RIC Allogeneic transplant vs. Myeloablative allogeneic transplant for Elderly (>55yr) High Risk AML

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- A 55 years old man with adverse karyotype AML (monosomy 7) and no co-morbidities has an HLA identical sibling. The patient has inquired if you would opt for full intensity or RIC allografting?

Rationale of conditioning

- Treat the underlying disease
- “Clear the way”
- Prevent rejection (immunosuppression of the host)
- Prevent/modify GvHD (immunosuppression of the Graft)

Myeloablation

- Busulfan 16mg/kg PO or 12,8mg/kg IV
- Whole body irradiation 11-14 Gy
- Combined with either above, Cyclophosphamide 120-200mg/kg

What is Reduced Intensity Conditioning?

- Anything less than full myeloablation
- Any attempt to reduce toxicity of chemotherapy or radiation
- Any immune manipulation or modulation
- Incorporation or “piggy-backing” of disease specific therapies and conditioning

Reduction of toxicity

- Reducing dose of busulfan or radiation
- Alternate immunosuppression:- e.g. changing cyclophosphamide to fludarabine
- Use of alternate myeloablative drugs:- e.g. intermediate dose melphalan
- Pharmacologic dosing:- maintaining steady state plasma levels of busulfan

Immune manipulation or modulation

- Acute-GvHD increases TRM
- Direct T-cell antagonists such as anti-thymocyte globulin, alemtuzumab, daclizumab in addition to cortico-steroids, methotrexate and cyclosporine/tacrolimus/mycophenolate mofetil
- Given in-vivo prior to or during the transplant vs. into the graft (in-the-bag)
- Have less effect on chronic-GvHD
- Chronic GvHD reduces incidence of relapse

Piggy-backing

- Disease specific agents such as Gemtuzumab Ozogamicin, imatinib and farnesyl transferase inhibitors
- Have less toxicity than conventional cytotoxics
- Allow better disease control, buying time for GvL effect
- Eradicate minimal residual disease

Why RIC?

- Efficacy of allogeneic haemopoietic stem cell transplant in the eradication of malignant disease
- Provide access to HST for patients with co-morbidities or advanced age who have an increased TRM from conventional myeloablation
- Disease demographics:- increased incidence of AML/MDS in older patients and worse prognosis disease in these patients
- In some diseases GvL effect is important and especially if MRD
- Allows the use of alternative donor/stem cell sources e.g. MUD’s & UCB

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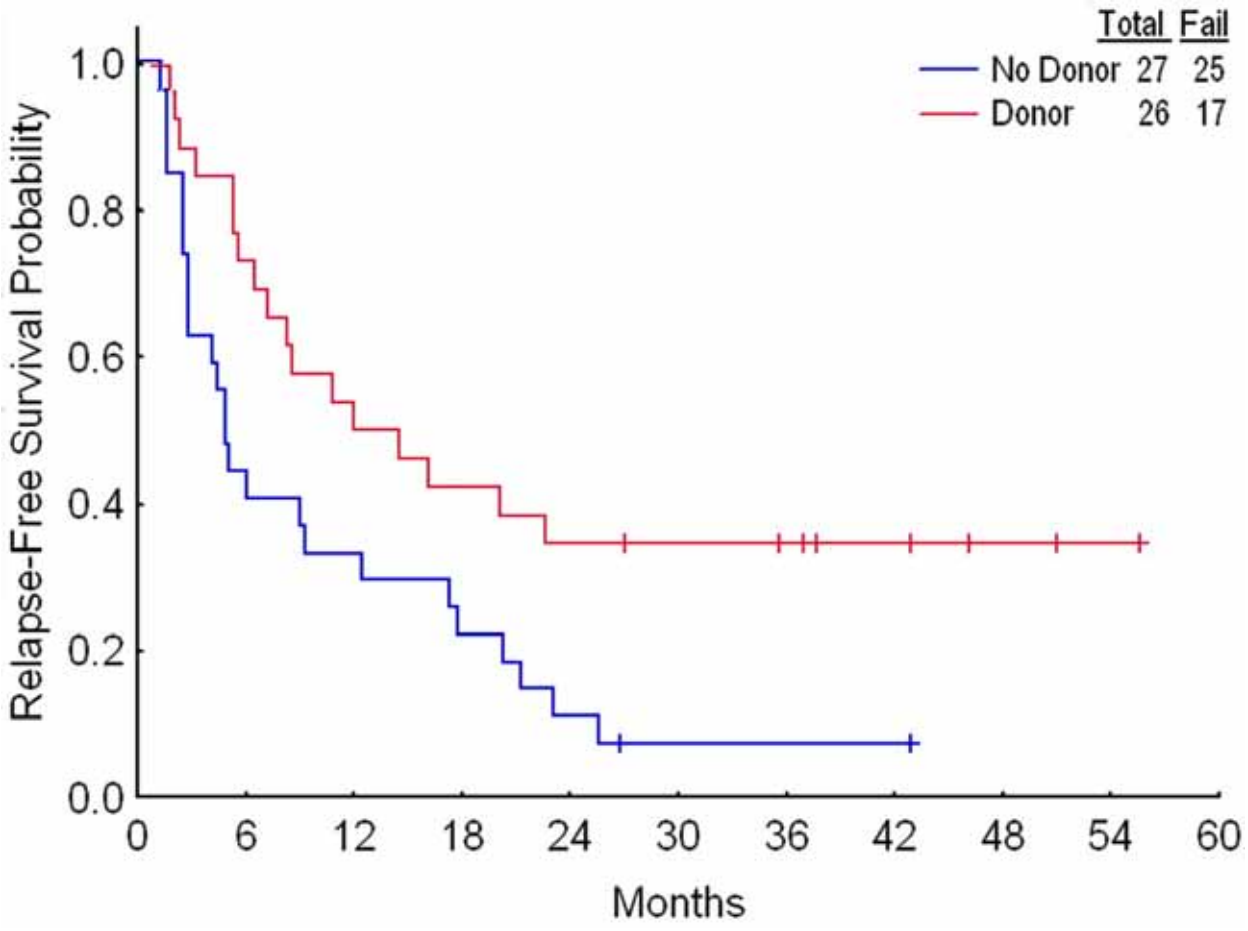

Estey, E. et al. Blood 2007;109:1395-1400

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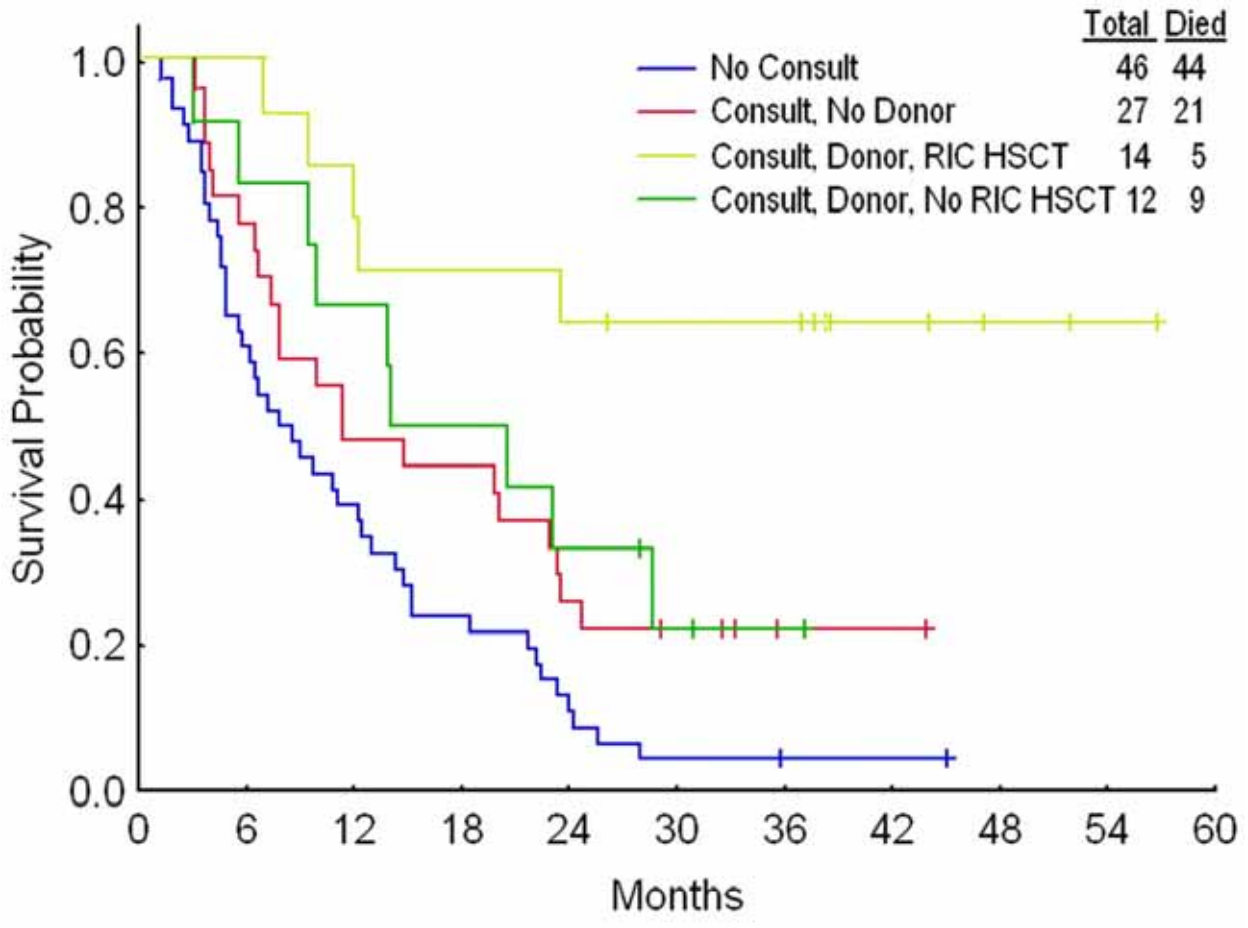

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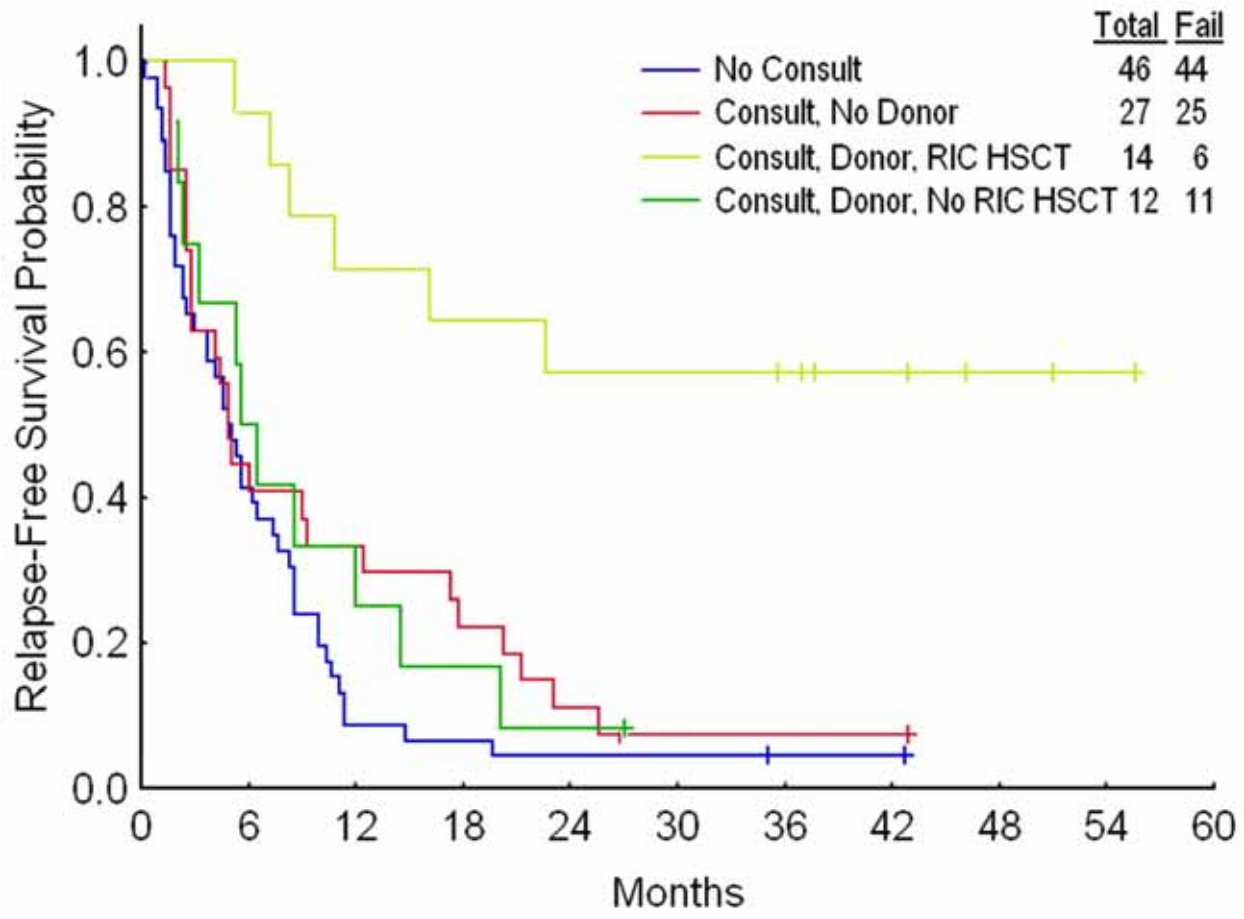

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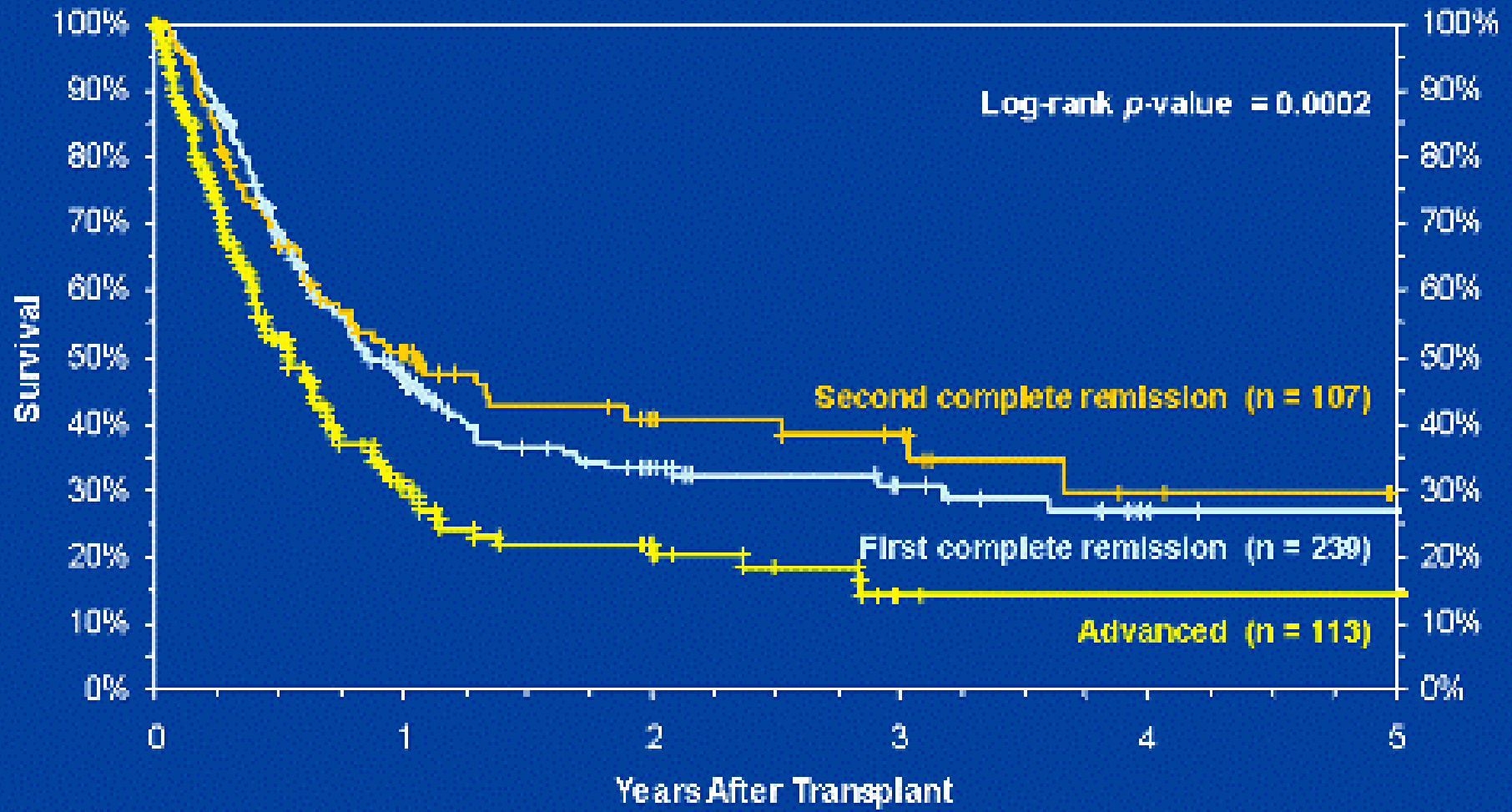
Why not RIC

- Some diseases need the chemotherapy or radiation dose (myeloablative dose)
- Active or progressive disease
- Refractory disease

Acute Myelogenous Leukemia

Survival of Older Adult (Age ≥ 55 Years) Marrow and PBSC Recipients with Non-Myeloablative Preparative Regimens, by Disease Stage 1998–2006



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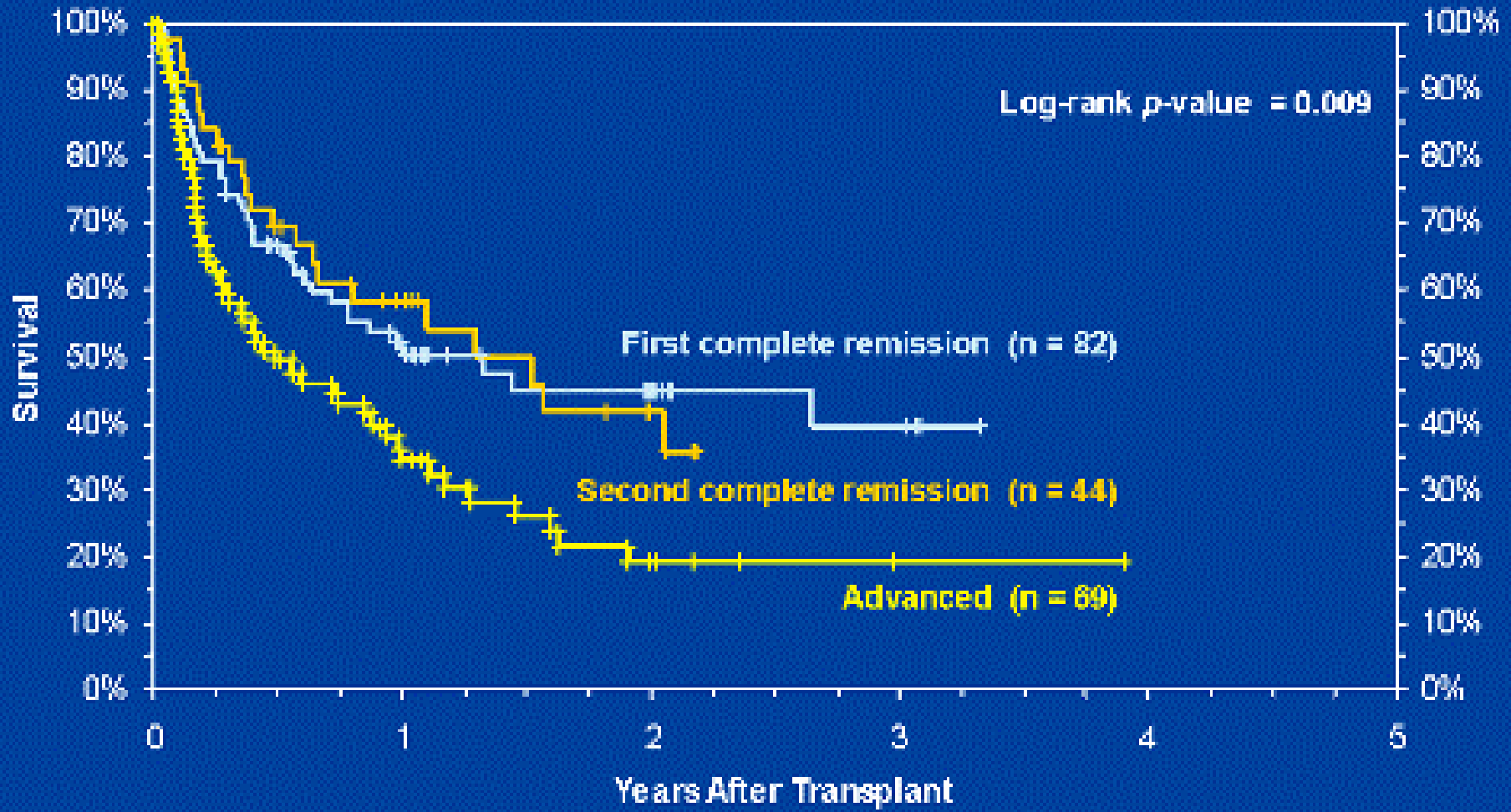
Acute Myelogenous Leukemia

Survival of Older Adult (Age ≥ 55 Years) Marrow and PBSC Recipients with Myeloablative Preparative Regimens, by Disease Stage 1998–2006



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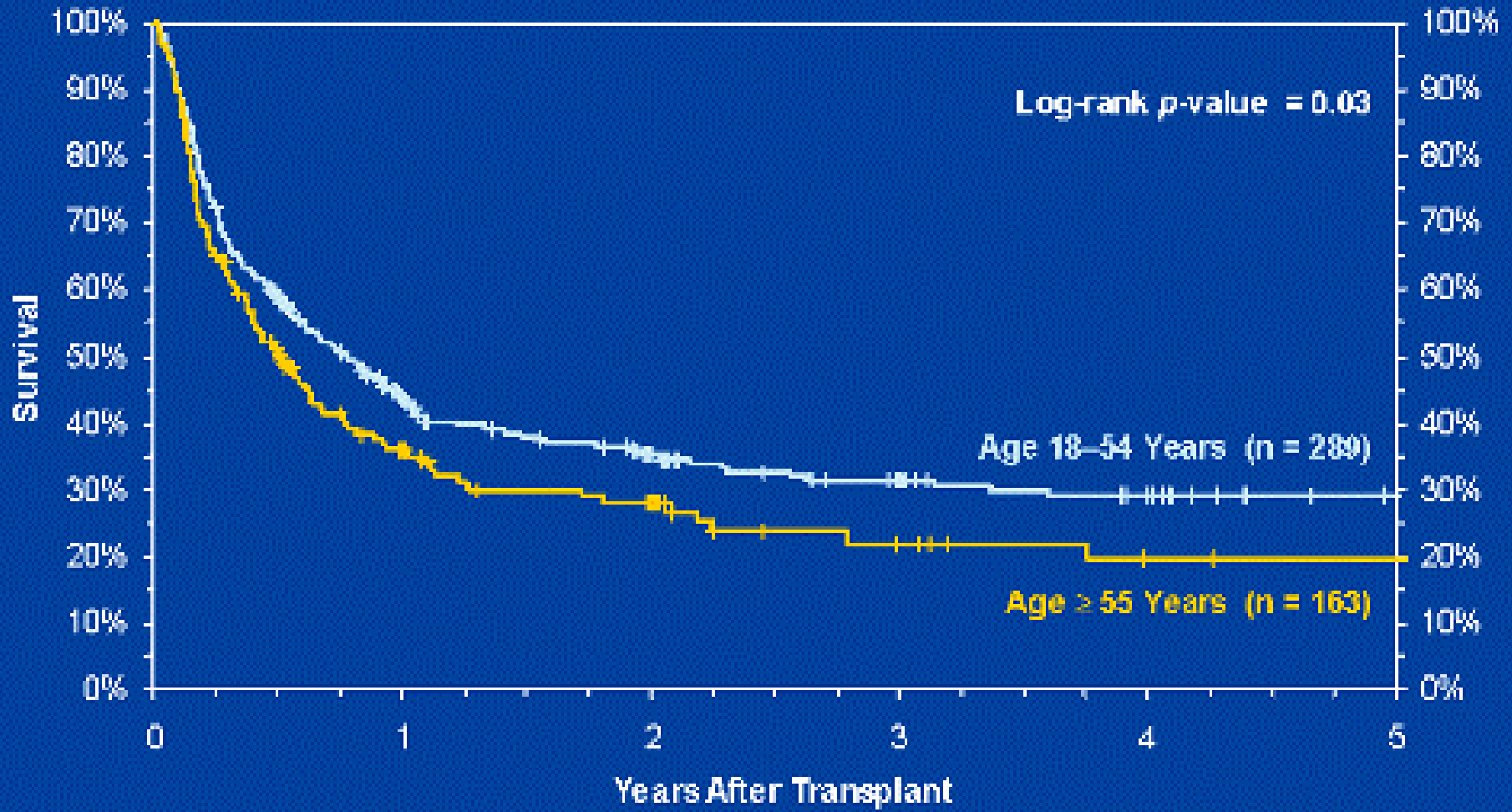
Myelodysplastic Syndromes

Survival of Adult (Age ≥ 18 Years) Marrow and PBSC Recipients with All Preparative Regimens, by Age at Transplant 1998–2006



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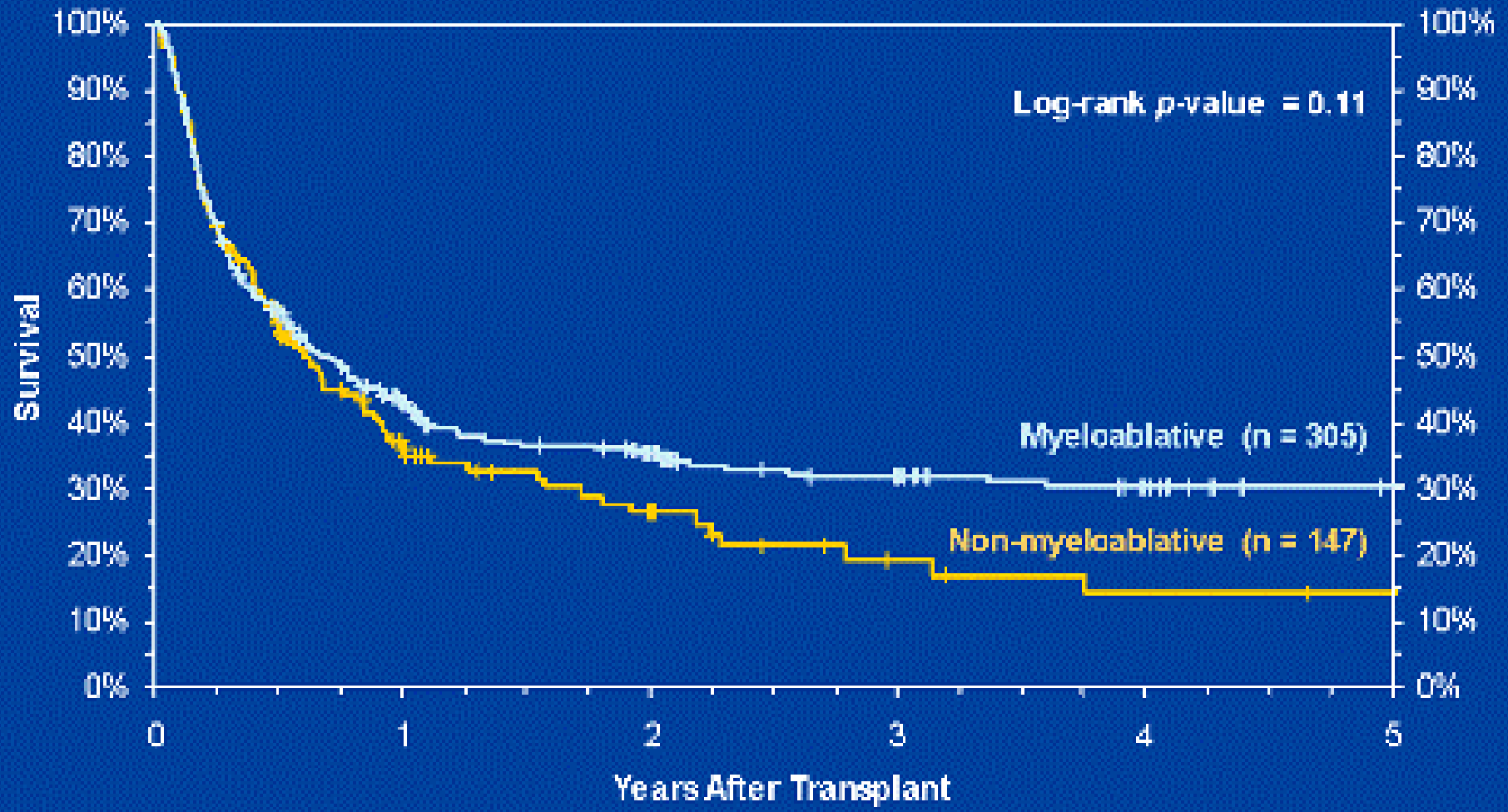
Myelodysplastic Syndromes

Survival of Adult (Age ≥ 18 Years) Marrow and PBSC Recipients with RAEB/RAEB-T by Conditioning Regimen 1998–2006



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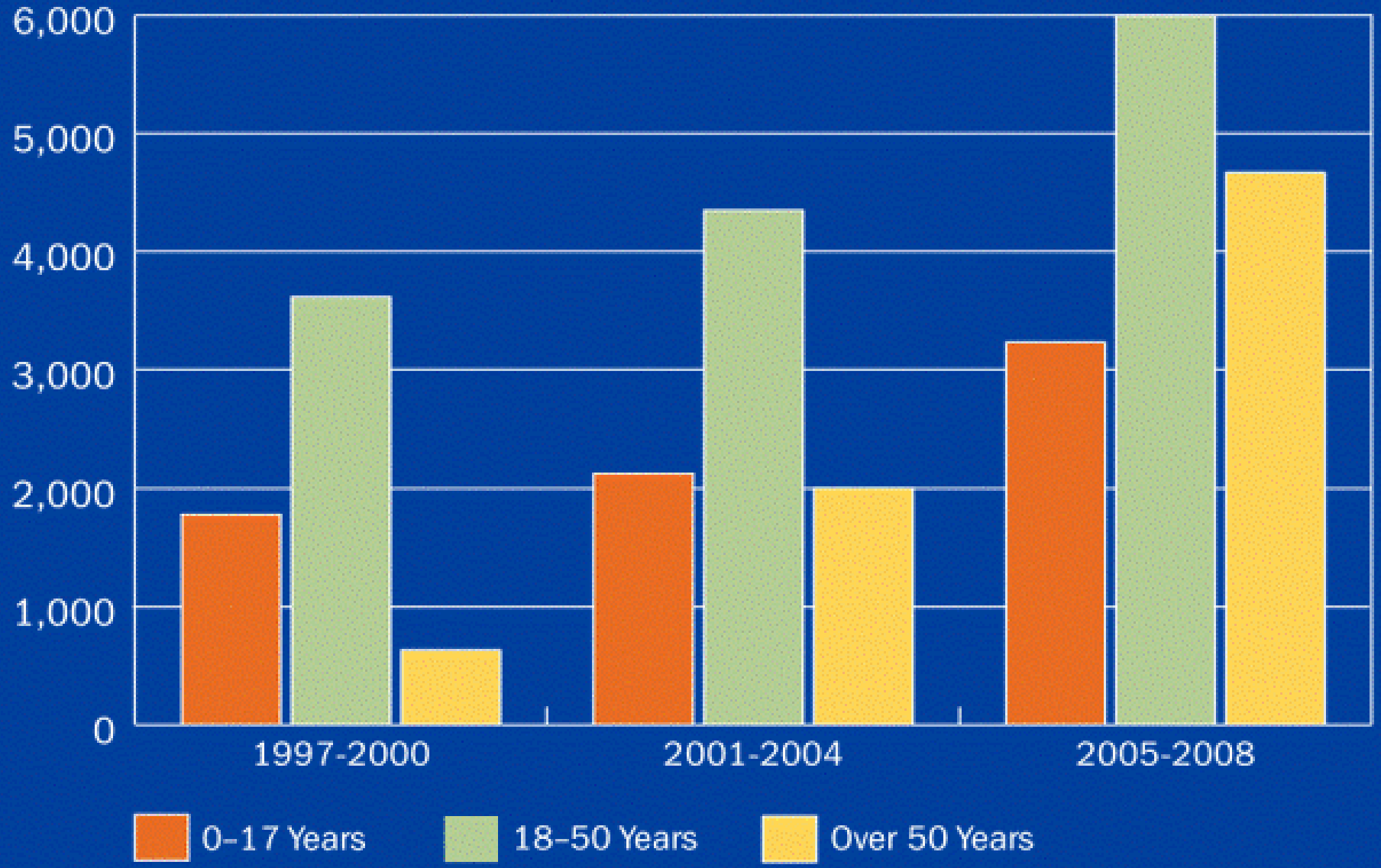
NMDP Transplants by Patient Age and Year



Case assumptions

- The patient is in CR

Decision

- This patient without significant co-morbidity but high risk disease can have a RIC allogeneic transplant because:
  - He is in CR
  - Age
- However I would concentrate on modifying the toxicity and on reducing the A-GvHD risk rather than reducing the dose intensity of the ablation
  - i.e. busulfan IV 6,4mg-8,6mg (or plasma level adjusted)
  - Substitution of cylclophosphamide by fludarabine
  - Addition of melphalan
  - T-cell modulation