Paradigm Change:

Can older refractory and relapsed AML patients undergo a successful stem cell transplant without entering complete remission first?

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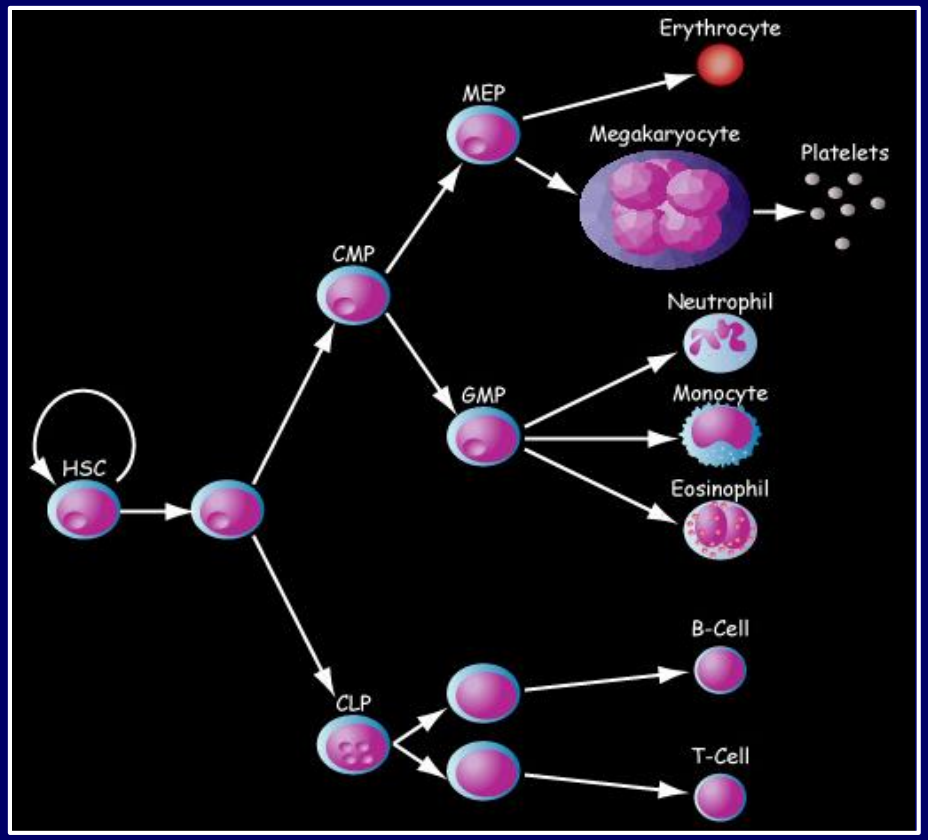
Agenda

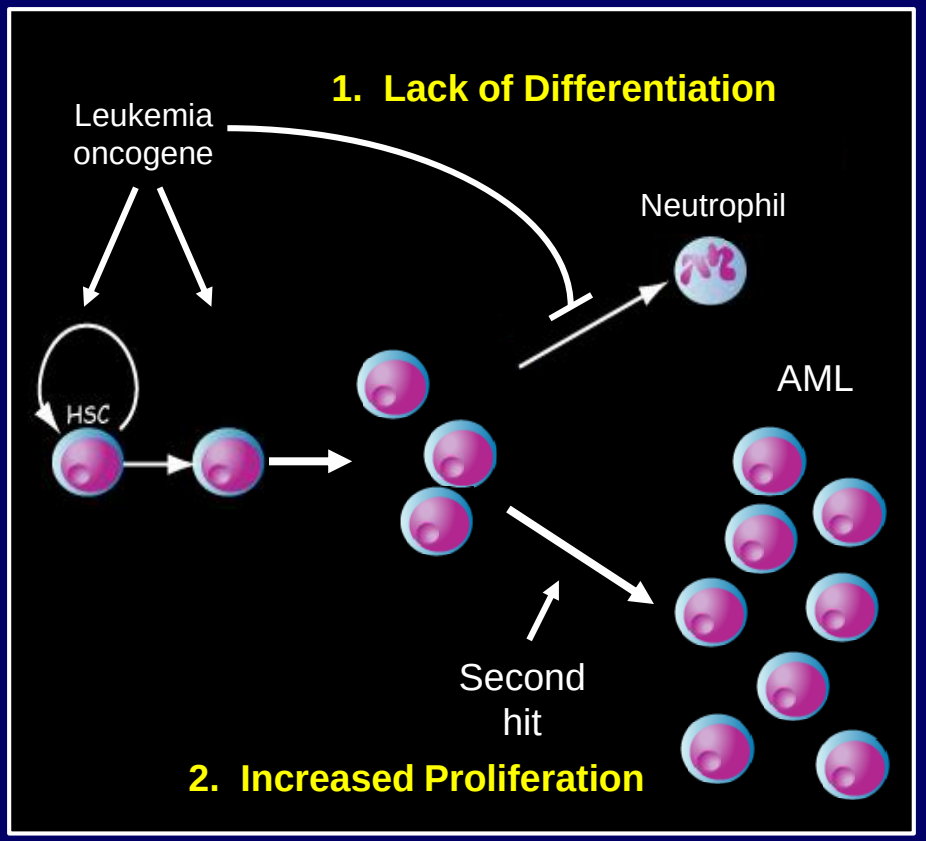
- AML background
- Current treatment approaches
- Radioimmunotherapy before HCT
  - Iomab-B overview
  - Clinical results to date
- Proposed phase III trial

Development of AML

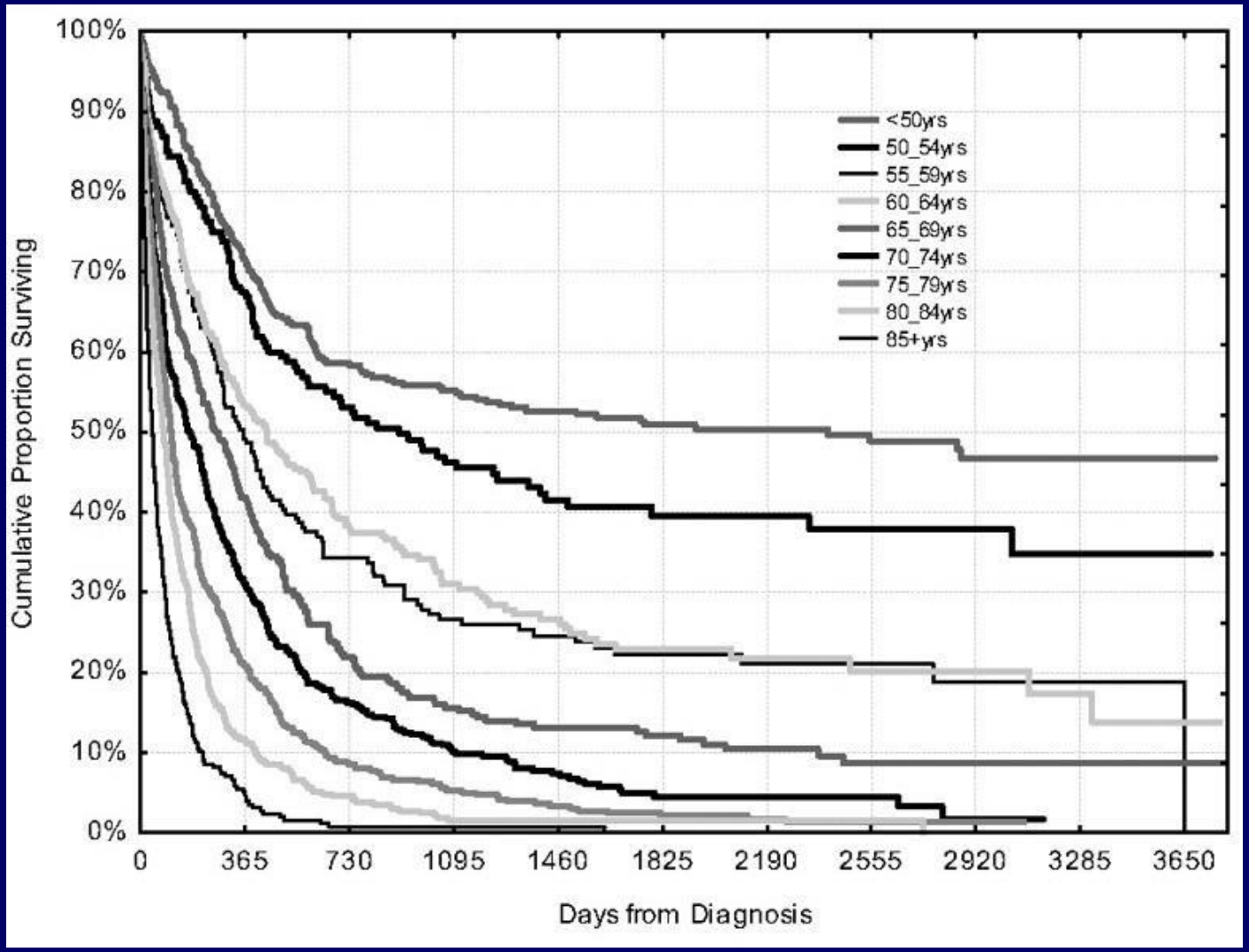
Normal Hematopoiesis



Leukemogenesis

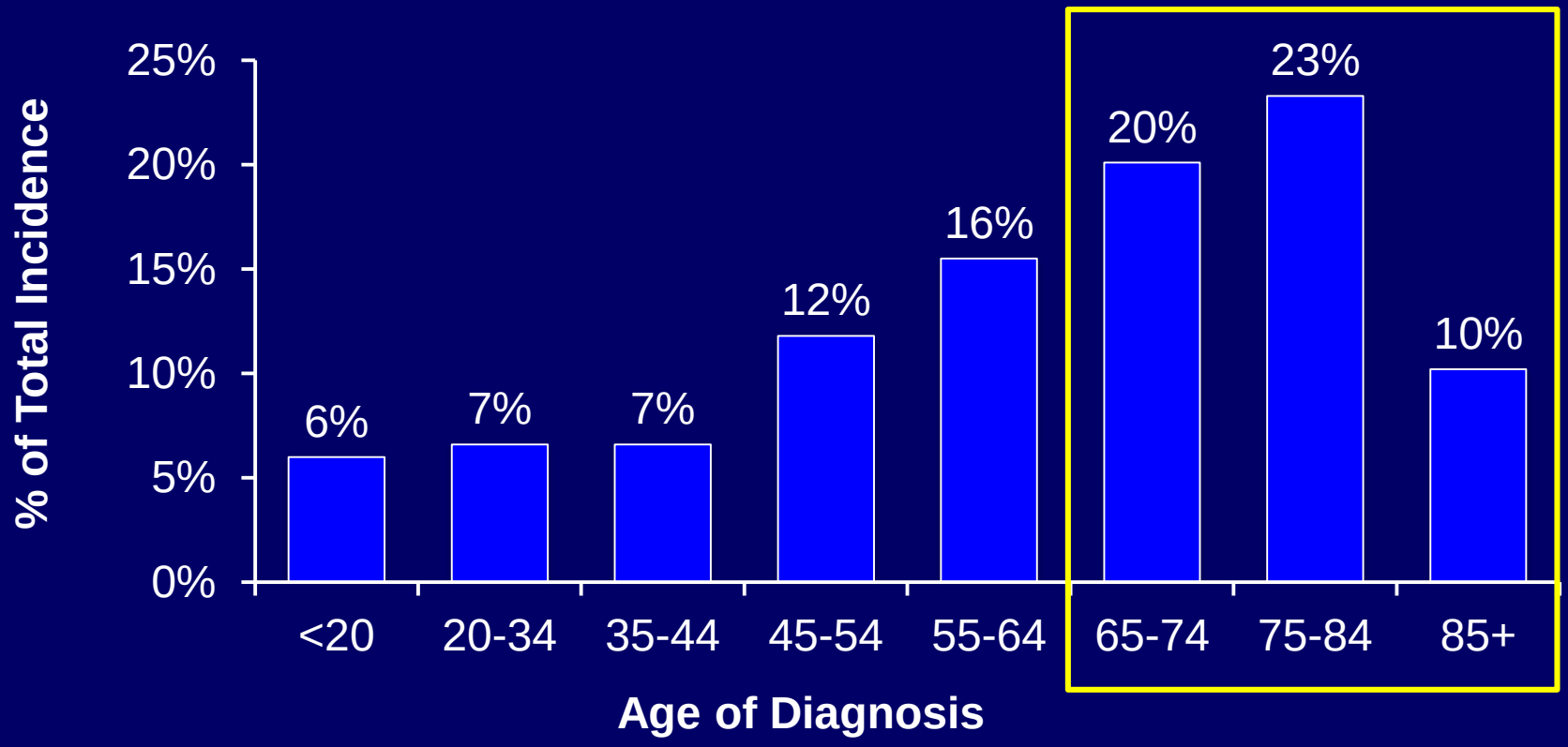


AML Survival by Age



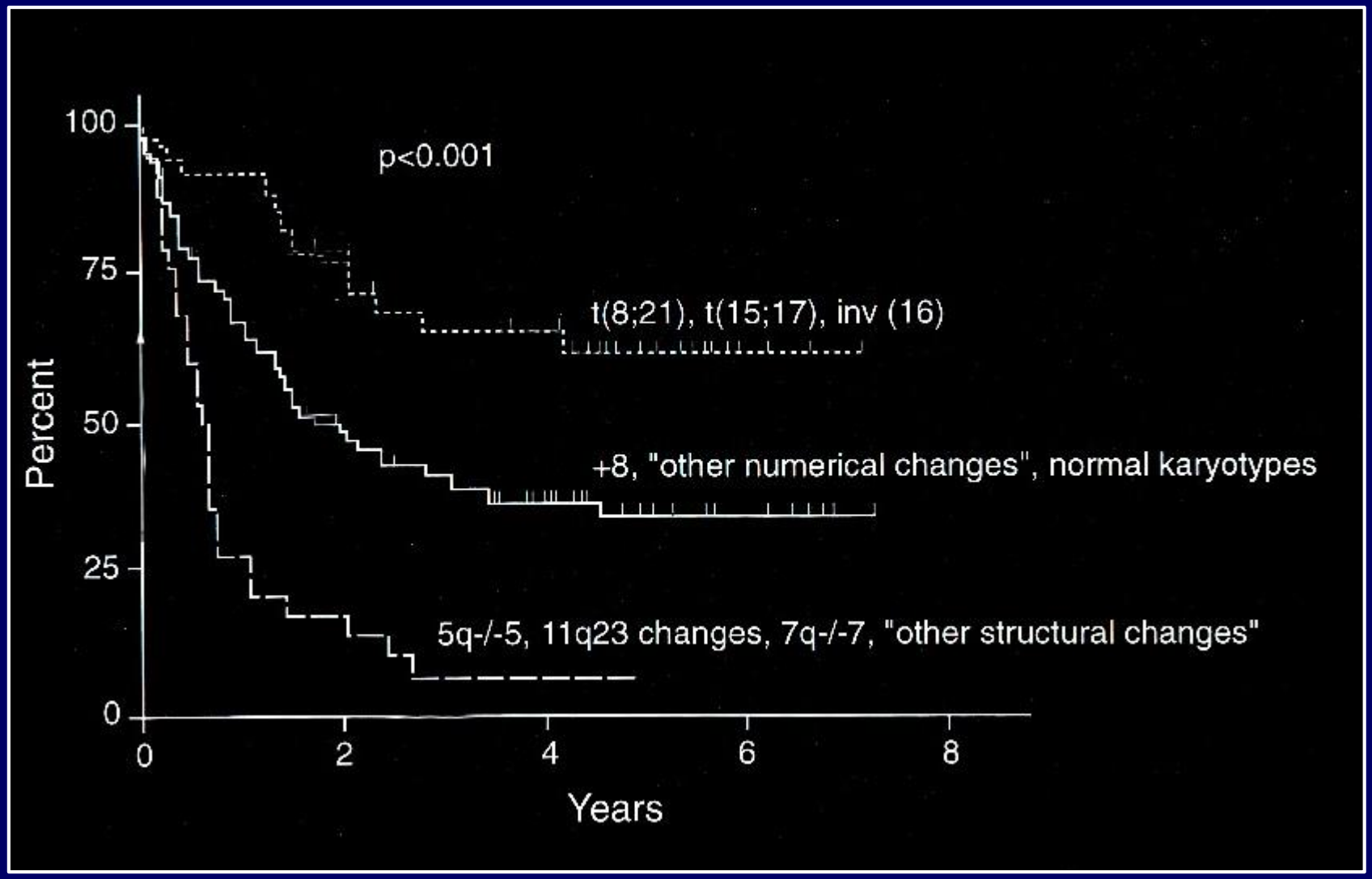
Juliusson G *et al. Blood* 2009;113:4179-4187.

2012 AML Incidence by Age Group



Source: NCI SEER US Cancer Database, AML.

AML: Cytogenetics Determines Survival



Bloomfield CD *et al. Cancer Res* 1998;58:4173-4179.

Risk Status Based on Cytogenetic and Molecular Abnormalities

Risk Status	Cytogenetics	Molecular Abnormalities
Better-risk	inv(16) or t(16;16) t(8;21) t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	t(8;21), inv(16), t(16;16): with c-KIT mutation
Poor-risk	Complex (≥ 3 clonal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 – non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)	Normal cytogenetics: with FLT3-ITD mutation

NCCN Guidelines Version 2.2013.

Phases of Leukemia Therapy

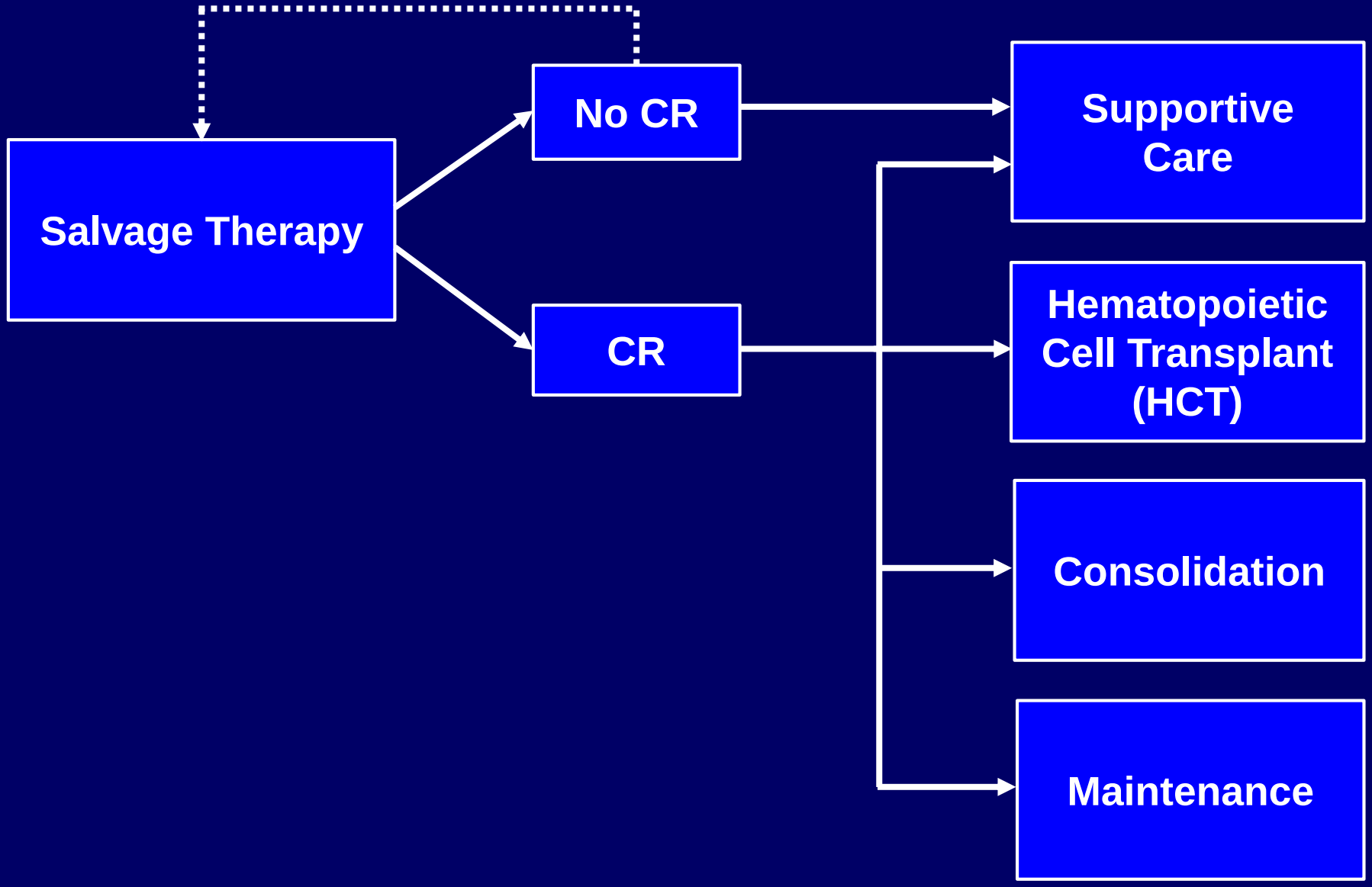
- **Induction**
  - Cytarabine + anthracycline
- **Postremission**
  - Consolidation chemotherapy
  - Hematopoietic cell transplantation (HCT)
  - Maintenance therapy

Treatment Outcome by Age

Age	< 56 yo	56-65 yo	66-75 yo	>75 yo
No. of patients	368	246	274	80
Response, no. (%)				
CR	235 (64)	113 (46)	108 (39)	26 (33)
Resistant disease	99 (27)	91 (37)	101 (37)	29 (36)
Median survival, mo. (95% CI)	18.8 (14.9-22.6)	9.0 (8.1-10.2)	6.9 (5.4-7.7)	3.5 (1.4-6.1)
Median DFS, mo. (95% CI)	21.6 (15.8-25.5)	7.4 (65.-8.8)	8.3 (6.3-10.2)	8.9 (5.8-10.8)

Appelbaum FR *et al. Blood* 2006; 107:3481-3485.

Managing Relapsed AML



Salvage Therapy for Relapsed AML

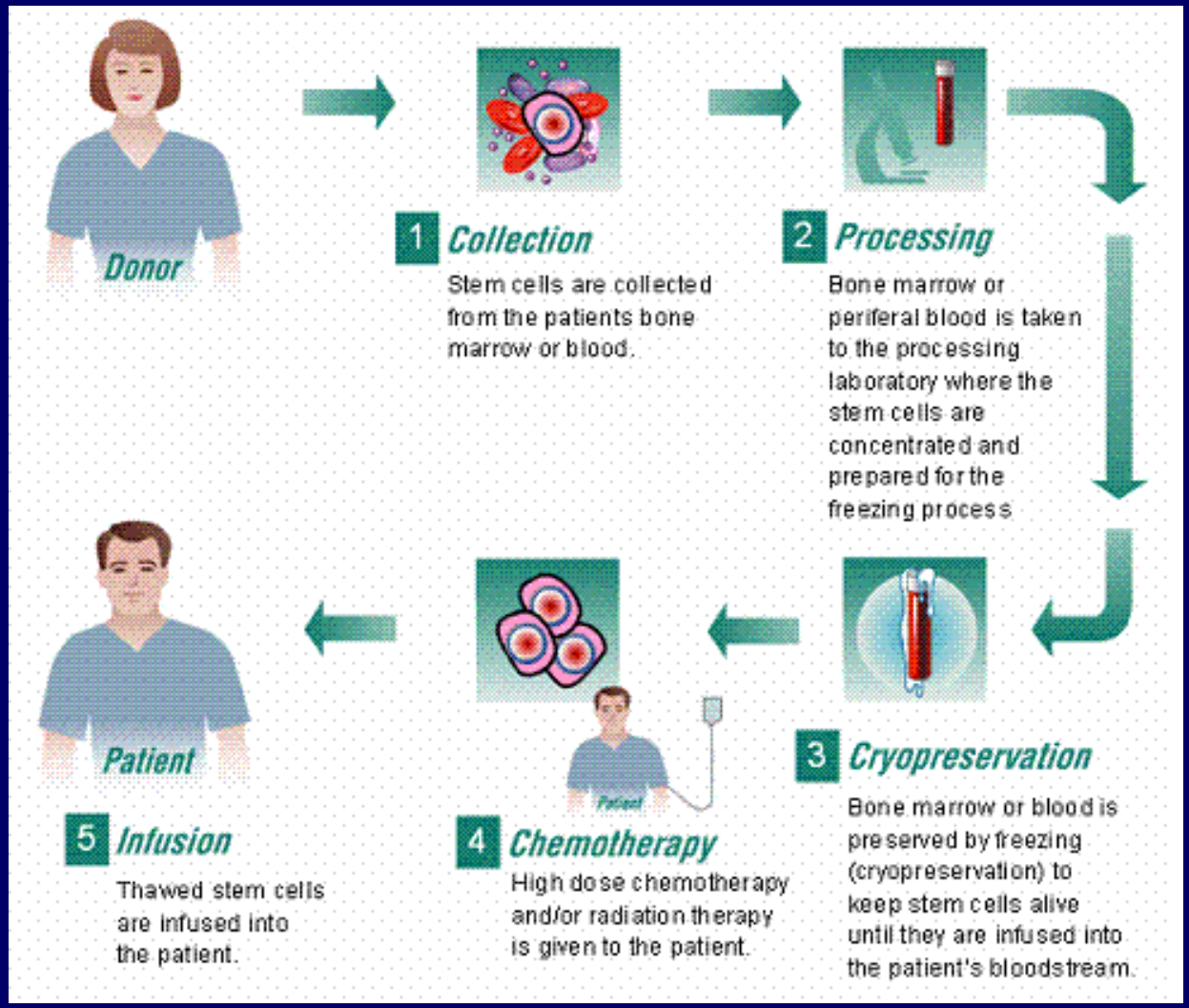
- No FDA-approved regimens
- Standard chemotherapy
  - High-dose cytarabine
  - Etoposide/mitoxantrone ± cytarabine (MEC)
  - Fludarabine/cytarabine/G-CSF ± idarubicin (FLAG-Ida)
  - Hypomethylating agents
- Investigational therapy
  - Antibodies, drug conjugates
  - Histone deacetylase inhibitors
  - Small molecule inhibitors (e.g., *flt-3*, *IDH*, etc.)
  - Others

Response to Salvage Chemotherapy for Relapsed AML

CR1 duration	< 1 year or 1º refractory	< 1 year or 1º refractory	1-2 years	> 2 years
# prior salvage attempts	≥1	0	0	0
N	58	160	30	15
CR Rate	<1%	14%	47%	73%

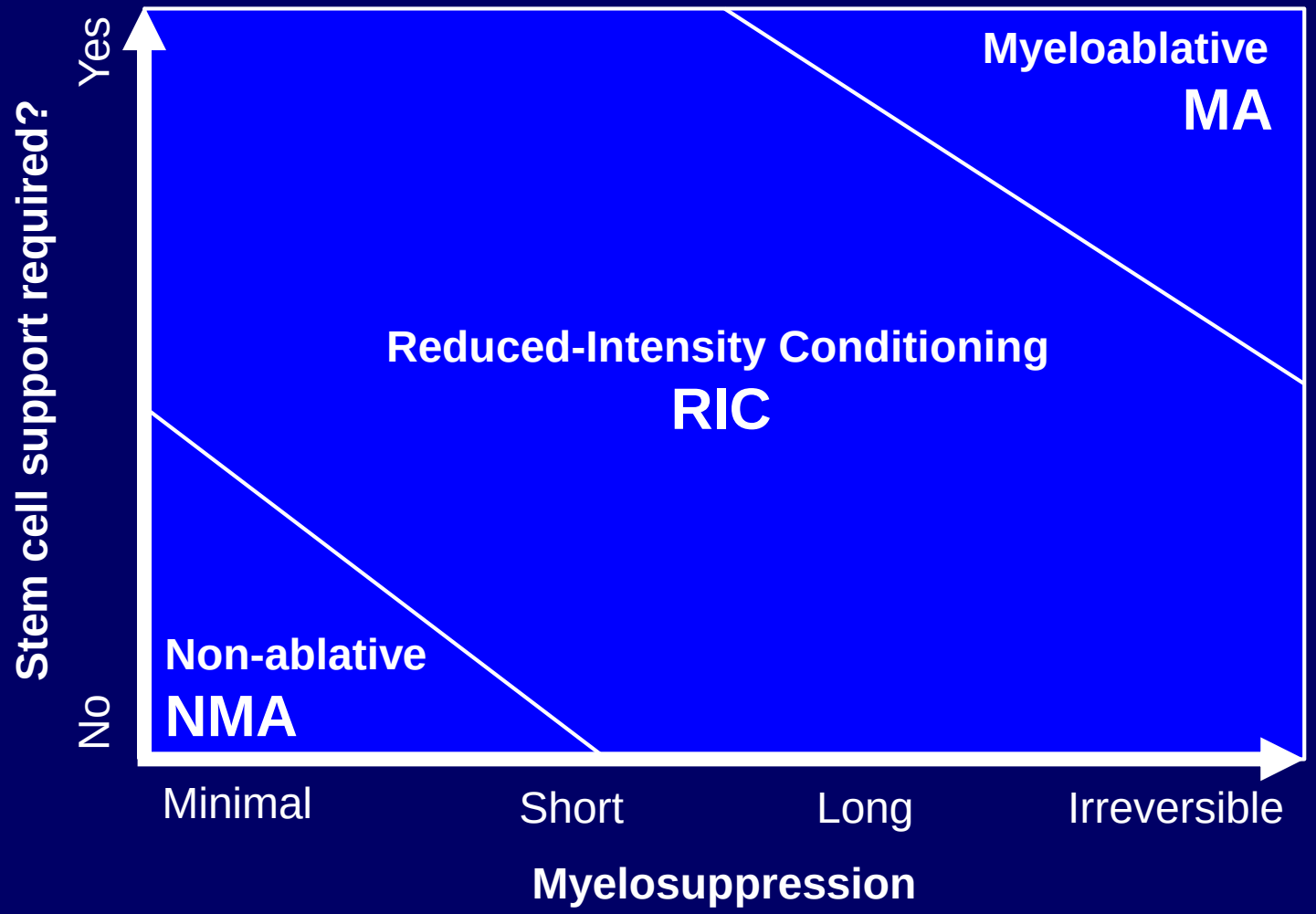
Estey E *et al. Blood* 1996; 88:756.

Hematopoietic Cell Transplant Procedure



http://biomed.brown.edu/Courses/BI108/BI108_2007_Groups/group07/stemcells/stcell04.html

Conditioning Regimens for Allogeneic HCT



Bacigalupo A *et al. Biol Blood Marrow Transplant* 2009;15:1628-33.

Stem Cell Sources for Allogeneic HCT

- Sibling donor (HLA-matched)
- Matched unrelated donor
- Umbilical cord donor
- Haploidentical donor

Outcome of HCT in CR2

- OS after HCT in CR2 for patients 18-50 yo:
  - 6 m: ~80%
  - 12 m: ~70%
  - 2 y: ~60%

BUT:

- Only ~15% enter CR2, so OS for all patients is:
  - 6 m: ~12%
  - 12 m: ~10%
  - 2 y: ~10%

Foreman SJ, Rowe JM. *Blood* 2013; 121:1077-1082.

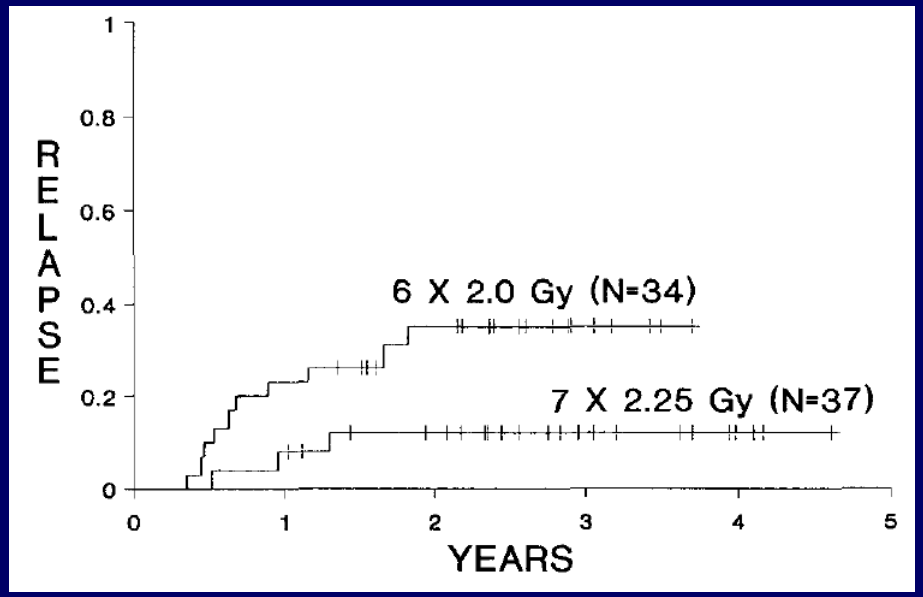
Impact of Disease Burden on HCT Outcomes

Disease burden	No. of patients	Median survival (mos.)	Median PFS (mos.)
Morphologic & cytogenetic remission	8	10.4	7.8
Morphologic remission only	6	4.6	2.9
Overt relapse	33	5.9	2.8

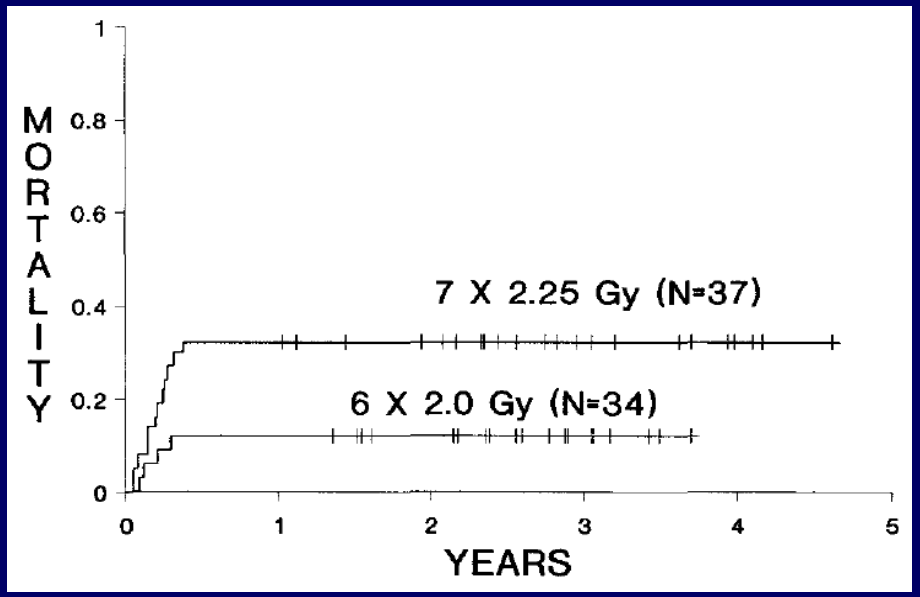
Kebriaei P *et al. Bone Marrow Transplant* 2005; 965-970.

Effect of TBI Dose on HCT Outcomes

Relapse Probability

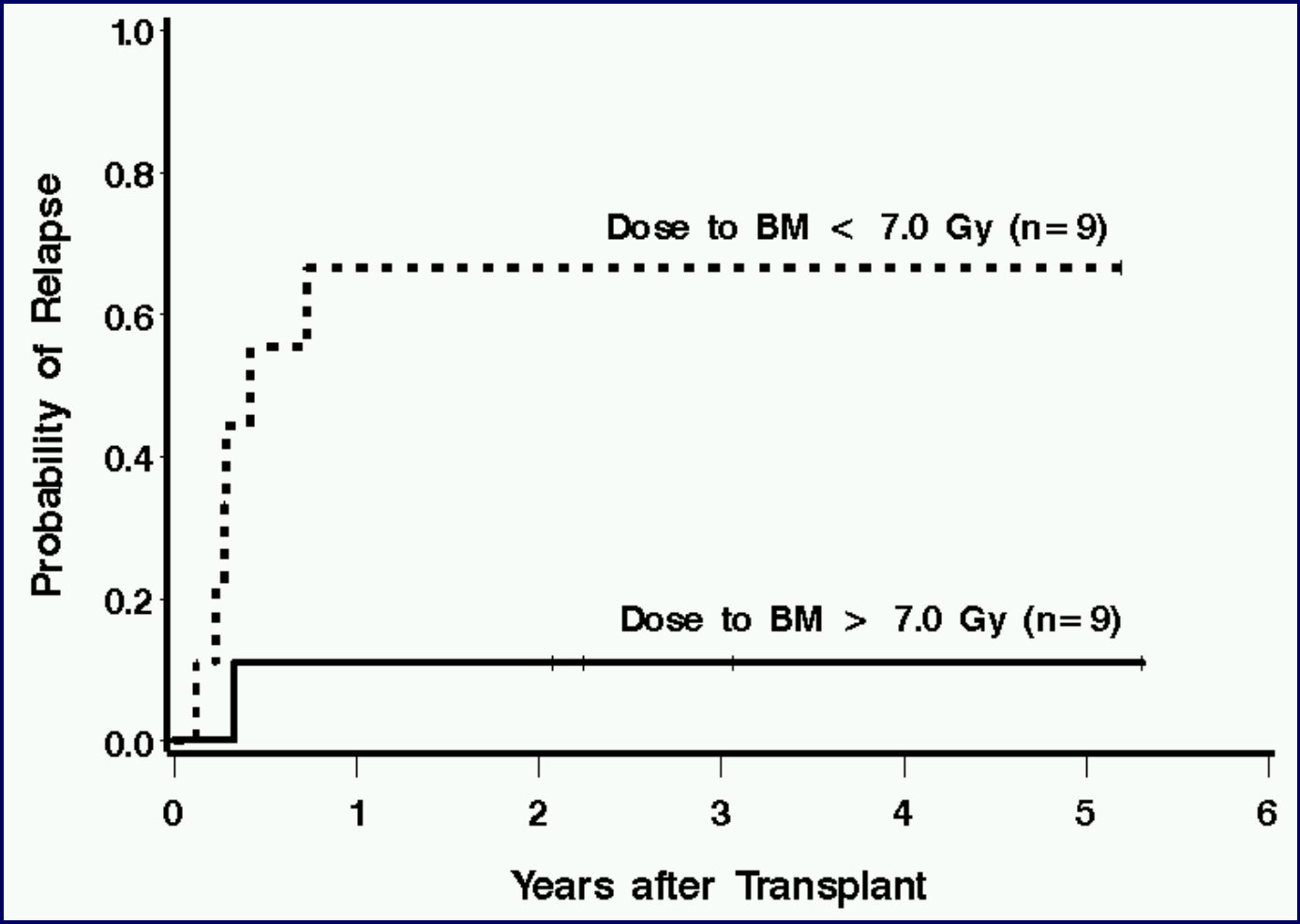


Mortality Probability



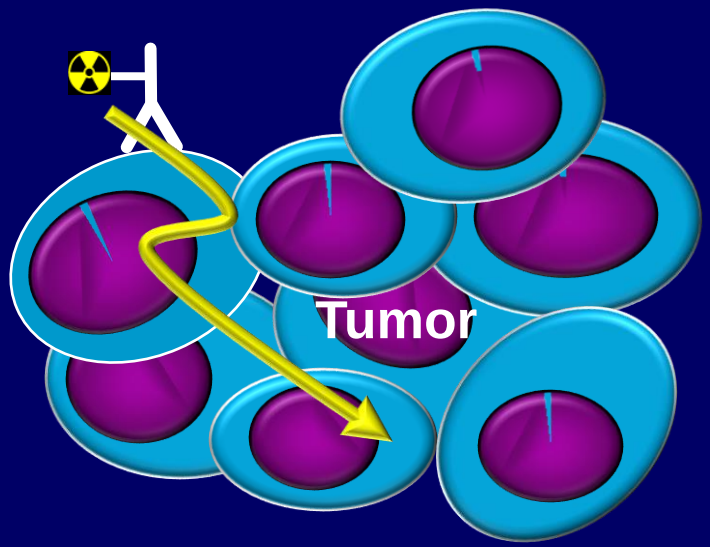
Clift RA *et al. Blood* 1990; 76:1867-71.

Relationship Between BM Dose and Relapse



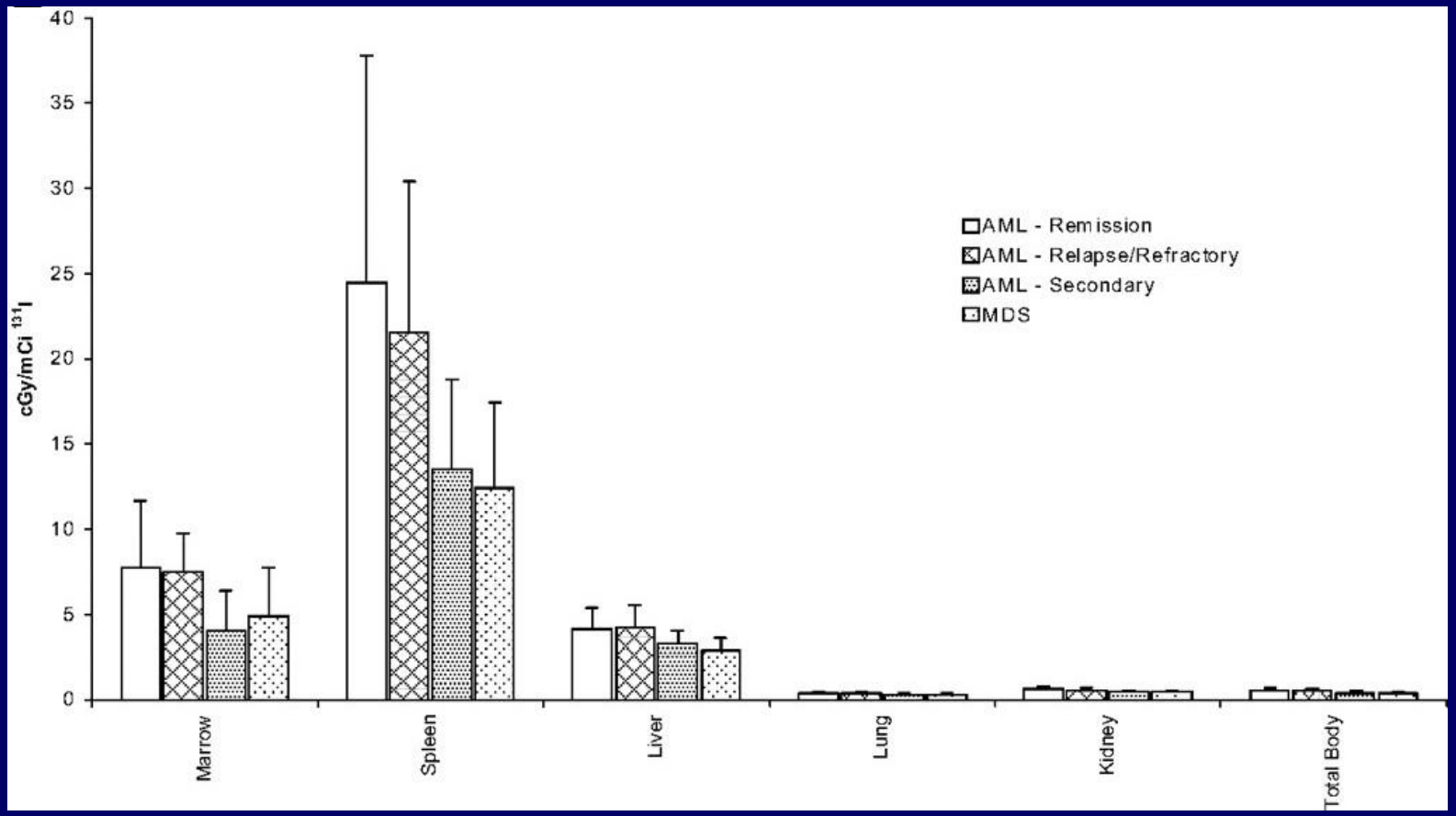
FHCRC data

Rationale for RIT in HCT Regimens



- AML is highly radiosensitive.
- TBI is effective in HCT regimens at high doses.
- TBI cannot be safely dose escalated.
- RIT can increase radiation doses to leukemia cells and normal bone marrow without increasing doses to normal tissues.
- Iomab-B consists of an anti-CD45 mAb that targets lympho-hematopoietic cells and the β-particle emitting radionuclide ^{131}I.

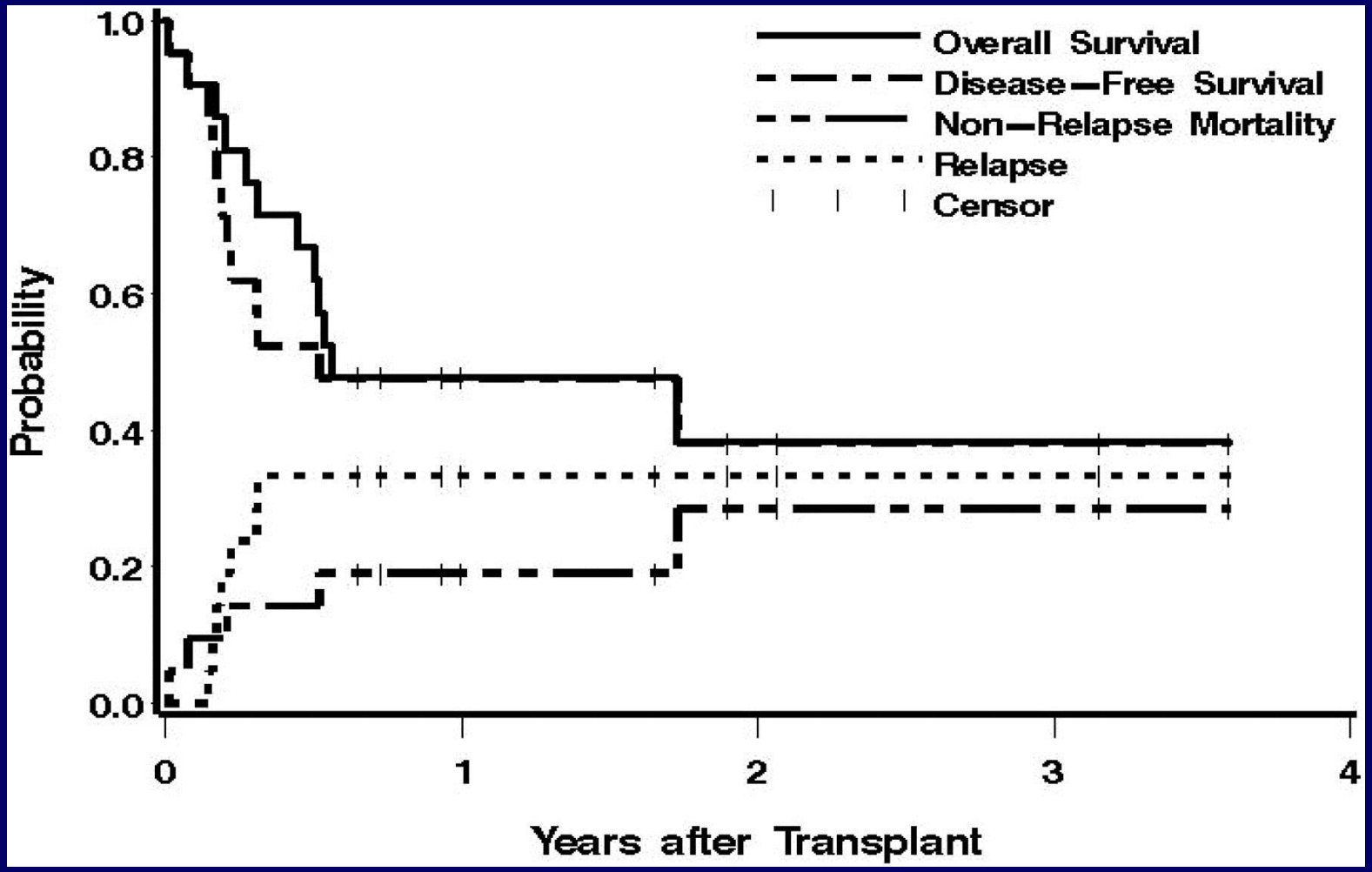
Iomab-B Biodistribution



Treatment at MTD (24 Gy to liver) delivers ~36 Gy to marrow and ~100 Gy to spleen.

Pagel JM *et al. Blood* 2009; 114:5444-5453.

Outcomes after Iomab-B at MTD

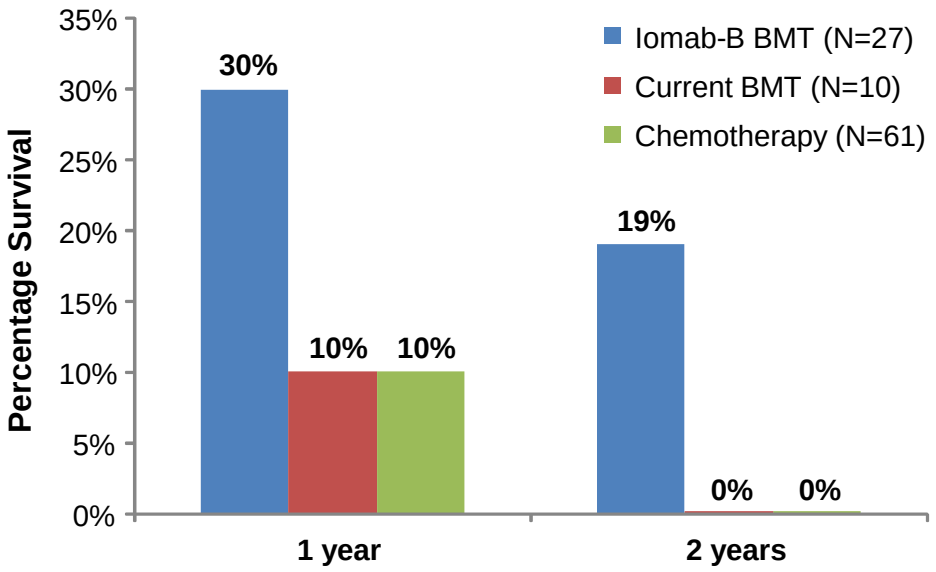


Pagel JM *et al. Blood* 2009; 114:5444-5453.

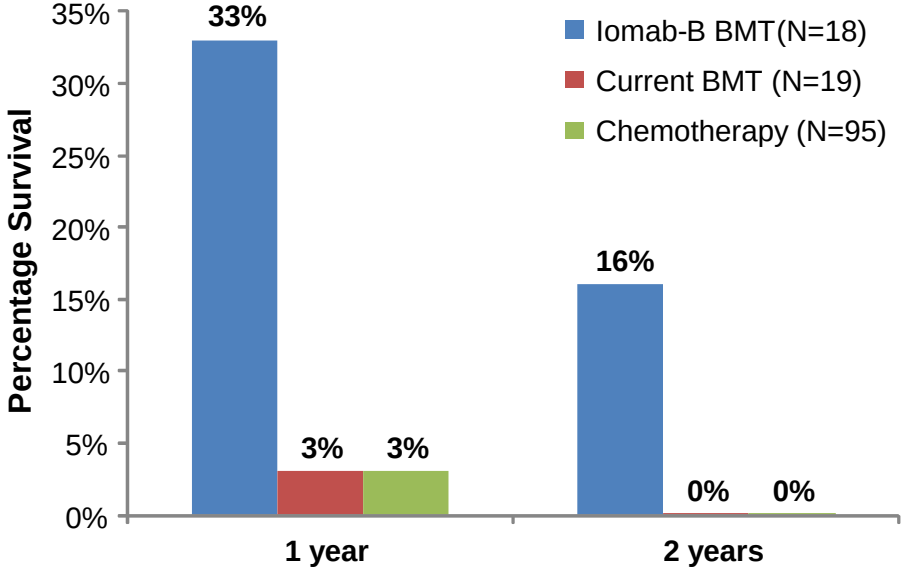
Compelling Results Enable Pivotal Phase III Trial

- Complete response rate: 100%
- Engraftment by Day 28: 100%
- Transplant related mortality: 14% (same as RIC)
- Non-relapse mortality (NRM):
  - Day 100: 10%
  - Overall: 20% (46% with myeloablative conditioning)

All relapsed/refractory AML patients > 50

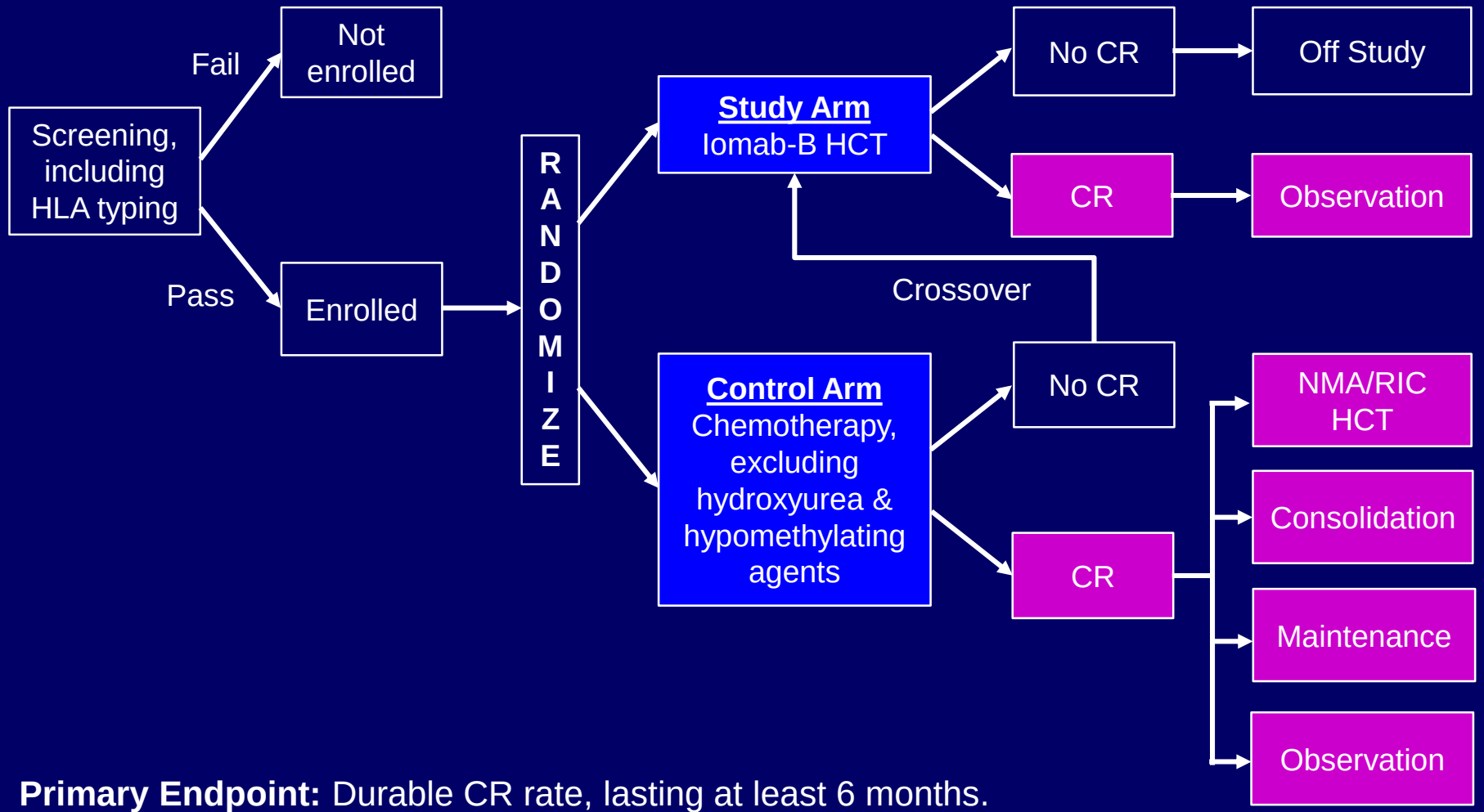


Rel/ref AML pts > 50 with poor cytogenetics



N = Number of patients treated
Iomab-B results from FHCRC clinical trials
Current BMT and Chemotherapy results from MD Anderson outcomes analysis.

Iomab-B Pivotal Trial Schema



Primary Endpoint: Durable CR rate, lasting at least 6 months.

Bone marrow aspirate and biopsy performed in all patients at ~1 and/or 2 months after the last day of intervention to determine response and at 6 months after CR has been established to confirm CR duration in groups labeled with ■.

Conclusions

- Poor response and toxicity of conventional salvage chemotherapy are barriers to HCT.
- Iomab-B can potentially increase anti-leukemic effects of conditioning without added toxicity.
- Phase III study will address whether RIT-based conditioning for HCT is superior to conventional management for relapsed/refractory AML.