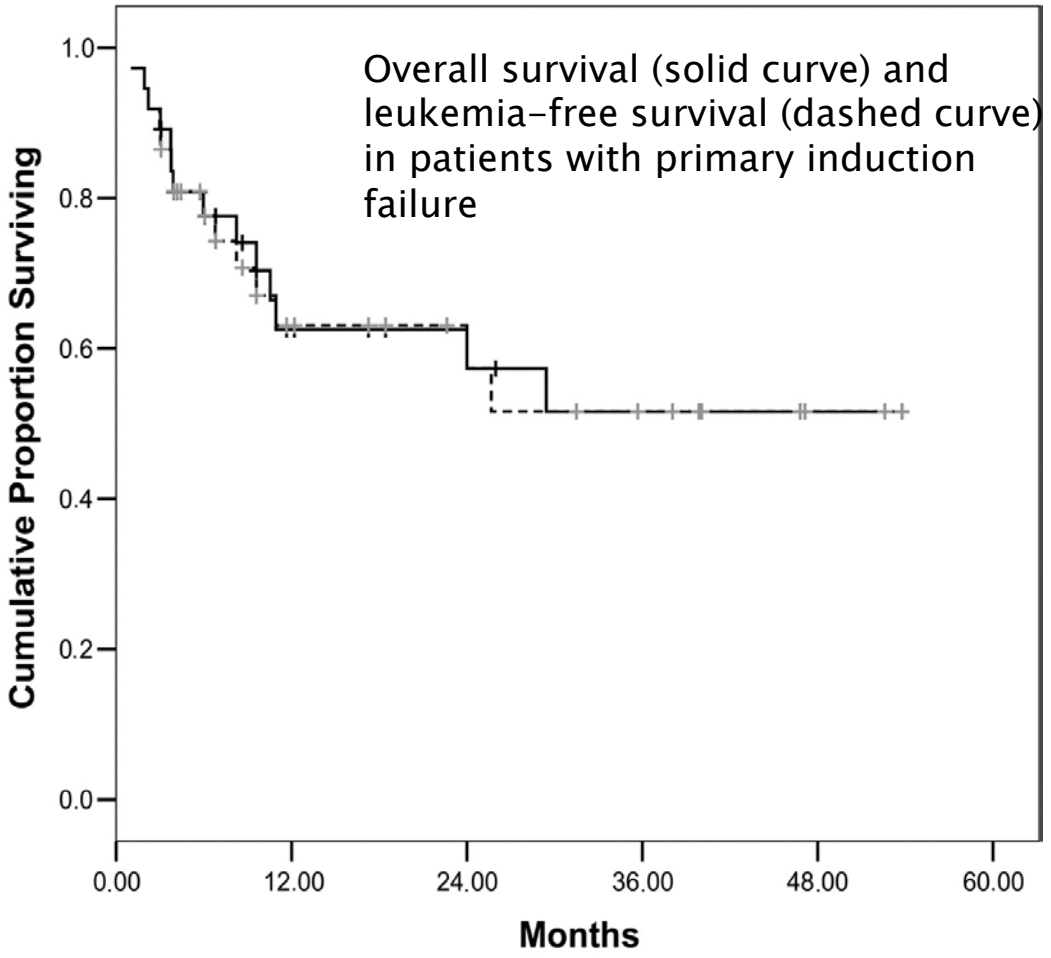
HCT in AML- Refractory disease

FLAMSA sequential strategy

FLAMSA

Fludarabine, Intermediate-dose ara-C, Amsacrine, followed after a 3 days' rest, by RIC HCT (4Gy TBI, Cy _ATG)
pDLI on D+120 w/u GVHD

- 25-month median f/up;
OS at 1, 2, and 4 years was 54%, 40%, and 32%;
respective LFS was 47%, 37%, and 30%.
Patients with PIF showed a 2-year OS of 62.5%.
OS was 87% in 17 patients receiving pDLT.



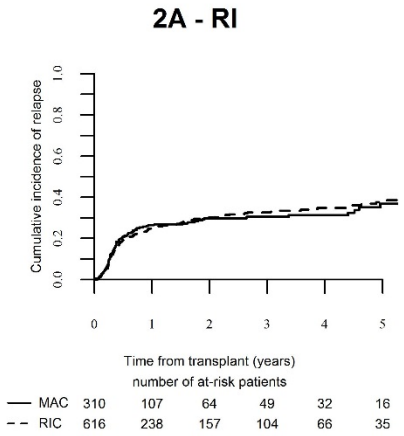
Christoph Schmid et al. Blood 2006;108:1092-1099

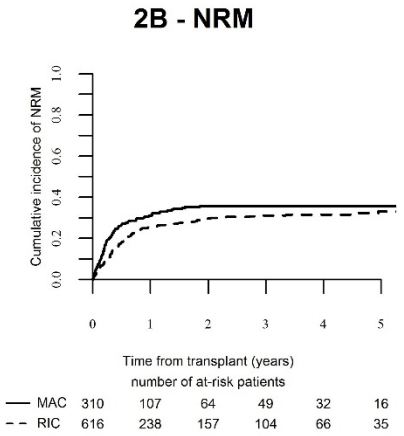
HCT in AML- Conditioning regimen

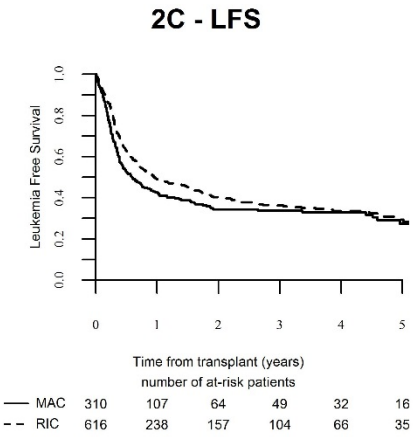
Retrospective data

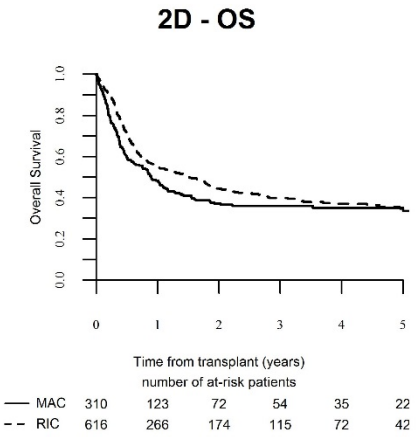
- Large study showed no significant outcome differences between RIC and MAC regimens after MMURD HCT in patients younger than 50 years
- Data support superiority of RIC regimen in older (>50 years) adults receiving transplant from MM-URD for AML

Concerns about increased relapse after RIC vs. MAC HCT- preliminary results of the BMT CTN 0901 study





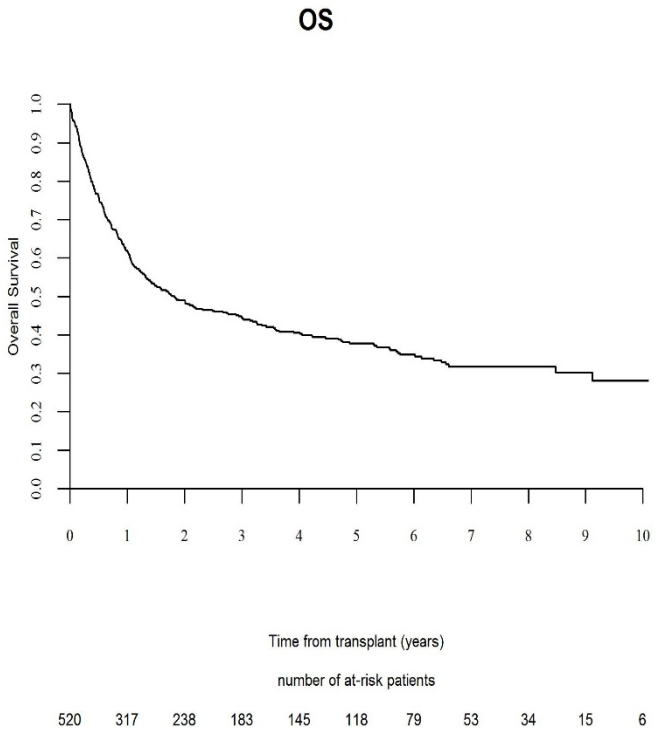


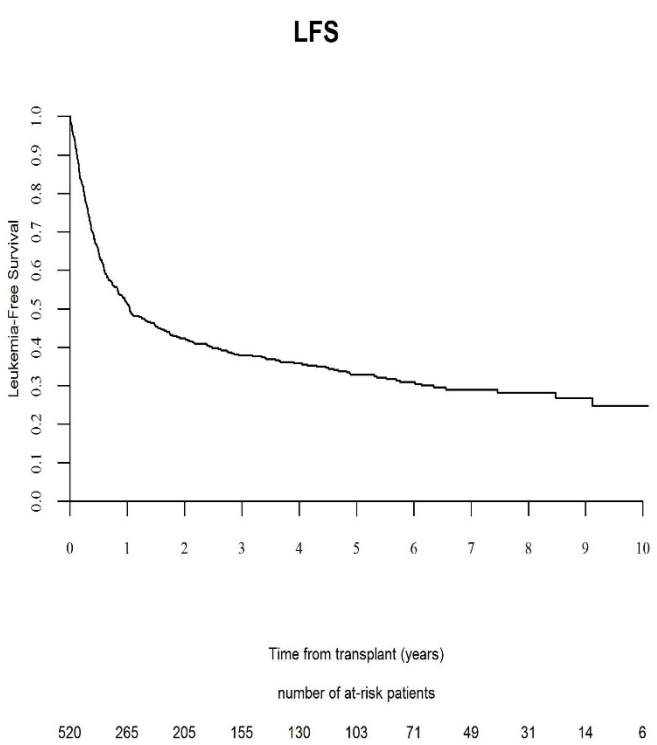


ALWP-EBMT, Haematologica 2016

HCT in AML- Novel conditioning regimen

Treosulfan based regimen in AML





- Treosulfan based conditioning regimen provides about 40% 5-year survival with low risk of early organ toxicity and acute GVHD
- The aim of future studies should be: to compare treosulfan to the currently available ablative regimens and to define the best treosulfan combinations

ALWP EBMT data, submitted 2016

Multicenter trial of myeloablative clofarabine and busulfan conditioning (CloBu4) for relapsed or primary induction failure AML. **Magenau et al. BMT 2017**

- Prospective multicenter phase II trial
- 71 patients, median age: 56 years
- Day 30 s/p HCT, 90% in morphologic remission
- NRM / relapse at 2 yrs was 25%/55%, respectively
- 2-year OS / EFS were 26% / 20%, respectively.
- EFS for PIF vs relapse (34% vs 8%), P< 0.01
- Multivariate analysis: CloBu4 vs contemporaneous cohort (CIBMTR) of AML not in remission who received MAC (n=105) - similar OS (HR: 1.33, 95% confidence interval: 0.92–1.92; *P*=0.12).

Case history

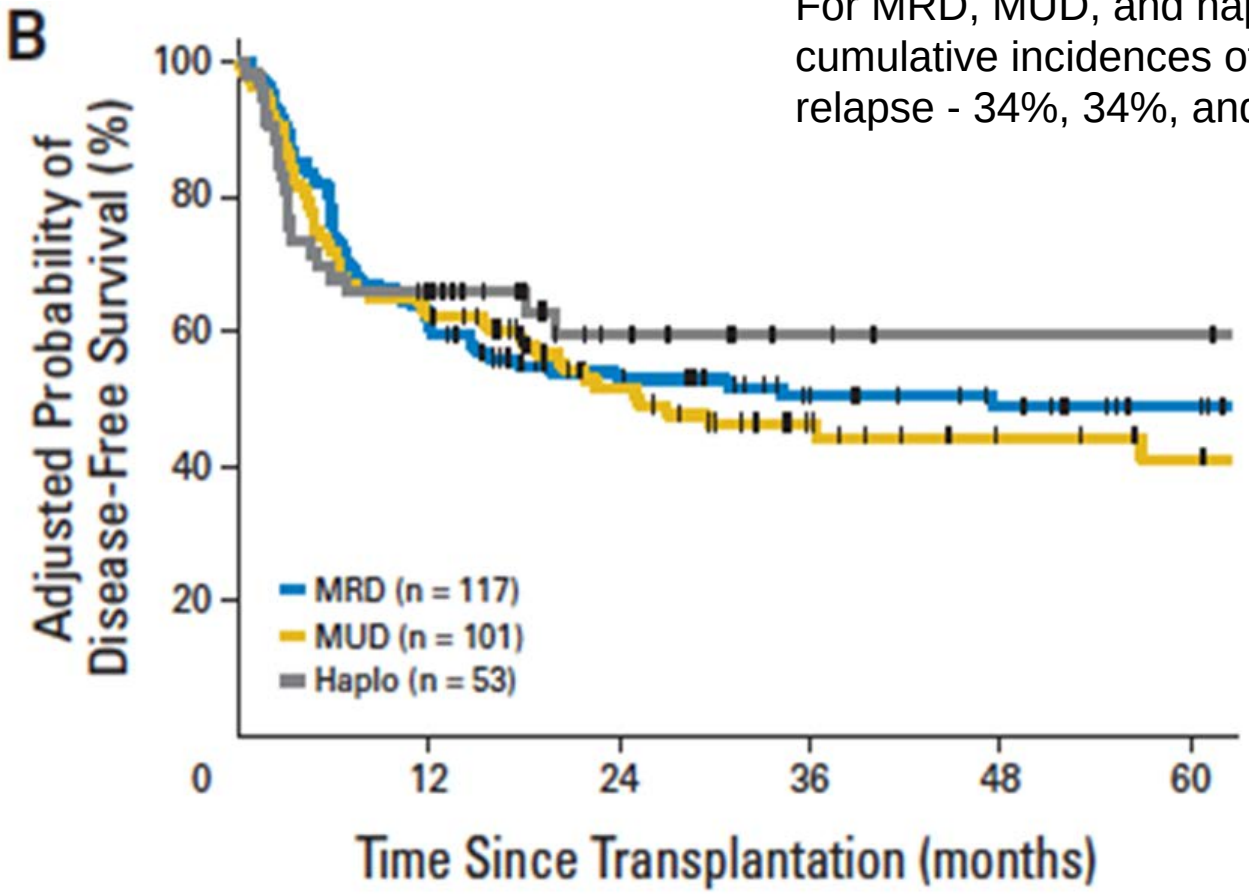
- Extensive discussion with patient/ family- outcome of elderly AML patient in CR1
  - ***transplant vs. no transplant***
- Risk of related M&M allo-SCT in elderly patients
- Decision- was to proceed with related haplo-SCT
- Haplo-SCT non-ablative regimen- Flu Cy TBI- 200 and post-SCT cytoxan
- GVHD prophylaxis- tacrolimus and MMF
- G-CSF from Day +5

HCT in AML- Alternative donor

Seminars in Hematology April 2016

T-cell-replete HLA-haploidentical HSCT for hematologic malignancies using PTCy results in outcomes equivalent to those of contemporaneous HLA-MRD and URD HSCT. Bashey. JCO, 2013

For MRD, MUD, and haplo HSCT: after 24-month cumulative incidences of NRM -13%, 16%, and 7%; relapse - 34%, 34%, and 33%, respectively (P, NS).



Impact of MRD positivity on survival post-transplant based on donor option

	Total	MRD+	Survival HR
UCB	112	31 (28%)	1.01
MURD	334	112 (36%)	2.14
MMURD	110	47 (43%)	1.94

Presence of MRD+ negatively impacted RR in MURD and MMURD but not RR or OS with CB

Frederick R. Appelbaum, BCP 2015

Case for maintenance therapy s/p HCT for myeloid malignancies.

- Relapse remains the major cause of treatment failure.
- Therapeutic options for patients who relapse after allo-HCT is limited
- Prognosis of patients relapsing after allo-SCT remains dismal
- Goal is to reduce the relapse rate and
- prolong survival

Stem cell Inv. 2016

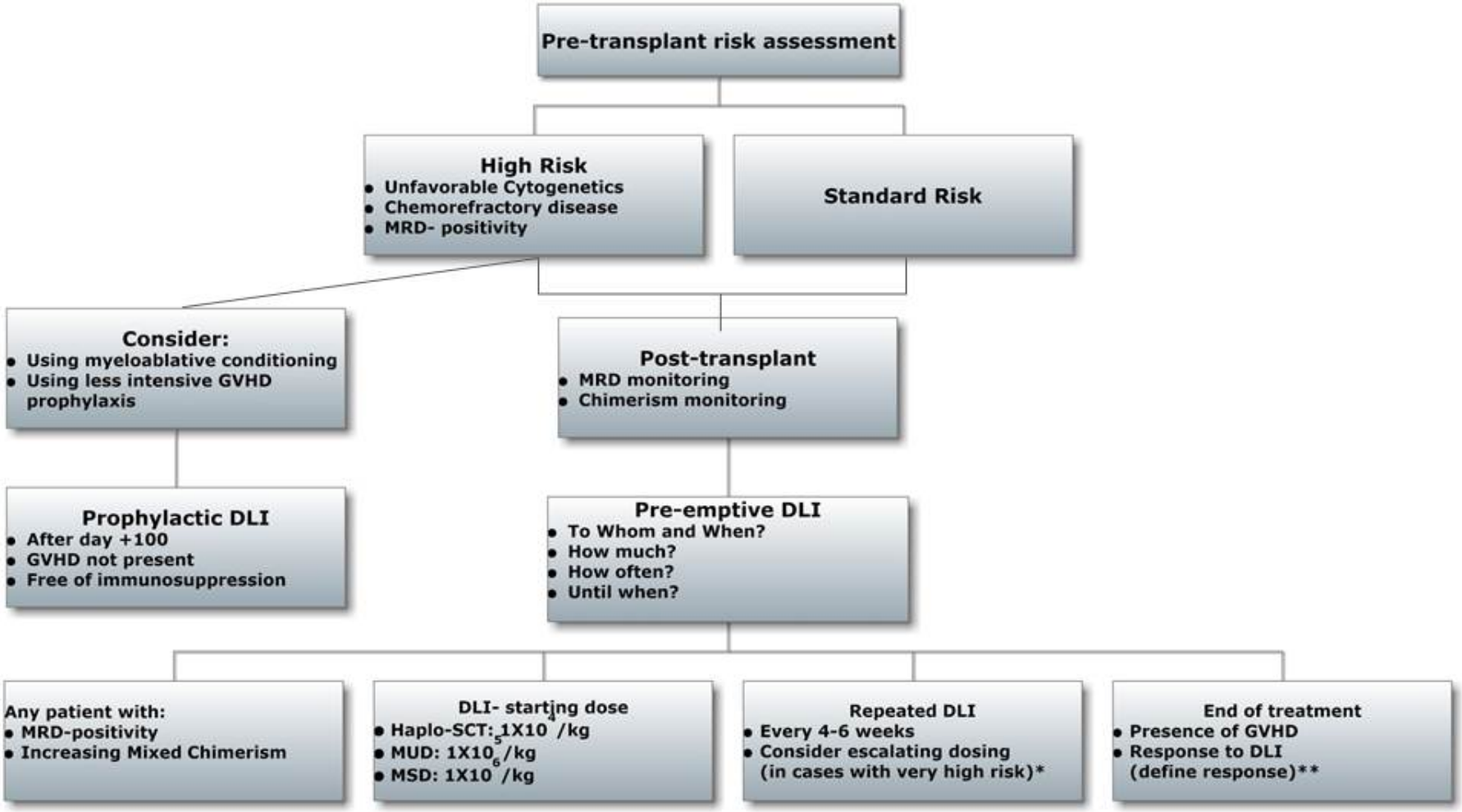
Characteristic of an ideal maintenance therapy

Characteristic
Active against the disease
Acceptable nonhematologic toxicity
Tolerated early after transplant
Nonmyelotoxic or with tolerable myelotoxicity
Drug interactions manageable
Will not inhibit graft-versus-tumor effect
Will not worsen graft-versus-host disease

Maintenance therapy options

Characteristic
DNMT inhibitors: Azacytidine Decitabine
Deacetylase inhibitors: Panobinostat
Tyrosine kinase inhibitors: Sorafenib Quizartinib Midostaurin

HCT in AML- Relapse managment after HCT



ALWP-EBMT, Bone Marrow Transplant 2016

Patient follow-up

- Patient tolerated Haploidentical transplant
- Minimal regimen related toxicity
- Received Azacytidine maintenance therapy
- D+365 MRD status was negative
- GVHD
  - Maximum acute and chronic GVHD at day 365: aGVHD none; cGVHD limited mild chronic gvhd

Take home message

- More patients are undergoing HCT for AML
- Better understanding of molecular biology of AML
- vel information will help identifying more patients needing HCT in CR1
- We are going to see more and more patients needing HCT in CR1
- HCT options are unlimited
- New era in managing post-transplant relapses- e.g. novel drugs to achieve disease control, second haplo-HCT
- The area of investigation will likely continue to be of interest in terms of optimizing transplant outcomes

Thank you!