# Should we transplant AML/MDS patients not in remission?

## Yes (but who and how?)

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# Disclosures

- I have no disclosures that are relevant to this presentation

# My opponent and I are on the same team…

The Leukidators

The glass is half full…

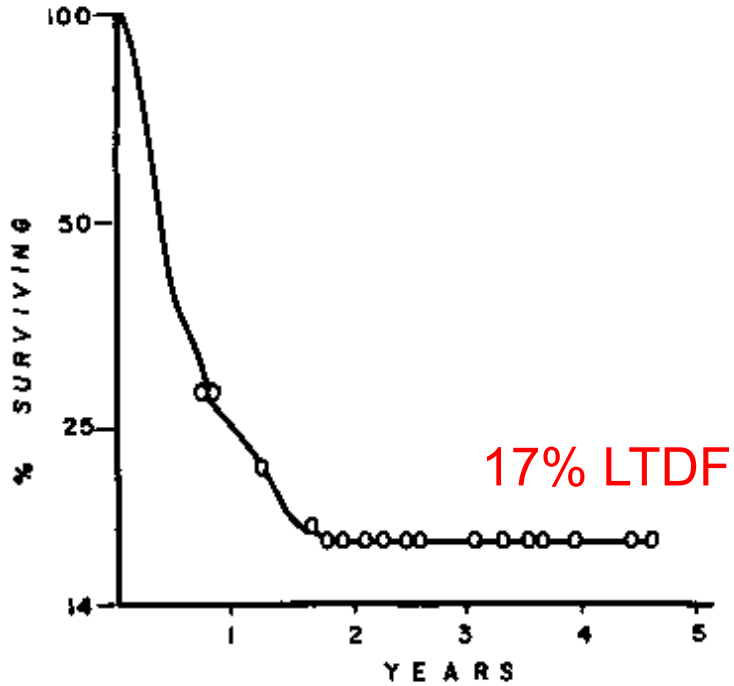
The glass is half empty…

# Case: 49 yo woman with presumed therapy related MDS-- RAEB-2

- h/o RA treated with hydroxychloroquine, gold and MTX; no other PMH
- Presented with pancytopenia and variably cellular BM c/w RAEB-1; normal karyotype
  - Progressive cytopenias—became RBC and transfusion dependent
  - Multiple bacterial infections
  - KPS maintained at 80-90%
- URD search revealed no 10/10 matches, but a single locus allele level mismatched donor identified
- Transplant 4/10/1998—**15% BM blasts pre-BMT/no circulating blasts**
  - Conditioning: Bu/Cy/Fludarabine (myeloablative)
  - Recurrent episodes of Cdiff post-BMT
  - Mild chronic GVHD
  - Normal CBC 2021
- Last f/u 6/21/22 with Rheumatology—doing well!

# One Hundred Patients With Acute Leukemia Treated by Chemotherapy, Total Body Irradiation, and Allogeneic Marrow Transplantation

By E. Donnall Thomas, C. Dean Buckner, Meera Banaji, Reginald A. Clift, Alexander Fefer, Nancy Flournoy, Brian W. Goodell, Robert O. Hickman, Kenneth G. Lerner, Paul E. Neiman, George E. Sale, Jean E. Sanders, Jack Singer, Mary Stevens, Rainer Storb, and Paul L. Weiden




17% LTDFS

Blood 49: 511-33 (1977)

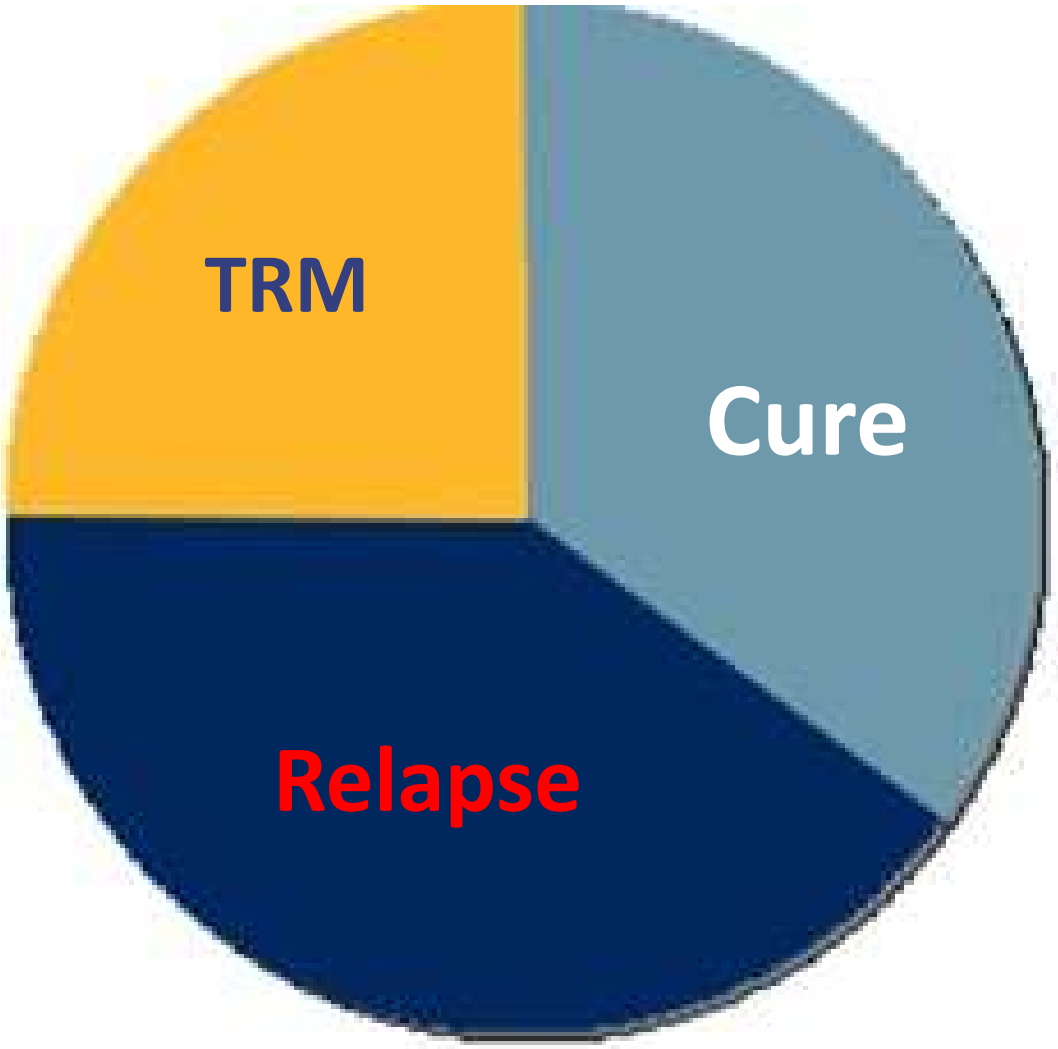
***1990: E. Donnall Thomas wins Nobel Prize in Medicine (with Joseph Murray)***

# My Arguments

- Allogeneic transplantation offers the only chance of cure for patients with high risk AML and MDS
- All *patients* with refractory AML/MDS are not the same
  - We can identify pts most likely (and unlikely) to benefit from transplantation
- Novel transplant approaches and new drugs offer hope to enhance the possibility of transplantation being curative for these pts
  - Enhance the transplant maneuver – GVL without GVHD or toxicity…
  - Post-transplant maneuvers to decrease relapse

# Outcomes after Allogeneic Transplantation

## The “transplant pie”




- Disease/disease status
- Conditioning therapy
- Donor type, matching
- GVHD prophylaxis
- Comorbidities, age
- Social support, distance from center, etc

# Which patients are most likely (or unlikely) to benefit?

# BMT CTN 0901: MAC vs RIC for AML/MDS

## Conditioning intensity matters

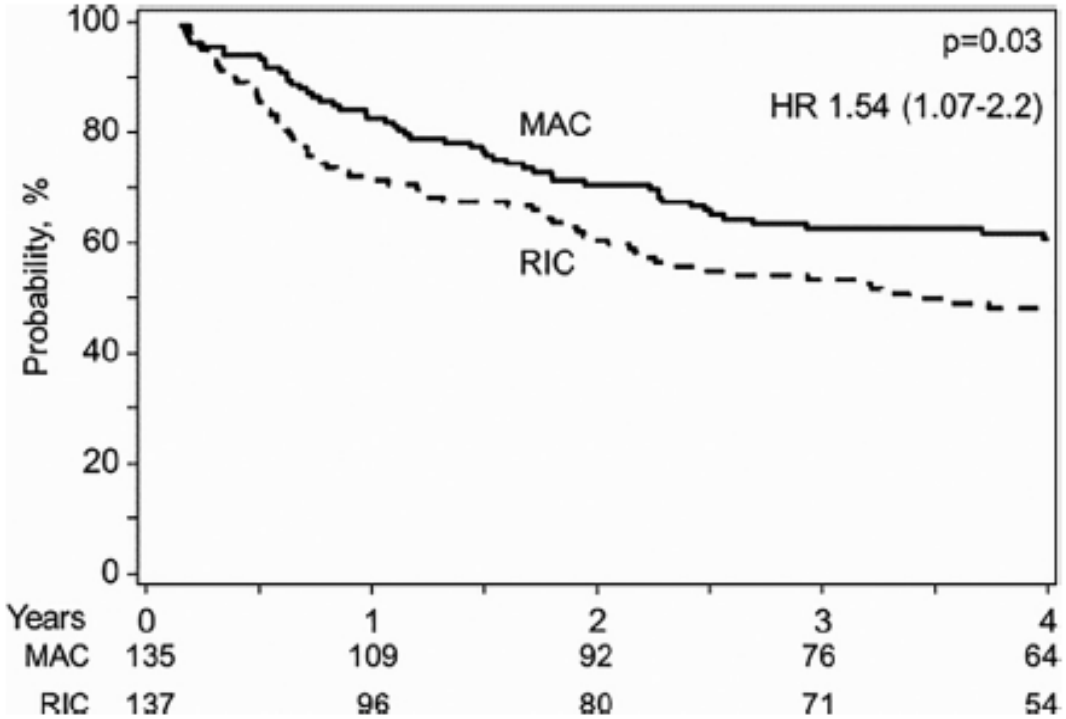



Figure 1. OS.

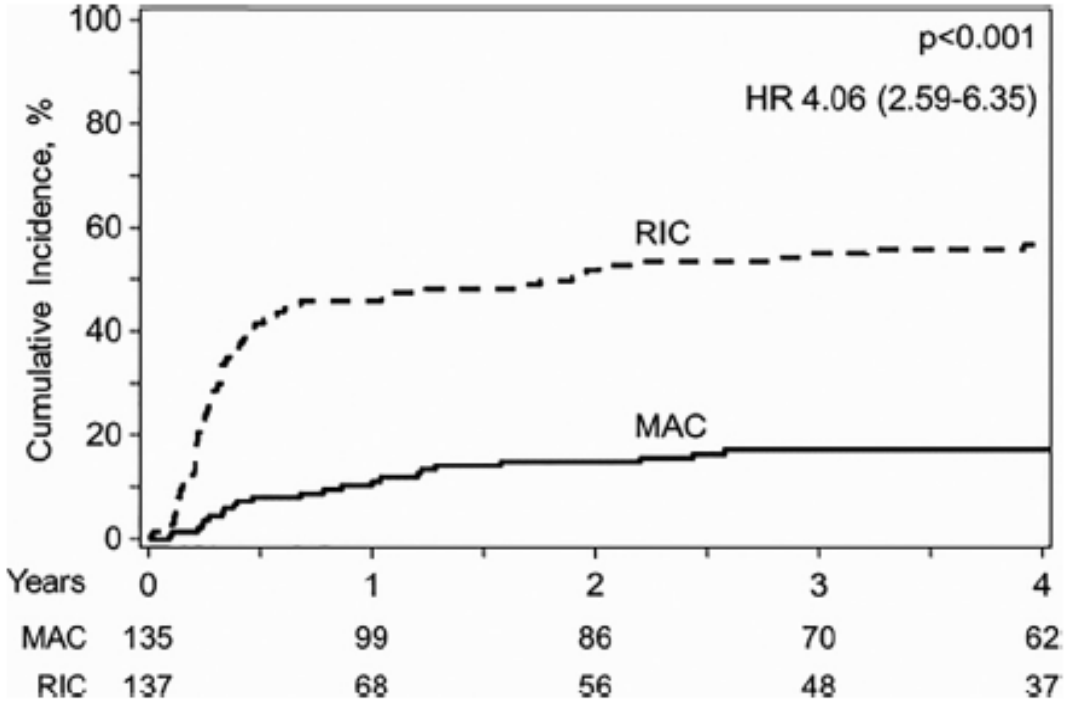



Figure 3. Relapse.

BL Scott et al. Transplantation and Cellular Therapy, 2021; 27: 483-88

# Hematopoietic Cell Transplant Comorbidity Index (HCT-CI)

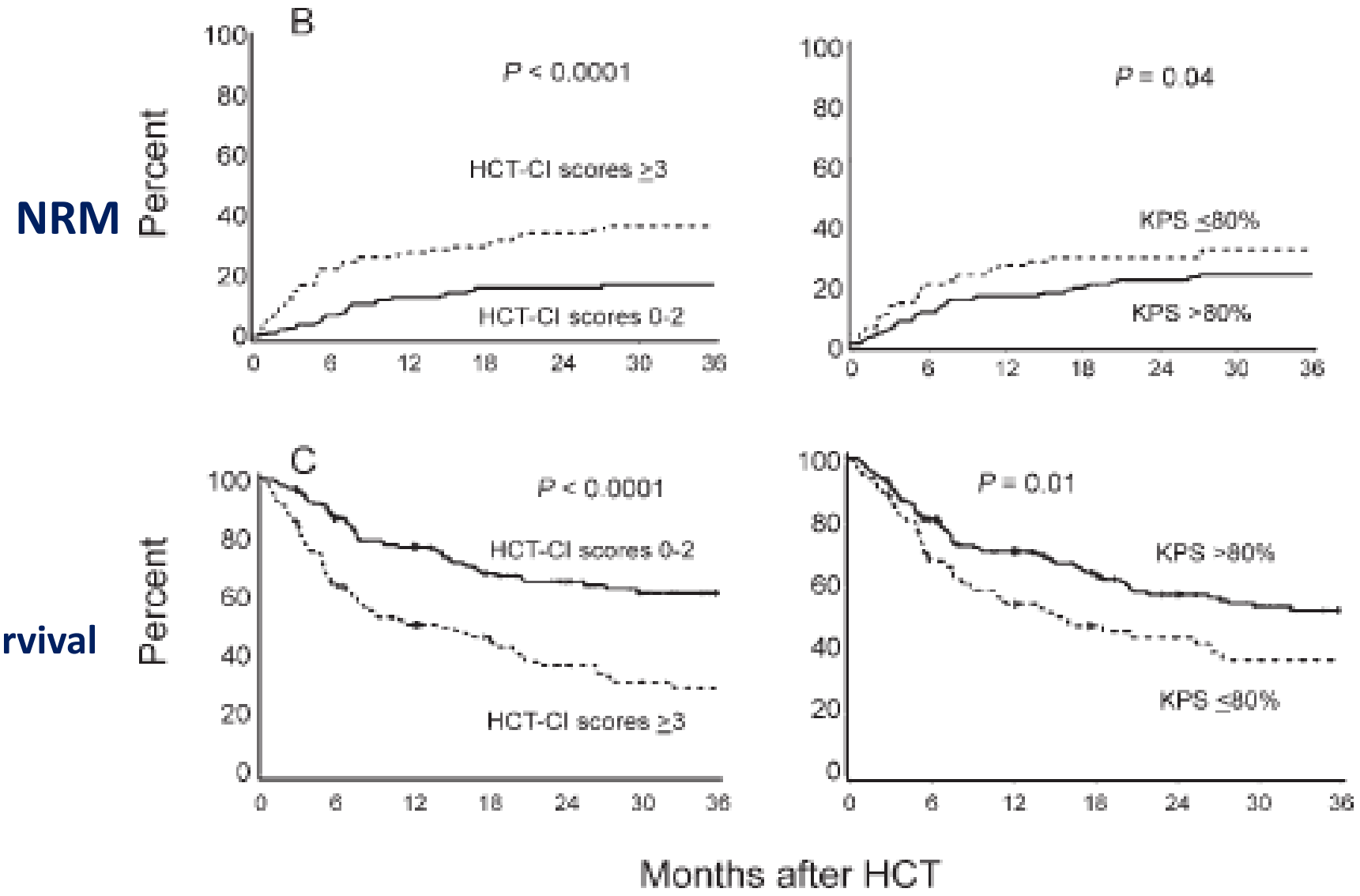
***Deciding who is a good candidate for transplantation***

| Comorbidity | Definitions of comorbidities included in the new HCT-CI | HCT-CI weighted scores |
|---|---|---|
| Arrhythmia | Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias | 1 |
| Cardiac‡ | Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50% | 1 |
| Inflammatory bowel disease | Crohn disease or ulcerative colitis | 1 |
| Diabetes | Requiring treatment with insulin or oral hypoglycemics but not diet alone | 1 |
| Cerebrovascular disease | Transient ischemic attack or cerebrovascular accident | 1 |
| Psychiatric disturbance† | Depression or anxiety requiring psychiatric consult or treatment | 1 |
| Hepatic, mild‡ | Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN | 1 |
| Obesity† | Patients with a body mass index > 35 kg/m$^2$ | 1 |
| Infection† | Requiring continuation of antimicrobial treatment after day 0 | 1 |
| Rheumatologic | SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica | 2 |
| Peptic ulcer | Requiring treatment | 2 |
| Moderate/severe renal‡ | Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation | 2 |
| Moderate pulmonary‡ | DLco and/or $FEV_1$ 66%-80% or dyspnea on slight activity | 2 |
| Prior solid tumor‡ | Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer | 3 |
| Heart valve disease | Except mitral valve prolapse | 3 |
| Severe pulmonary‡ | DLco and/or $FEV_1$ ≤ 65% or dyspnea at rest or requiring oxygen | 3 |
| Moderate/severe hepatic‡ | Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN | 3 |



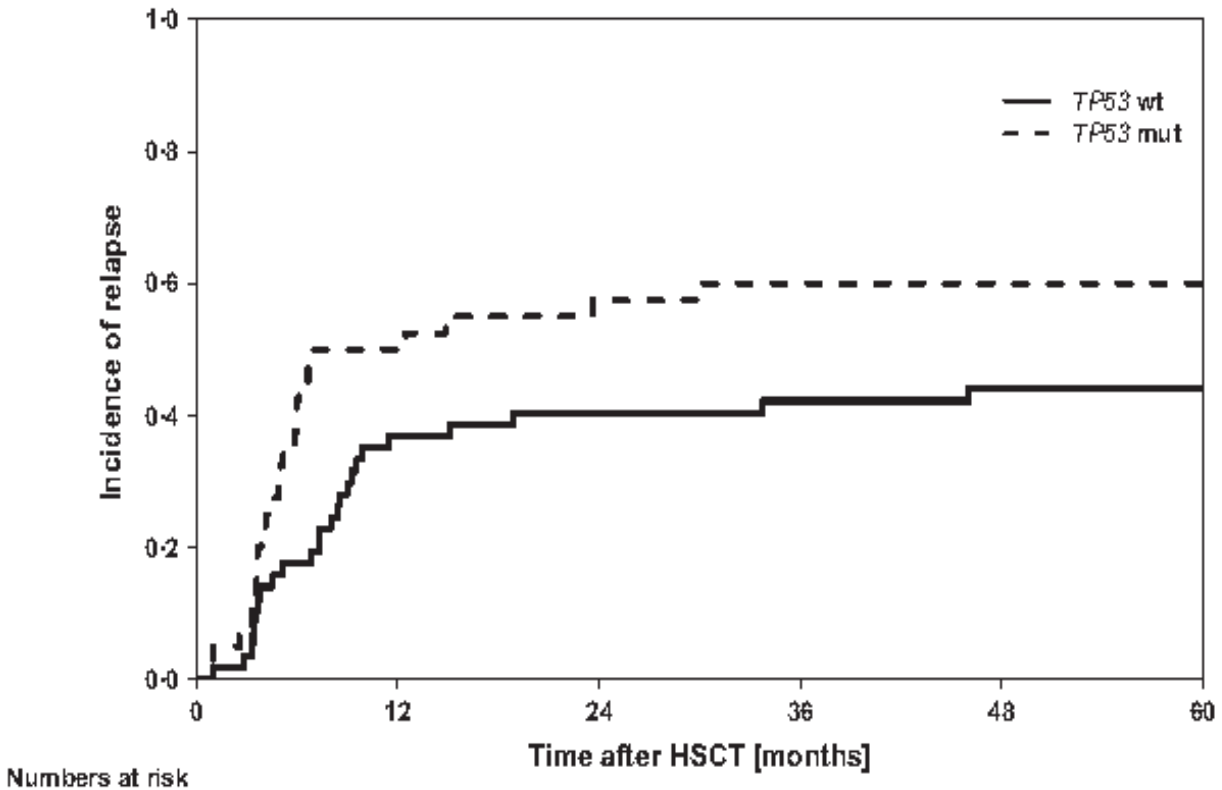
ML Sorror et al. Blood 106: 2912 (2005)

# HCT-CI and KPS predict NRM and Survival



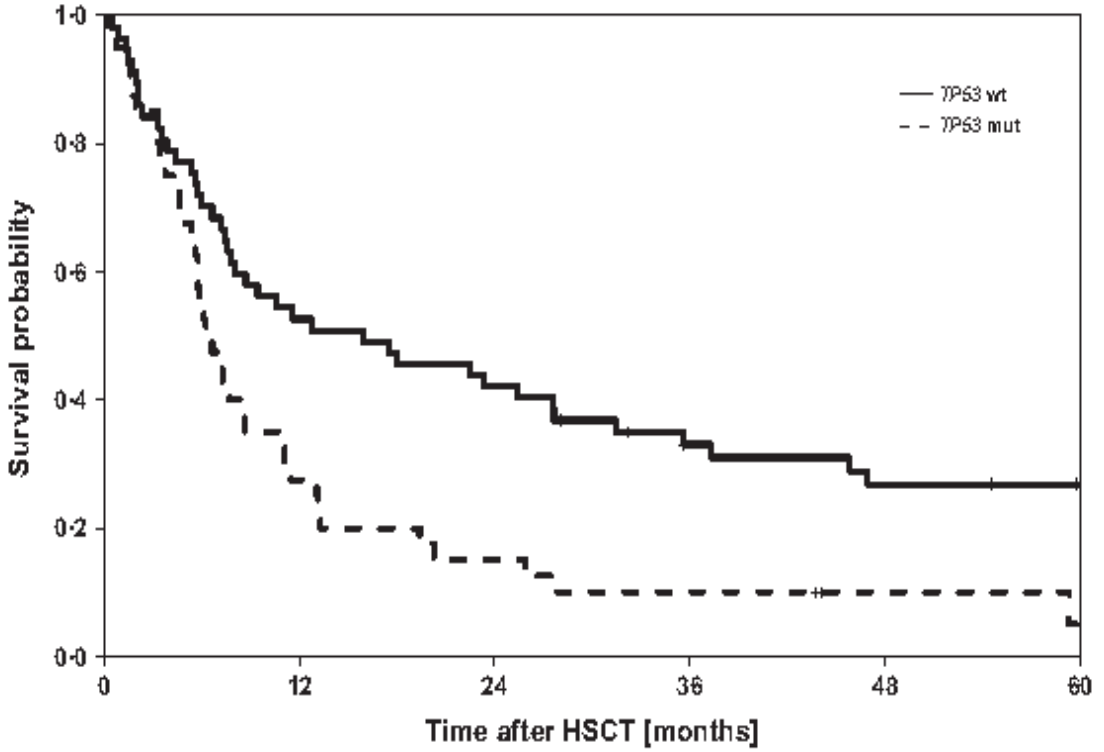

Sorror M, et al. *Cancer.* 2008;112(9):1992-2001.

# Adverse genetic profiles lead to poor transplant outcomes




Numbers at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| *TP53* wt | *N* = 57 | 20 | 16 | 12 | 11 | 9 |
| *TP53* mut | *N* = 40 | 7 | 4 | 3 | 1 | 1 |

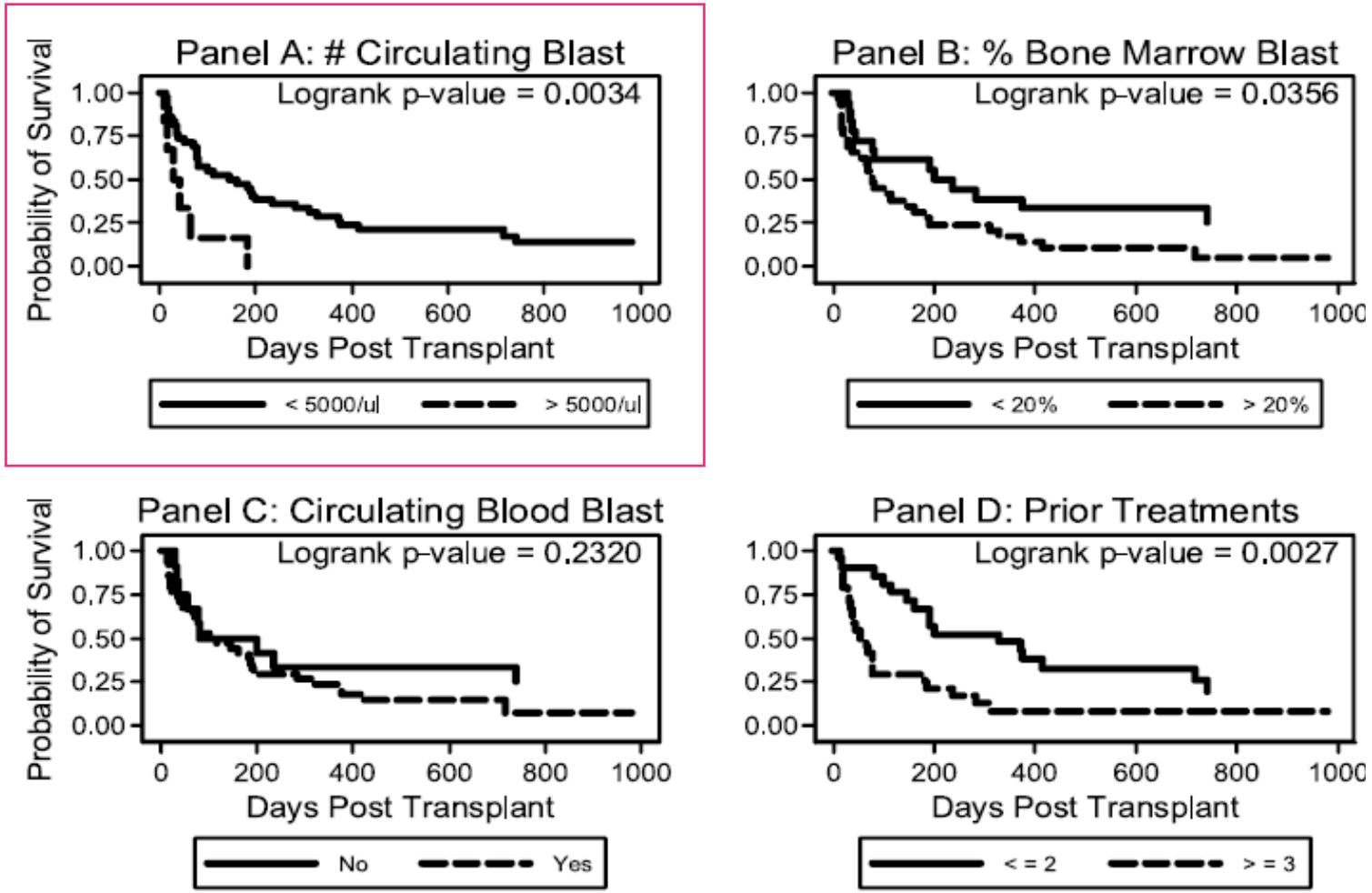



Numbers at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| *TP53* wt | *N* = 57 | 30 | 24 | 16 | 13 | 11 |
| *TP53* mut | *N* = 40 | 11 | 6 | 4 | 2 | 1 |

JM Middeke et al. Br J Haem, 2016; 172: 914-22

# Pre-transplant disease burden also matters…




W Blum et al. *BBMT*. 2006; 12: 61-67.

# Summary of impact factors we need to consider

- Age, KPS
- Comorbidities
- Ability to receive a myeloablative conditioning regimen
- Underlying genetics
- Disease burden

# How can we make transplantation more effective?

- Transplant approaches that optimize GVL without increasing GVHD
  - Graft engineering
  - Adoptive immunotherapy post-transplant

- More effective pre-transplant therapy to achieve deeper remission prior to initiation of conditioning therapy
  - *Incorporation of radio-immunotherapy into conditioning therapy*

- Post-transplant maintenance approaches
  - *Analogy with Ph+  and FLT3 mutated leukemias*

# Graft Engineering: Orca-T Study

- Strategy
  - Myeloablative conditioning
  - Administration of CD34+ progenitors + Tregs on day 0
  - Conventional T cells given on day +2
  - Single agent immunoprophylaxis for GVHD (tacrolimus or sirolimus)
- Methods
  - Multicenter study in high risk hematologic malignancies
  - HLA matched related (n=72), matched unrelated donor (n=62) or mismatched URD (n=4)
  - Comparator cohort of historical controls matched for disease/status, donor type and all receiving tacrolimus + MTX for GVHD prophylaxis

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# Orca-T: Results and Conclusions to Date

| *parameter* | *CIBMTR Control* | ***Orca-T*** |
|---|---|---|
| n | 375 | **138** |
| Median follow-up in months (range) | 31 (4-50) | **10 (1-65)** |
| Grade ≥ 3 aGVHD at Day +180* (95% CI) | 16% (2-19) | **4% (0-9)** |
| Moderate to Severe cGVHD through Day +365** (95% CI) | 38% (33-44) | **5% (0-10)** |
| Relapse at 1 year | 35% (30-40) | **21% (9-34)** |
| Non-relapse mortality at 1 year (95% CI) | 10% (7-13) | **4% (0-8)** |
| GVHD and Relapse-Free Survival at 1 year (95% CI) | 34% (30-39) | **71% (61-78)** |
| Overall survival at 1 year (95% CI) | 68% (63-73) | **90% (82-94)** |

- Enables safe delivery of myeloablative conditioning with reasonable toxicity profile
- Clinically significant GVHD outcomes appear favorable
- GVL effects appear to be preserved

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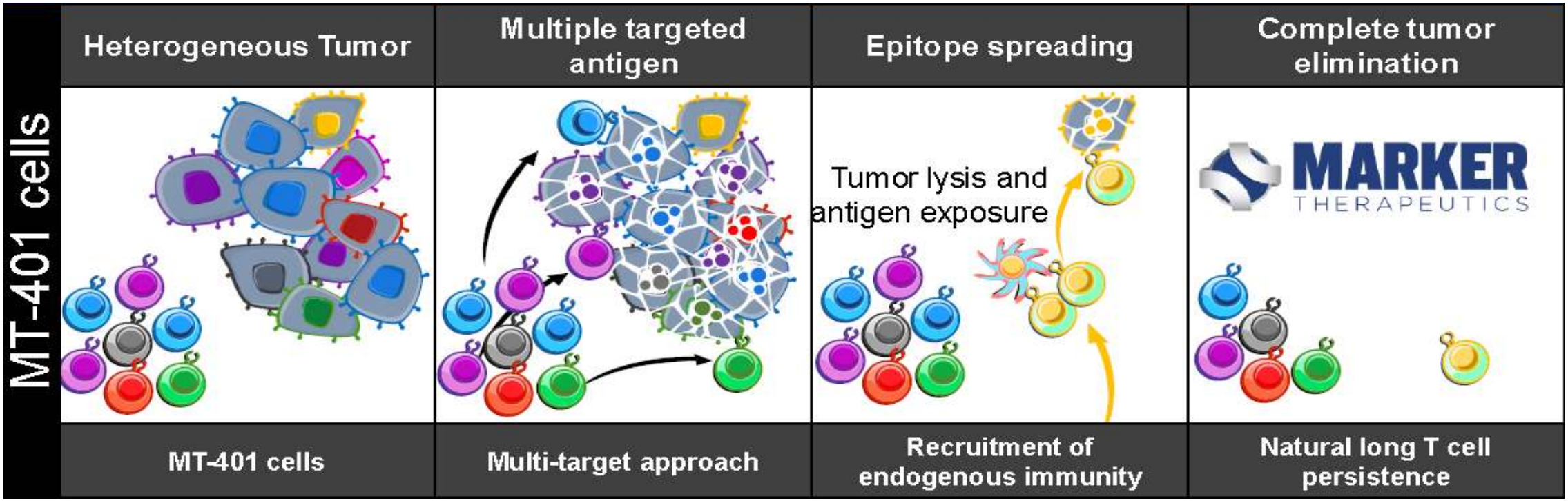
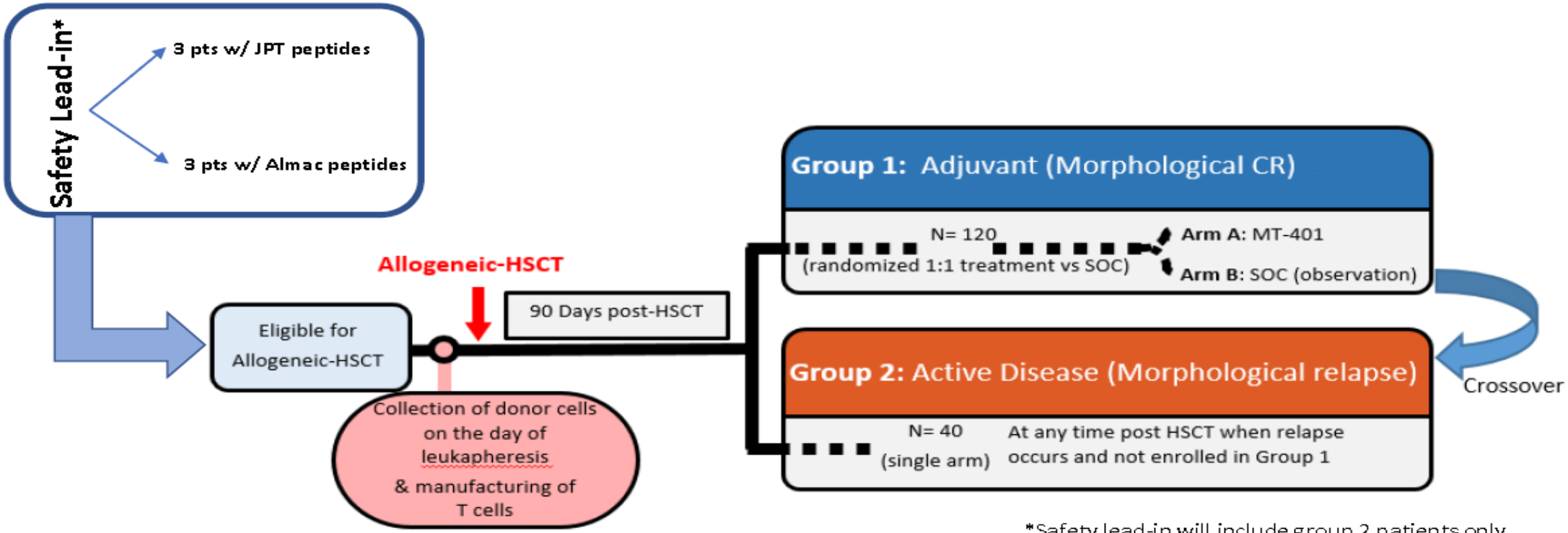
# Post-transplant Leukemia Antigen-directed NK cell therapy

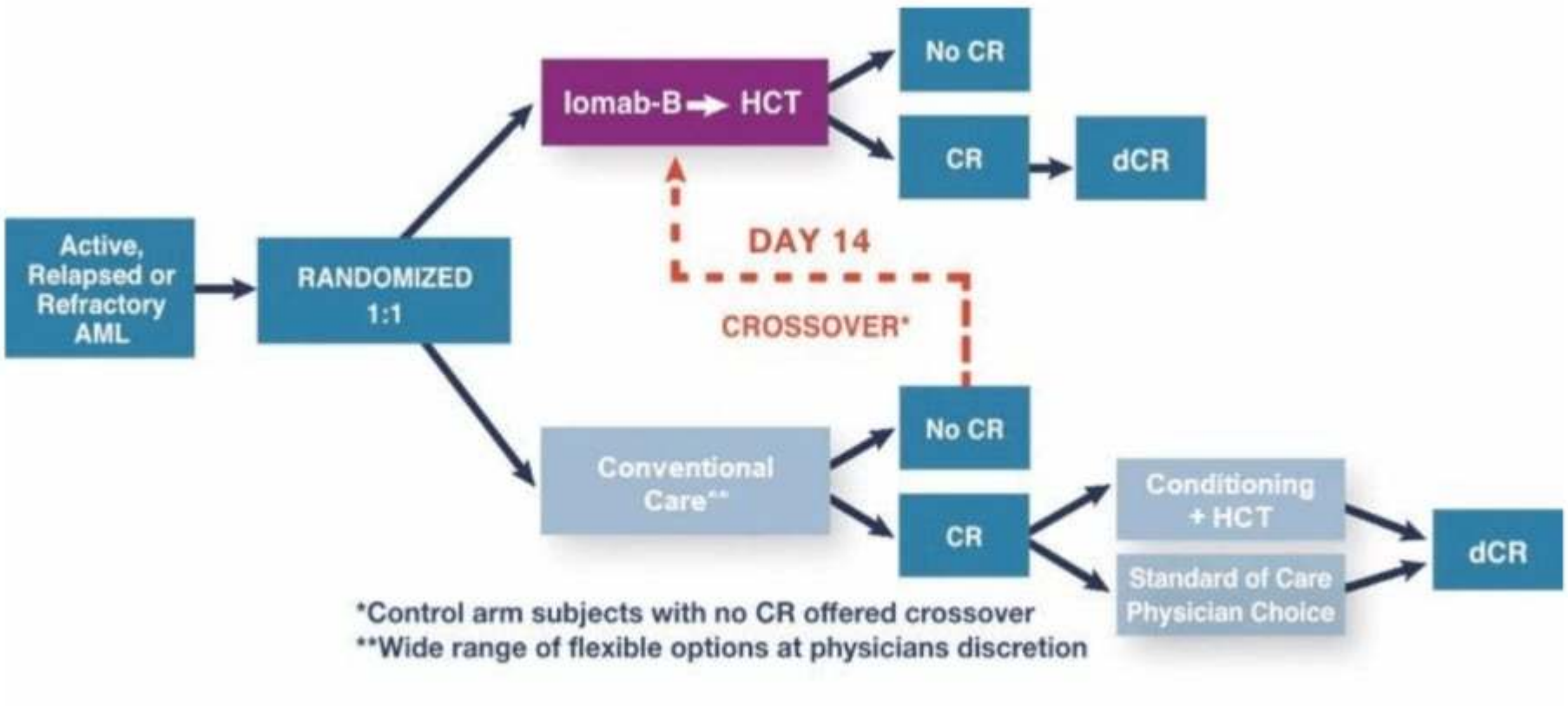


# Study Schematic: Phase 2 with Safety Lead-in




- Patients in Group 1 – Arm B who relapse after Day 90 may cross over to Group 2 to receive MT-401
- Patients may be identified post-HSCT and enter Group 2 if the same donor is available to provide cells for manufacturing MT-401 and eligibility is fulfilled
- If relapse occurs less than 90 days post-HSCT and T cells have been manufactured and stored, the patient may receive MT-401 and be included in a subgroup analysis of Group 2.
- Group 2 patients may receive MT-401 even if CR is achieved post-bridging therapy, but will be analyzed separately.

# SIERRA Trial: CD45-directed radio-immunotherapy incorporated into conditioning for older pts with refractory AML



# What about other pre- or post-transplant therapies?

- Incorporation of venetoclax into initial induction/consolidation therapy, e.g. FLAG-IDA + venetoclax (CD DiNardo, et al. J Clin Oncol, 2021; online 5/27/21)

- Mogalizumab trial (anti CD-47) to induce remission in higher risk pts prior to transplant (blocking “don’t eat me” signal)

- Investigations of post-transplant “maintenance” strategies, especially for those with targetable mutations
  - FLT3, IDH1/2, 11q23 translocations, etc
  - HMA +/- venetoclax for those without a targetable mutation

# What are the take-home points?

- Refractory MDS/AML is a bad situation, but some patients can be cured with allo-transplantation

- Patients who should be considered for allo-transplantation
  - Young and fit for a myelo-ablative conditioning regimen
  - Limited disease burden immediately prior to conditioning
  - Few comorbidities
  - Lack of high risk genetic changes such a *TP53* mutation and/or complex karyotypes
  - Presence of a targetable mutation may be a plus

- Novel transplant and non-transplant approaches should always be considered for this patient population

# Thanks for your attention!

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