BHS Training Course and Seminars
Seminar 6

Managing Relapse and Maintenance Therapy after Allogeneic Stem Cell Transplantation

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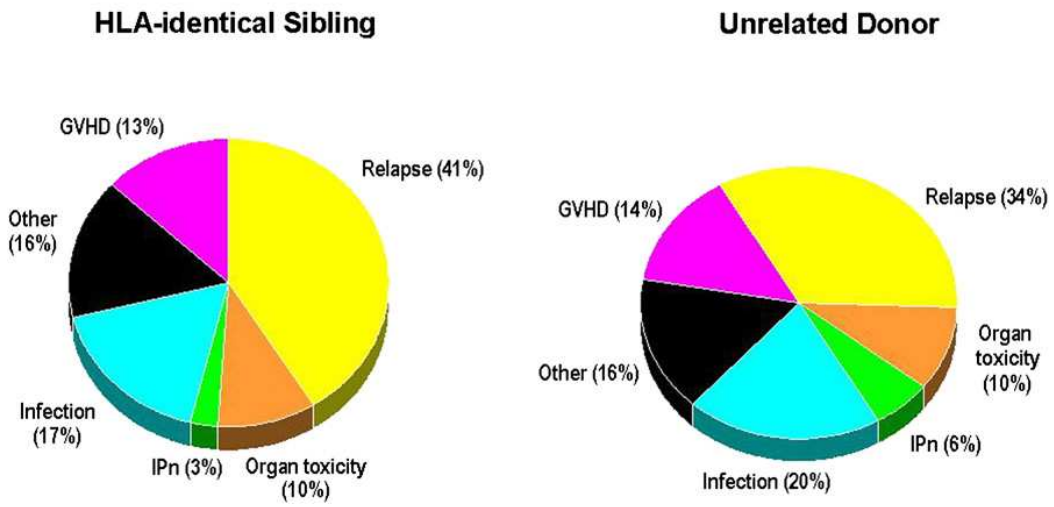
Allogeneic Stem Cell Transplantation

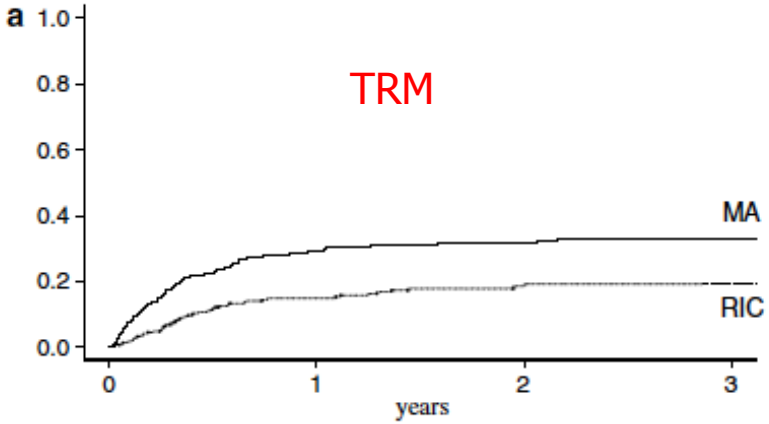
- Relapse is the main cause of TREATMENT FAILURE

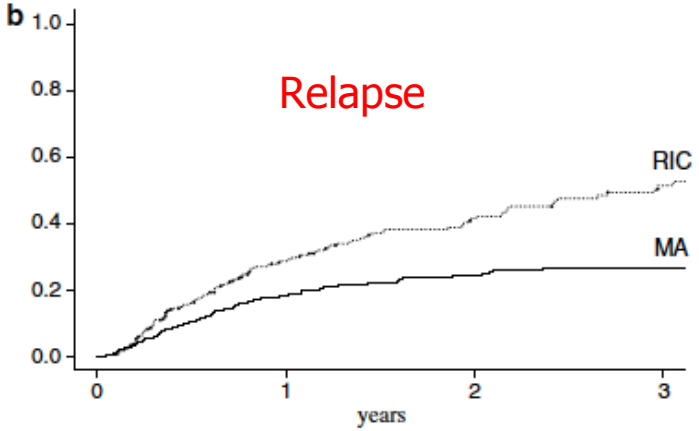
CIBMTR: Causes of Death after Allogeneic Transplantations Done in 2001-2006



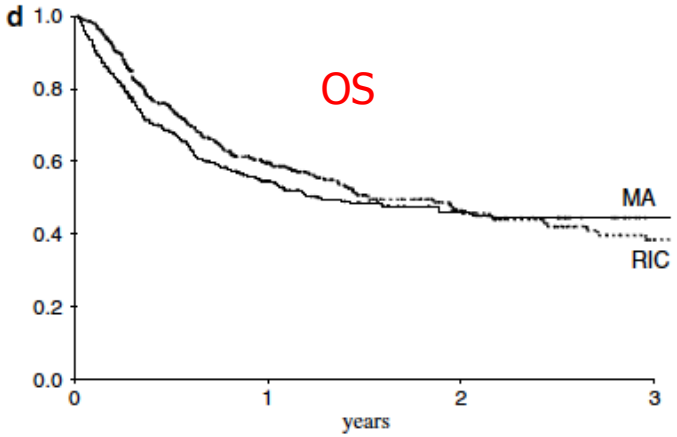
- Prognosis is poor
- No consensus
- Insufficient graft-versus-tumor effect

Increased relapse risk after RIC

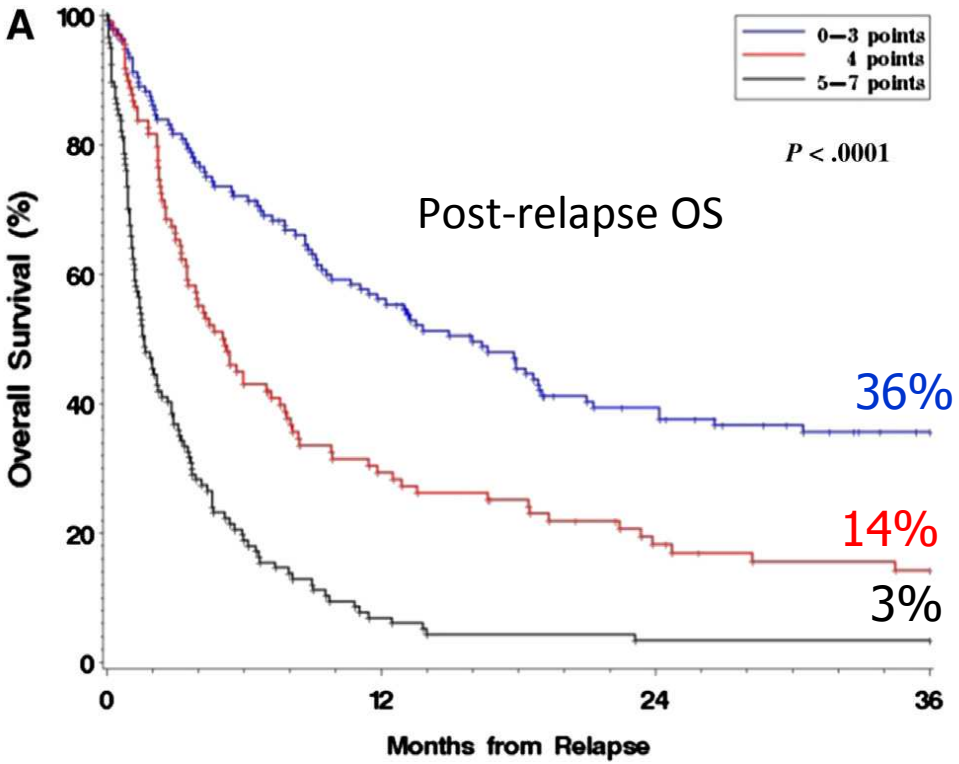




Aoudjhane et al, Leuk 2005



Prognosis of relapse



Thanarajasingam et al., BBMT 2013

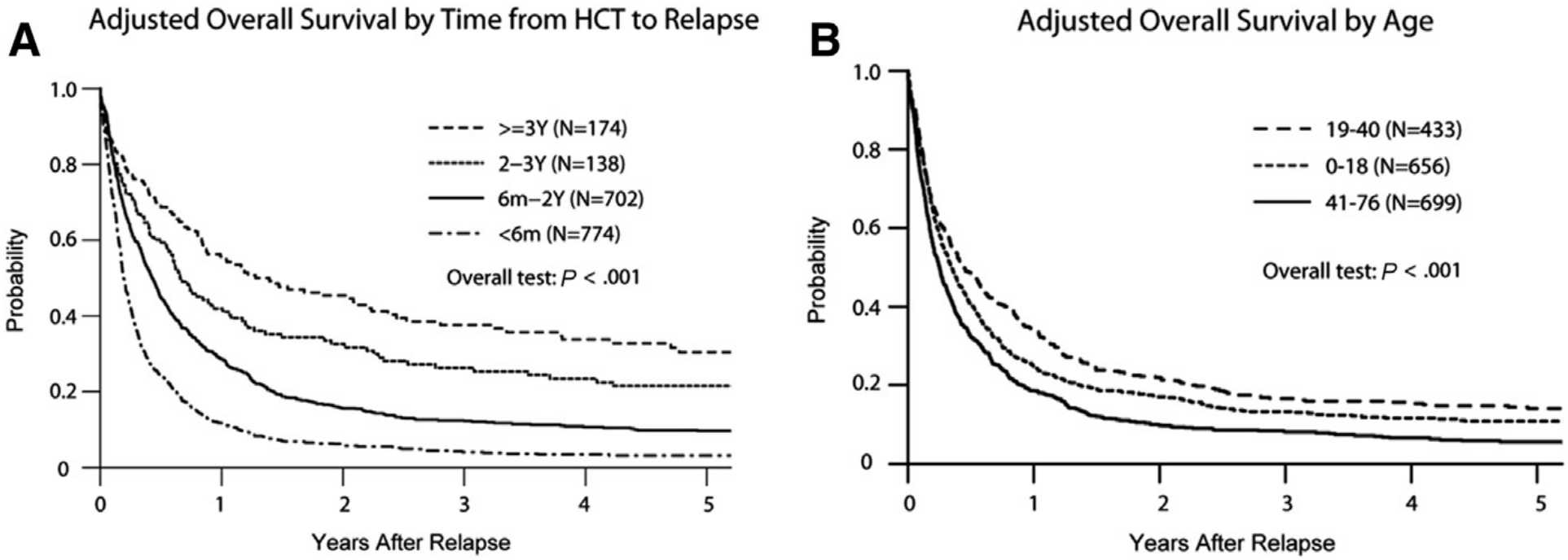
Prognostic factors

- Time to relapse
  - > 24 mo, 6-24 mo, 3-6 mo, <3 mo
- Disease-risk index
  - Low: indolent NHL, CLL, CP-CML
  - Int: aggressive NHL, MDS
  - High: high-risk AML
- Conditioning intensity
- Prior GvHD

Other Factors not included

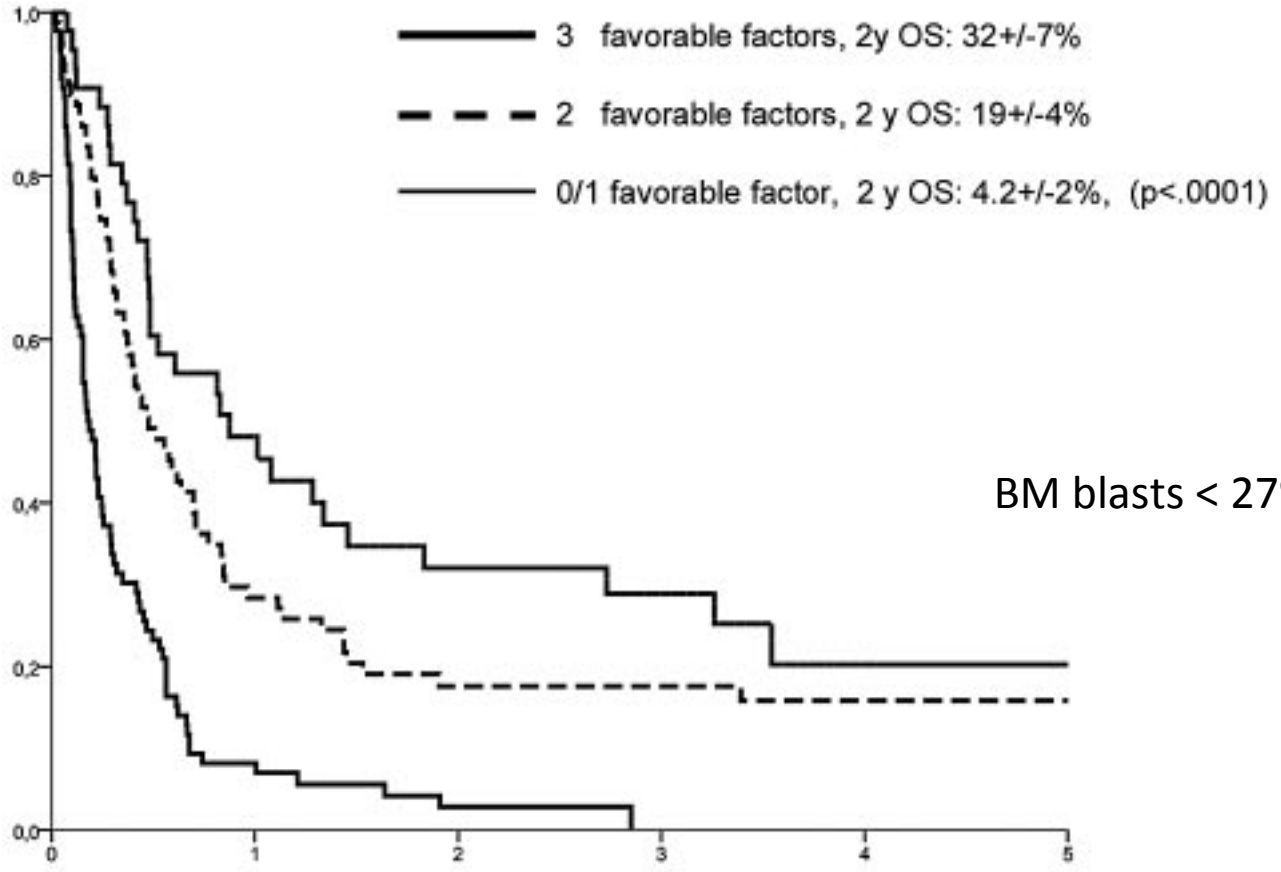
- Age
- CR Achievement after relapse

Interval from SCT and Age



Bejanyan et al., BBMT 2015

BM blasts at relapse in AML

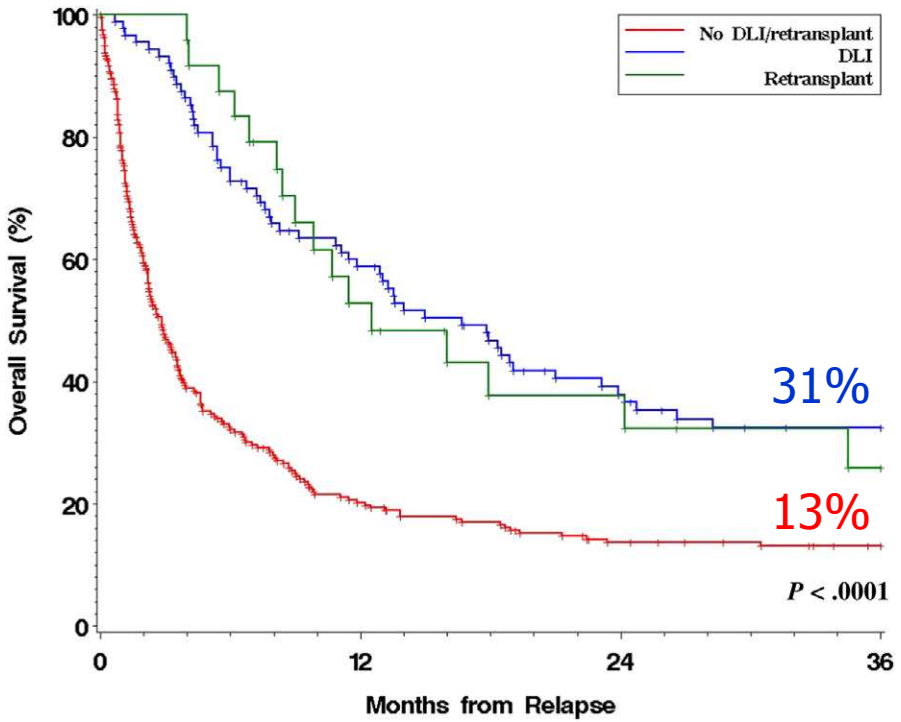


BM blasts < 27%

Schmid et al., Blood 2012

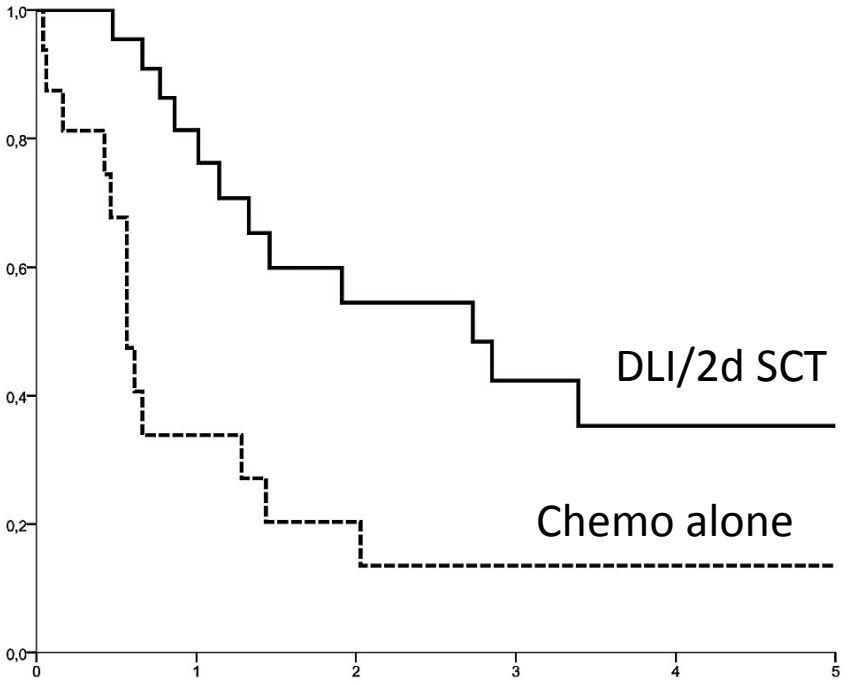
Cell-based Therapy
Especially in CR patients

All diseases



Thanarajasingam et al., BBMT 2013

AML



Schmid et al., Blood 2012

Treatment Options

- Withdrawal of immunosuppression
- Tumor burden reduction:
  - Standard chemotherapy
  - Inhibitors
  - Targeted therapy
  - Immunomodulatory drug
- Donor leukocyte infusion
- Second Allogeneic Stem Cell Transplantation
- T-cell engeneering (CAR-T)
- Vaccines
- Supportive Care

Early Intervention, Better Ouctomes
Early Detection

Minimal Residual Disease

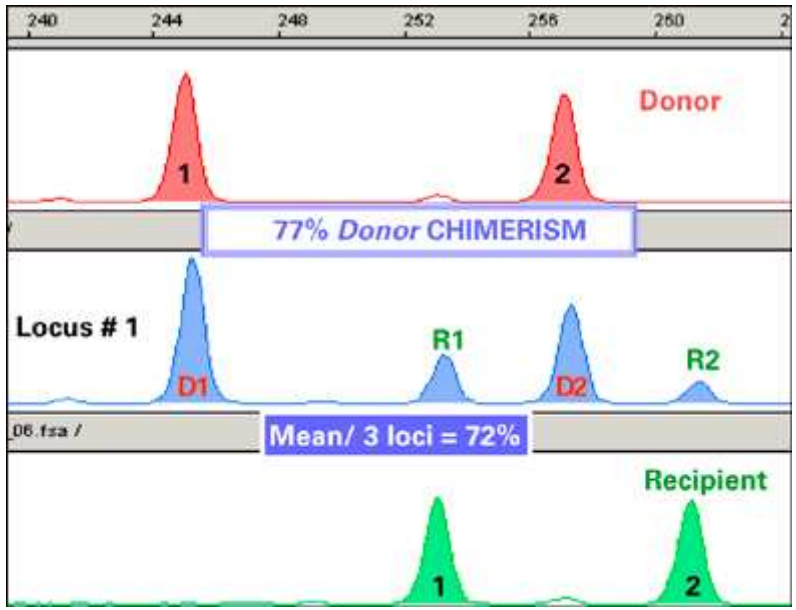
Table 1. Diagnostic Methods to Monitor Residual Disease and Relapse of Hematologic Malignancies after alloHSCT

	Tumor Marker Detection					Chimerism	
Method	*Chromosomal Banding*	*FISH*	*Flow Cytometry*	*Antigen Receptor PCR*	*Translocation or Other RT-PCR*	*XY FISH*	*qPCR/STR-PCR*
Applicability	Subset of all types	Subset of all types	ALL; most AML; CLL; myeloma	ALL; lymphoma; CLL	CML; Subset of ALL; subset of AML; subset of lymphoma	Sex mismatched alloHSCT	All types with differences in donor/recipient polymorphisms
Sensitivity	10^{-1}	10^{-2}	10^{-3}-10^{-4}	10^{-4}-10^{-5}	10^{-3}-10^{-6}	10^{-2}	10^{-3}-10^{-6}

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction; qPCR, quantitative real-time PCR; RT-PCR, reverse transcription PCR; STR, short tandem repeats.

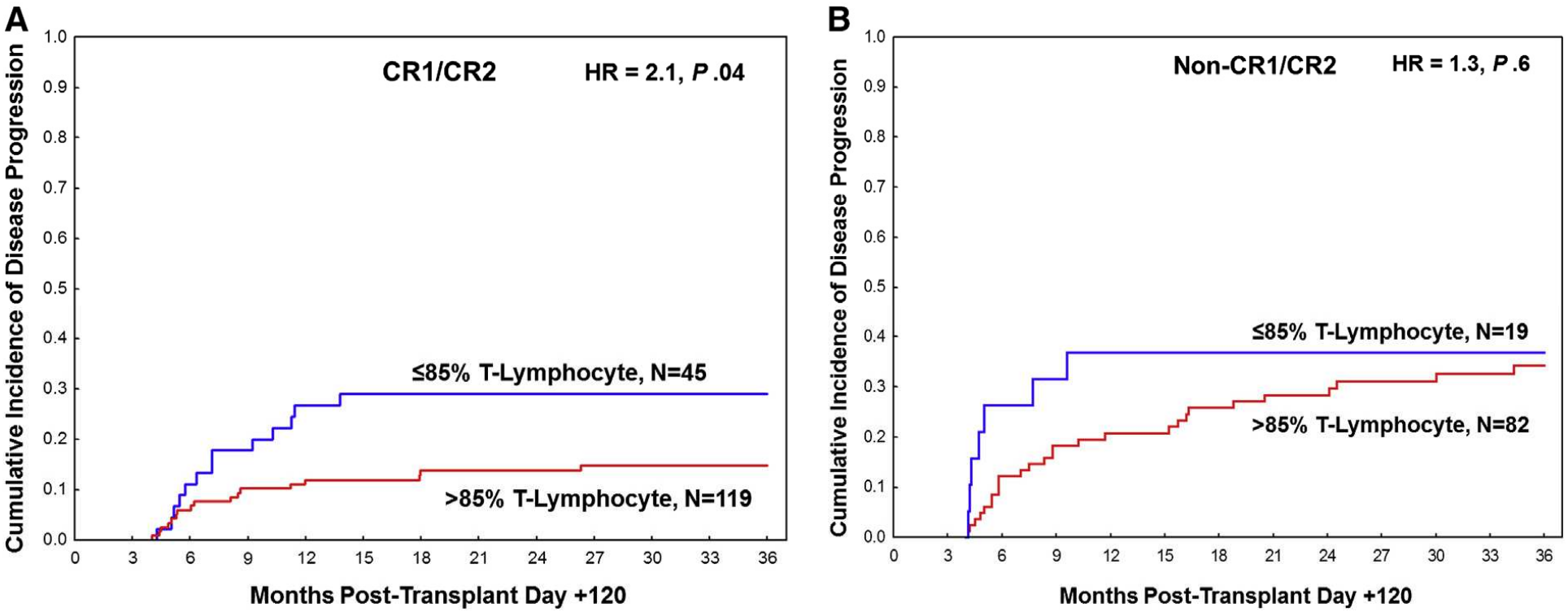
Chimerism

- Short-tandem repeats (STR-)PCR specific to an individual
- Engraftment marker and not a tumor-specific marker
- Better specificity using lineage specific chimerism as CD34+ for AML, CD19+ for CLL, CD138+ for MM
- Increased mixed chimerism after RIC



GvT acts through T-cells
⇒ Full donor T-cell chimerism may have a stronger GvT effect

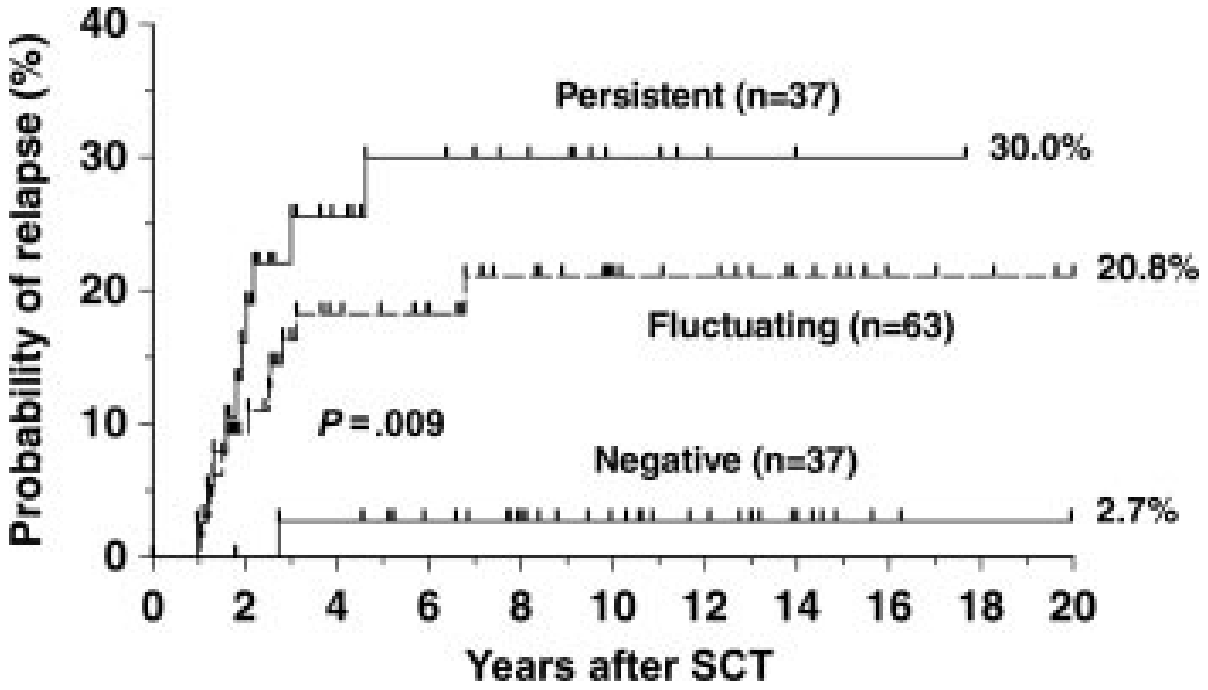
Chimerism at day +100 and relapse



Lee et al BBMT 2015

Conversion to Full Donor Chimerism is associated with response
Every 3 months the first year

BCR-ABL

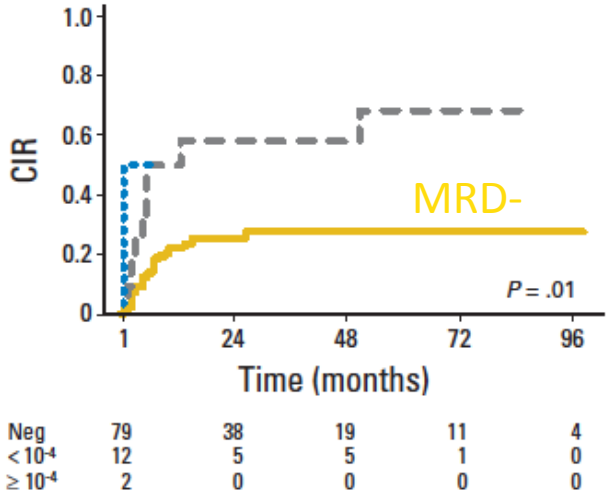


Kaeda et al. Blood 2006

Monitoring every 3 months on PB for CML
Monitoring every 2-3 months on BM for ALL

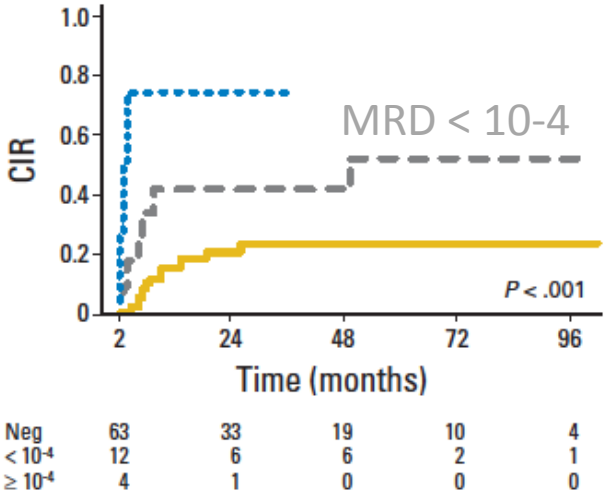
ASO-PCR in ALL

D+30



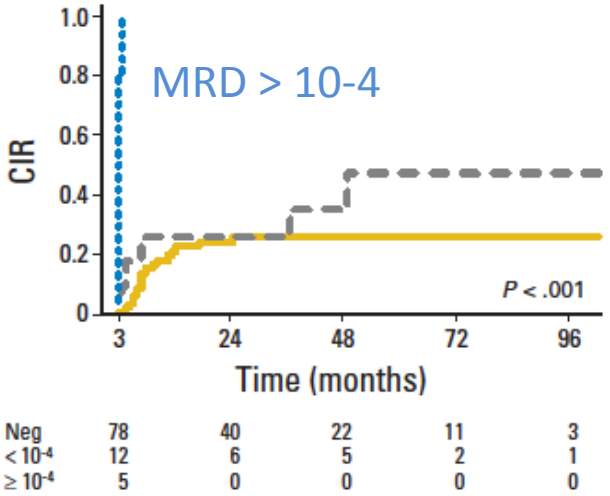
Neg	79	38	19	11	4
$< 10^{-4}$	12	5	5	1	0
$\geq 10^{-4}$	2	0	0	0	0

D+60



Neg	63	33	19	10	4
$< 10^{-4}$	12	6	6	2	1
$\geq 10^{-4}$	4	1	0	0	0

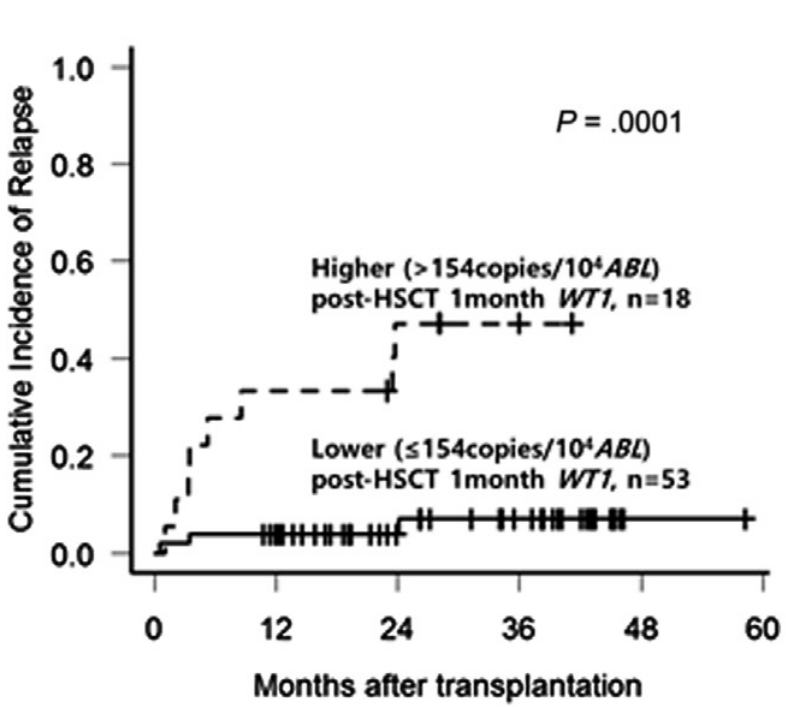
D+90

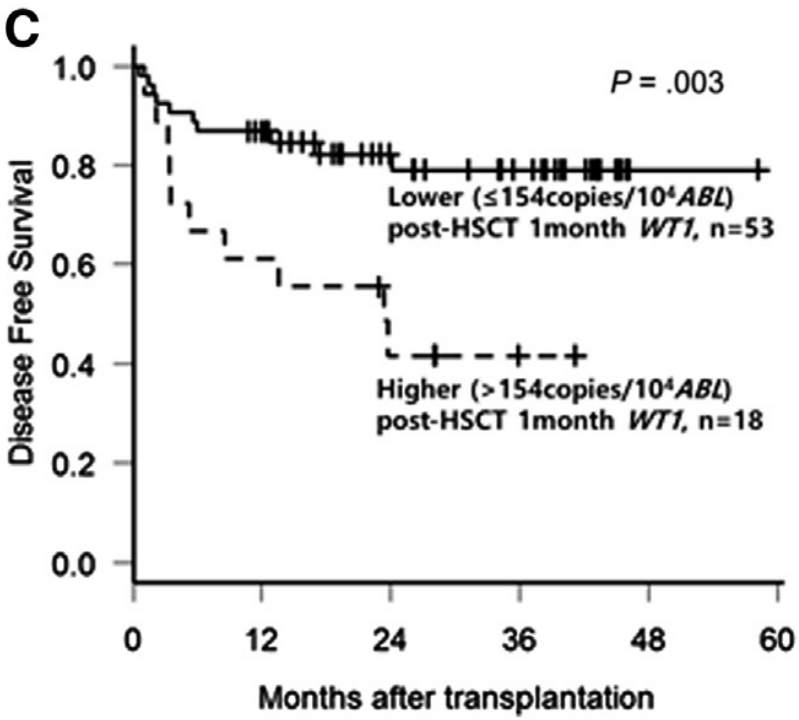


Neg	78	40	22	11	3
$< 10^{-4}$	12	6	5	2	1
$\geq 10^{-4}$	5	0	0	0	0

Bader et al. JCO 2015

WT1 in AML





Yoon et al. BBMT 2015

Treatment Options

- Withdrawal of immunosuppression
- Tumor burden reduction:
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  - Inhibitors
  - Targeted therapy
  - Immunomodulatory drug
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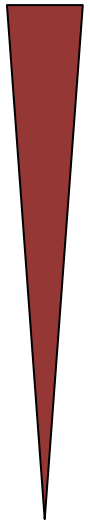
DLI

Donor Leukocyte Infusion (DLI)

Single leukapheresis of the donor with peripheral leukcocytes product containing lymphocytes, granulocytes, monocytes…

– CML	
– Chronic Phase	60-80%
– Accelerated/blastic	35%
– Low grade lymphoma	70-80%
– CLL	75%
– MM	45%
– Hodgkin lymphoma	40-45%
– AML/MDS	15-30%
– ALL	0-20%
– Aggressive lymphoma	10-20%



Decreased Efficacy

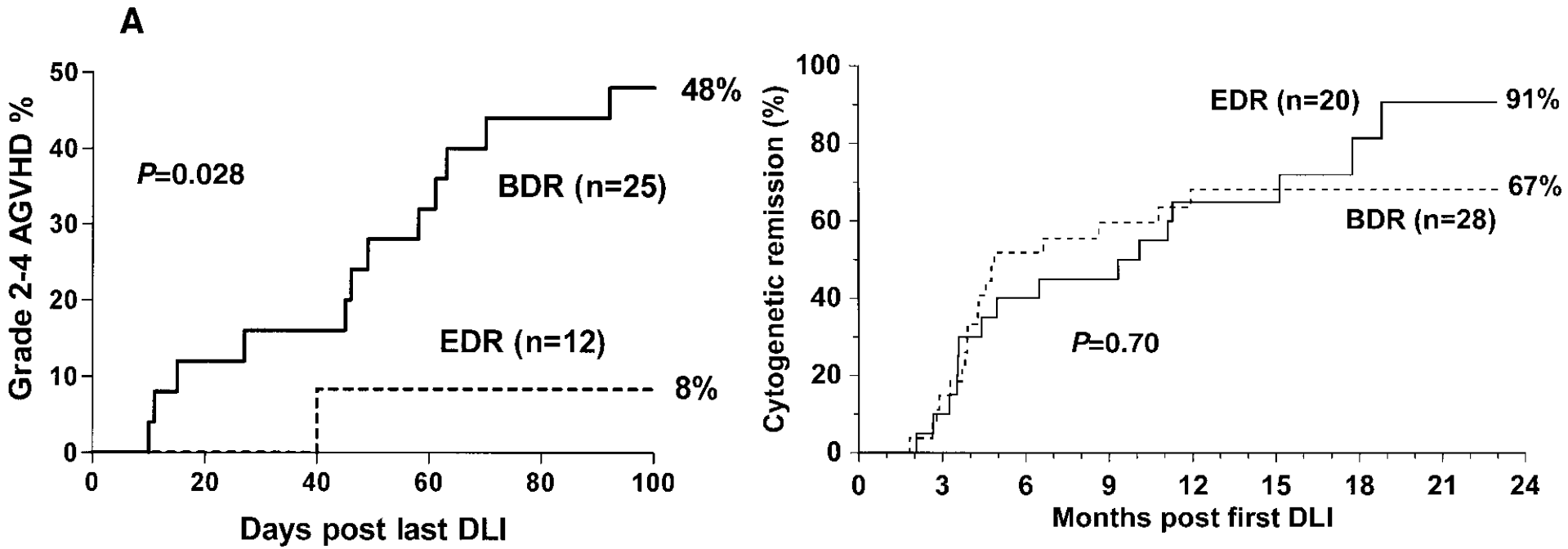
Complications :
-GvHD
-Aplasia
-TRM 5-44%

Donor Leukocyte Infusion (DLI) Dose

Low (~10^6 CD3+/kg)	High (~10^7 CD3+/kg)
– MRD	– Frank Relapse
– Mixed Chimerism	
– Indolent disease	– Aggressive disease
– Unrelated	– Sibling
– Early after SCT	– Delayed after SCT
– History of GvHD	– No history of GvHD

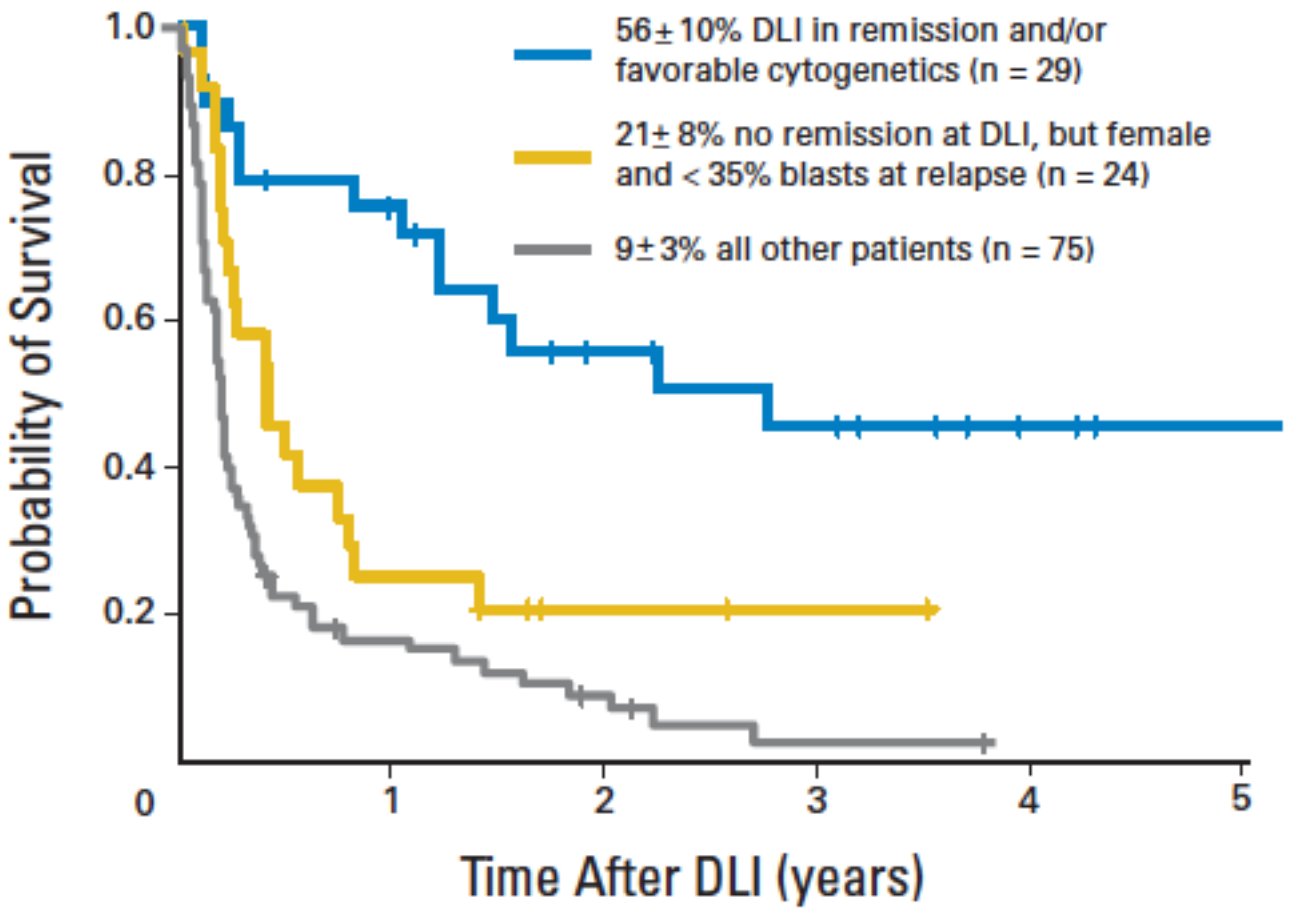
Dose-escalated DLI

- Sibling : $10^7 \rightarrow 5 \times 10^7 \rightarrow 10^8$ CD3+/kg
- Unrelated : $10^6 \rightarrow 5 \times 10^6 \rightarrow 10^7$ CD3+/kg
- Every 2-3 months in the absence of GvHD



Dazzi et al. Blood 2000

Prognosis after DLI in AML



Schmid et al., JCO 2007

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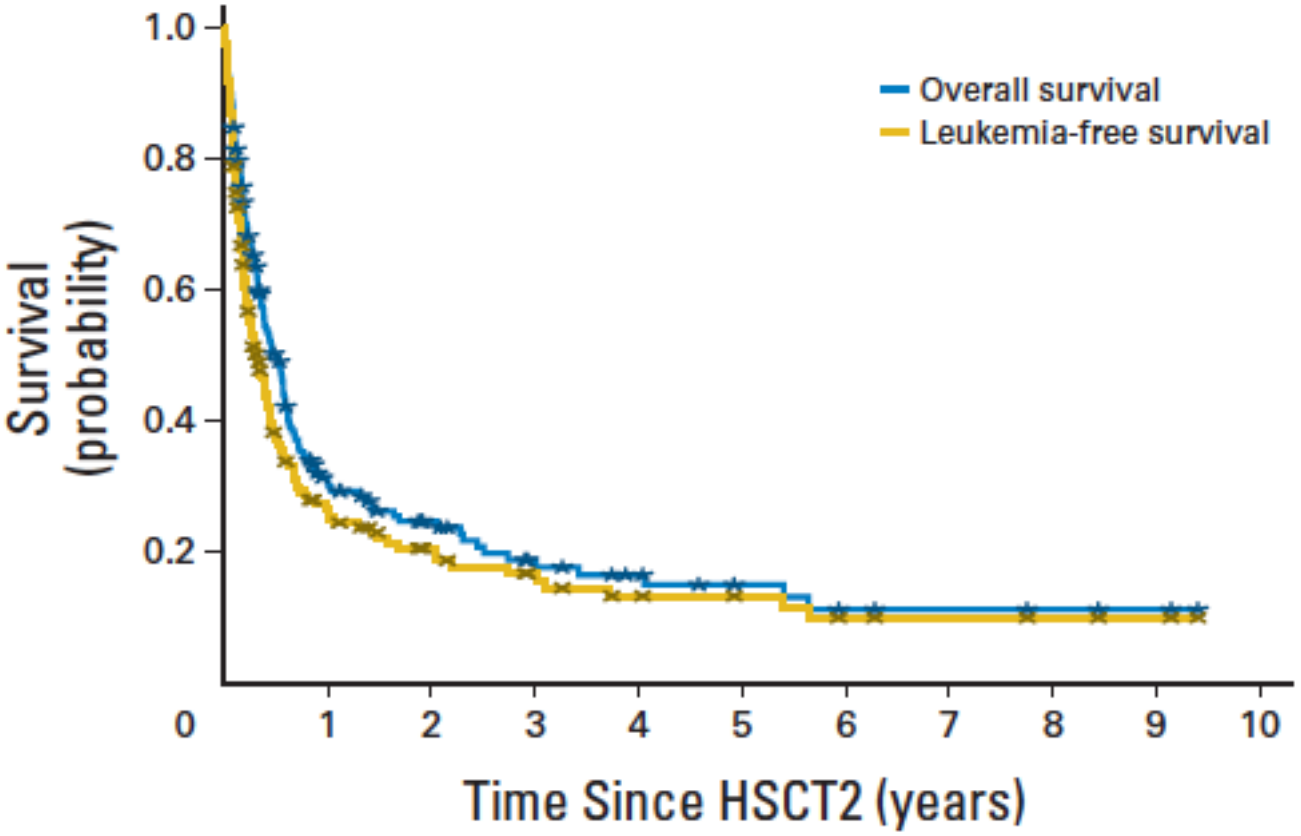
Second allo-SCT

Second Allo-SCT

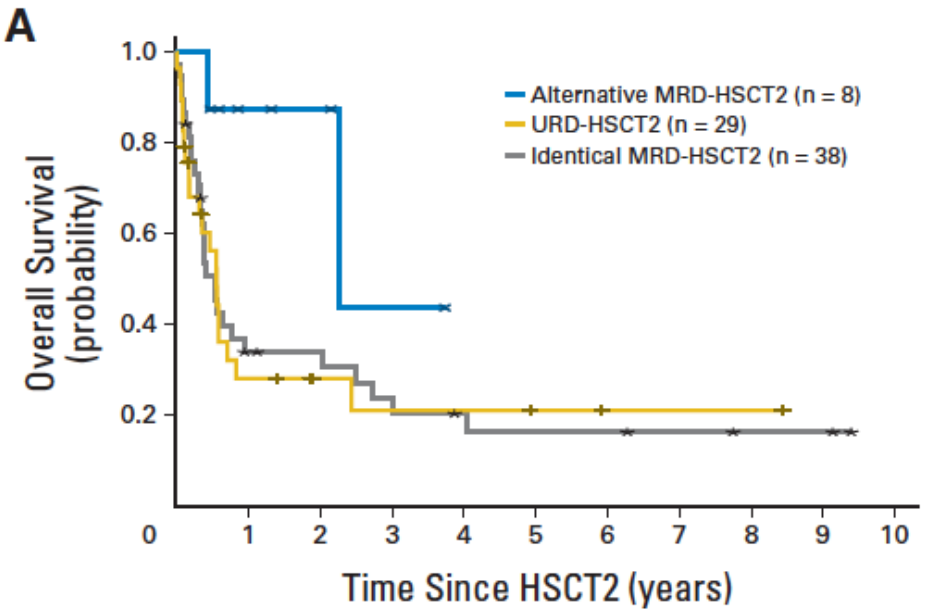


Duration of CR
CR at SCT2

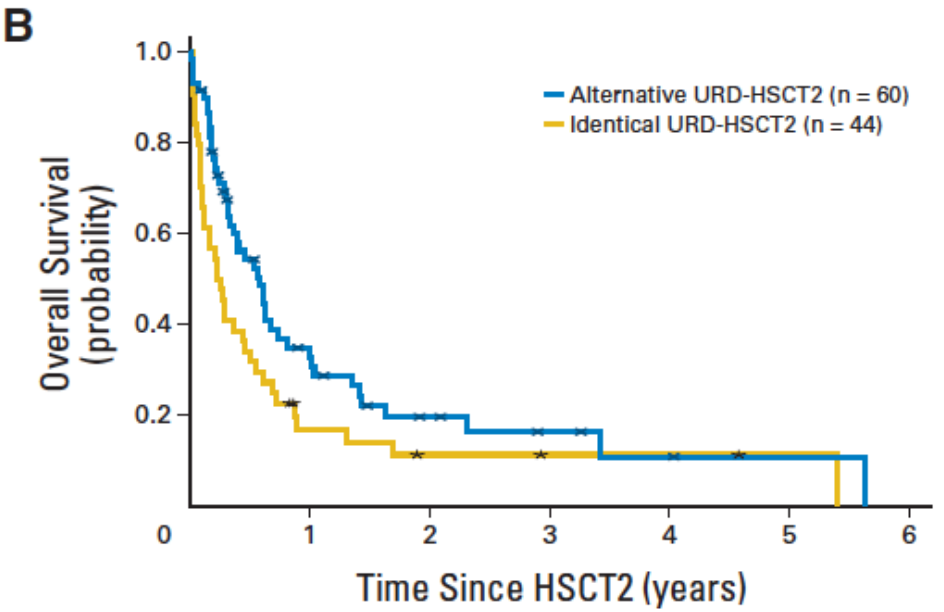
Christopeit et al., JCO 2013

Second Allo-SCT Donor Change

MRD at HSCT1



URD at HSCT1



Christopeit et al., JCO 2013

How to improve Cell-Based Therapy

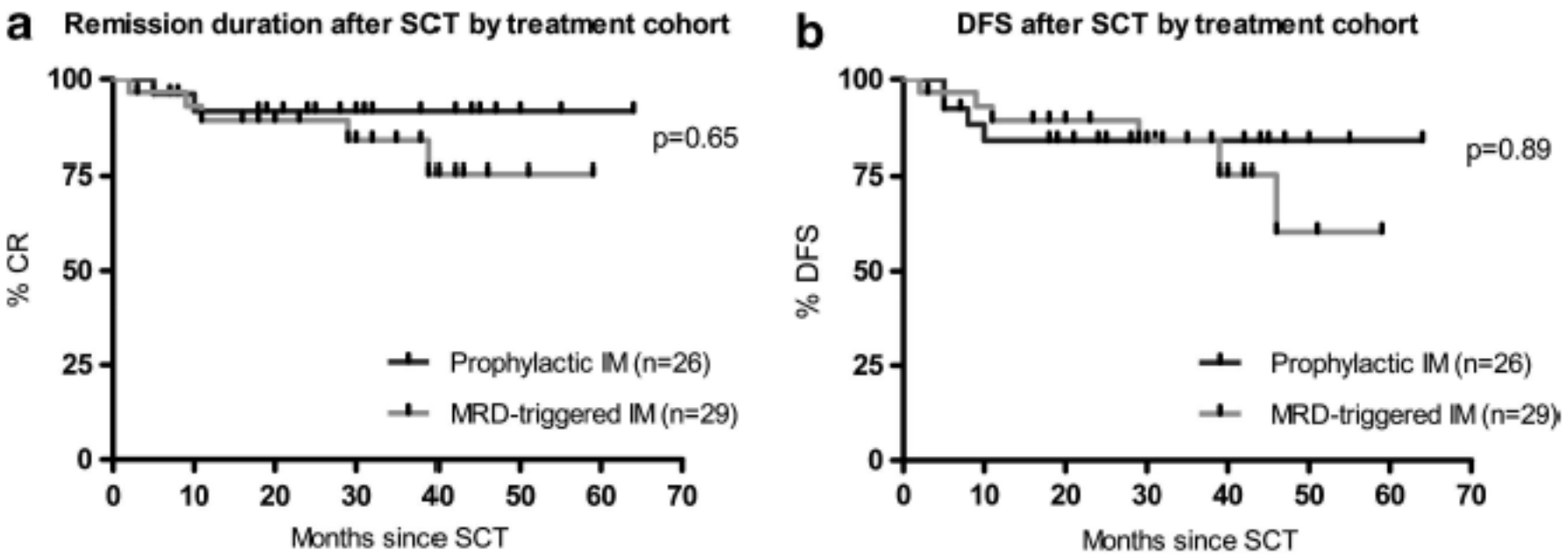
Tumor Burden Reduction
-Standard Chemotherapy
-Inhibitors
-Immunomodulatory Drugs
-Targeted Therapy

Relapse

Maintenance Therapy

Inhibitors : Tyrosine Kinase Inhibitors ALL

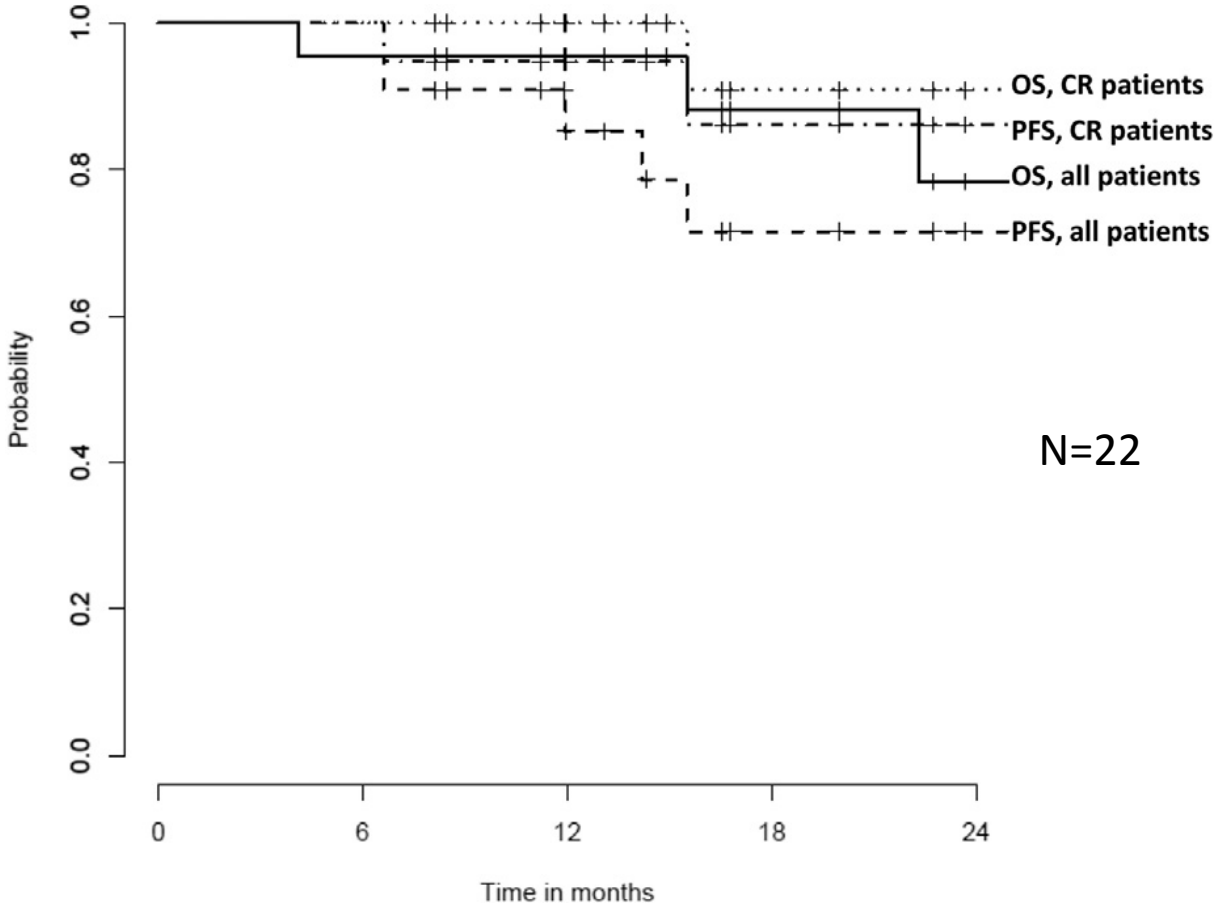
Glivec given systematically around D+60 versus MRD-triggered



Pfeifer et al., Leukemia 2013

Inhibitors : FLT3 Inhibitors
AML

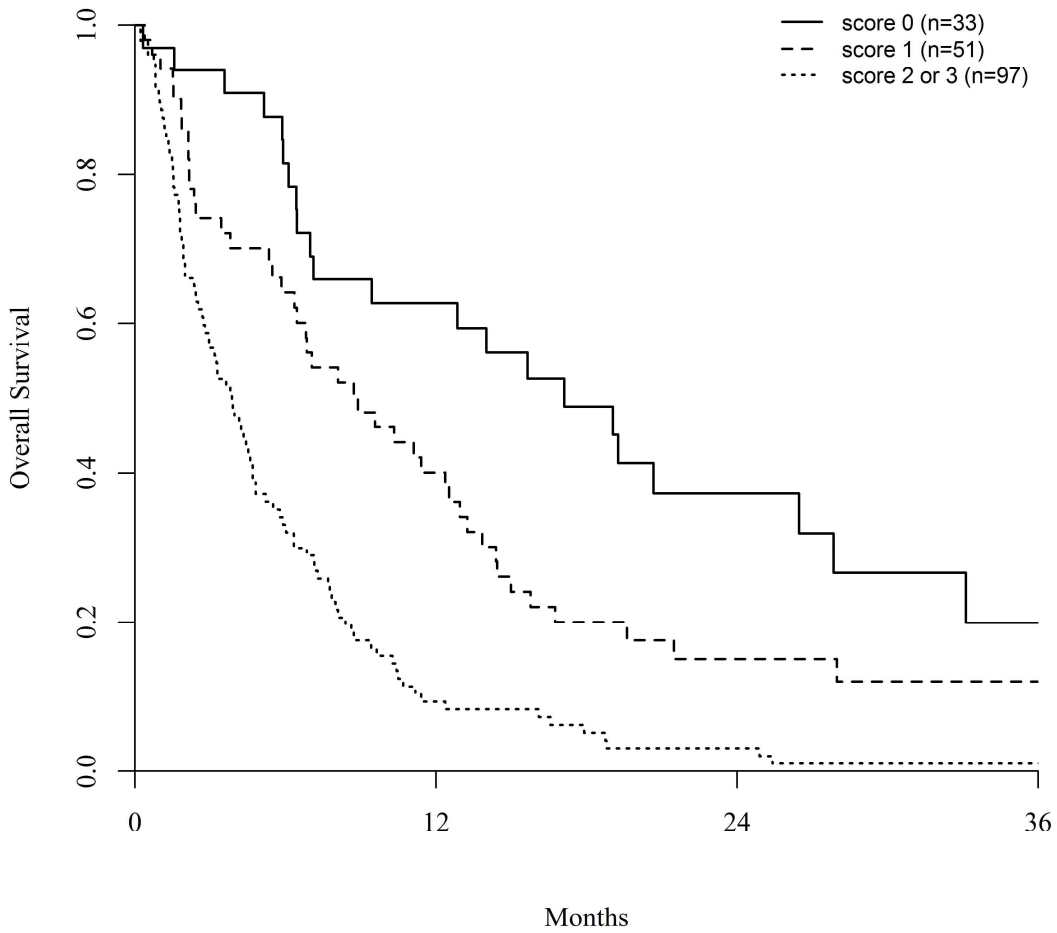
Sorafenib started around D+45 and D+120



N=22

Chen et al., BBMT 2014

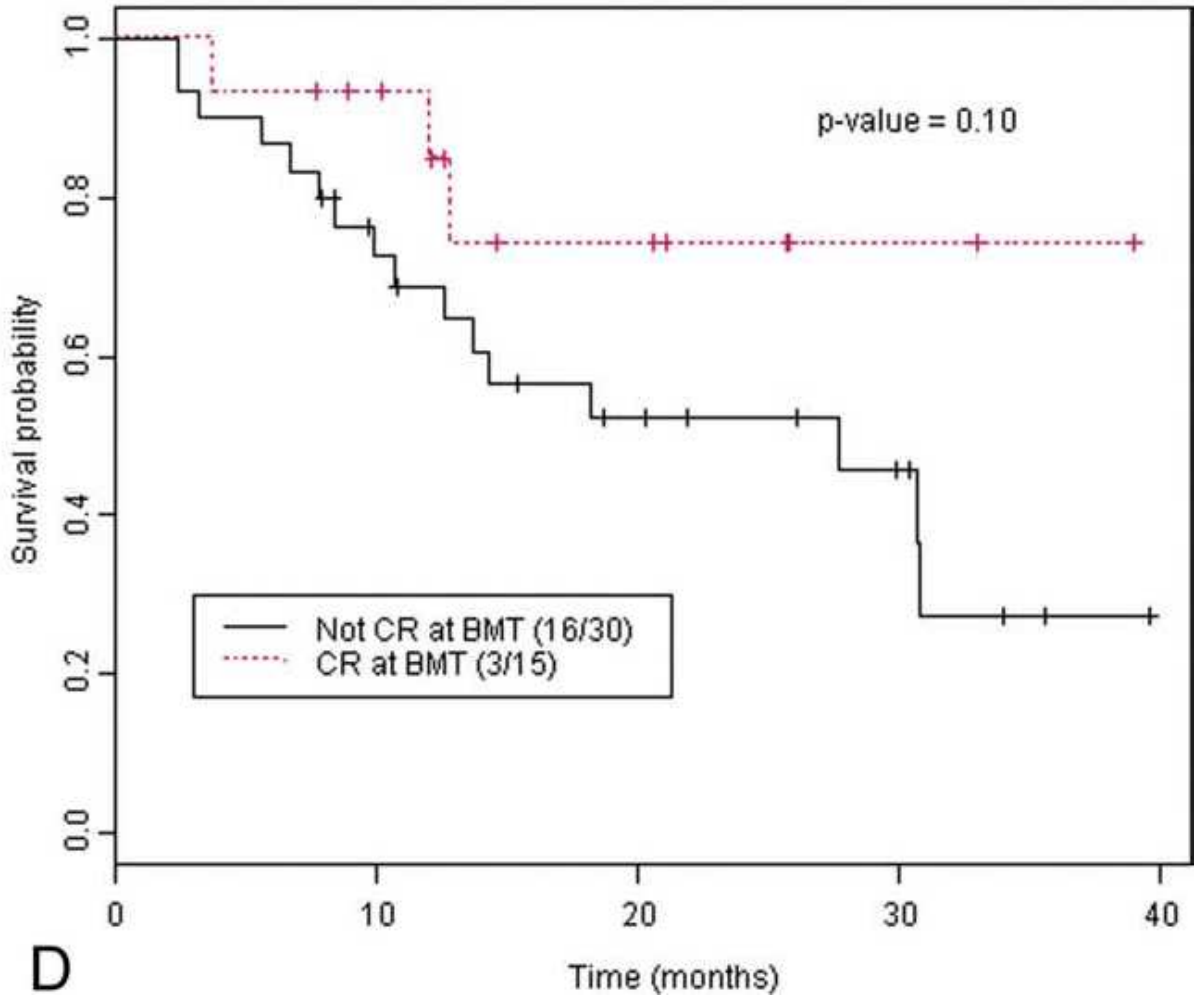
Immunomodulatory Drugs
Azacytidine for relapsed AML/MDS



Relapse <6 mo, 6-12 mo, > 12 mo
Blasts at relapse > 20%

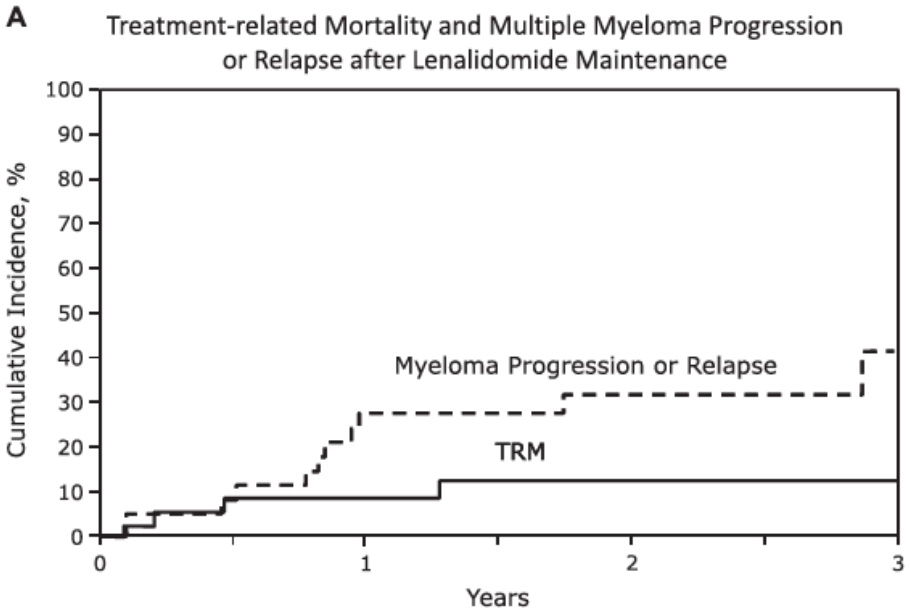
Craddock et al., Haematologica 2016

Immunomodulatory Drugs
Azacytidine as maintenance in AML

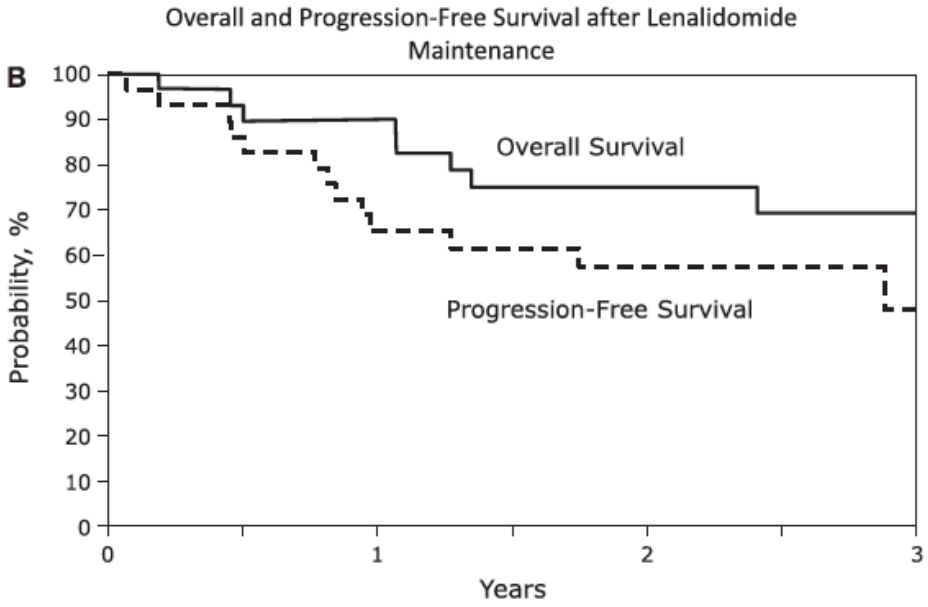


De Lima et al., Cancer 2010

Immunomodulatory Drugs
Lenalidomide as maintenance in MM

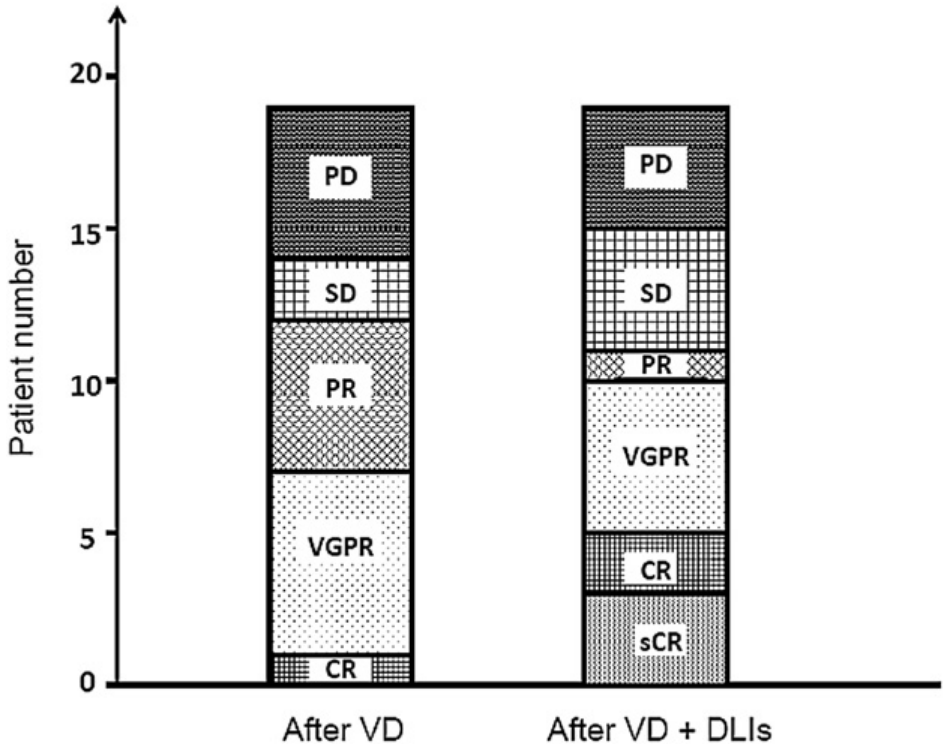


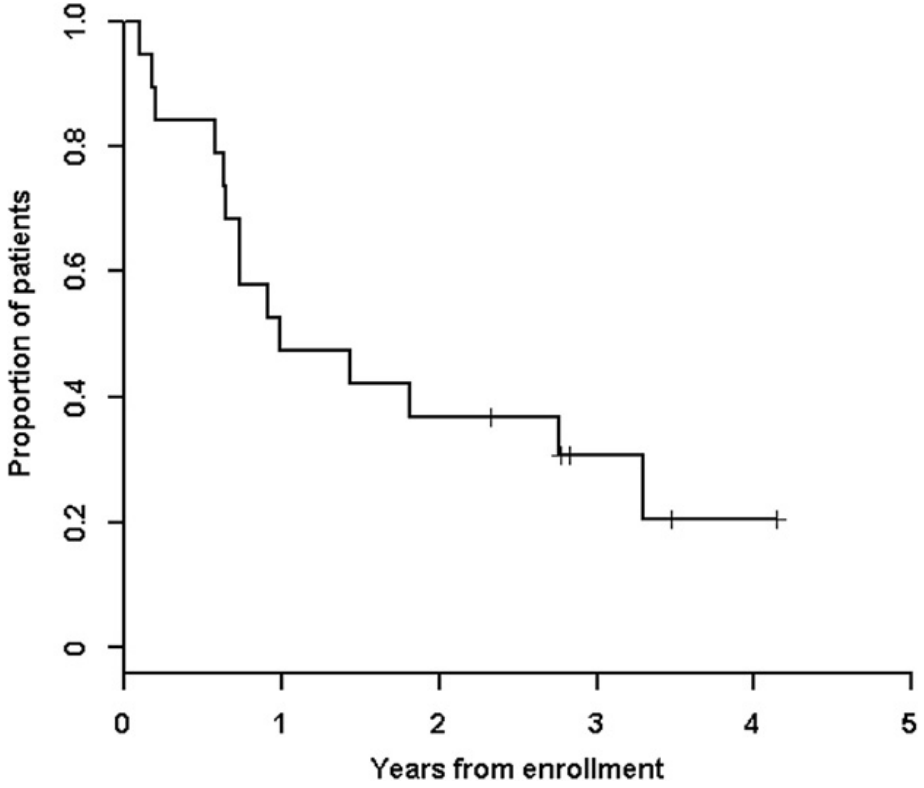
High-risk MM
Len 10 mg/day
aGvHD



Alsina et al., BBMT 2014

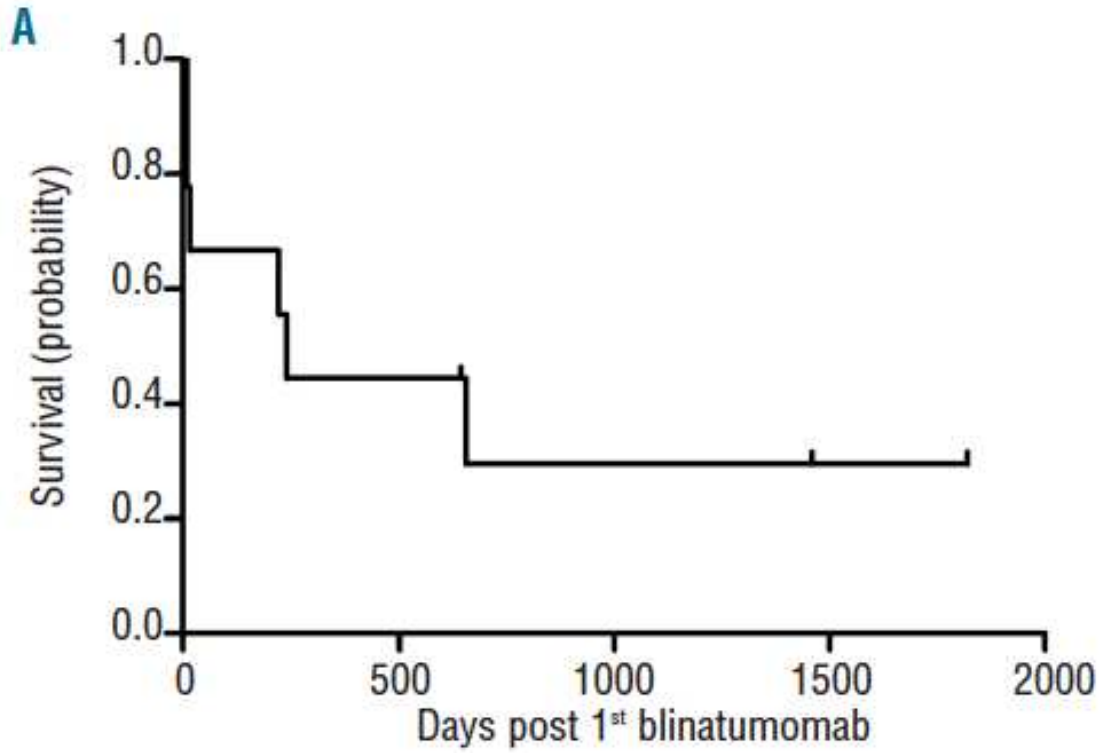
Immunomodulatory Drugs
Bortezomib+DLI in relapsed MM

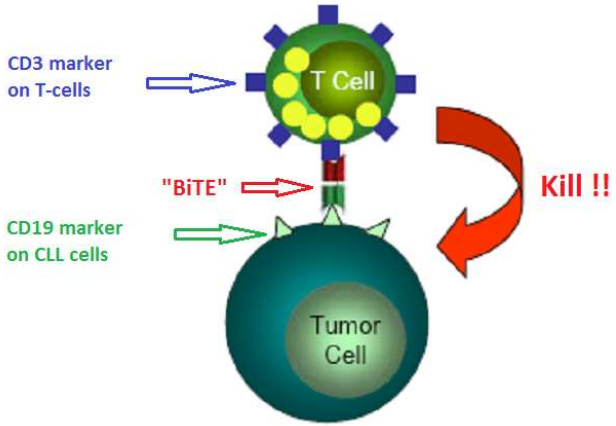




Montefusco et al., BBMT 2013

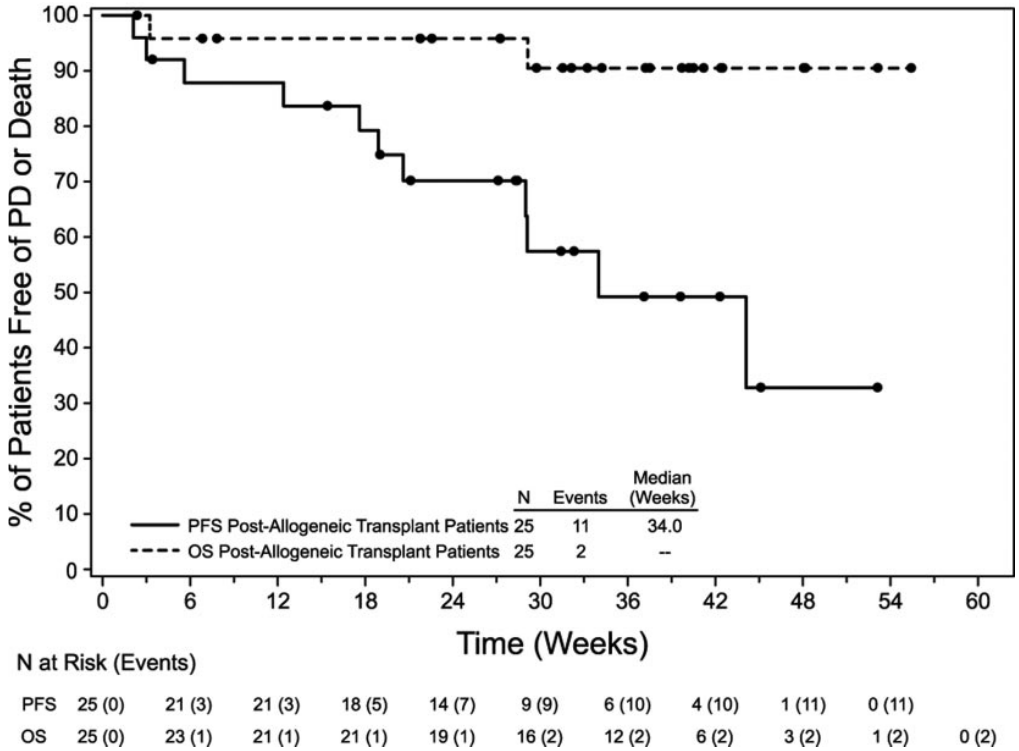
Targeted immunotherapy
Blinatumomab in relapsed ALL

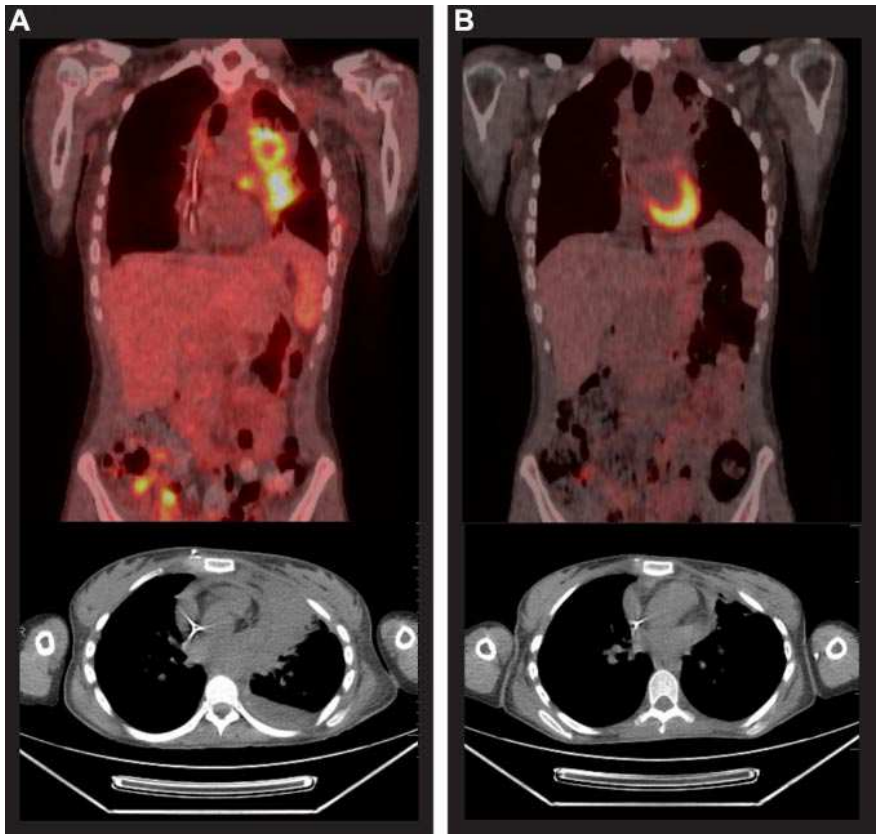




Schlegel et al., Haematologica 2014

Targeted immunotherapy
Brentuximab Vedotin in relapsed HD





Gopal et al., Blood 2012

Other Options

Gemtuzumab in AML
Inotuzumab in ALL
Check-point inhibitors : Nivolumab and Ipilimumab
Ibrutinib in CLL, MCL
Ruxolitinib in MF
HDAC inhibitors
And others

Conclusions

Relapse remains the major cause of treatment failure

Early detection of relapse by monitoring of chimerism and specific molecular marker

Management of relapse

- Withdrawal of immunosuppression
- Tumor burden reduction
- Cell-based therapy

Prevention of relapse = Maintenance

- Small molecule inhibitors
- Immunomodulatory drugs
- Targeted therapies

References

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