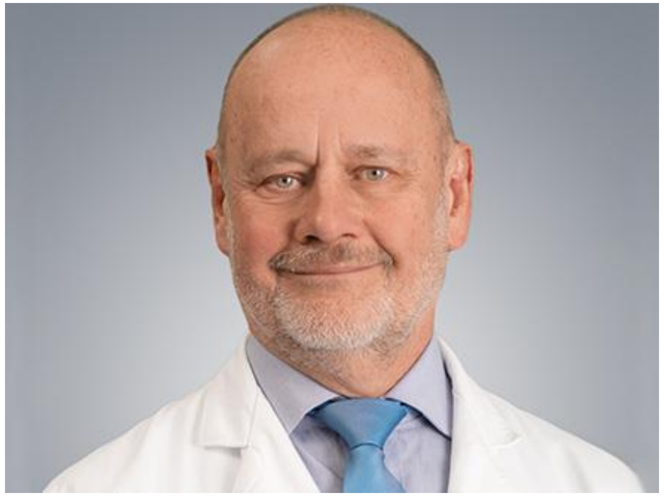
What to Do When Cancer Comes Back After Transplant or CAR T-cell Therapy

Celebrating a Second Chance at Life Survivorship Symposium

May 3-9, 2025



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Managing Post-Transplant Relapse: A Guide for Patients & Families

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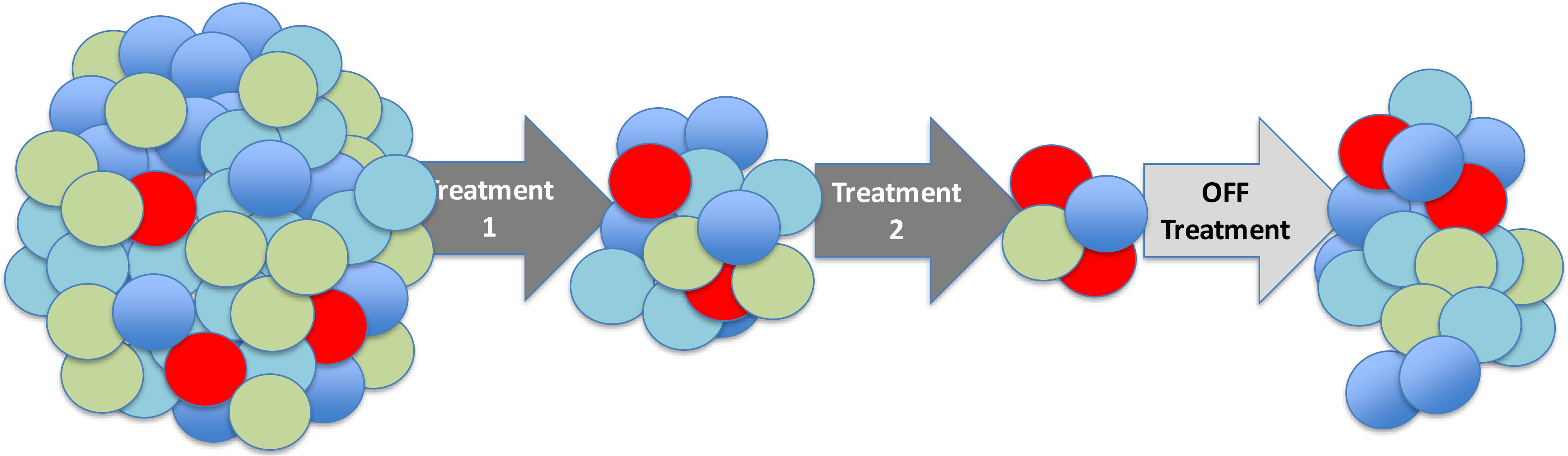
May 2025

Why Does Cancer Relapse?

Cancer stem cells survive chemotherapy and repopulate tumors after treatment.

The tumor is a heterogeneous mixture of cancer cell types

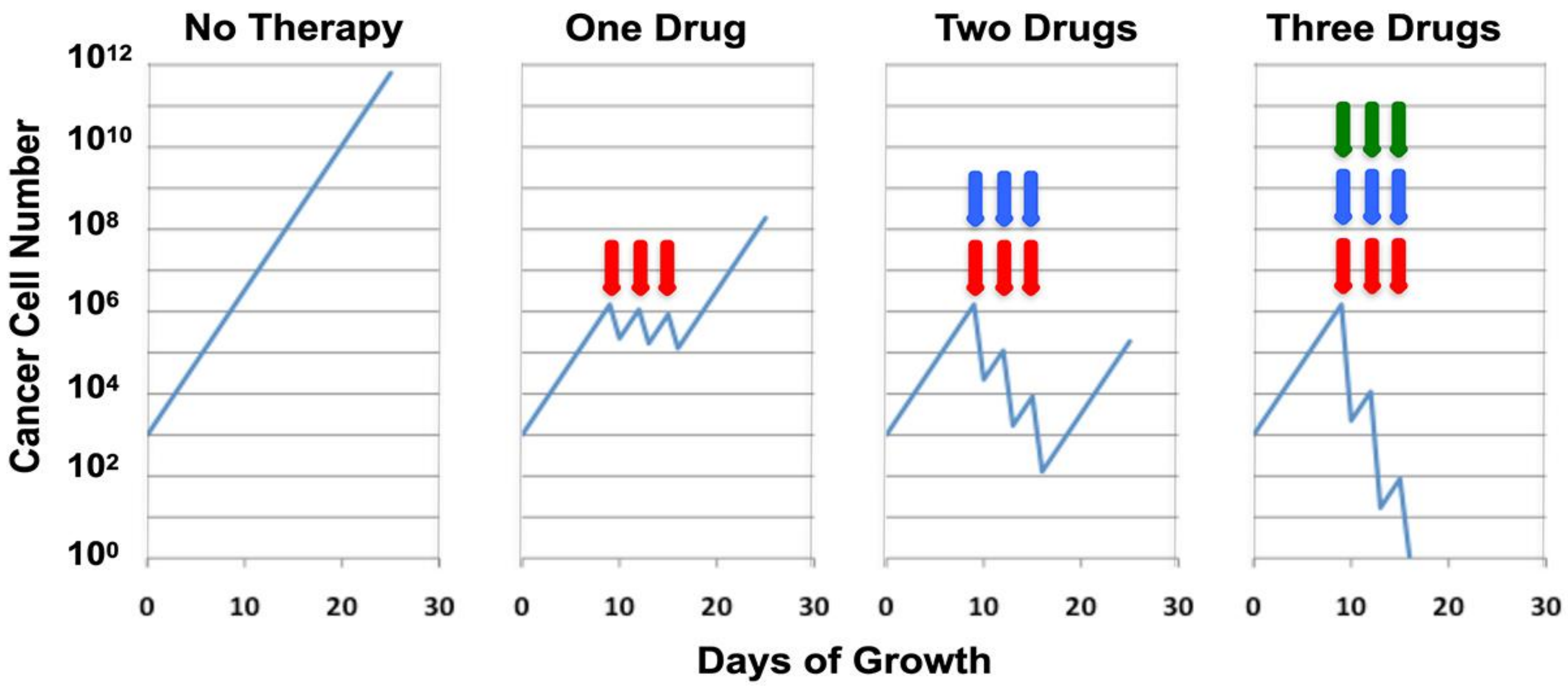


Cancer Stem Cells (red) are rare but are more resistant to chemotherapy

Tumor regrows from stem cells once treatment stops

Why Does Cancer Relapse?

Treatment failed to eliminate the last cancer cell



https://globalforum.diaglobal.orgissue/august-2021

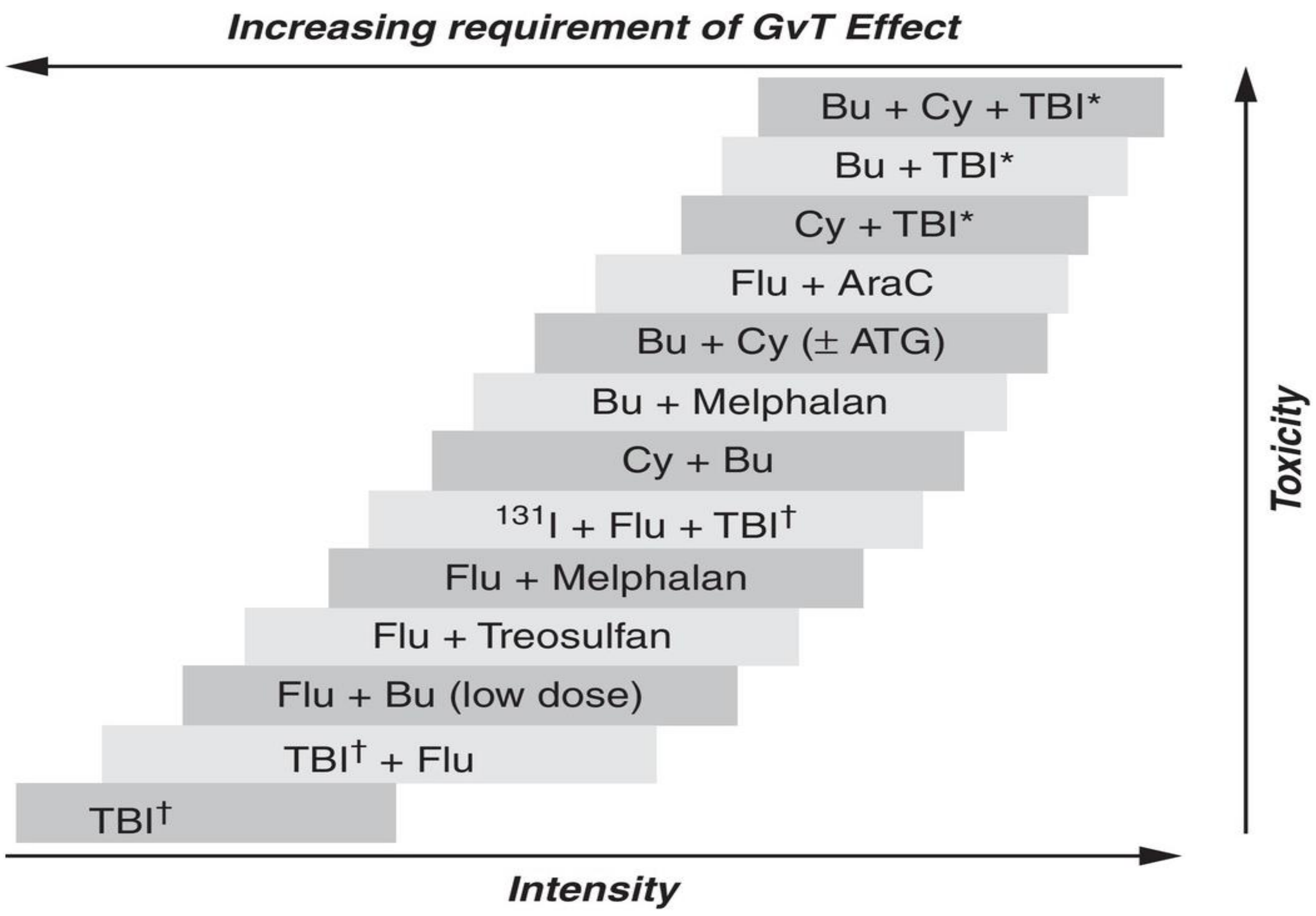
Autologous vs. Allogeneic Transplant

Key differences in relapse risk and treatment options

- The cancer burden in auto-transplantation is reduced or eliminated only by the intensity of the chemotherapy given before transplant.

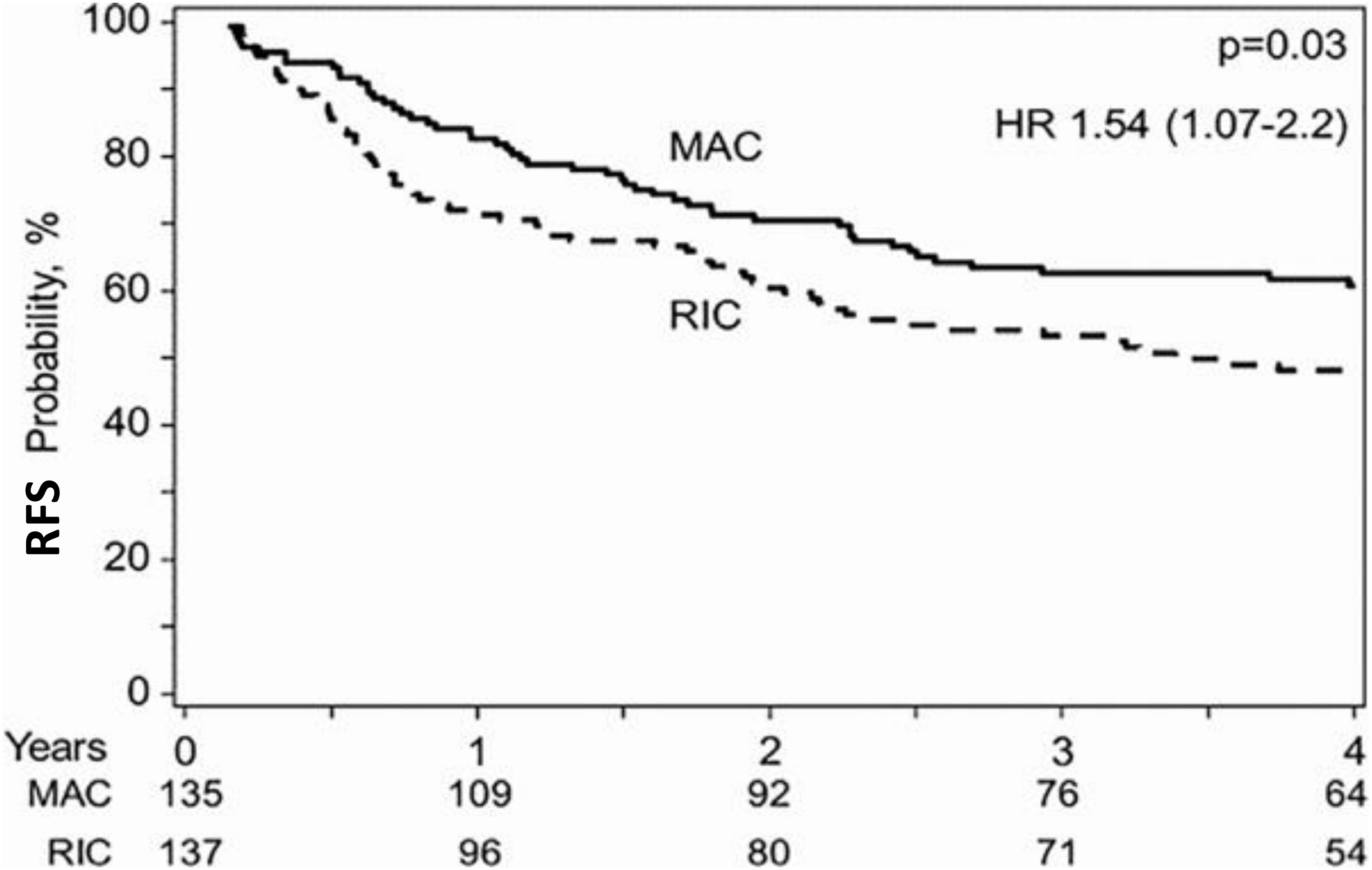
- The graft-versus-leukemia effect of allogeneic transplant can eliminate minimal residual leukemia cells that survived the conditioning regimen.

Different Pre-BMT Conditioning Regimens Vary in Intensity



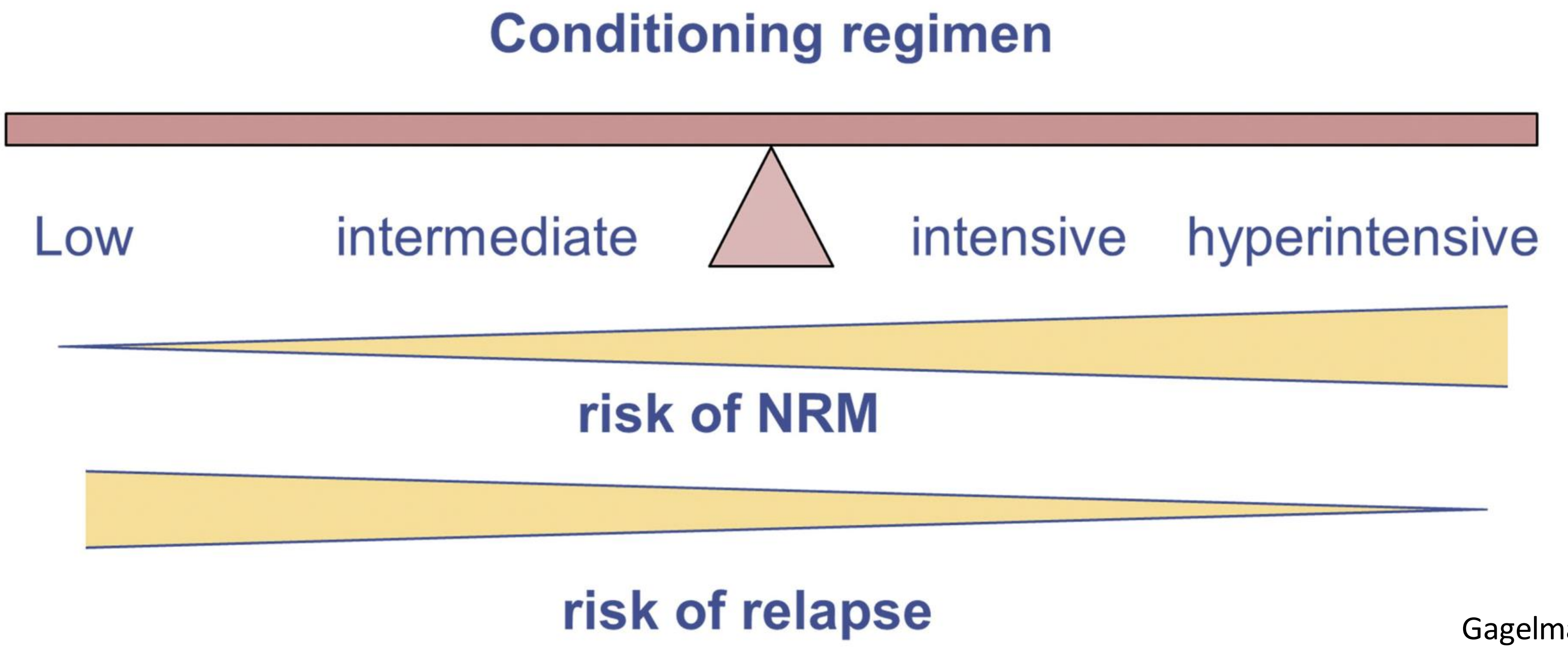
Hematopoietic Stem Cell Transplants Cambridge Press 2007. Chapter 27: [Charles Craddock]

More Intensive Conditioning Leads to Better Leukemia Eradication in Allo-BMT



Scott et al Transplant Cell Ther. 2021 **27**(6):483.e1–483.

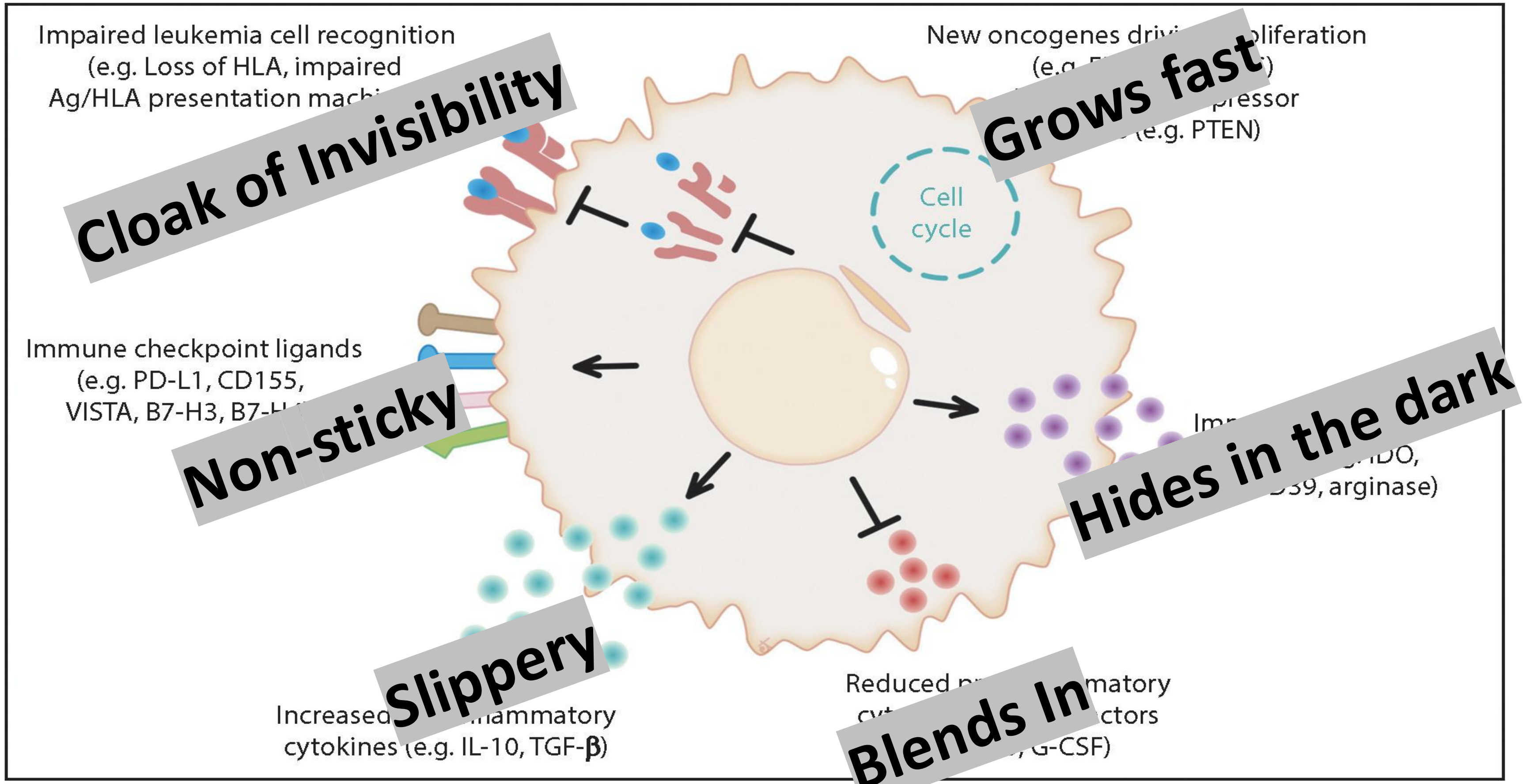
Increasing the Intensity of the Conditioning Regimen in Allo-BMT Decreases Relapse Risk but Increases Treatment-Related Mortality.



Gagelmann and Kröger
Haematologica 2020
https://doi.org/10.3324

Mechanisms of Relapse in Allo-BMT

Immune escape by residual leukemia cells



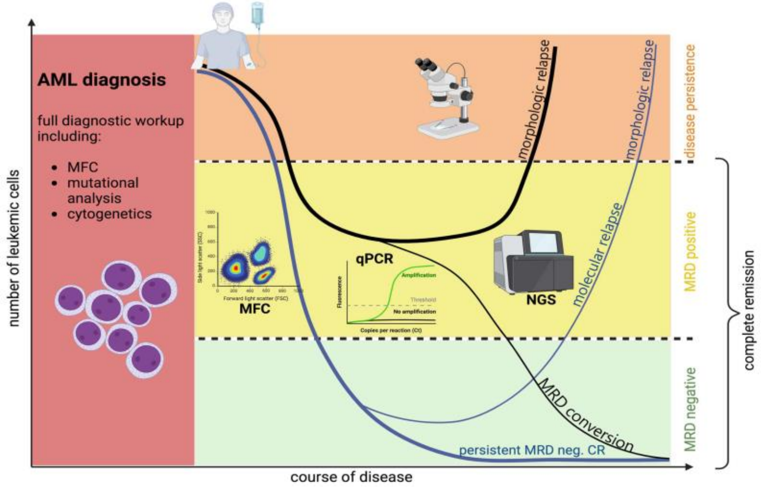
Zeiser and Vago 2019 Blood **133**: 1294

Signs of Relapse

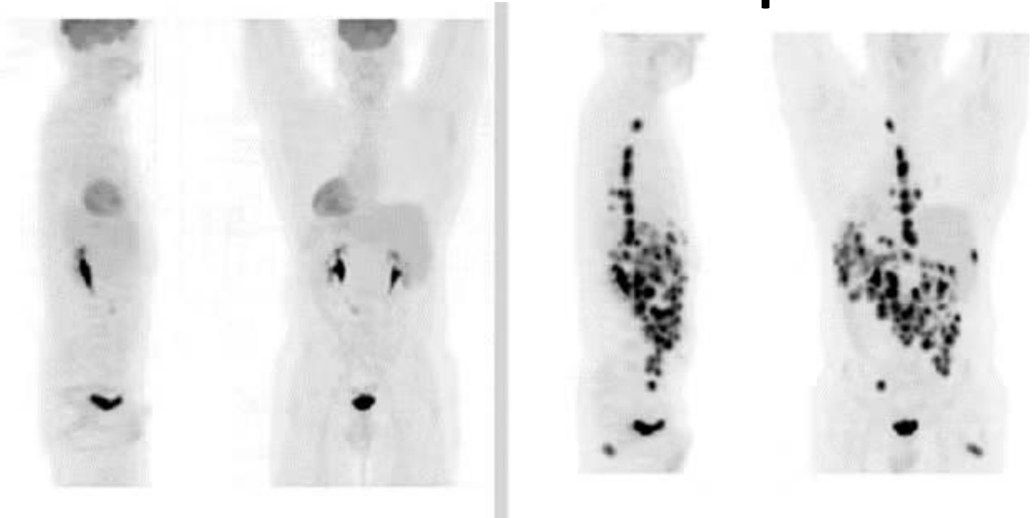
- Fatigue
- Weight Loss
- Night Sweats
- Swollen Lymph Nodes
- Bone Pain
- Abnormal Lab Results.

Diagnostic Tests for Relapse

Bone marrow biopsy, PET/CT scans, and molecular markers.



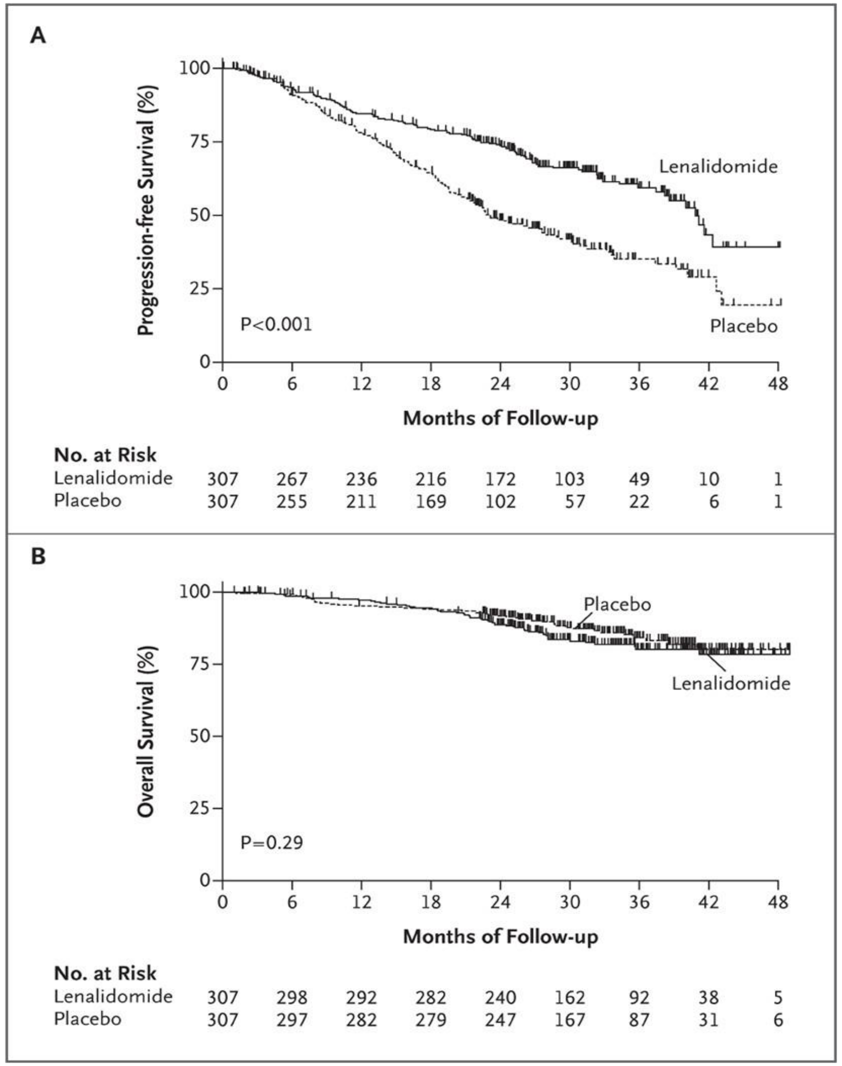
Remission PET **Relapse PET**



PCR testing and DNA sequencing to detect cancer-specific mutations in blood or BM that anticipate clinical relapse

Maintenance Therapy to Prevent Relapse

The Role of Maintenance Therapy in Myeloma

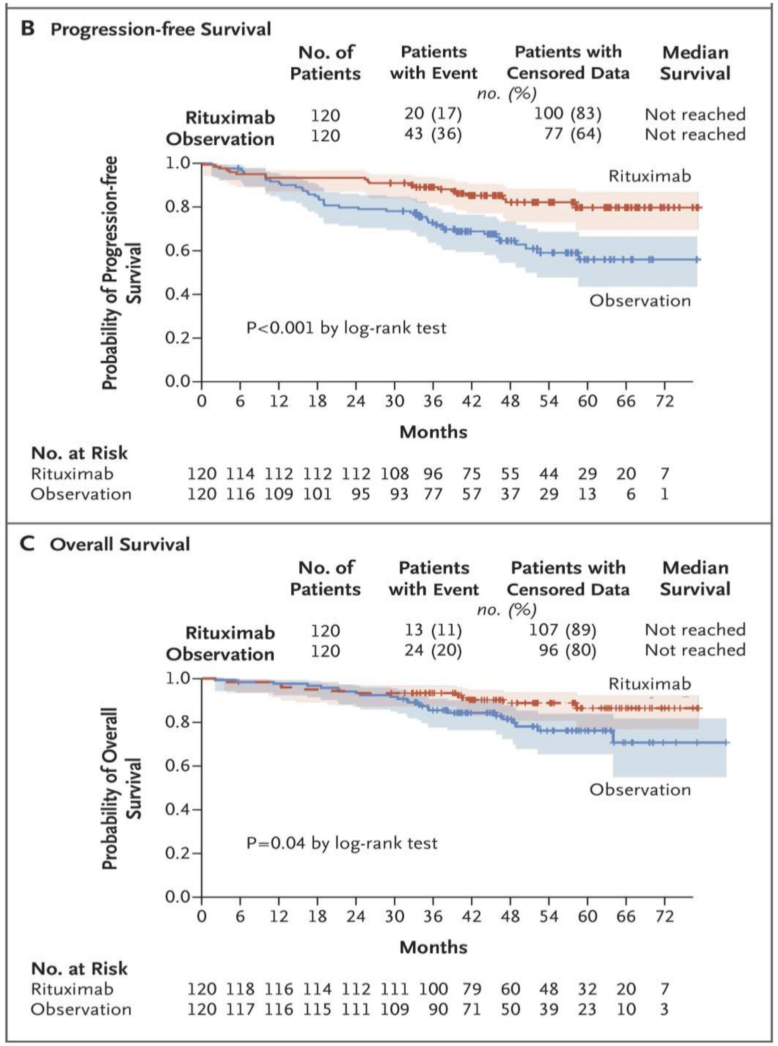


- Ongoing treatment to reduce the risk of relapse.

Lenalidomide maintenance reduces the risk of disease progression at 4 years from 80% to 63% in multiple myeloma patients undergoing autologous stem cell transplant

Attal et al. N Engl J Med 2012. **366**:1782-1791

The Role of Maintenance Therapy in Lymphoma

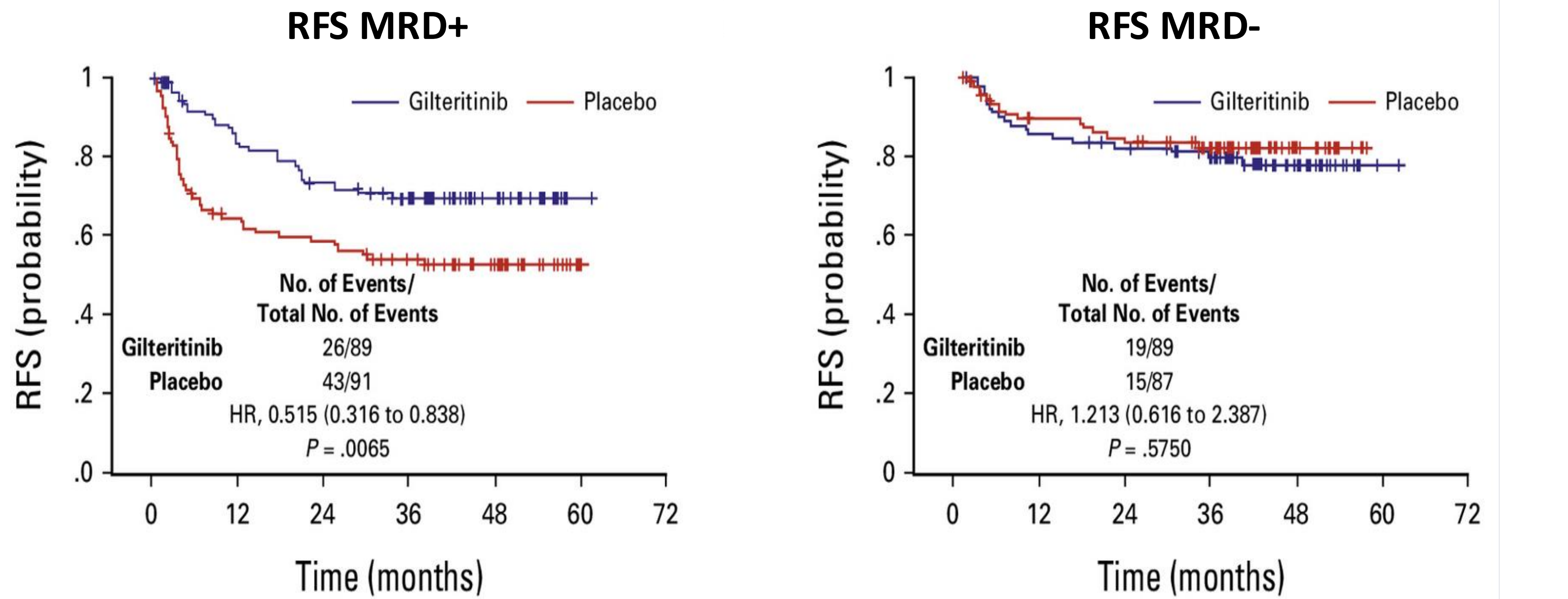


Ongoing treatment to reduce the risk of relapse.

Rituximab maintenance reduces the risk of disease progression at 4 years from 45% to 20% in mantle cell lymphoma patients undergoing autologous stem cell transplant

Le Gouill et al. N Engl J Med 2017. **377:**1250-1260

The Role of Maintenance Therapy in AML & Allo-BMT



Gilteritinib maintenance reduced the risk of AML progression at 5 years from 30% to 12% in Flt3+ AML patients who are MRD[+] before or immediately after allogeneic stem cell transplant but did not benefit patients who were MRD[-].

Levis et al. JCO 2024;. **42:**1766

Immunotherapy to Treat Relapse

- **CAR T-cell therapy** treats relapse after auto- or Allo-transplant
- **Immune-checkpoint blockade therapy** has been used with relapse after allo-BMT, but it may cause GvHD
- **Hypomethylating drug therapy** can make leukemia more susceptible to recognition by the immune system.
- **Additional donor immune cells or a second Allo transplant** can be used if patients relapse late after the transplant.

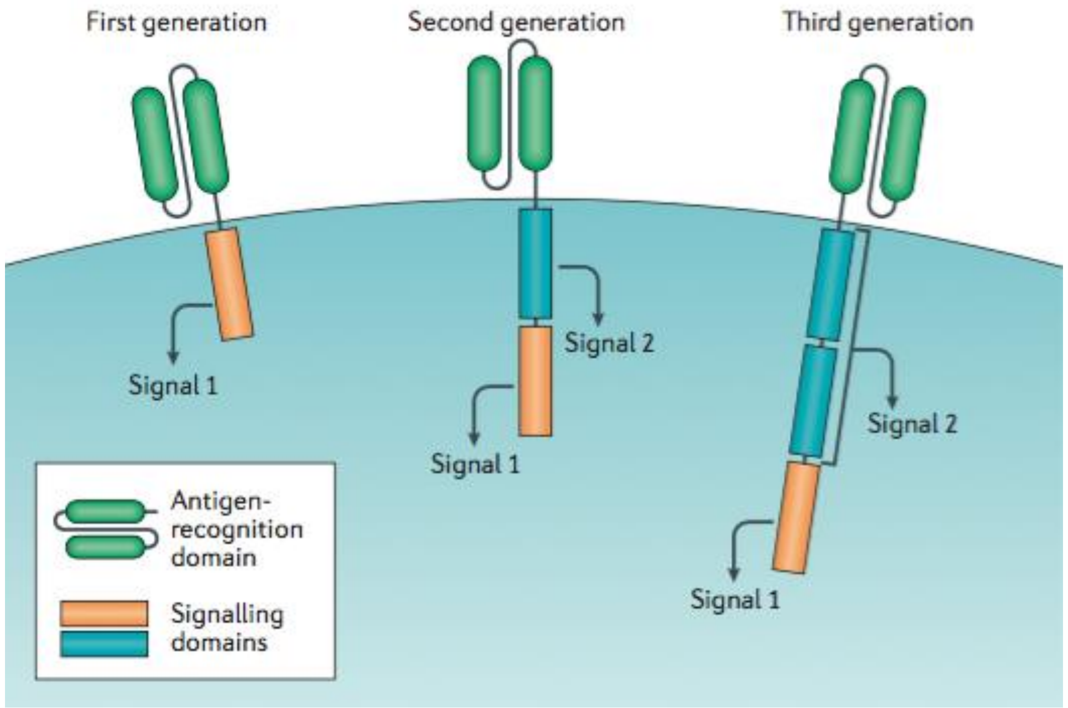
CAR T-Cell Therapy

- A breakthrough for relapsed lymphoma and multiple myeloma.
- FDA-approved products use a patient’s own lymphocytes to manufacture a population of cancer-targeted killer T cells

Chimeric Antigen Receptor (CAR) T Cells: How They Are Made

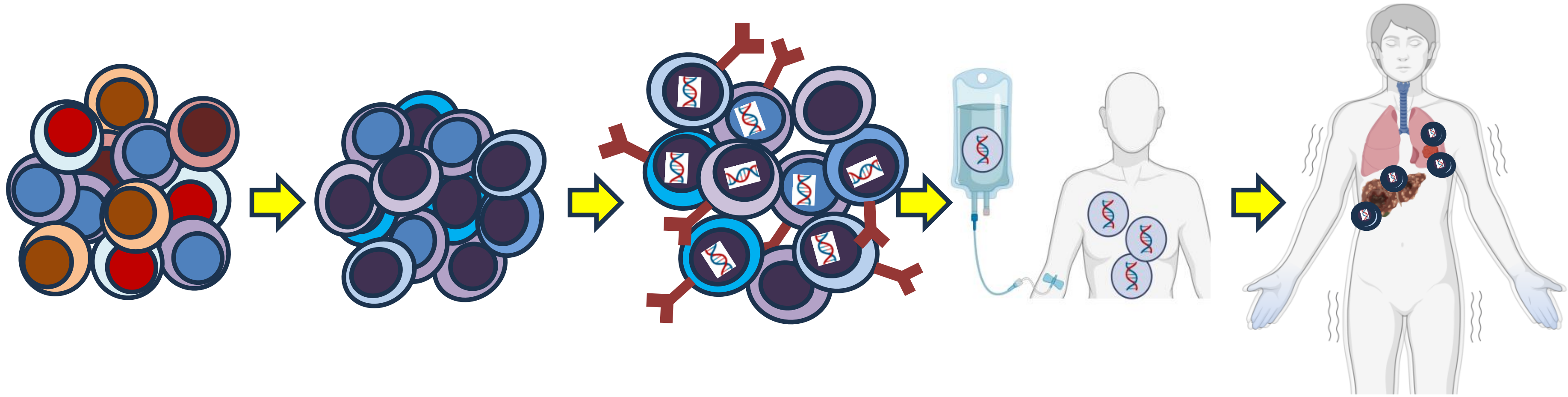
Signal 1→ activation (CD3ζ)
Signal 2→ co-stimulation

2nd gen→ 4-1BB or CD28
3rd gen→ 4-1BB + CD28



Jackson HJ, et al. Nat Rev Clin Oncol. 2016. **13**:370-383.

The Steps in Chimeric Antigen Receptor Cell Therapy



Harvest cells from patient or volunteer donor

Selection of cells for CAR cell manufacturing

Genetic modification of cells

Infusion of CAR cells

CAR cells home to disease sites with local effects

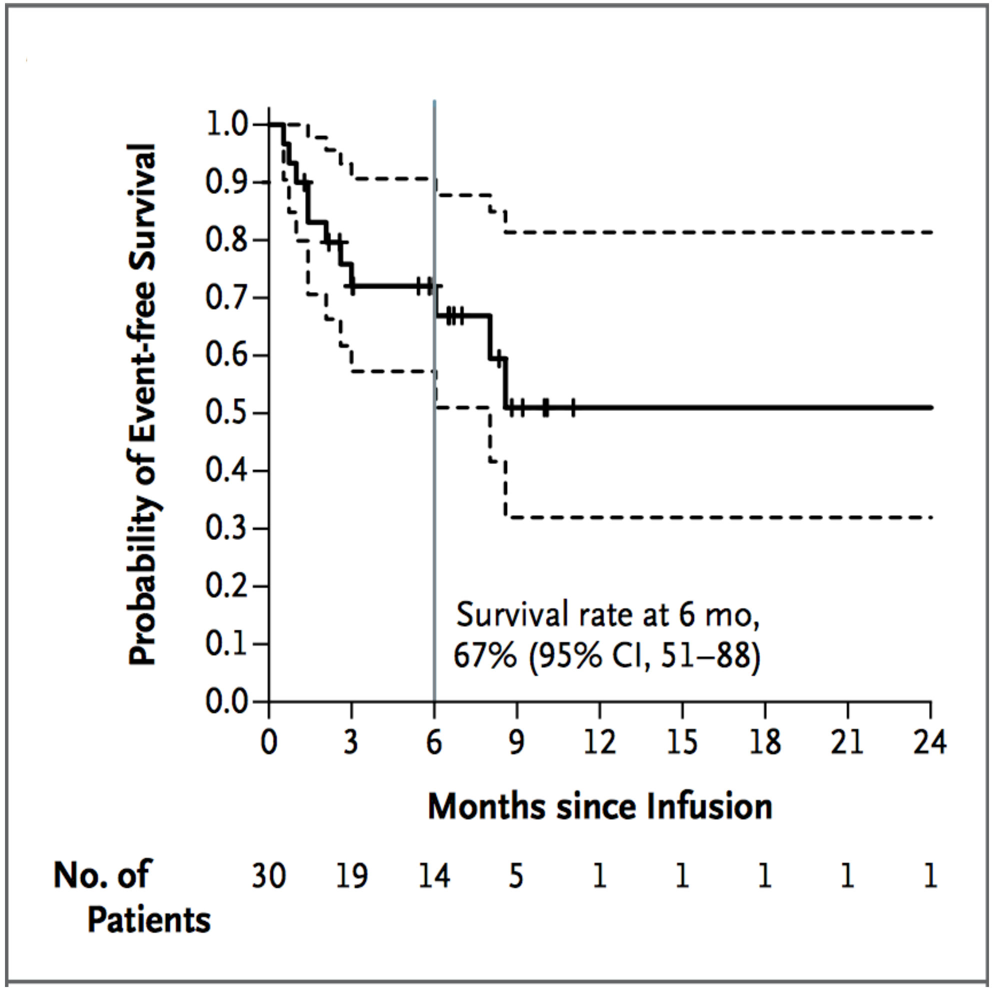
CAR T-cell Therapy Cures Pediatric ALL

Pediatric Patients were 83% of subjects

- Median Age 11 years
- 72% had prior allogeneic transplant
- 88% had 2 or more relapses
- 80% had detectable Leukemia

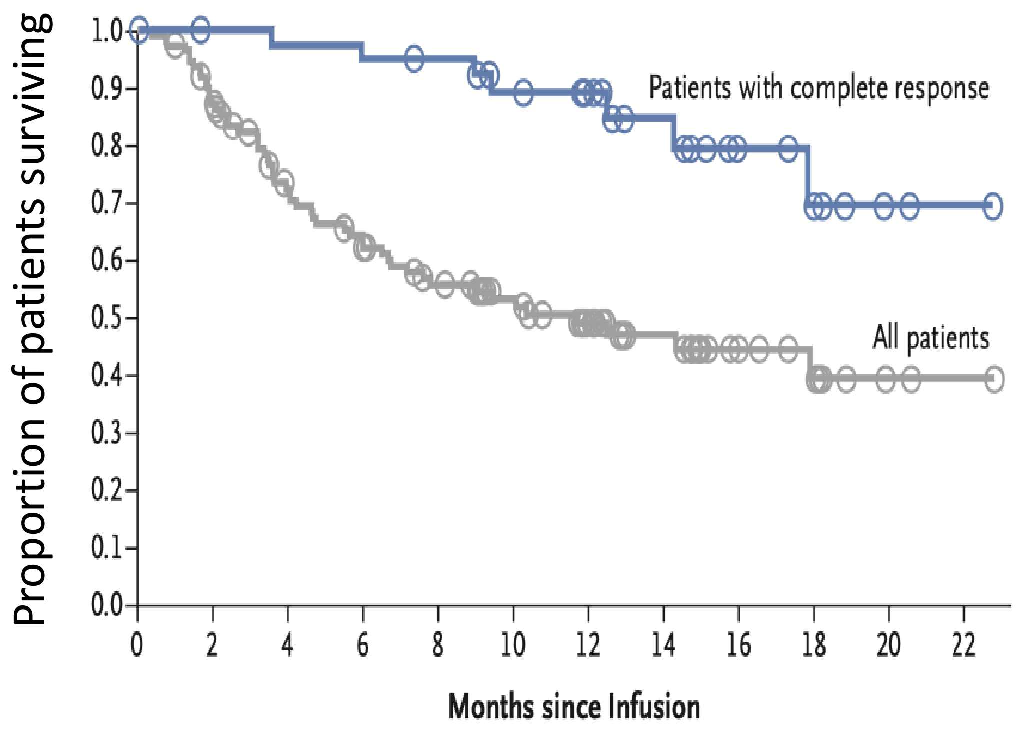
Adult patients were 17% of subjects

- Median age 47 years
- No allogeneic transplants
- 60% had primary refractory disease



Maude SL et al. N Eng. J Med 2014. **371**:1507-1517.

Tisa-cel CAR-T (Kymriah) leads to durable remissions in a fraction of relapsed/refractory adult lymphoma patients



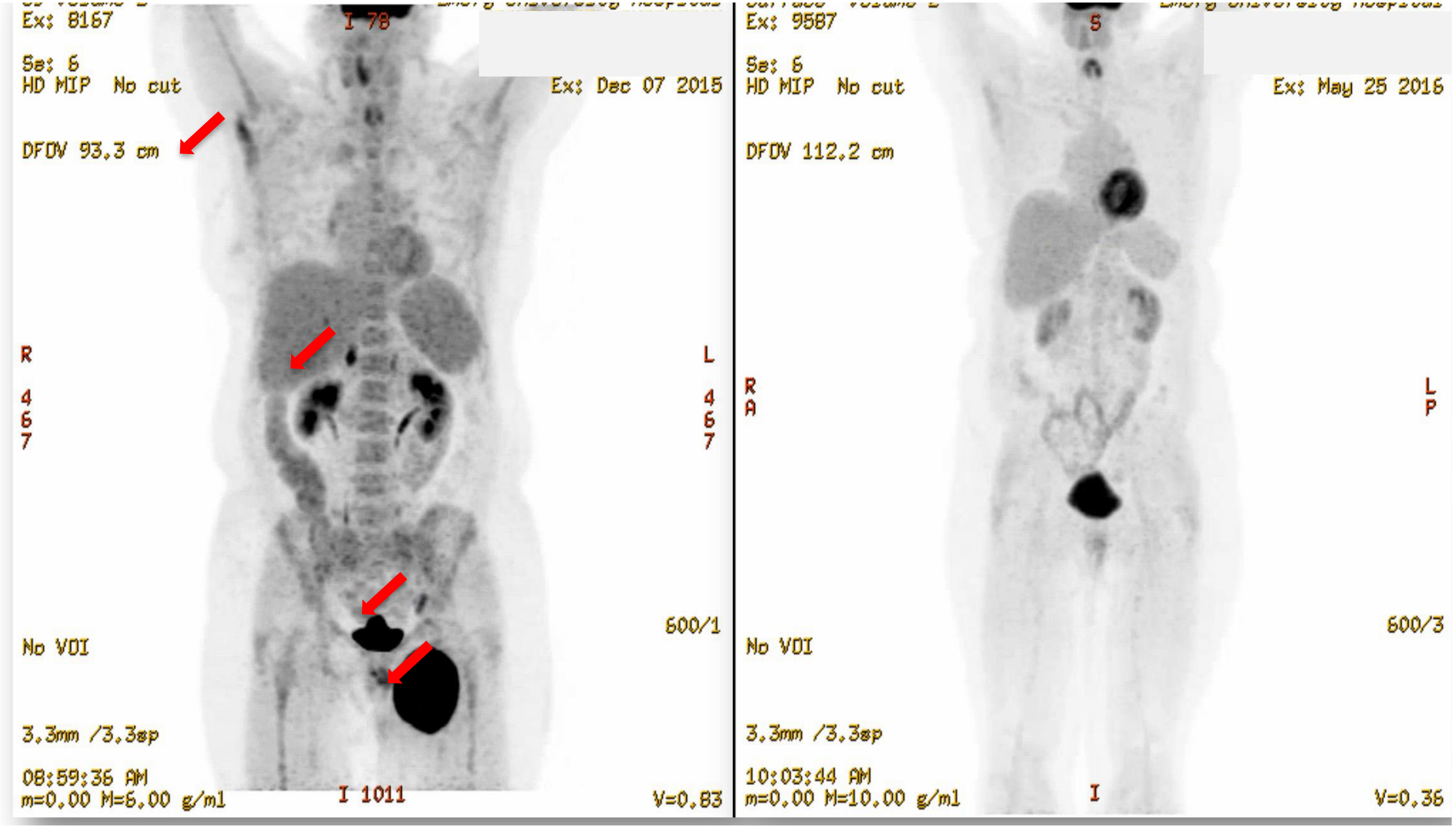
Tisa-cell (Kymriah) was effective across different groups of lymphoma patients:

- >age 65
- Males and females
- More aggressive disease
- High-risk molecular mutations

It tended to be less effective for patients with very bulky disease

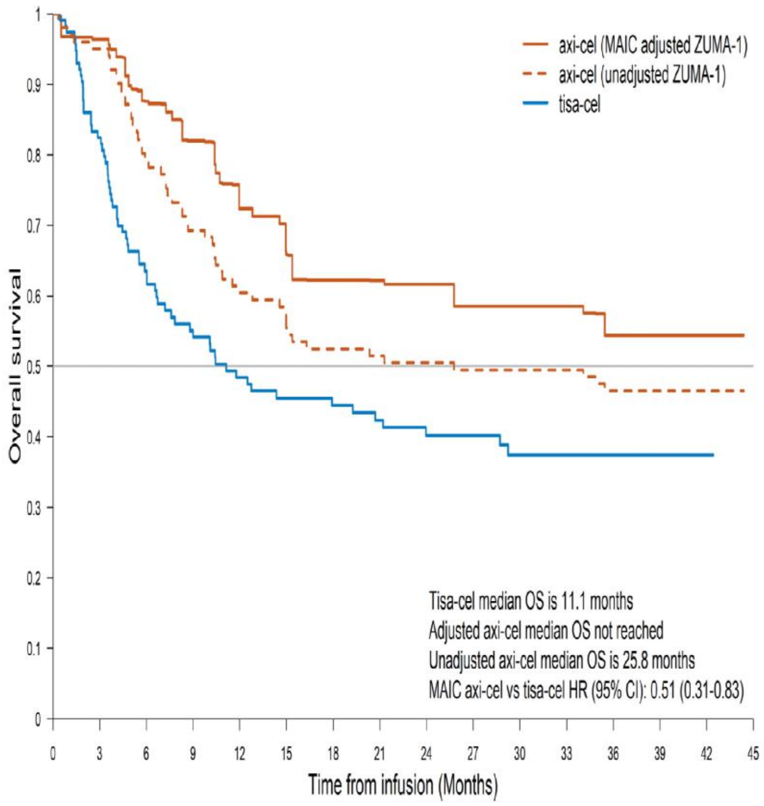
Schuster et al. NEJM 2019.

Complete regression of DLBCL three months following Tisa-cel CART therapy

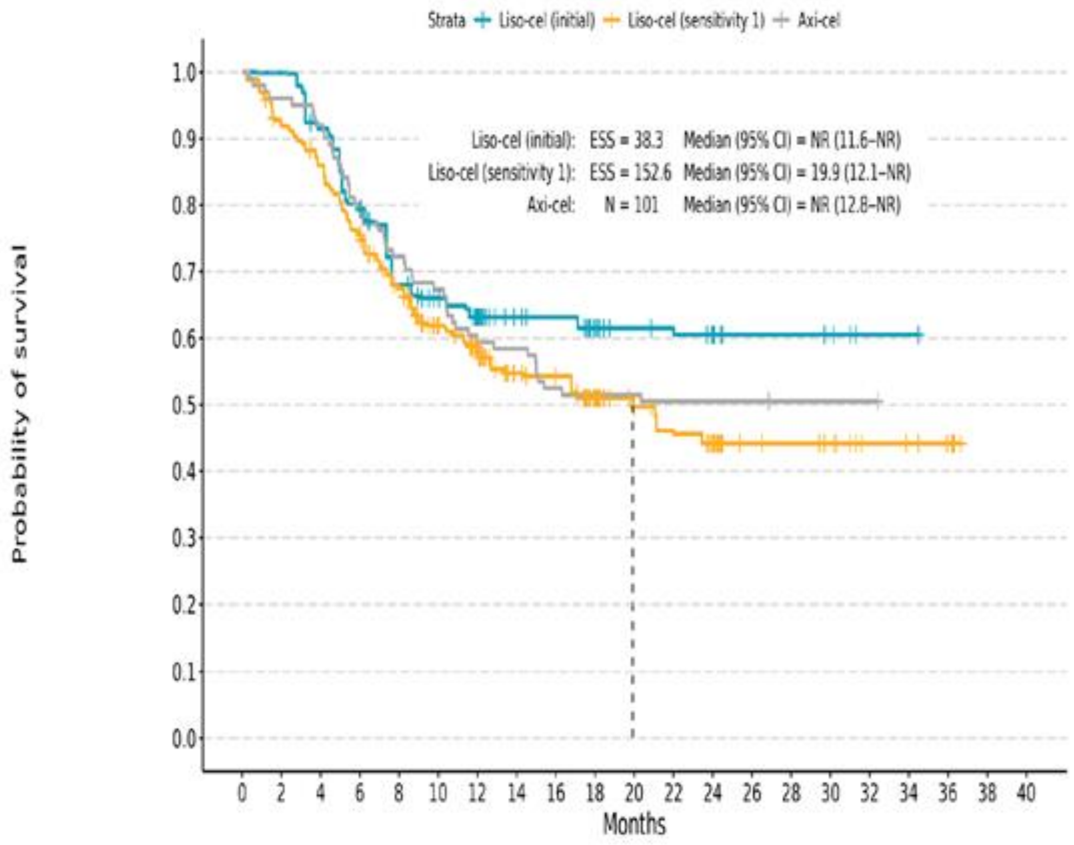


Waller, unpublished

Liso-cel (Breyanzi) and Axi-cel (Yescarta) are superior as 3rd line therapy for relapsed large cell lymphoma compared to Tisa-cel (Kymriah)

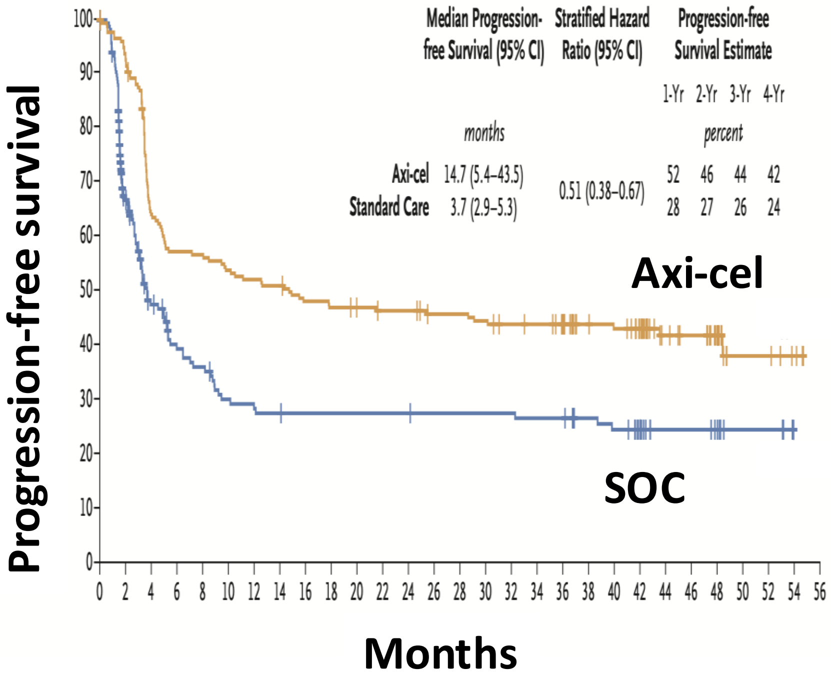


Maloney et al. J Hematol Oncol. 2021 **14**:140

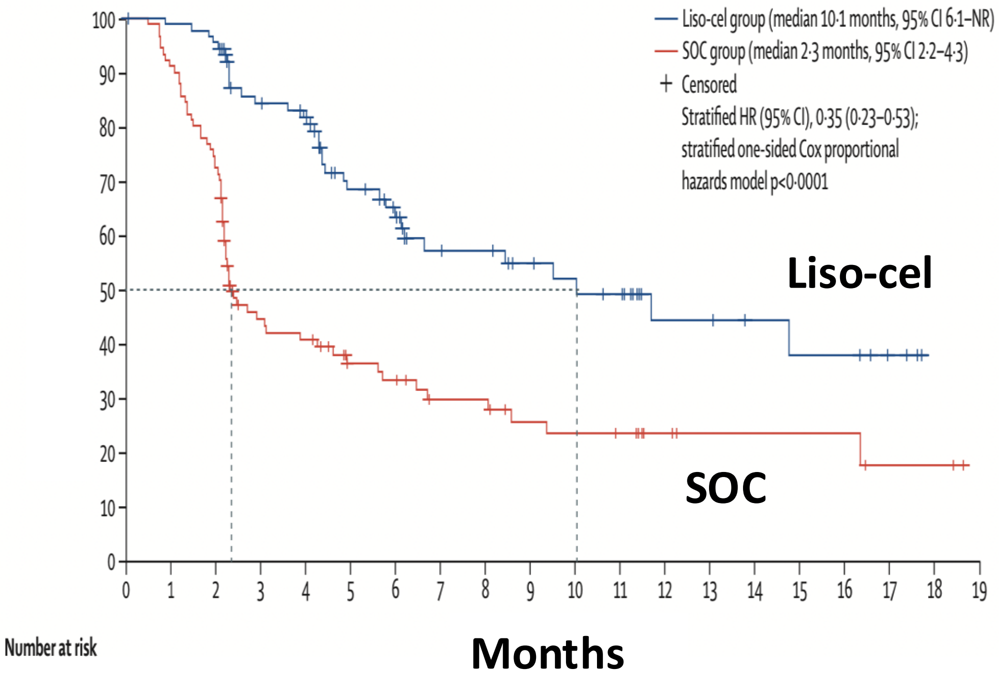


Oluwole et al. BBMT. 2020 26:1581

Axi-cel (Yescarta) and Liso-cel (Breyanzi) are superior to auto-transplant as 2nd line therapy for patients with relapsed B-cell lymphoma

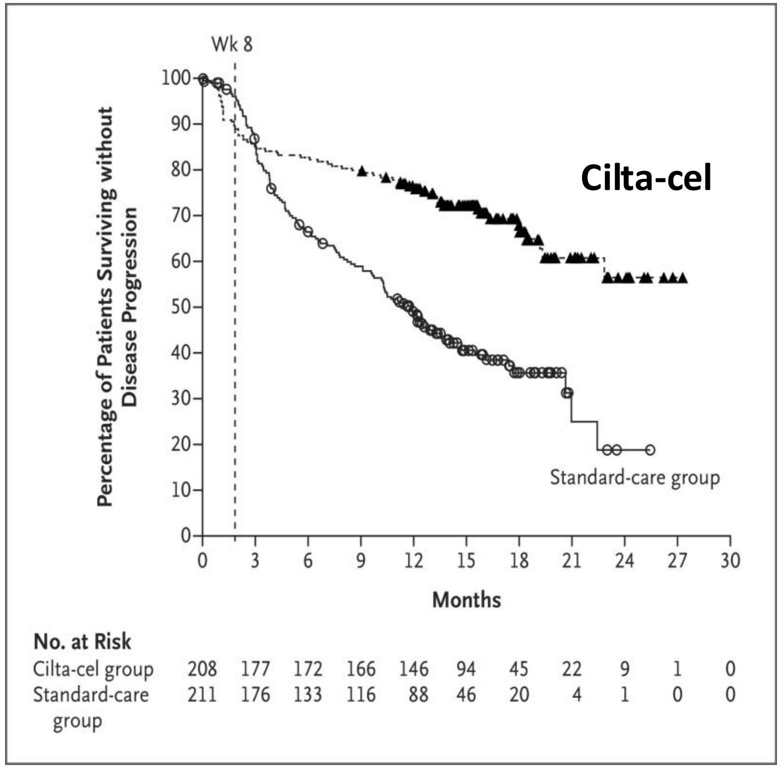


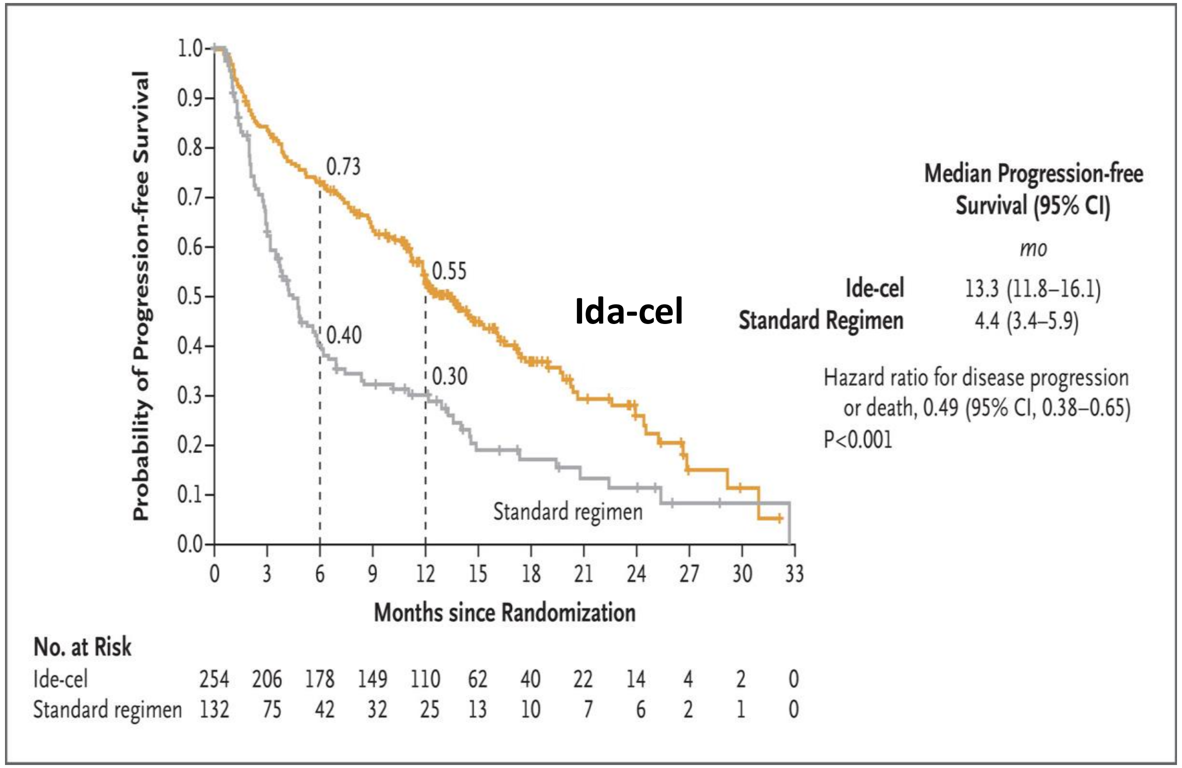
Westin et al. 2023 NEJM **389**: 148



Manali Kamdar Lancet Oncology 2022

BCMA CAR T for Lenalidomide-refractory multiple myeloma: Cilta-cel (Carvykti) or Ide-cel (Abecma) versus standard-of-care treatment

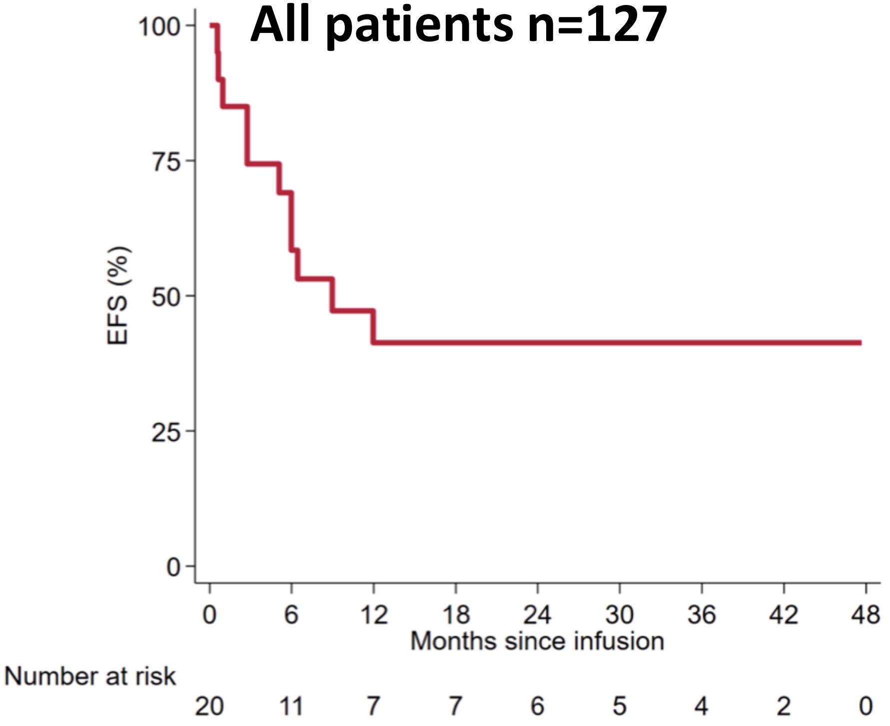


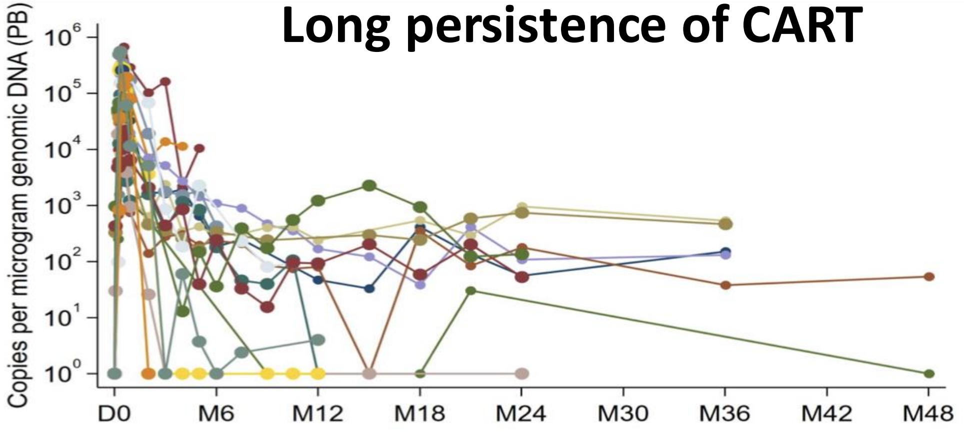


San-Miguel 2023 NEJM **389**: 335

Rodriguez-Otero 2023 NEJM **388**:1002

Efficacy and Safety of Obe-cel (Aucatzyl) in adult B-ALL patients





Low toxicity

	Overall (n=127)	<5% BM blasts (n = 36)	5–75% BM blasts (n = 51)	>75% BM blasts (n = 40)
12-month EFS	50%	65%	55%	27%
≥G3 CRS	2%	0%	4%	3%
≥G3 ICANS	7%	0%	6%	15%

Roddie, et al. Abstract #222 ASH 2023

NEJM paper

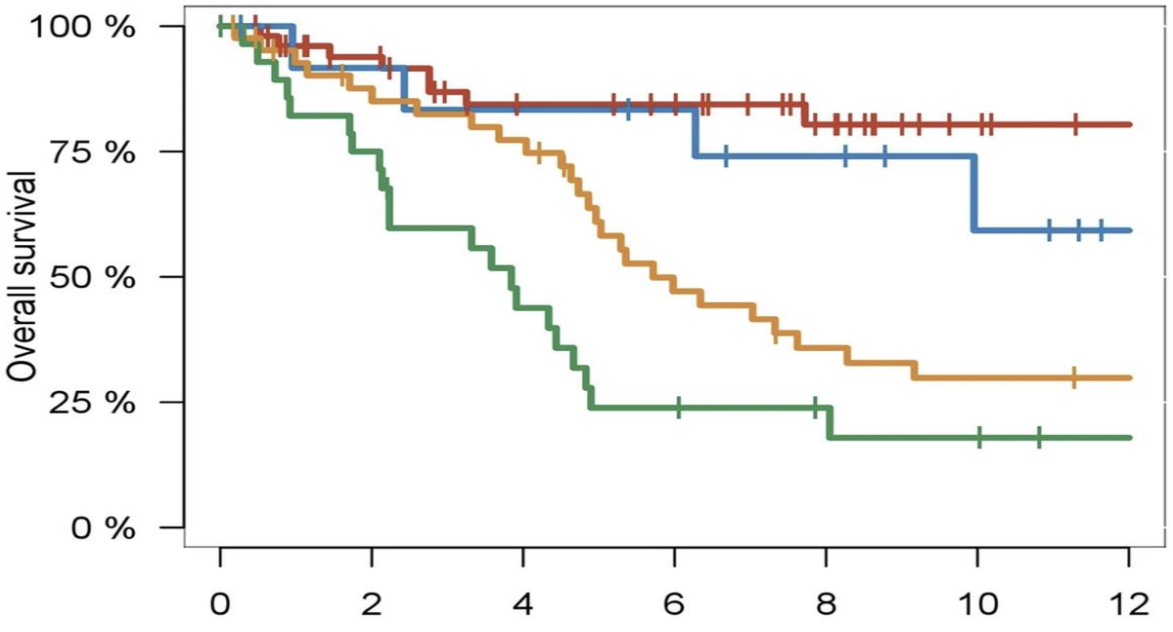
Managing Relapse after CAR T-cell Therapy

What are the options for myeloma or lymphoma patients who relapse after CAR T?

- Bi-specific antibodies- reactivate T cells
- Allogeneic Transplant- start over with a 2nd graft
- Second CAR T- target a different antigen

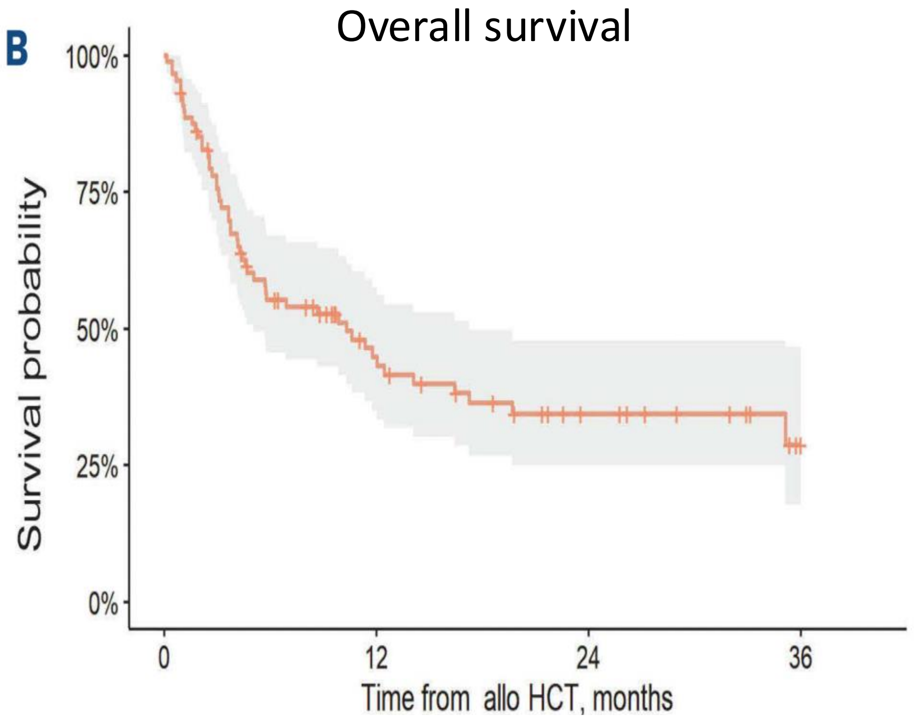
Bispecific Antibodies

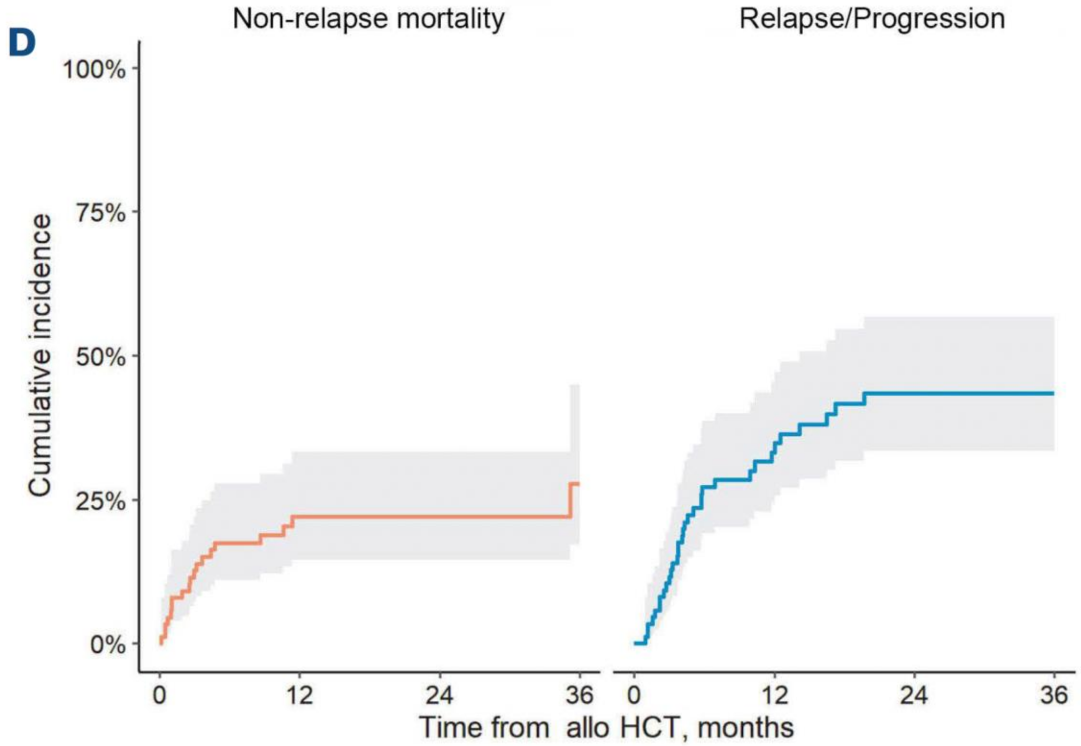
Antibodies that link T cells to tumor cells are effective as salvage therapy after CAR-T



Merz. 2024 Blood Cancer Journal

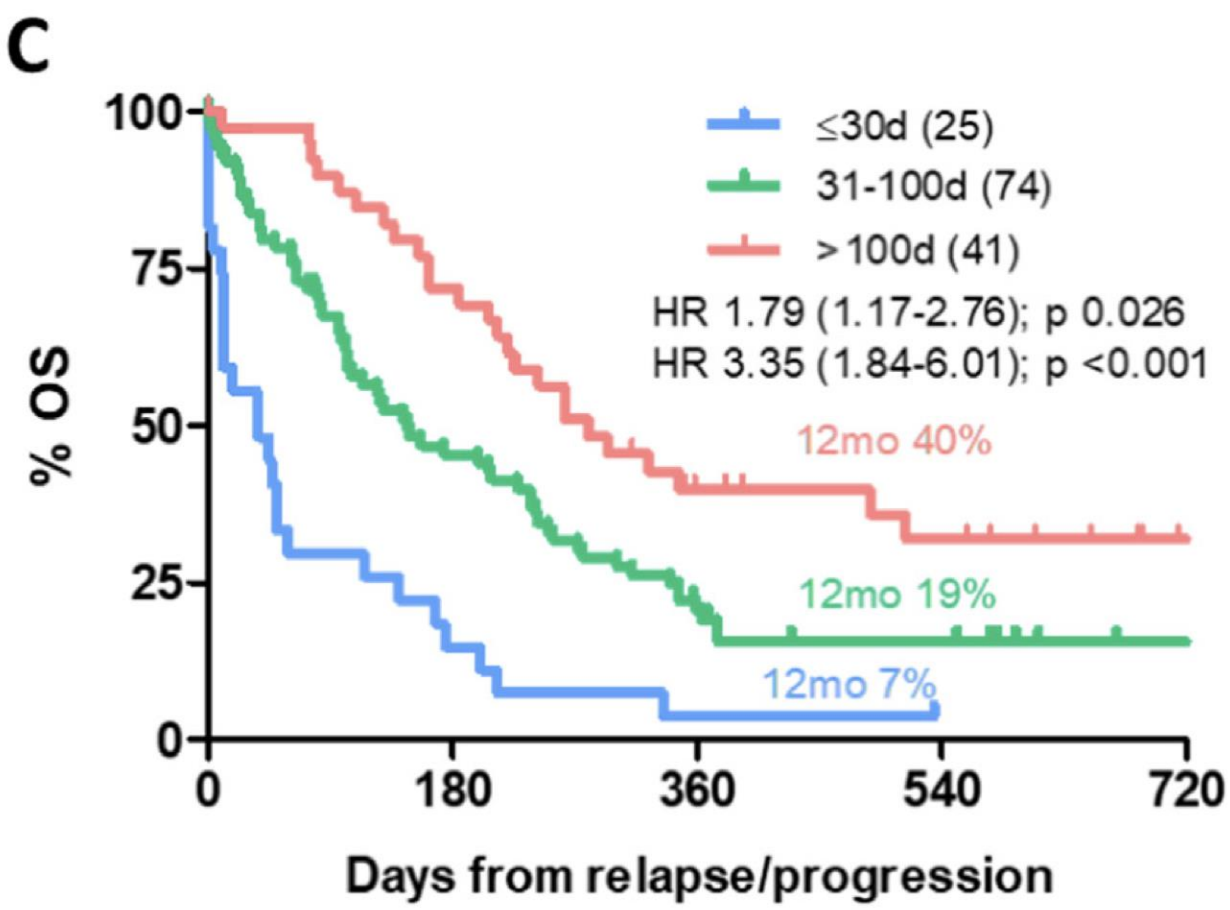
Allo-BMT Can Salvage 1/3 of Patients with Lymphoma that has relapsed after CAR T





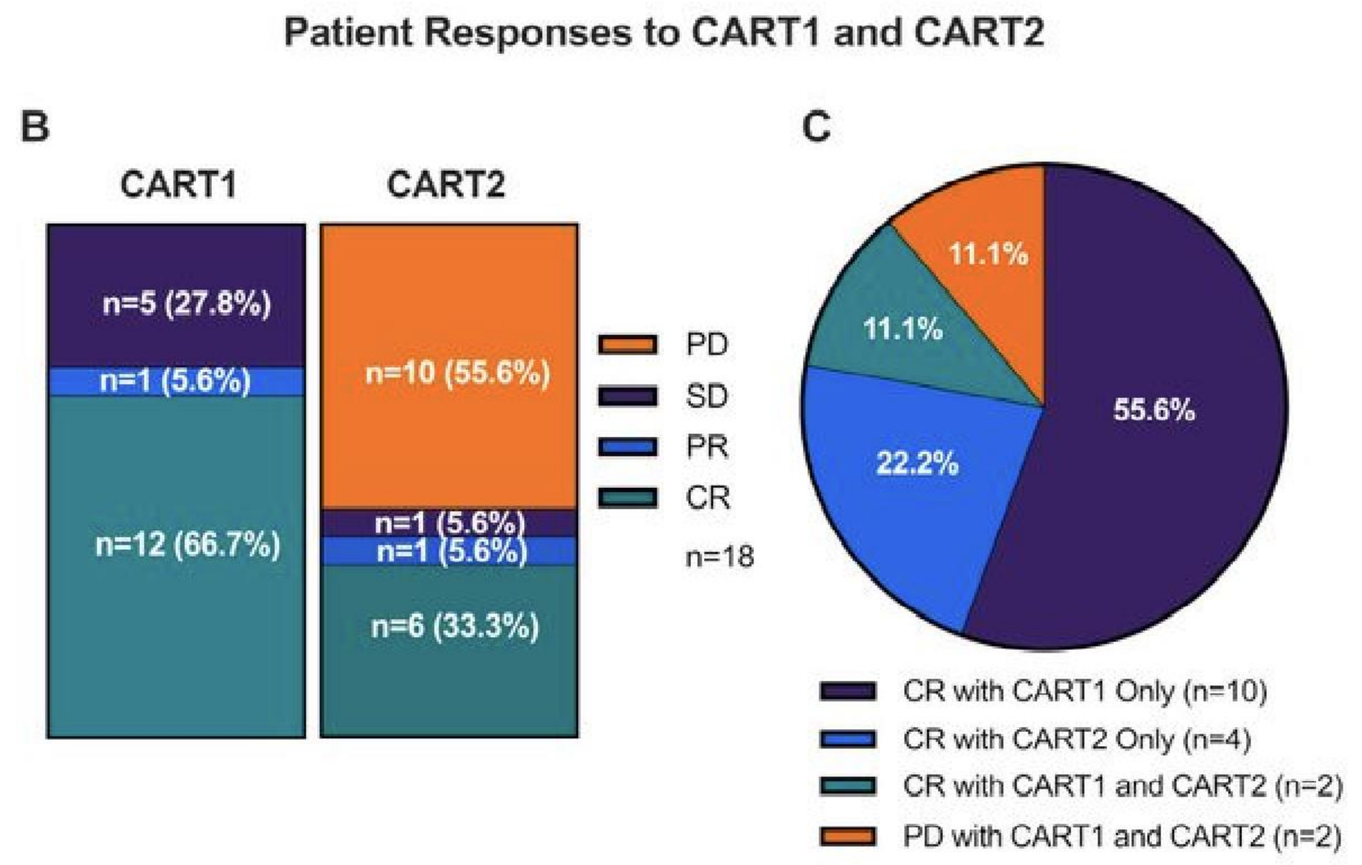
Zurko et al. Haematologica 2023

Late Relapse after CAR T for Lymphoma Had Better Survival



Derigs et al. TCT 2023

One Third of Patients Who Didn't Respond to Initial CAR T Benefit from a Second CAR T



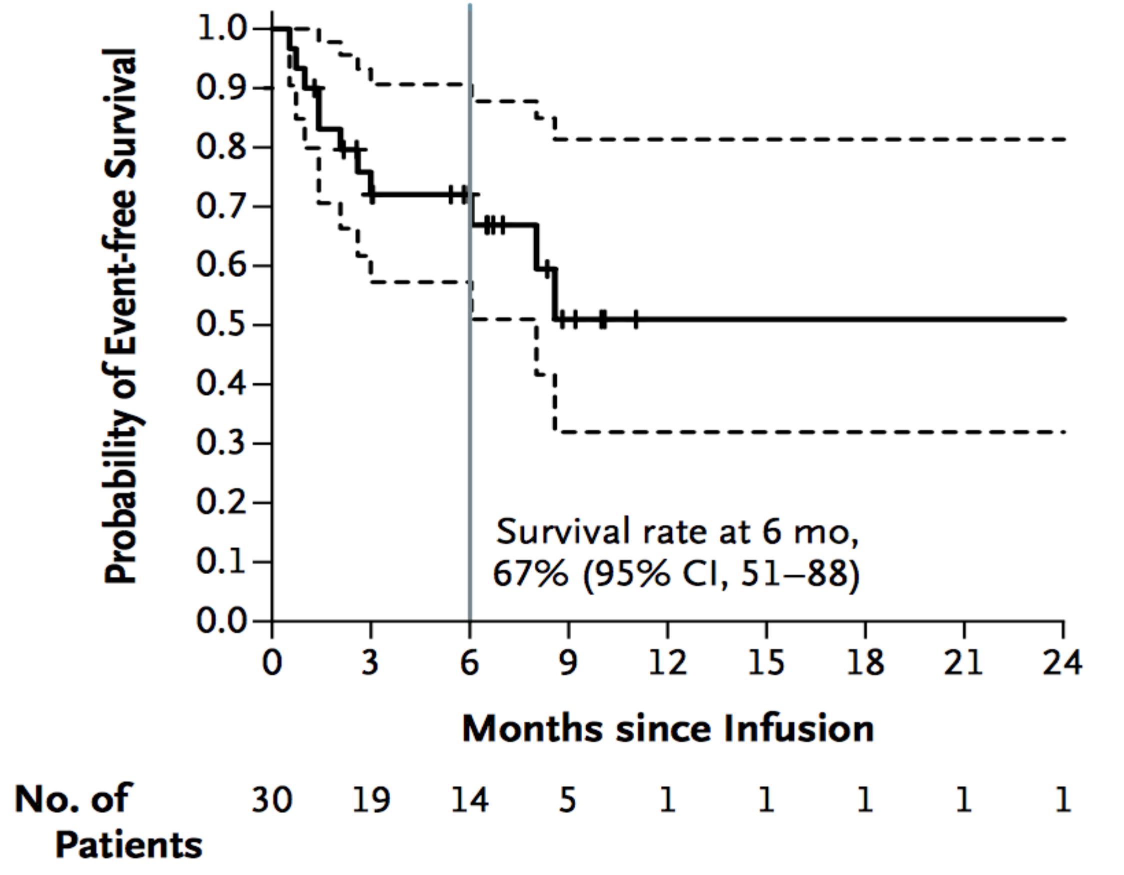
Holland et al. J Immunother Cancer 2022

What Are the Options for Relapse after Allo-BMT?

- **CAR T** for CD19+ relapsed B-cell acute lymphoblastic leukemia (B-ALL)
- **Second Allo-BMT** for patients with a late relapse (any malignancy)
- **Hypomethylating drug therapy** for relapse with minimal detectable leukemia or MDS (AML and MDS)

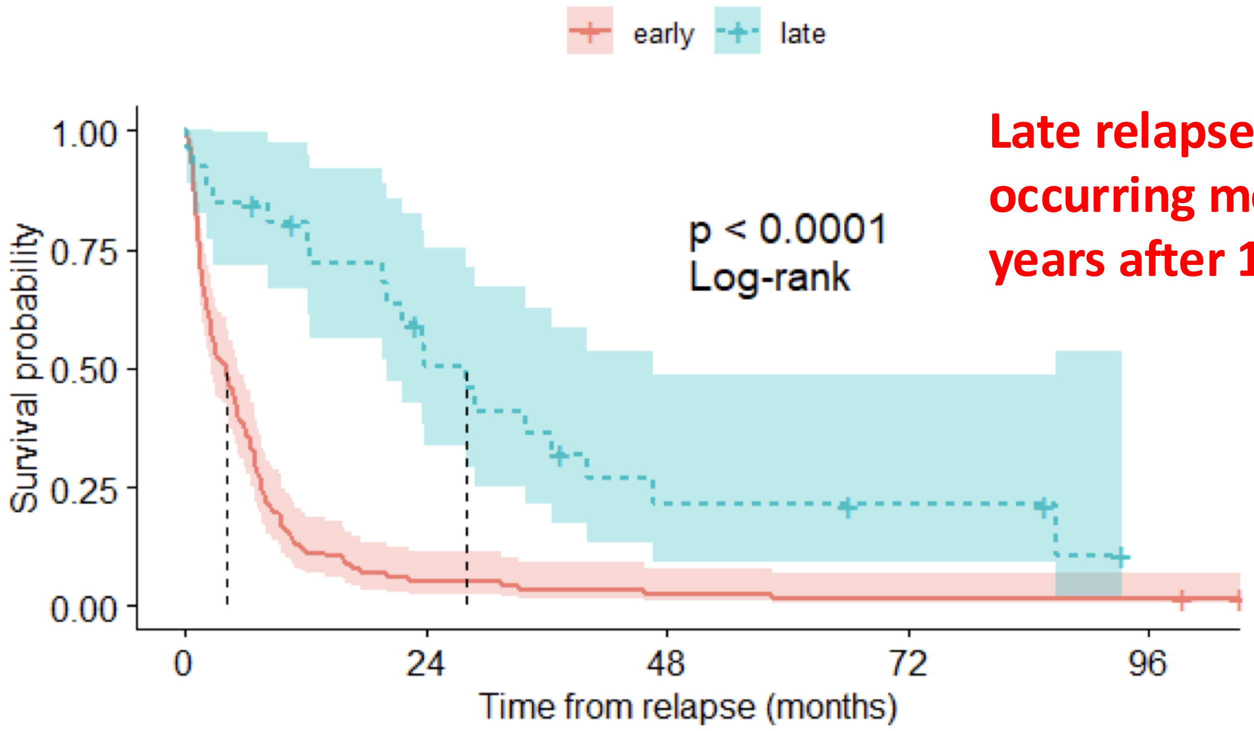
CAR-T B-cell for Acute Lymphoblastic Leukemia Relapsed after Allo-BMT

72% of pediatric patients relapsed after allo-BMT



Maude SL et al. N Eng. J Med 2014. **371**:1507-1517.

Very Poor Survival with Second Allo Transplant for Early Acute Myeloid Leukemia Relapse



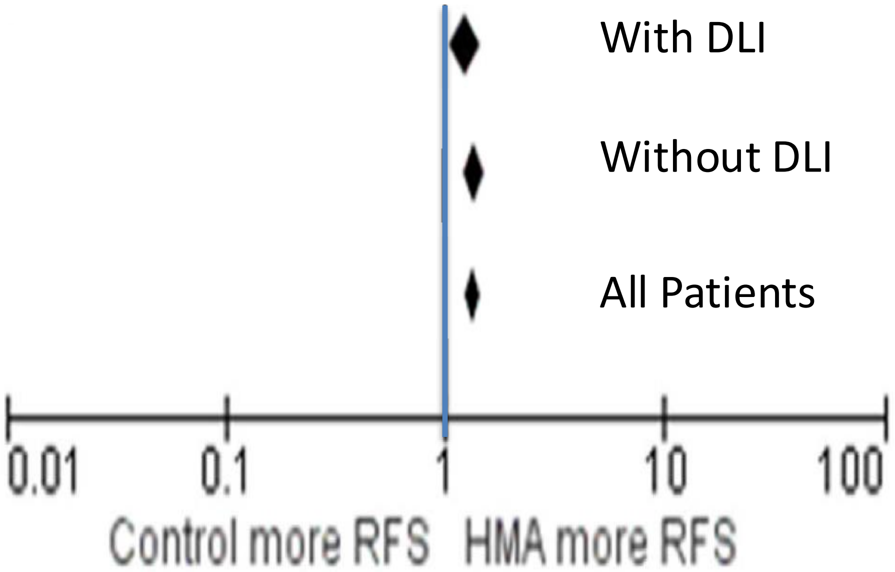
Late relapse defined as occurring more than 2 years after 1st allo-BMT

Early relapse	116	6	3	2	2
Late relapse	26	11	4	3	0

Antier et al. Cancers 2024

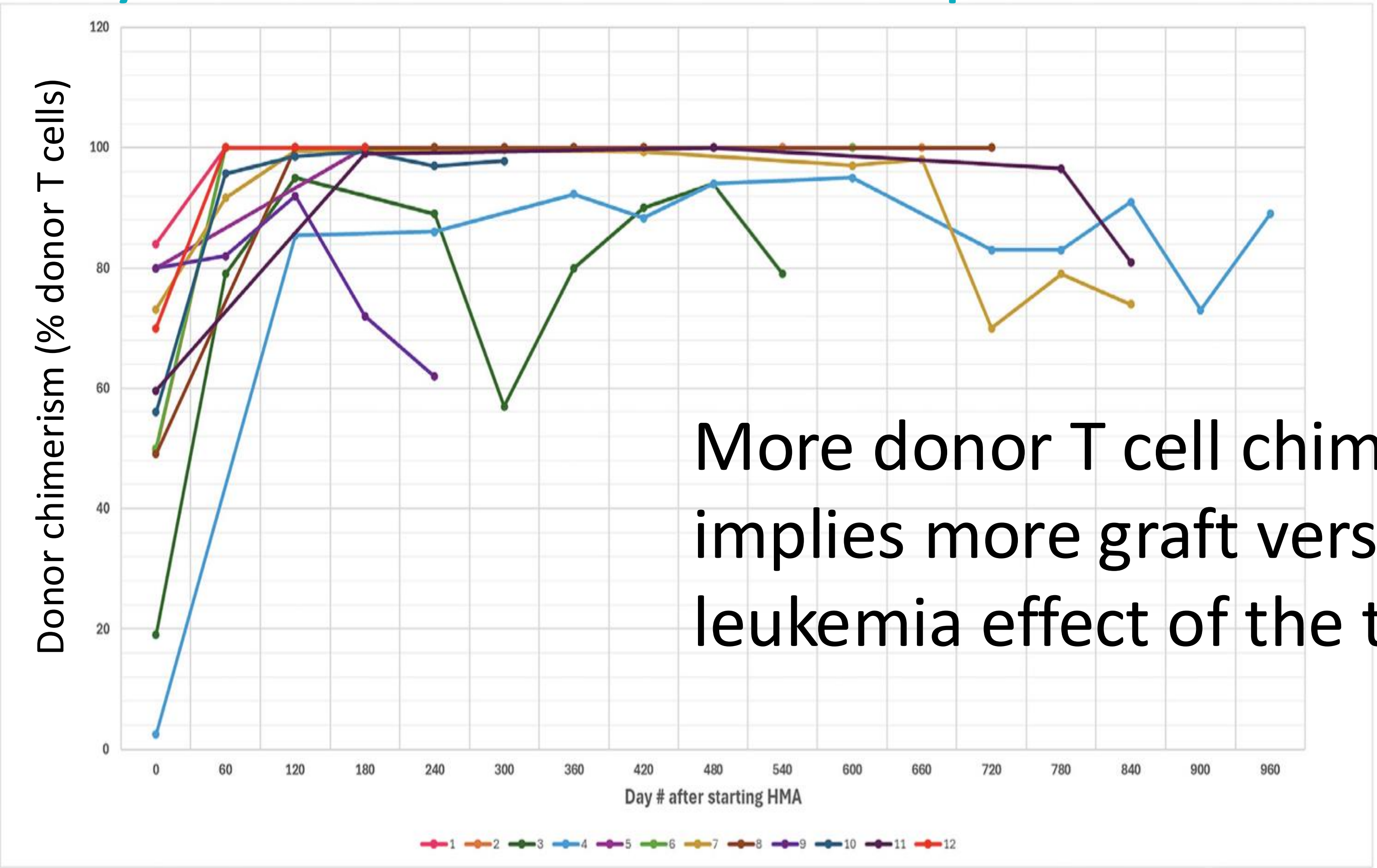
Post-transplant Hypomethylating drug therapy (HMA) can Improve Survival in patients with relapsed AML after Allo-BMT

	HMA		Control			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Subtotal (95% CI)		62		120	29.5%	1.33 [1.09, 1.62]		
Subtotal (95% CI)		202		333	70.5%	1.50 [1.32, 1.70]		
Total (95% CI)		264		453	100.0%	1.44 [1.30, 1.61]		



Kungwankiattichai Frontiers in Immunology 2022

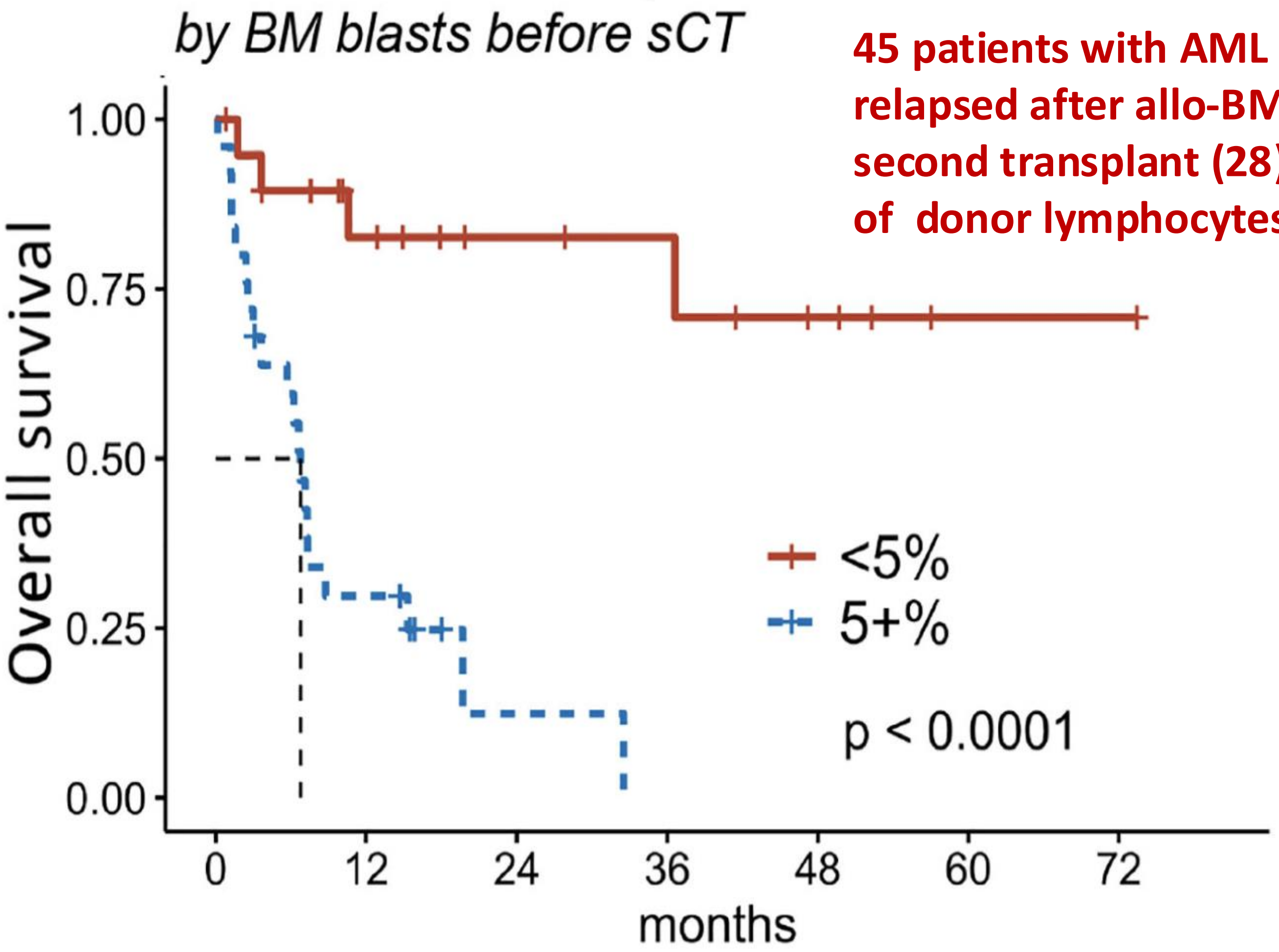
HMA Treatment Leads to Elimination of Residual Host-type T cells in Myelofibrosis Patients Relapsed after Allo-BMT



More donor T cell chimerism implies more graft versus leukemia effect of the transplant

Ngo et al. TCT 2024

Second Transplant or Donor Leukocyte Infusion (DLI) is Effective with Relapsed AML If the Disease Burden is Low



45 patients with AML or MDS relapsed after allo-BMT received a second transplant (28) or an infusion of donor lymphocytes (17)

Brambilla et al. TCT 2021

Role of Lifestyle in Preventing Relapse

- A diet that promotes a diverse gut microbiome (diet with varied fiber and nuts) has been associated with less gut inflammation, better anti-cancer immunity
- Psychological stress may increase inflammation and impede the success of donor T cells in fighting cancer.

Coping with Fear of Relapse

- Recognize that the fear of relapse is inevitable
- Acknowledge that there is a limit to what patients or doctors can do to prevent relapse
- Live in the moment
- Don't rely on annual CT scans or marrow biopsies for permission to have hope

Supportive Care Strategies

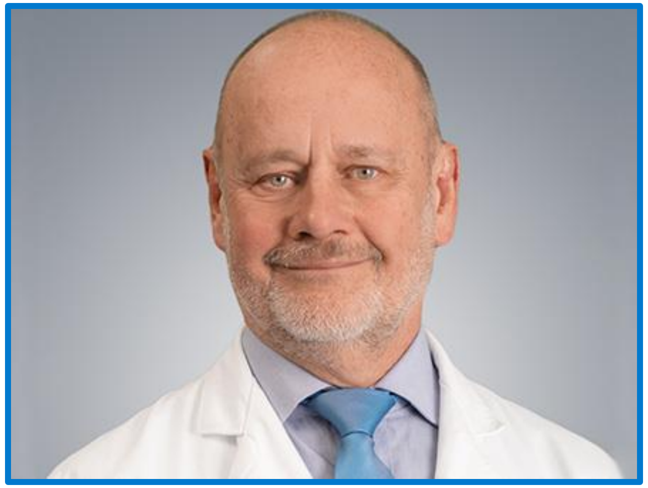
The Role of the Caregiver

- Provide emotional and practical support.
- Discuss the test results with the doctors.
- Ask for a “Plan A” and “Plan B” if relapse occurs.
- Seek a second opinion at a higher volume transplant center or seek out a clinical trial.
- Fear of relapse is stressful for caregivers: seek support as well!

Summary & Key Takeaways

- “An ounce of prevention is worth a pound of cure”
- Targeted maintenance therapy after BMT can prevent relapse
- CAR T is more effective than auto-BMT for relapsed lymphoma
- CAR T can follow allo-BMT and cure 40%-50% of patients with relapsed B-ALL
- Allo-BMT can follow CAR T and salvage 33% of B-ALL patients with very early signs of relapse

Questions?



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