



# “Minimal Residual Disease in Hematologic Malignancies”

Leukemia Research Foundation  
November 10, 2021

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Rush University, Chicago*

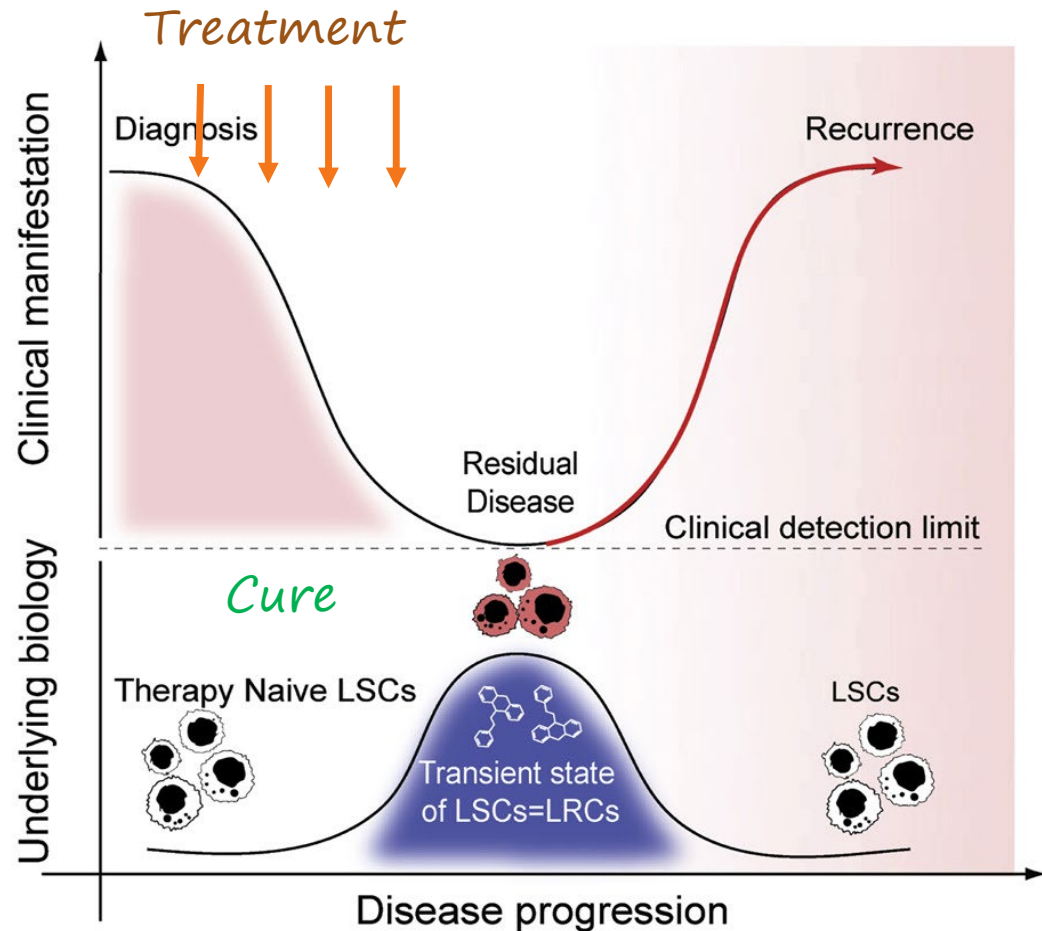
# Disclosure

- *Honoraria from Novartis and Blueprint (advisory board)*

- 
- *We all want cure*
  - *Hematologic malignancies are curable!*
  - *However, cure requires sequential therapies*

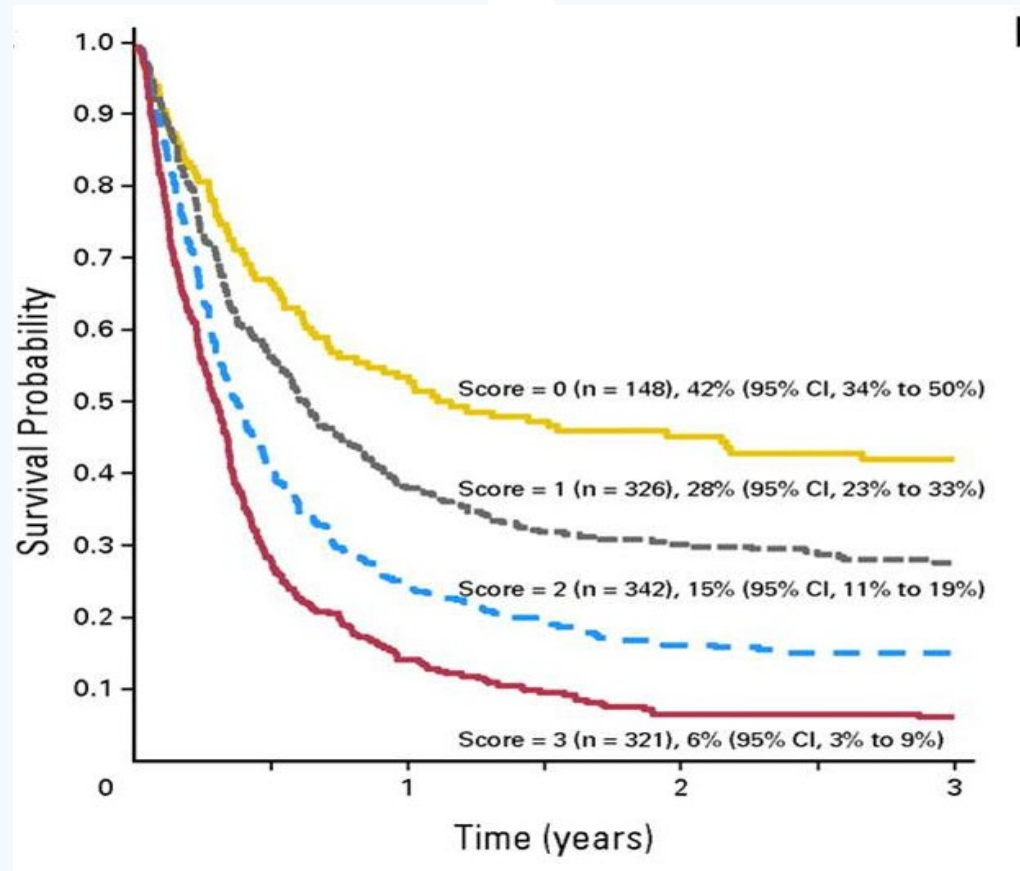
# Each Phase/Cycle of Chemo/radiation therapy

- Decreases tumor burden
- Increases chance of cure
- However, some patients relapse



AlloHCT outcomes is poor in AML patients if they are not in CR

OS Overall 19% at 3 years

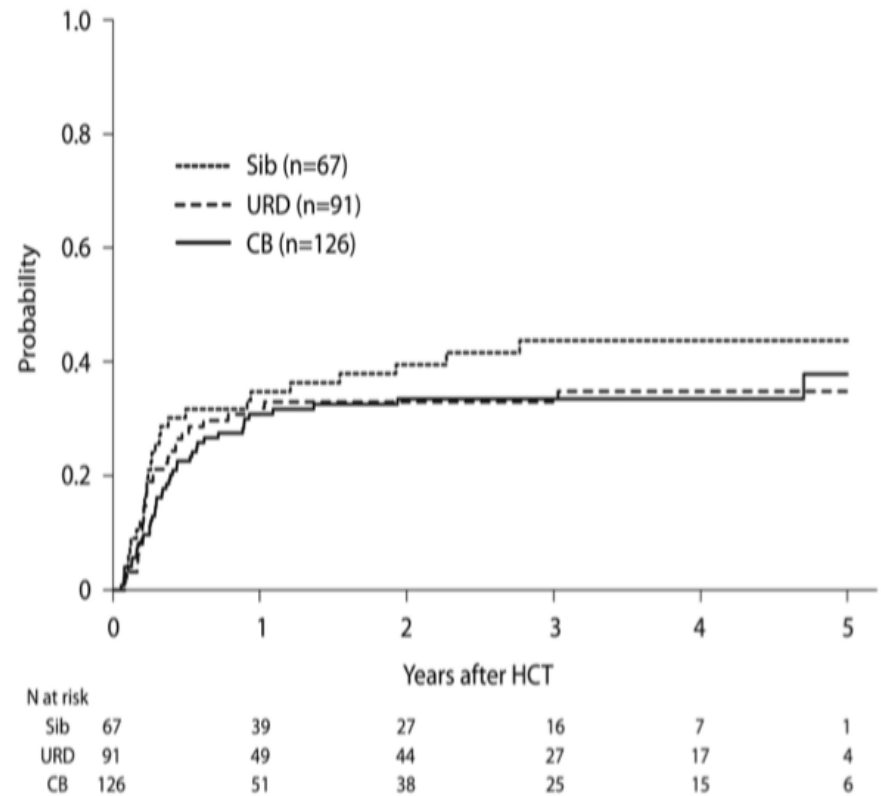
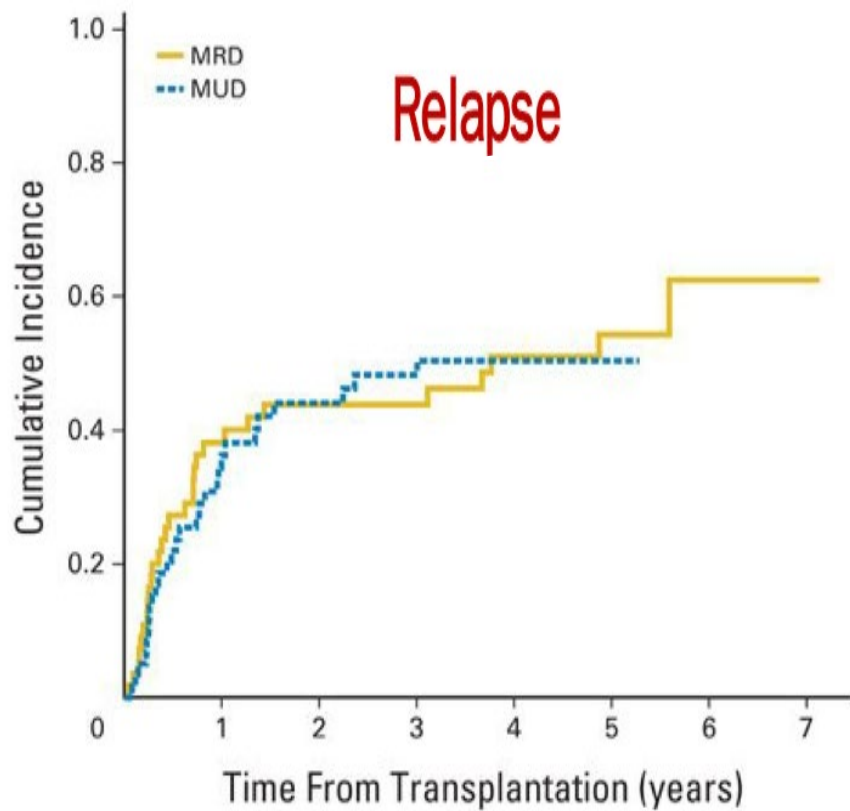


Duval M et al. J Clin Oncol 2010

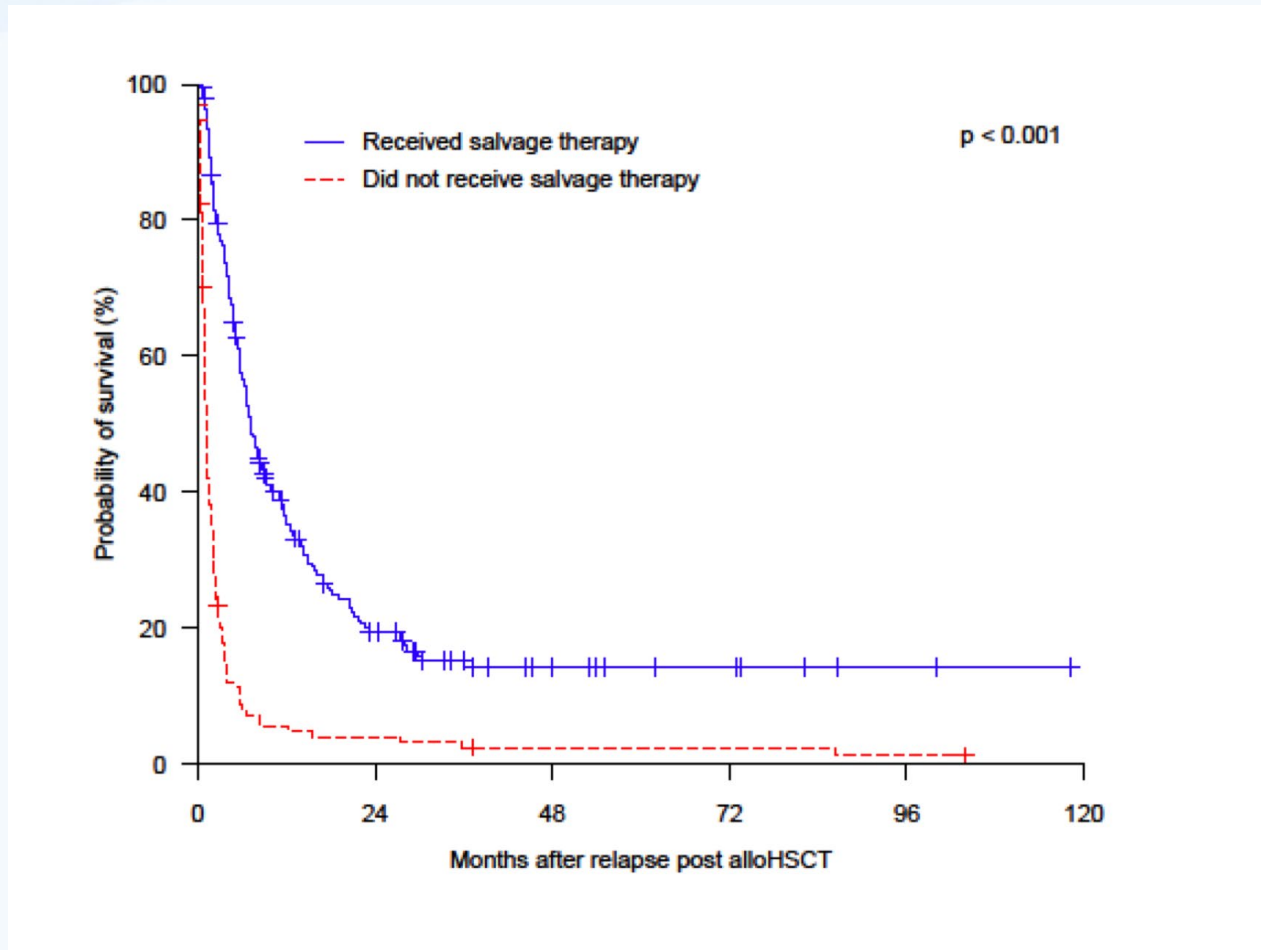
# Relapse is a Common Problem

Prospective Phase II HCT Study  
in Older AML

FLT3 AML, Graft Source, CIBMTR



# Treatment of Relapse is Not very Successful

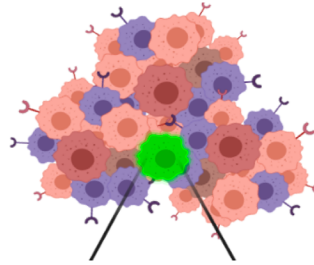


# What We Learned

- CR is important for success (cure)
- However, CR is not cure for most Hematologic Malignancies
- Relapse is still a common problem in patients in CR
- Treatment of relapse is difficult
  
- Then our goal should make sure to do everything to **PREVENT** relapse
  
- One of Most Important Thing: **PREDICT** Who will have a higher chance to relapse



# What is MRD?



## Minimal/Measurable Residual Disease (MRD)

Detection of rare neoplastic cells (<1%) during post-treatment follow-up, by using complementary approaches:

### Multiparametric Flow Cytometry (MFC)

Immunophenotypic analysis to detect abnormal expression of specific antigens

- sensitivity  $10^{-3} - 10^{-4}$
- applicability >95%



### Next Generation Flow (NGF)

- sensitivity  $< 10^{-5} - 10^{-6}$
- applicability >99%

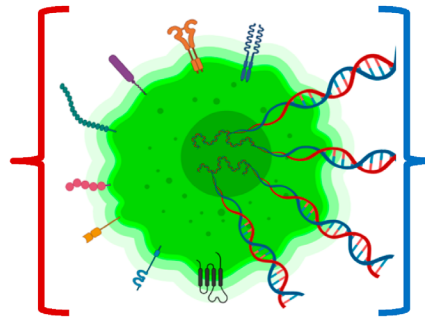
### Molecular diagnostics (PCR, RT-qPCR)

Genetic analysis to detect specific DNA signatures

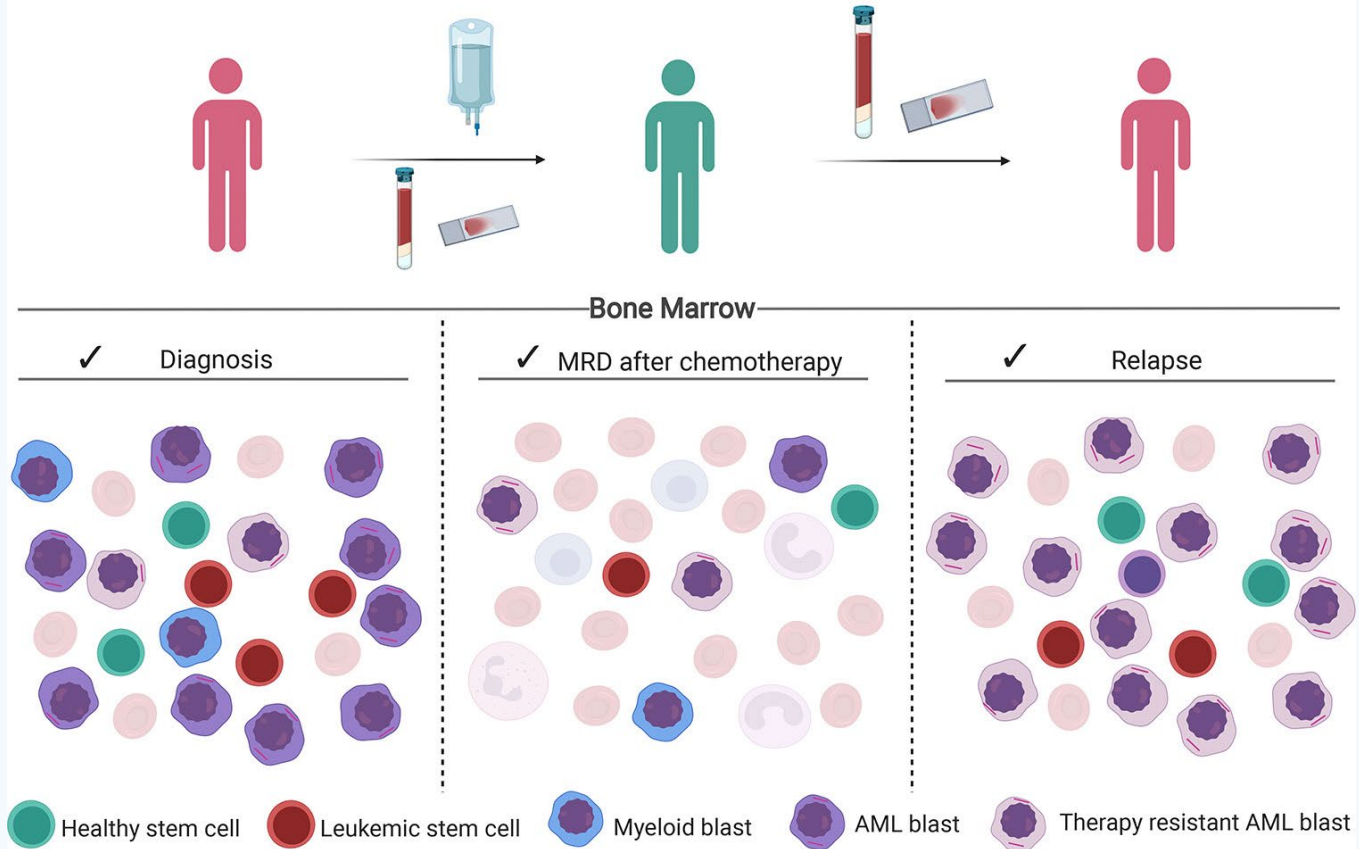
- sensitivity  $10^{-3} - 10^{-6}$
- applicability >90%



### Next Generation Sequencing (NGS), Digital PCR (ddPCR)



## Disease progression in AML

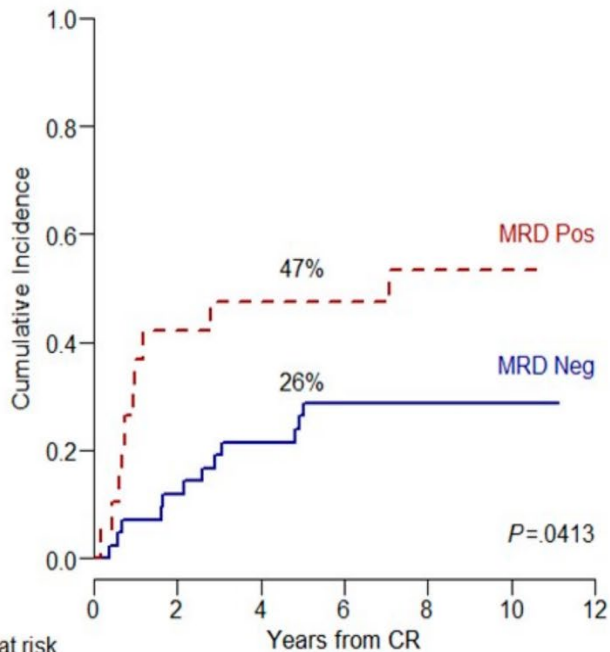


# MRD in Acute Lymphoblastic Leukemia

## Cumulative incidence of relapse

### according to w10–22 MRD risk model:

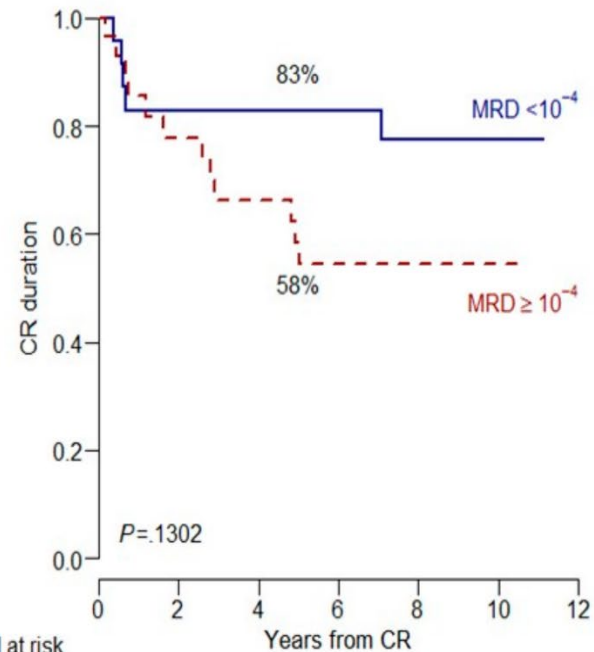
- MRD Pos:  $\geq 10^{-4}$  w10–16 and/or positive w22
- MRD Neg:  $< 10^{-4}$  w10–16 and negative w22



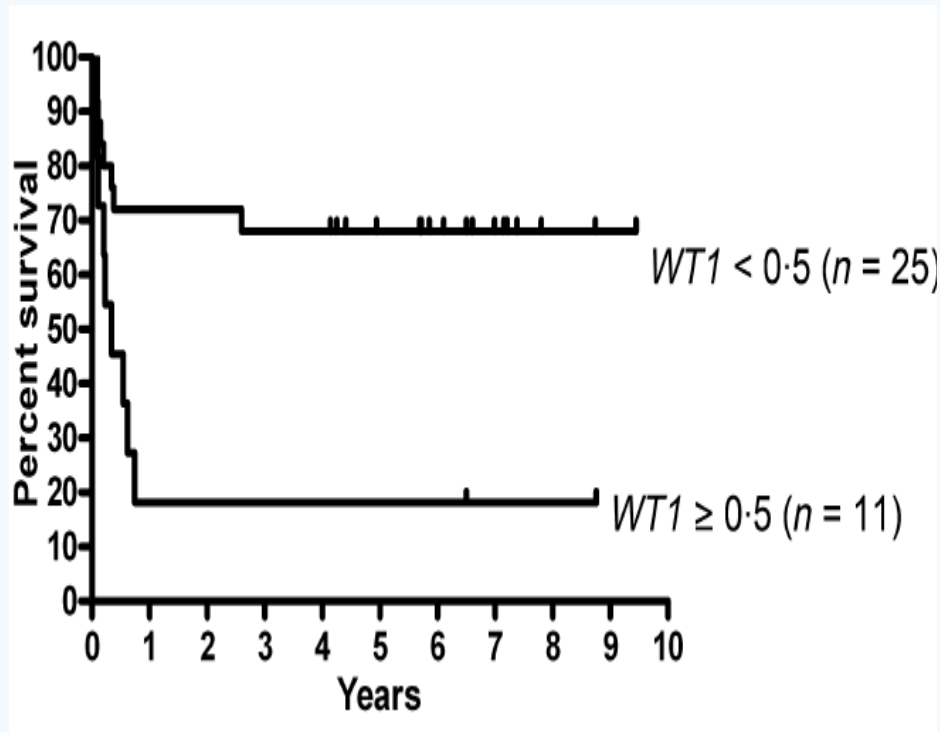
## CR duration

### according to w4 (EOI) and w10 MRD:

- MRD  $< 10^{-4}$  at w4 and w10
- MRD  $\geq 10^{-4}$  at w4 and/or w10



# MRD in Acute Myeloid Leukemia



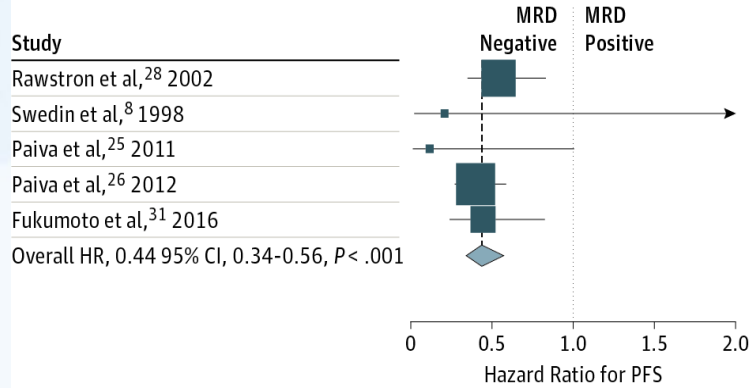
130 children  
Relapse;  
48% high WT1 levels vs.  
8% of normal WT1 levels

Jacobsohn DA, et al Br J Haematol  
2009;

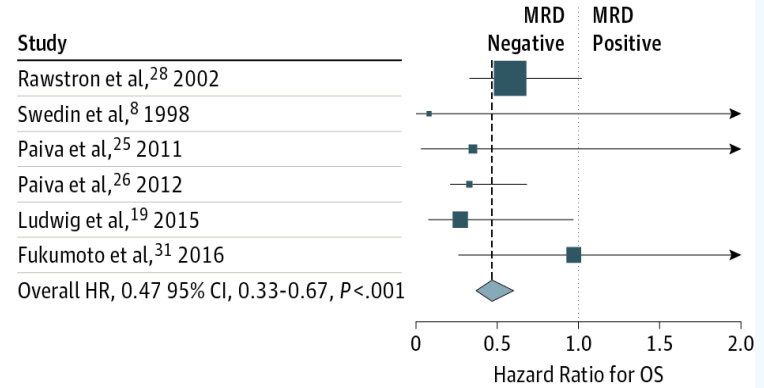
Woehlecke C, et al J Cancer Res  
Clin Oncol

# MRD in Multiple Myeloma in CR: A meta-analysis

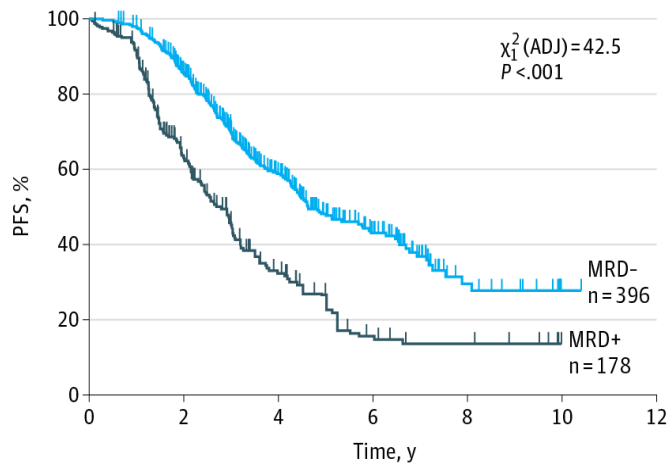
**A** CRs only: OS hazard ratio forest plot



**B** CRs only: OS hazard ratio forest plot

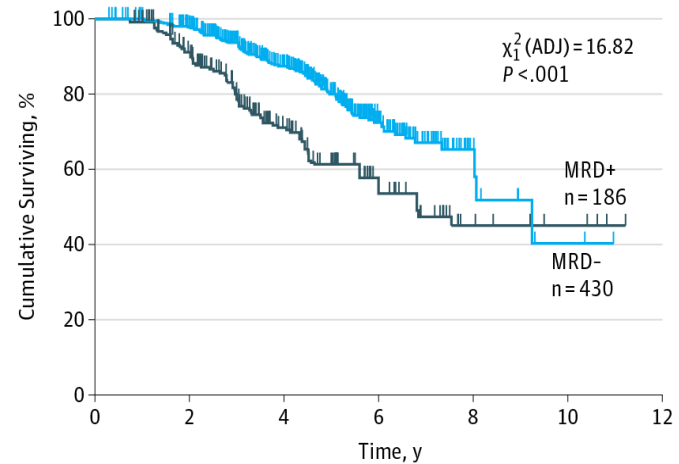


**C** CRs only: OS by MRD status

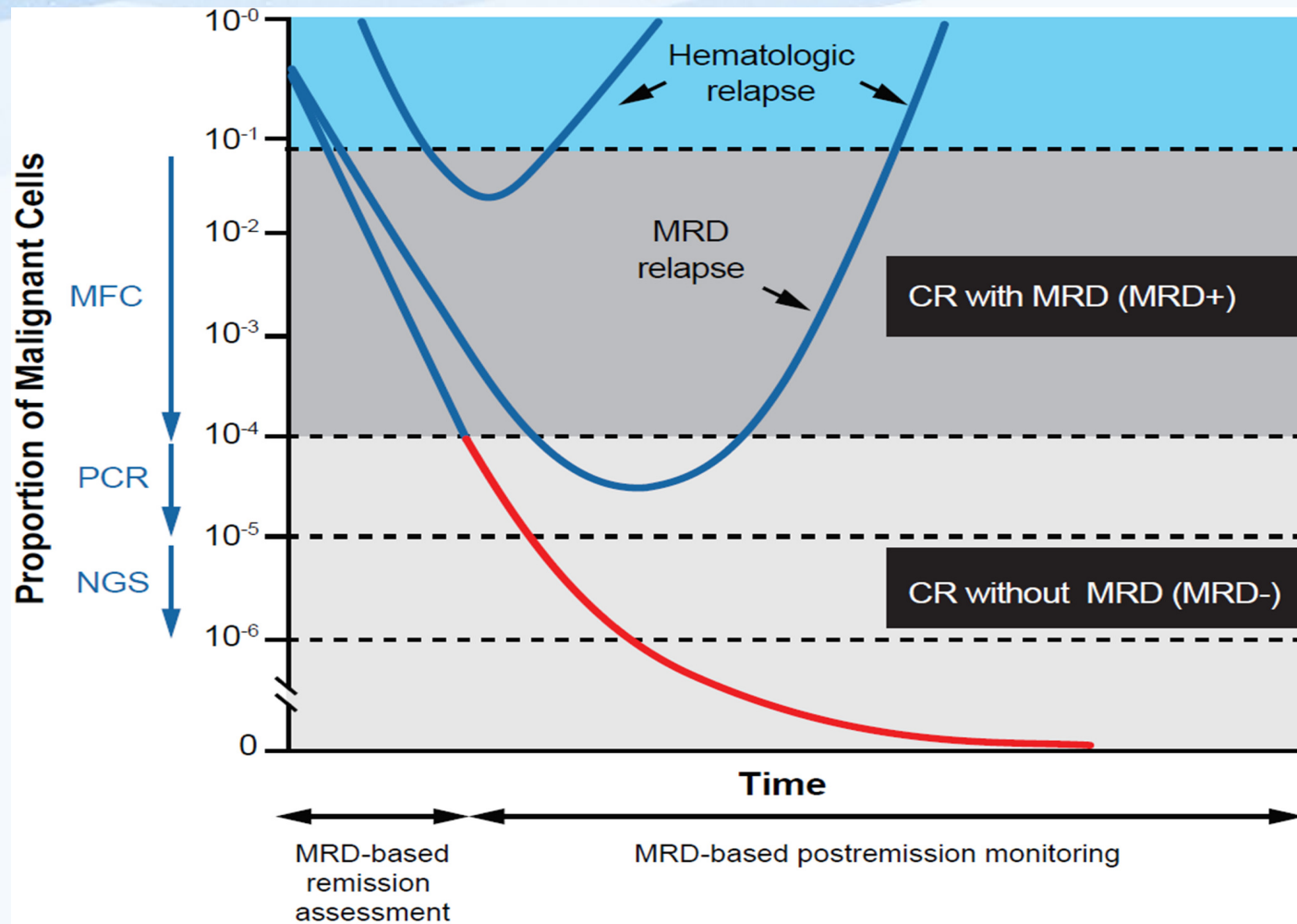


No. at risk	0	2	4	6	8	10	12
MRD -VE	314	156	65	16	1		
MRD +VE	93	34	12	7	0		

**D** CRs only: OS by MRD status



No. at risk	0	2	4	6	8	10	12
MRD -VE	389	261	85	11	2		
MRD +VE	155	78	28	8	4		



Short et al Am J Hematol 2019

# What We Learned

- *MRD is poor prognostic*
- *MRD positive patients will tend to have more relapse in most (if not all) hematologic malignancies*

# Methods for MRD Detection

Method	Case Applicability	Sensitivity	Pros and Cons
Karyotyping	~50%	1/20	<ul style="list-style-type: none"> <li>+ Widely available</li> <li>+ Well-standardized</li> <li>- Slow turnaround time</li> <li>- Labor intensive</li> <li>- Requires pre-existing abnormal karyotype</li> </ul>
FISH	~50%	1/100	<ul style="list-style-type: none"> <li>+ Useful for numeric cytogenetic abnormalities</li> <li>+ Relatively quick turnaround time</li> <li>- Labor intensive</li> <li>- Requires pre-existing abnormal karyotype</li> </ul>
RT-qPCR	~40-50%	1/10,000 – 1/1,000,000	<ul style="list-style-type: none"> <li>+ Widely available</li> <li>+ Well-standardized</li> <li>+ Relatively inexpensive</li> <li>- Single gene assessed per assay</li> <li>- Mutations occurring outside of primer-spanning regions of gene will be missed</li> </ul>
MFC	~ All	1/10,000 – 1/1,00,000	<ul style="list-style-type: none"> <li>+ Widely available</li> <li>+ Relatively quick turnaround time</li> <li>+ Widely applicable</li> <li>- Not fully standardized</li> <li>- Analysis and interpretation require high-level expertise</li> </ul>
NGS	>95%	1/10,000 – 1/1,000,000	<ul style="list-style-type: none"> <li>+ Simultaneous assessment of numerous targets</li> <li>+ Can detect mutations in any sequenced portion of a gene</li> <li>+ Very widely applicable</li> <li>- Not widely available</li> <li>- Slow turnaround time</li> <li>- Not standardized</li> <li>- Expensive (particularly to achieve high sensitivity)</li> <li>- Analysis and interpretation require high-level expertise</li> </ul>



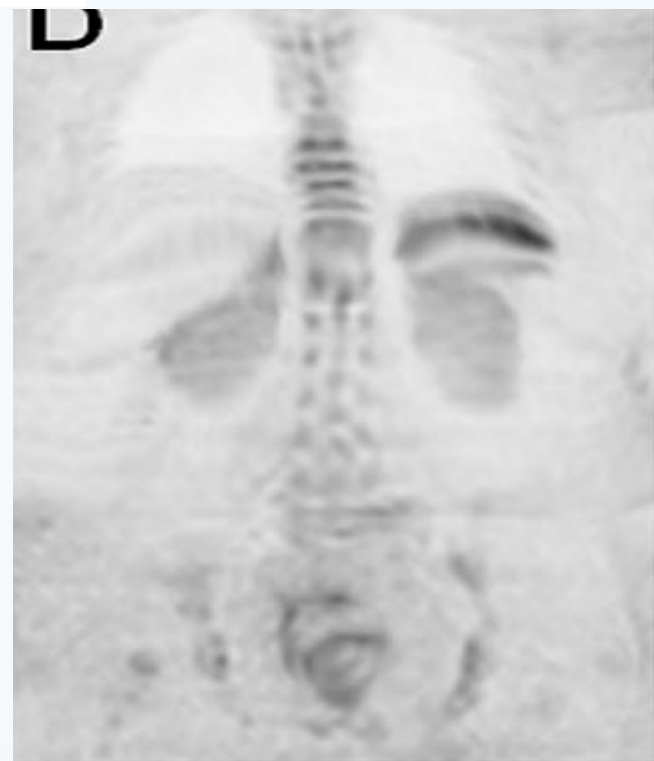
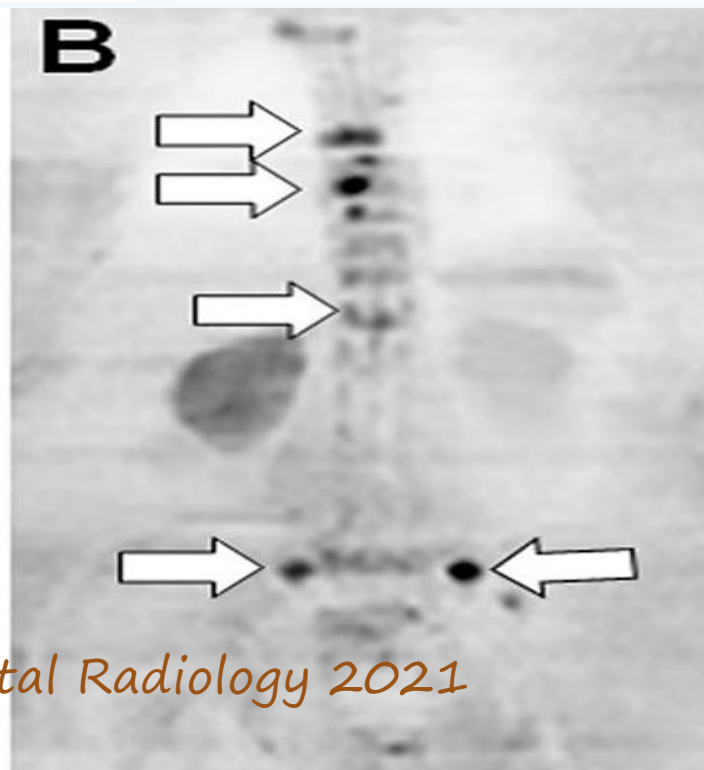


PET/CT

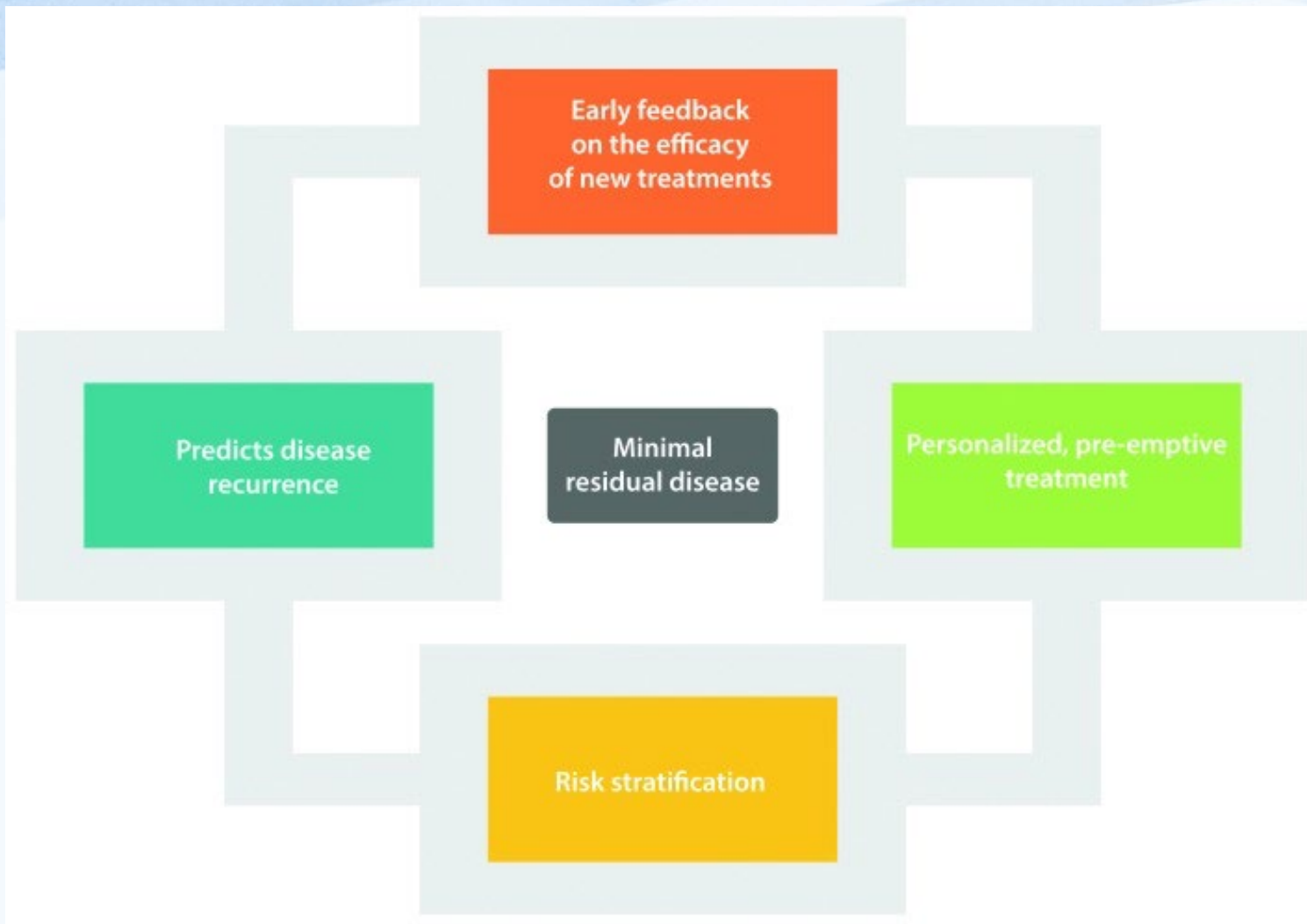


Images in  
MM

WB MRI



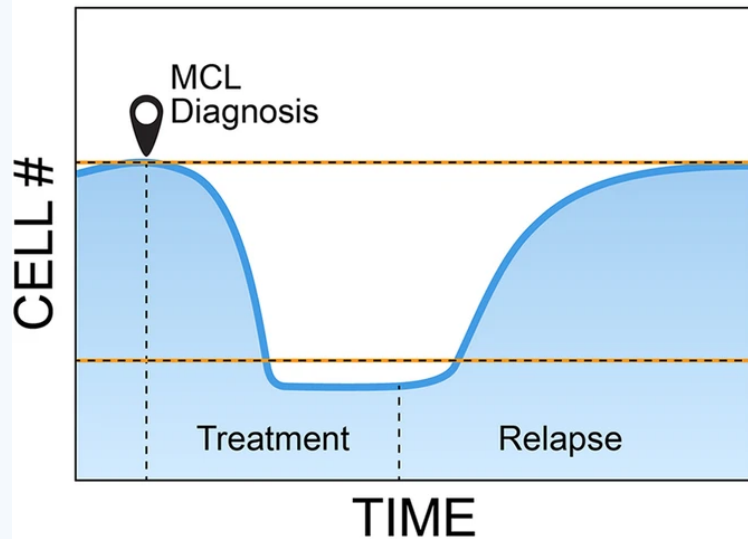
Lecouvet et al. Skeletal Radiology 2021



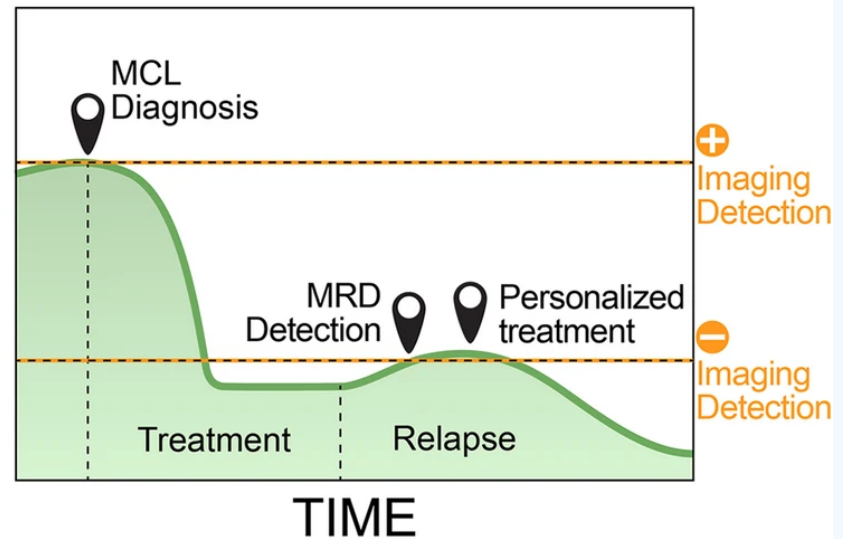
*Ferrero et al Haematologica 2017*

# Minimal Residual Disease (MRD)

## Before MRD Detection



## After MRD Detection

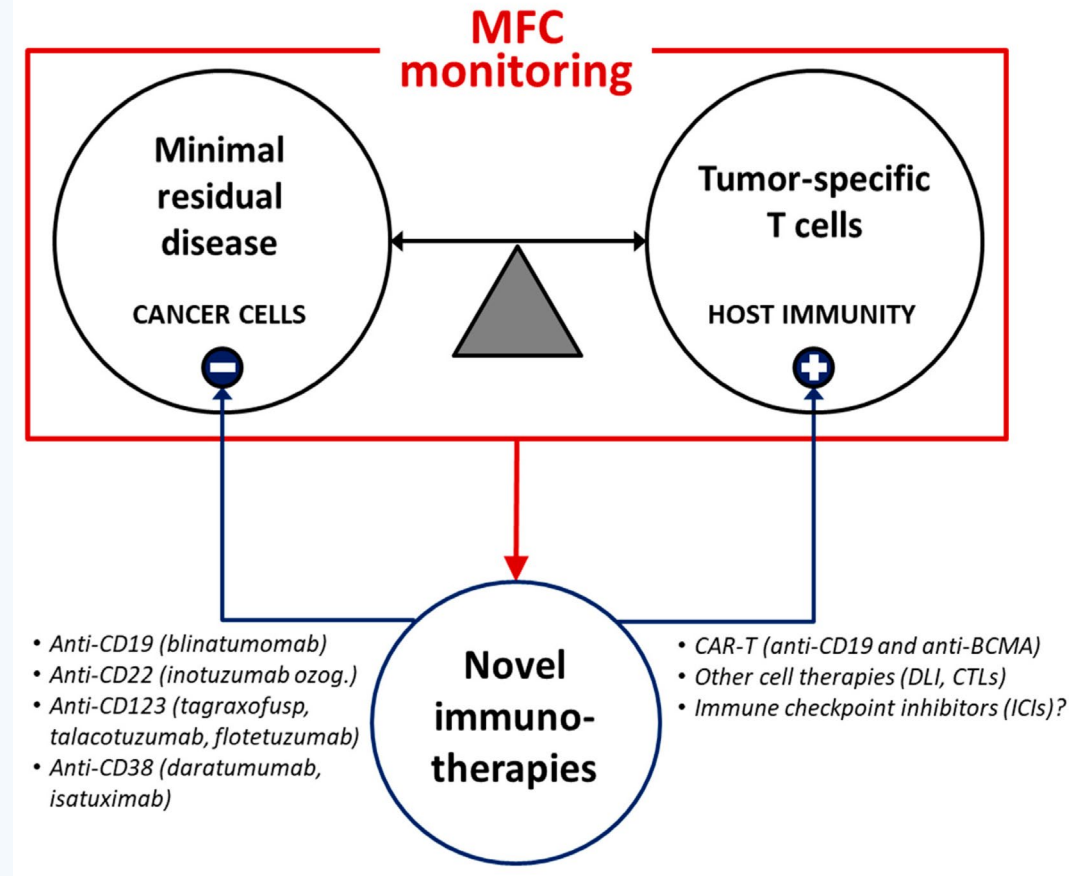


Visual Art: © 2020 The University of Texas MD Anderson Cancer Center

Jung et al J Hematol and Oncol 2020

# How to Treat MRD? What Can we Do?

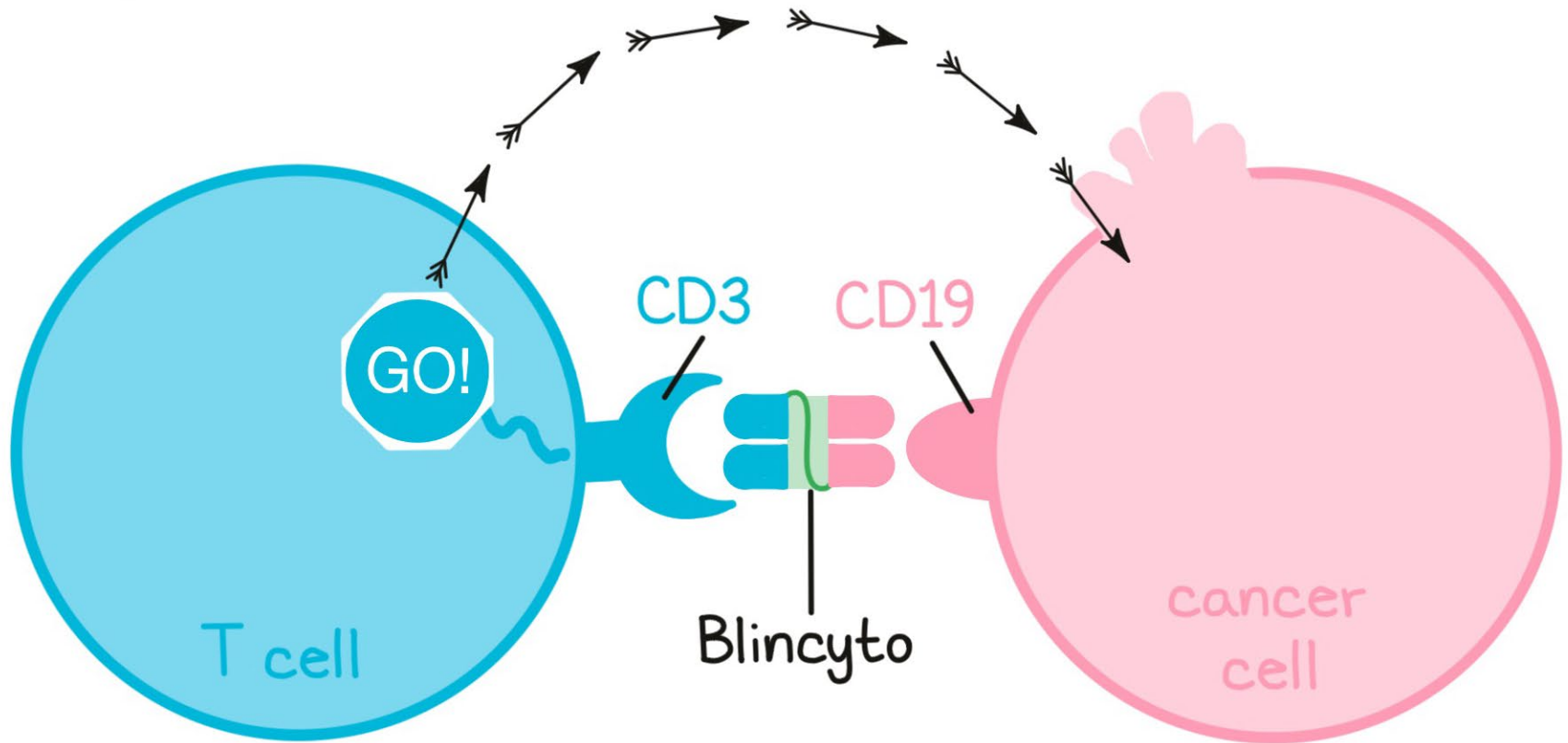
- Targeted Therapies
- Hematopoietic Cell Transplantation
- Immunotherapies
- CART cells
- Combination of all of these



# What Can We Do?

-Augment Patients Own Immune System

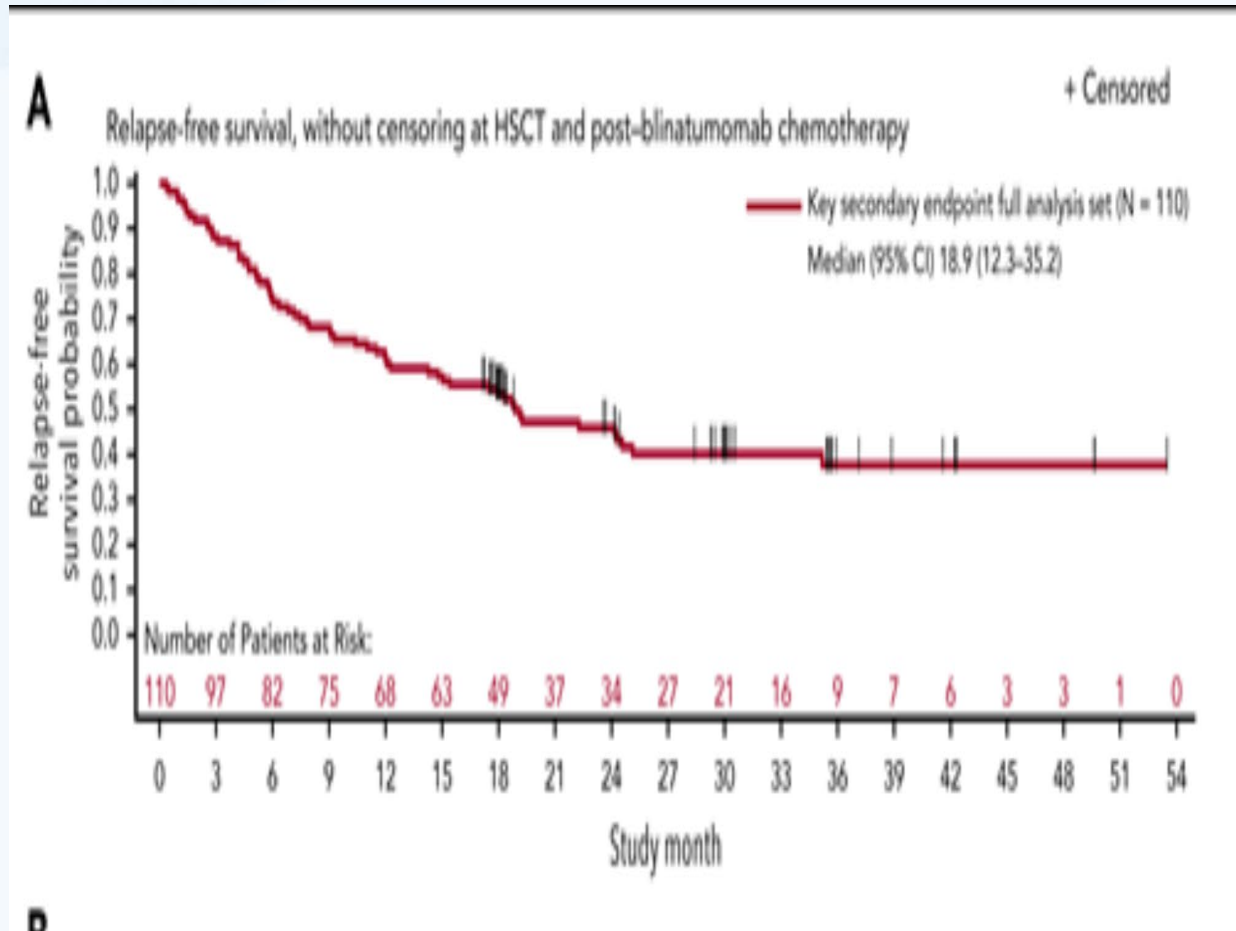
Blincyto: how it works



UCIR.org

Understanding Cancer Immunotherapy Research- <https://www.ucir.org>

# Blinatumumab Induces MRD negative state and improves Outcomes



Gokbuget et al Blood 2018

# How Does Hematopoietic Cell Transplantation Work?

If Donor is Patient her/himself = Autologous HCT.

Very high dose Chemo/radiation      cancer ~~cells~~

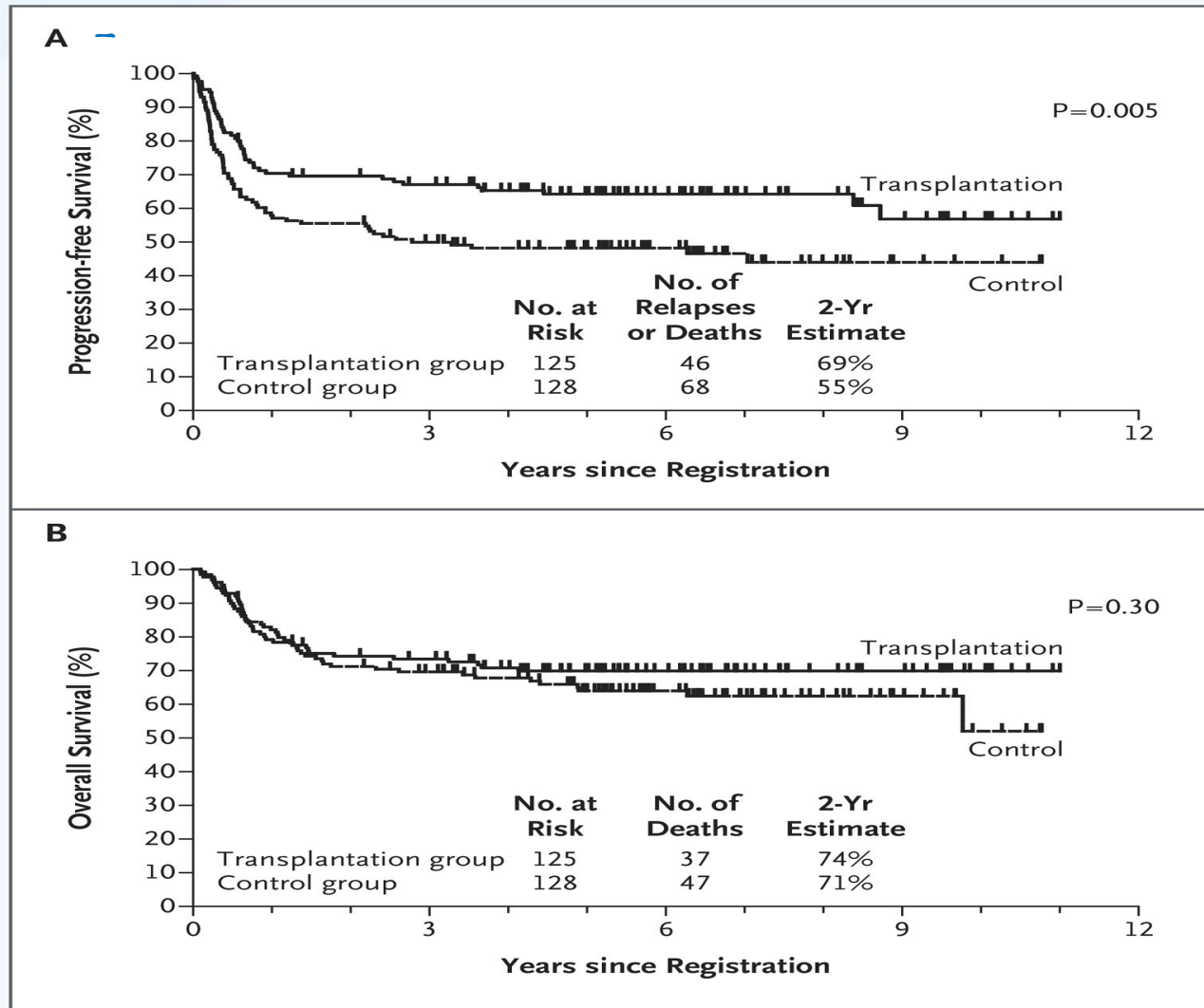
If Donor is another individual = Allogeneic HCT

Chemo/Radiation therapy + Other Person Immune Cells      cancer ~~cells~~



# What Can We Do?

-Autologous HCT Bone Marrow Transplantation for consolidation of NHL





# What Can We Do?

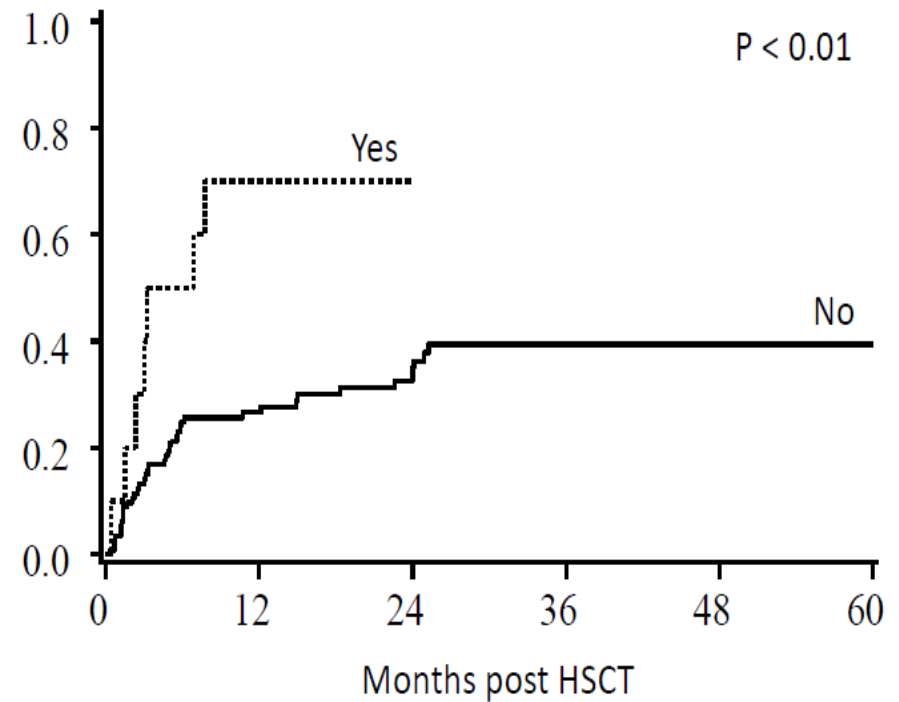
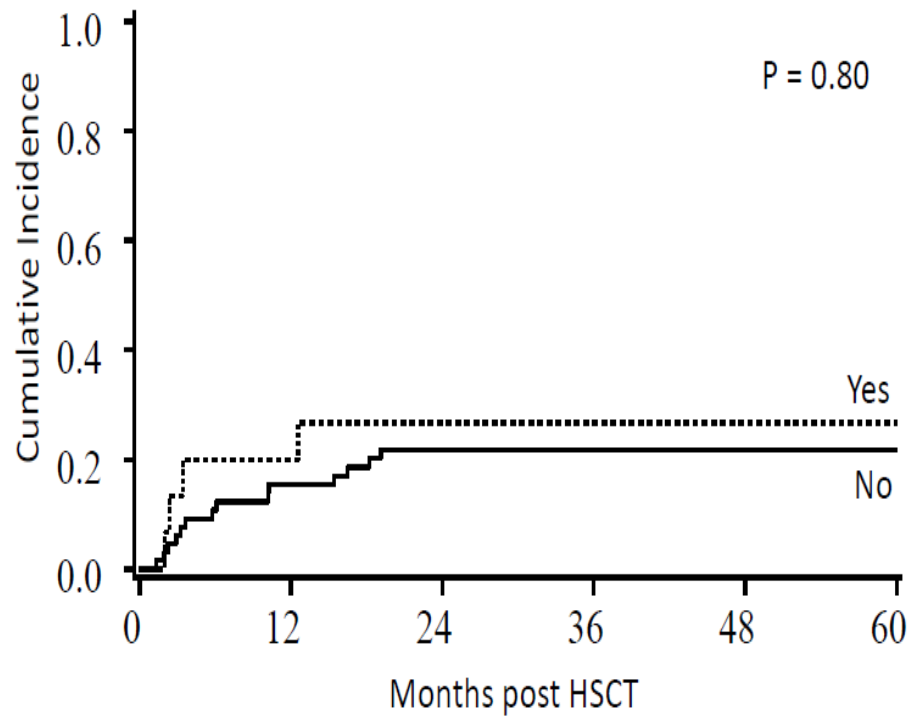
-Allogeneic HCT

-Increase Intensity of Chemo/Radiation Therapy

**MAC**

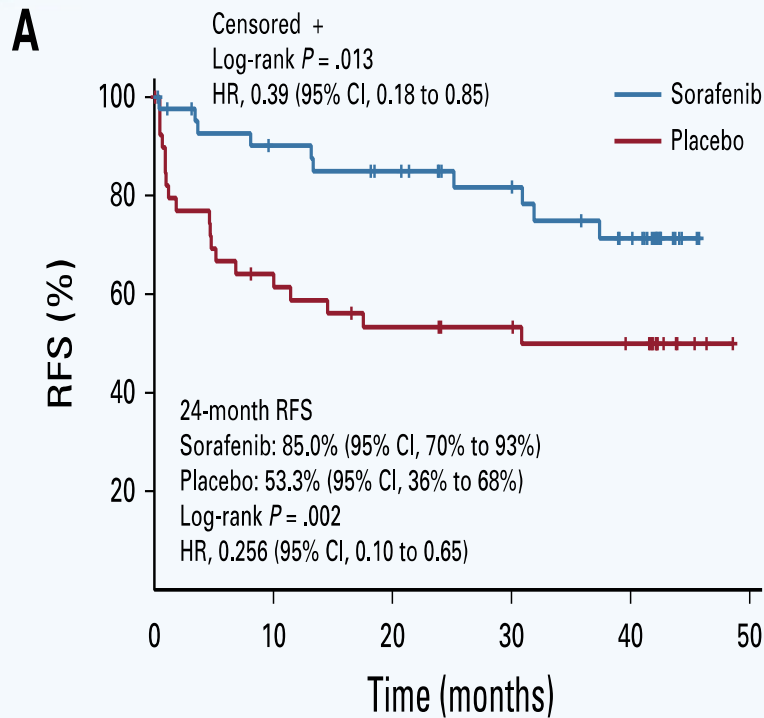
*Relapse*

**RIC**

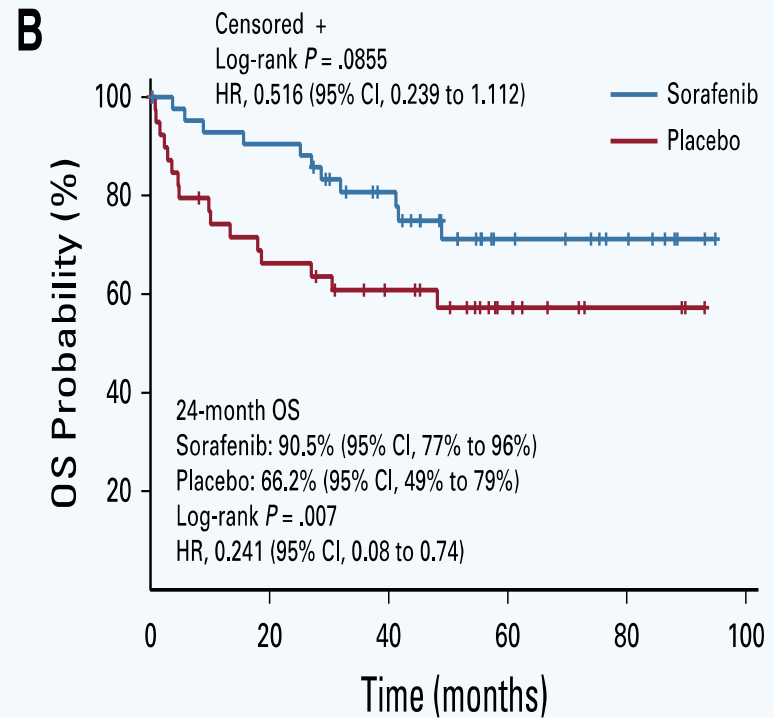


# What Can We Do?

## -Targeted Maintenance Therapy after HCT



No. at risk:		0	10	20	30	40	50
Placebo	40	24	19	17	14	0	
Sorafenib	43	35	31	25	18	0	

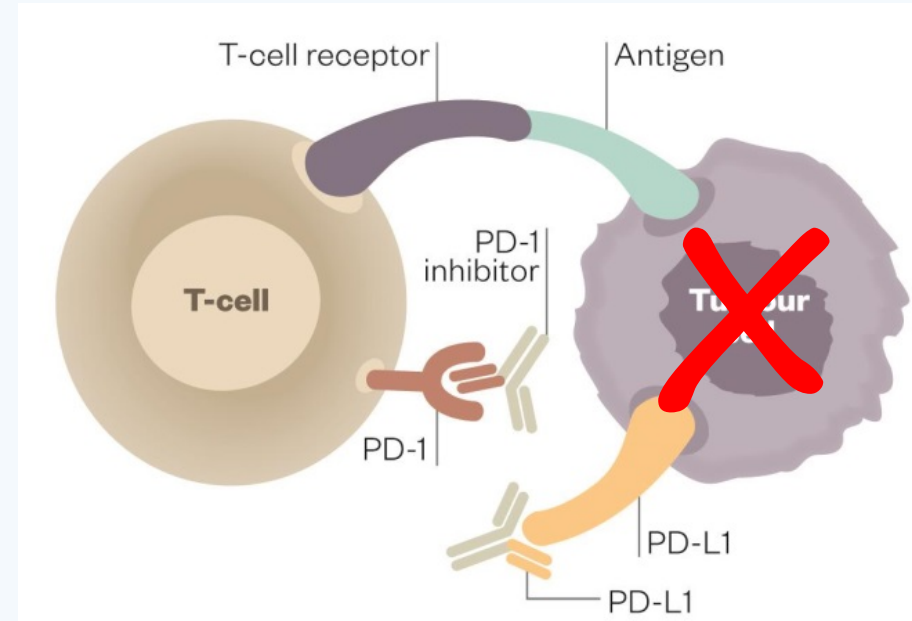
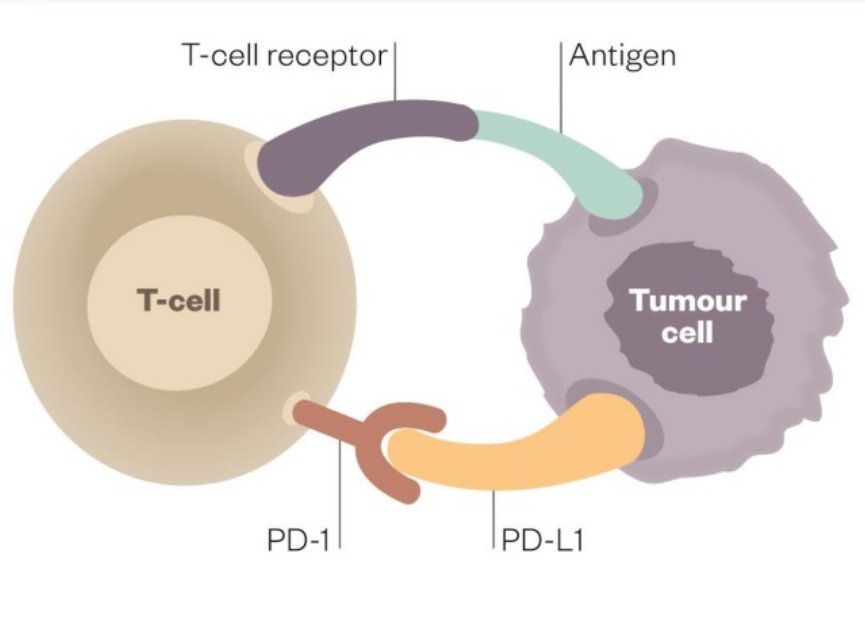


No. at risk:		0	20	40	60	80	100
Placebo	40	25	19	9	3	0	
Sorafenib	43	38	28	12	7	0	

# What Can We Do?

Augment Patient Own Immune Cells (in the body)

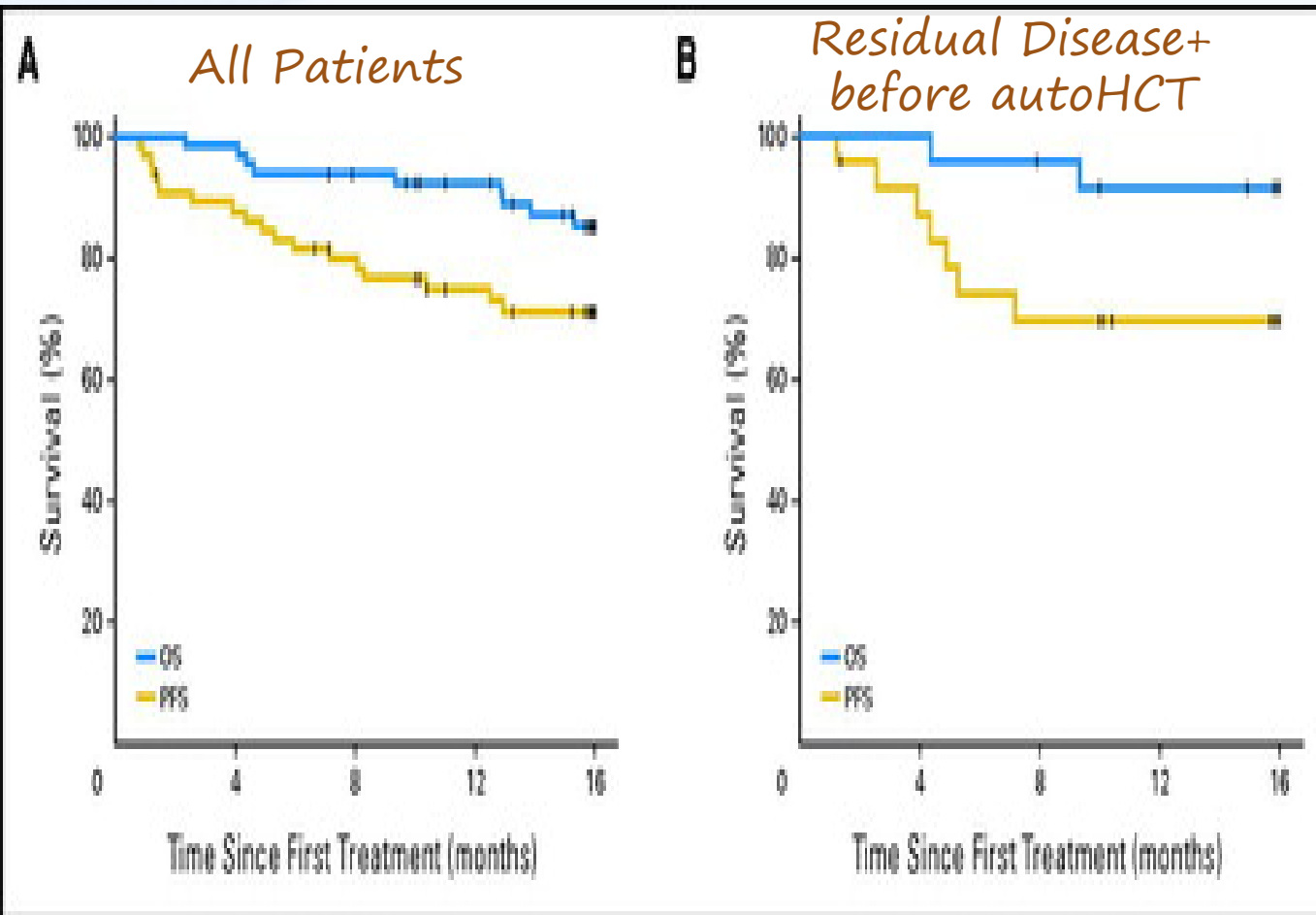
-PDL-1 inhibitors



# What Can We Do?

## Augment Patient Own Immune Cells (in the body)

-PDL-1 inhibitors (Pidilizumab) after autologous HCT for NHL



Residual Disease+  
After autoHCT

N=35 patients

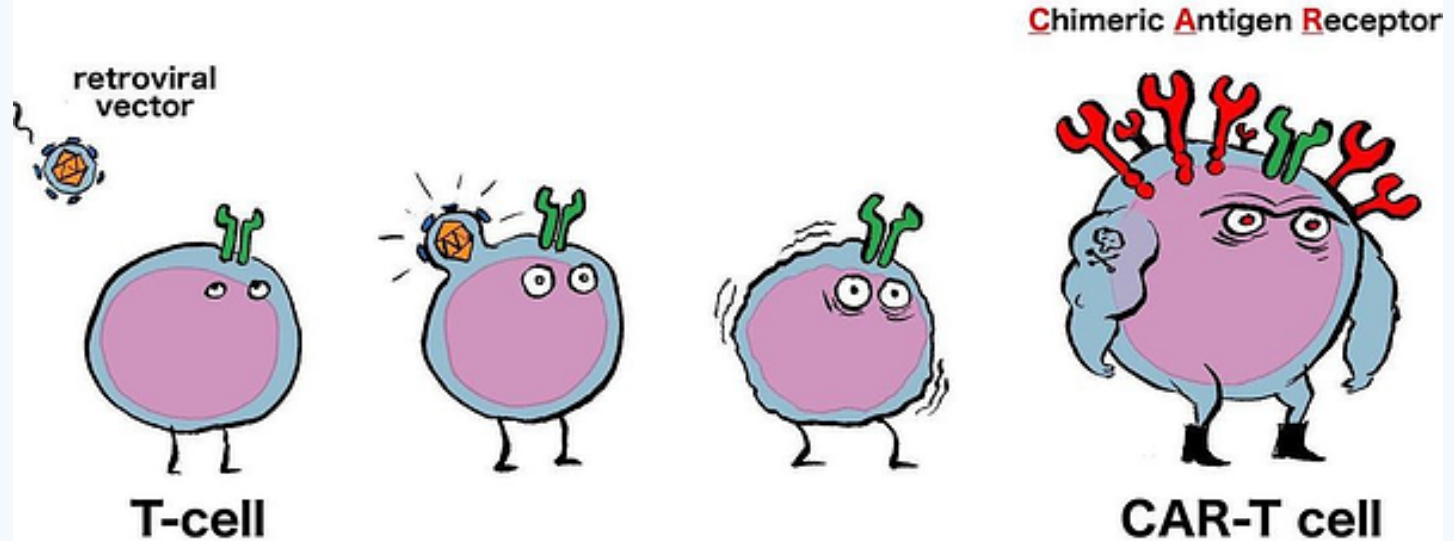
ORR=51%

CR= 34%

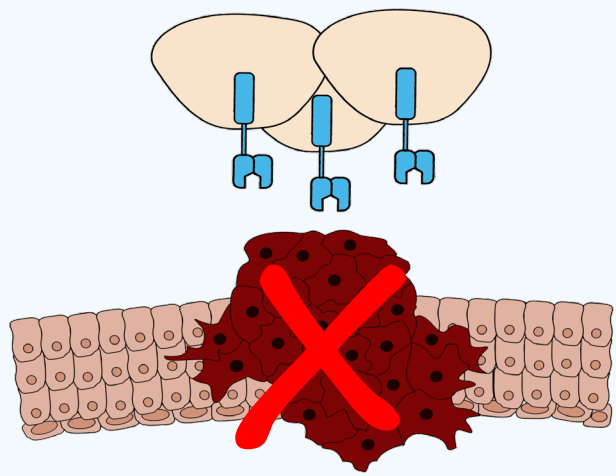
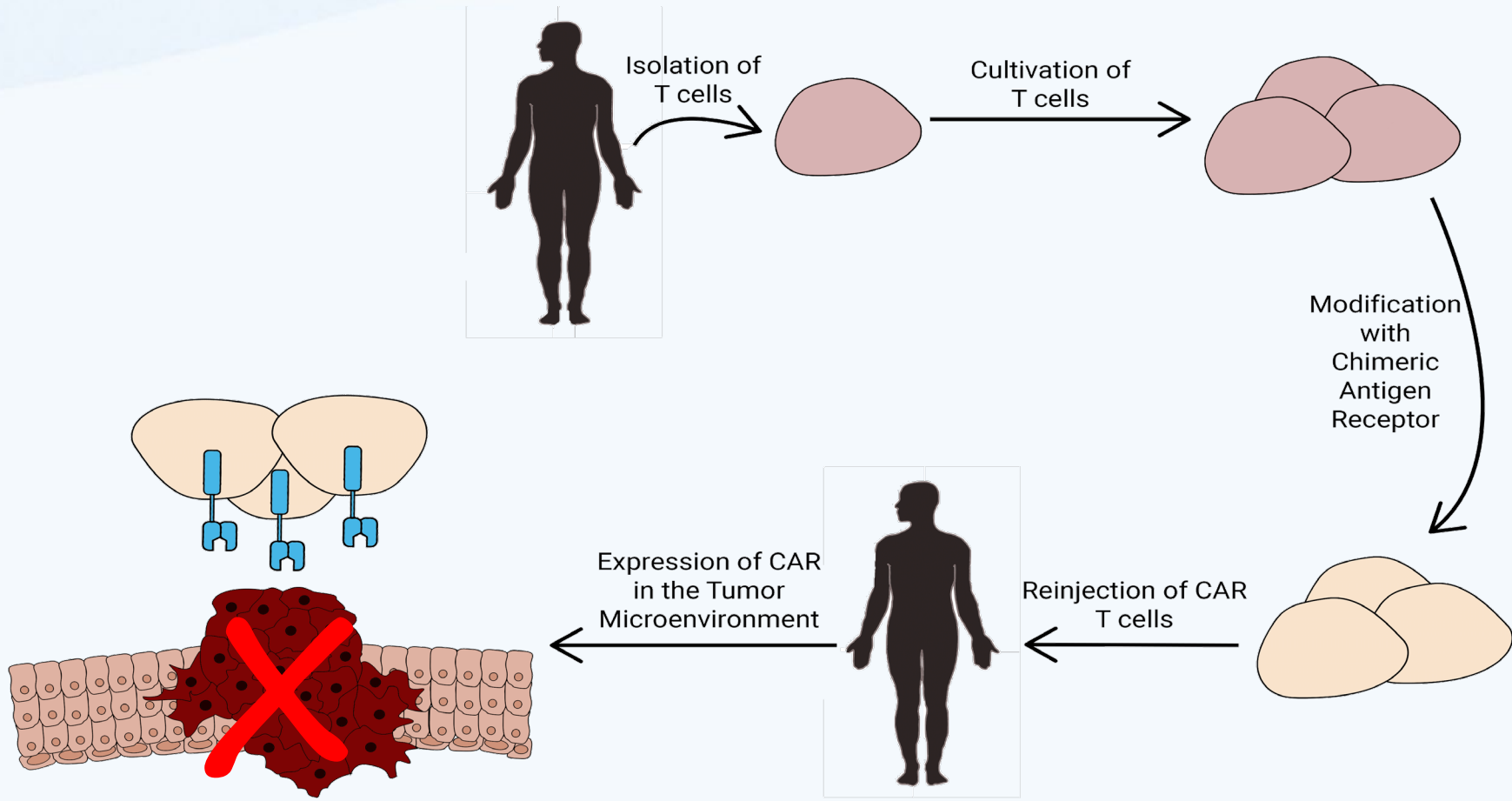
# What Can We Do?

-Augment patient Own Immune Cells (out of Body)

## Generating super-soldiers the production of CAR-T cells



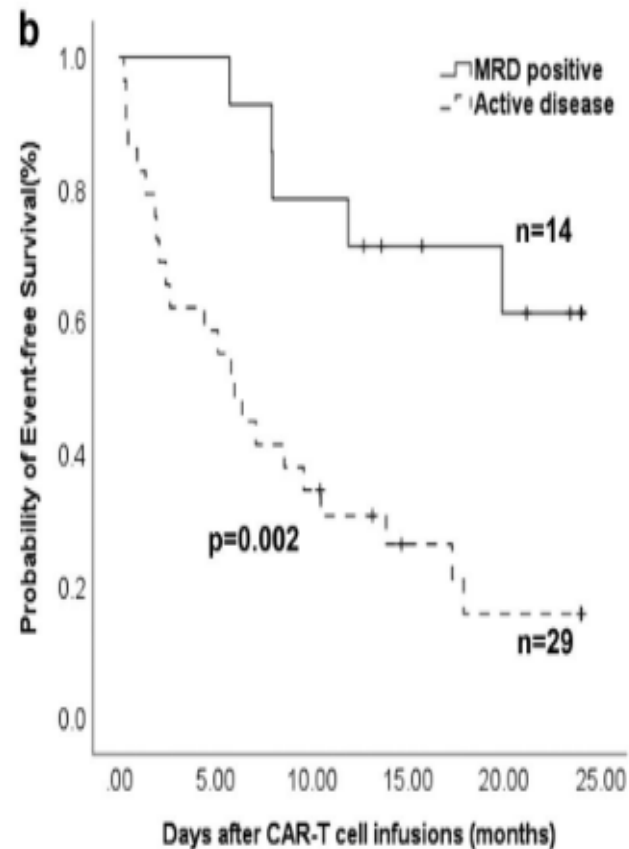
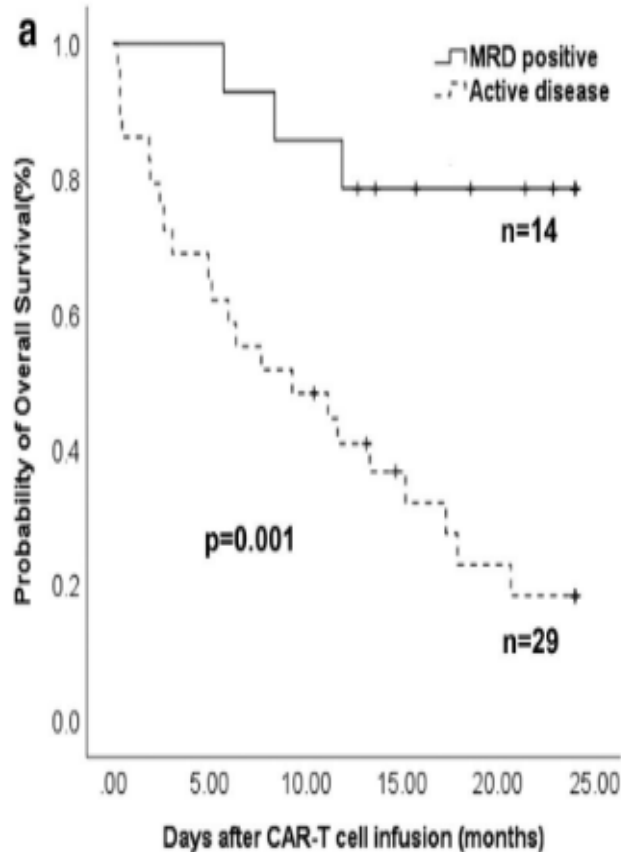
[facebook.com/pedromics](https://facebook.com/pedromics)



# What Can We Do?

-CART cells

Augment patient Own Immune Cells (out of Body)



Lu et al Cancer Immunol Immunotherapy 2021

# Conclusions

- *MRD helps us to tailor treatment for individual patient*
  - *Therefore we can prevent relapse in patients who needs more therapy*
  - *We can also decrease unnecessary t*
- *MRD detecting tecniques have been improving*
- *Treatment of MRD “arsenal” has been expanding*