“A Bridge Over Troubled Waters”

Using Bridge to Transplant as Criteria for FDA Drug Approval

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Establishing the Playing Field

Our Common Goals

- Cure all patients.

- Don’t hurt them while doing it.

- Don’t spend much money.

Establishing the Playing Field

Overall Criteria for Approval

“Clinical Benefit”

- Primary and possibly only criteria
- Provides diverse endpoints/definition
- Balances toxicity
- Allows for varied clinical trial designs
- Eliminates discussion of “classical” versus “non-classical” endpoints
- More patient input needed

Establishing the Playing Field

Overall Criteria for Approval

"Clinical Benefit"

Compared to what?

- Randomized trials useful
- Historical comparisons valid alternative
  - With subgroups may be only approach
  - Best outcomes for "standard practice"
- Equivalencies should be considered

“Clinical Benefit”

- Provides diverse endpoints/definition
  - Survival & Disease Free Survival
  - Response Rate
    - Definitions may vary
    - Methods of measurement may vary
  - Time to progression (when relevant)
  - “Bridge to Better Treatment”
  - Quality of Life – Multiple ways to define

“Bridge to Better Treatment”

The Question:

Does a drug’s ability to achieve a ‘disease state’ that allows a patient to undergo HSCT (or alternative) provide a sufficiently robust measure of clinical benefit for FDA approval?

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Breakdown:

1) Is there an advantage of HSCT for patients with relapsed and/or refractory leukemia over no therapy or conventional chemotherapy?

2) Does the status or extent of disease

   a) whether a patient receives a HSCT

   b) the outcome after HSCT

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Some Data

Prospective, randomized trials comparing HSCT to chemotherapy for relapsed and/or refractory patients lacking

But, consensus based on single arm trials is that HSCT is the only, currently available cure for patients with relapsed or refractory AML and early relapse or refractory ALL

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Prognostic Factors for These Patients

- Time interval a patient is in CR1
- Initial cytogenetics
- CR1/CR2 compared to $\underline{\geq}$ CR3
- Disease status at the time of HSCT

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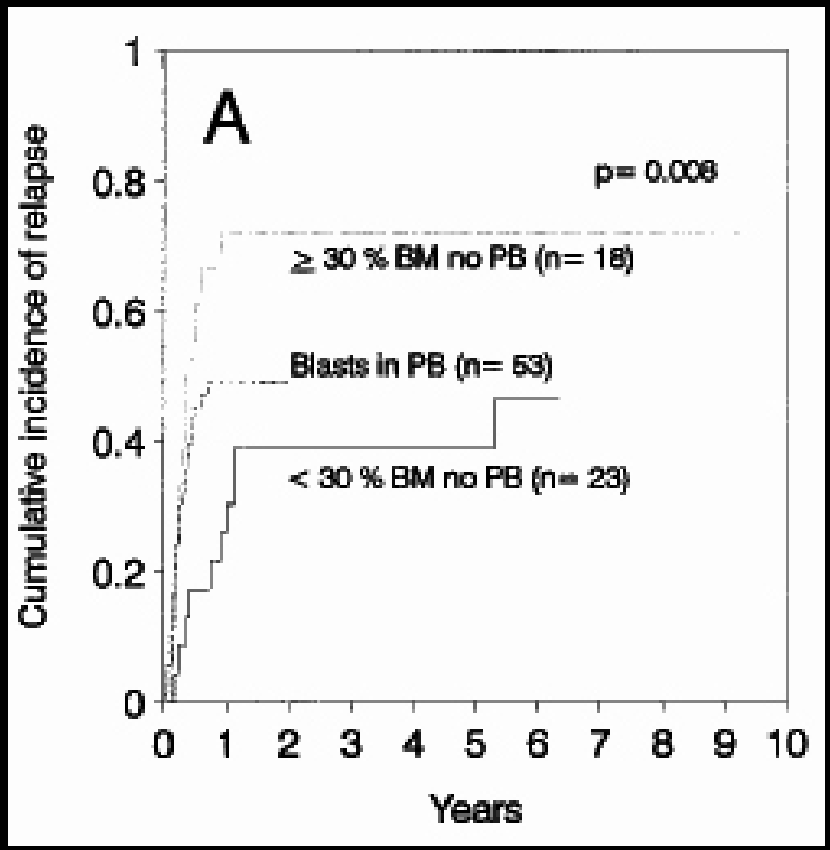
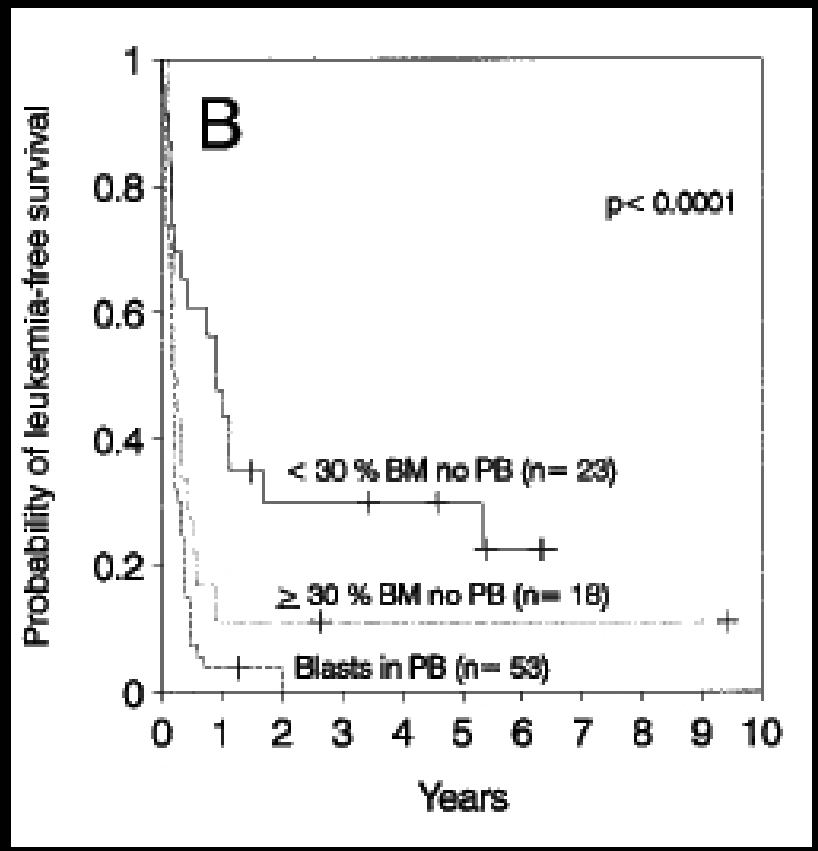
Disease status at the time of HSCT

174 patients (median age 20 (0.5 to 54 years); 74 AML, 91 ALL, 9 Hybrid)





Sierra et al., Blood, 89: 4226; 1997

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Disease status at the time of HSCT

Nemecek et al., BMT, 34: 799; 2004

58 children with relapsed AML

Outcomes with allogeneic HSCT

Overall DFS at 5 years: 24% (95% CI 14-36%)

Patient Status at HSCT	DFS
CR2	58% (27-80%)
Untreated first relapse	36% (11-63%)
Refractory Disease	9% (2-21%)

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Disease status at the time of HSCT

Nemecek et al., BMT, 34: 799; 2004

Outcomes with allogeneic HSCT

Patient Status at HSCT	Non-Relapse Mortality
CR2	0%
Untreated first relapse	27% (0-54%)
Refractory Disease	17% (5-30%)

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Disease status at the time of HSCT

Nemecek et al., BMT, 34: 799; 2004

Multivariable Regression Analysis

Phase	DFS			Relapse		
	HR	95% CI	P	HR	95% CI	P
CR2	0.3	0.1-0.7	0.008	0.3	0.1-0.8	0.02
UFR	0.5	0.2-1.2	0.14	0.4	0.1-1.0	0.06
RD	1	-	-	1	-	-

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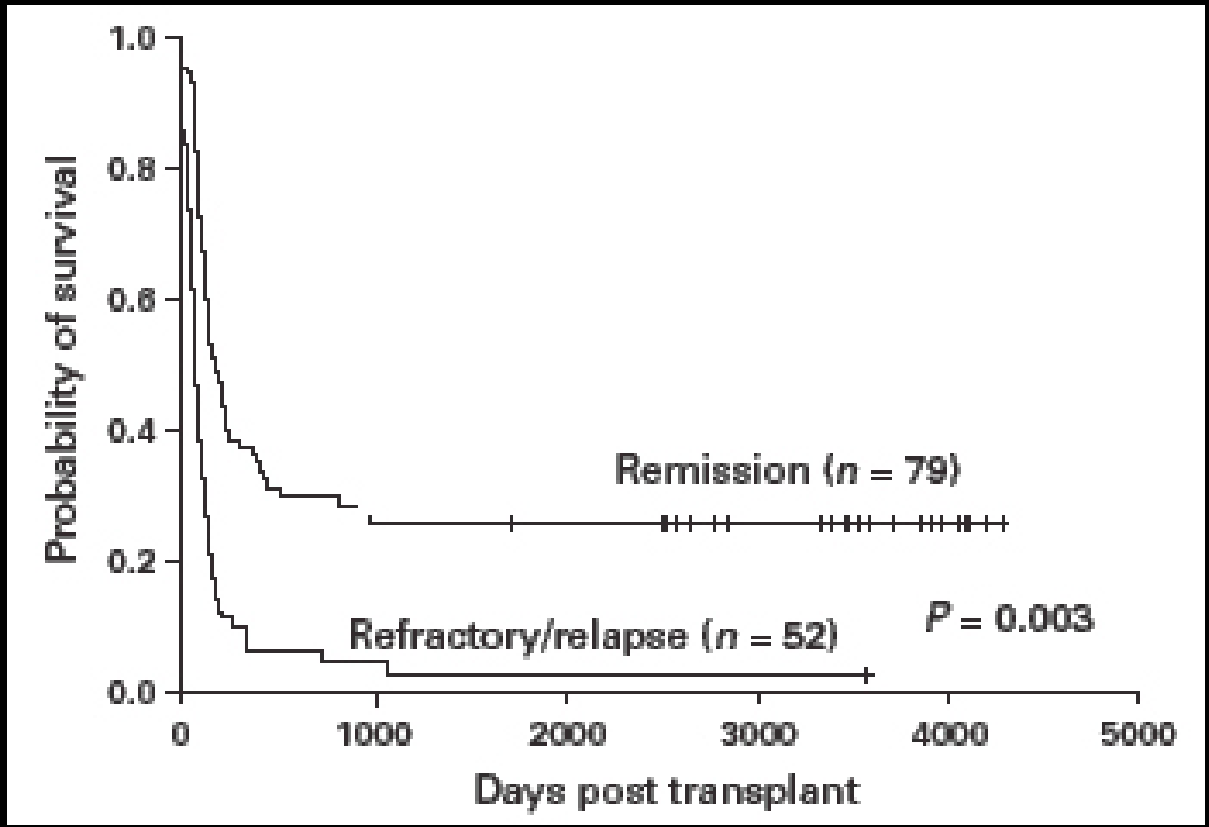
Disease status at the time of HSCT

Goldman et al., BMT 25: 943; 2000



(Retrospective Analysis/16 AML, 42 ALL)

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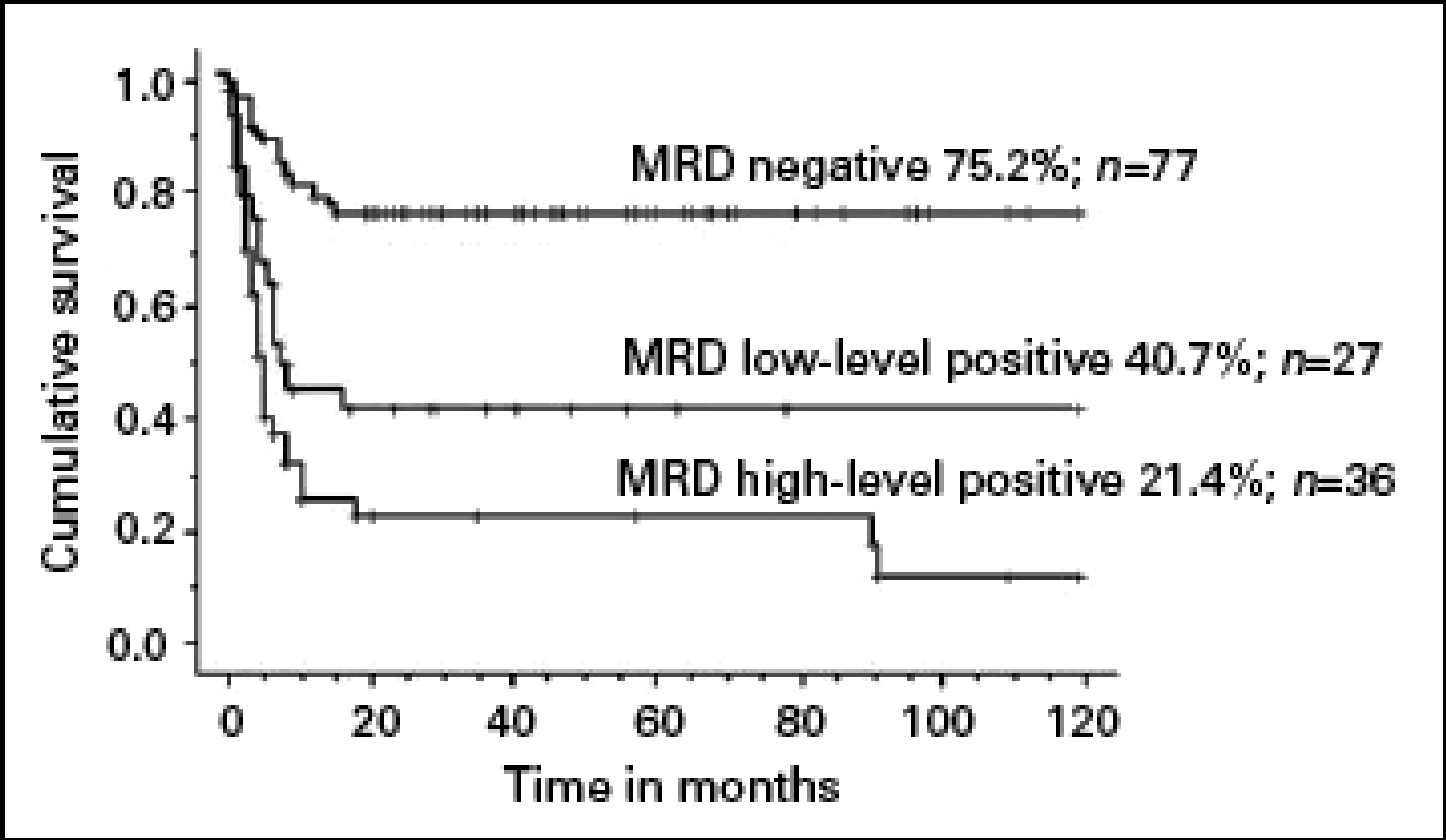
Disease status at the time of HSCT

Krejci et al., BMT, 32: 349; 2003

142 patients, 85 in ≥CR2



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Disease status at the time of HSCT is critical for autologous HSCT in APL

De Bottom et al., JCO, 23: 120; 2005

A retrospective analysis of 122 patients with relapsed APL

23 received allogeneic HSCT

50 received autologous HSCT

49 received Consolidation ± maintenance

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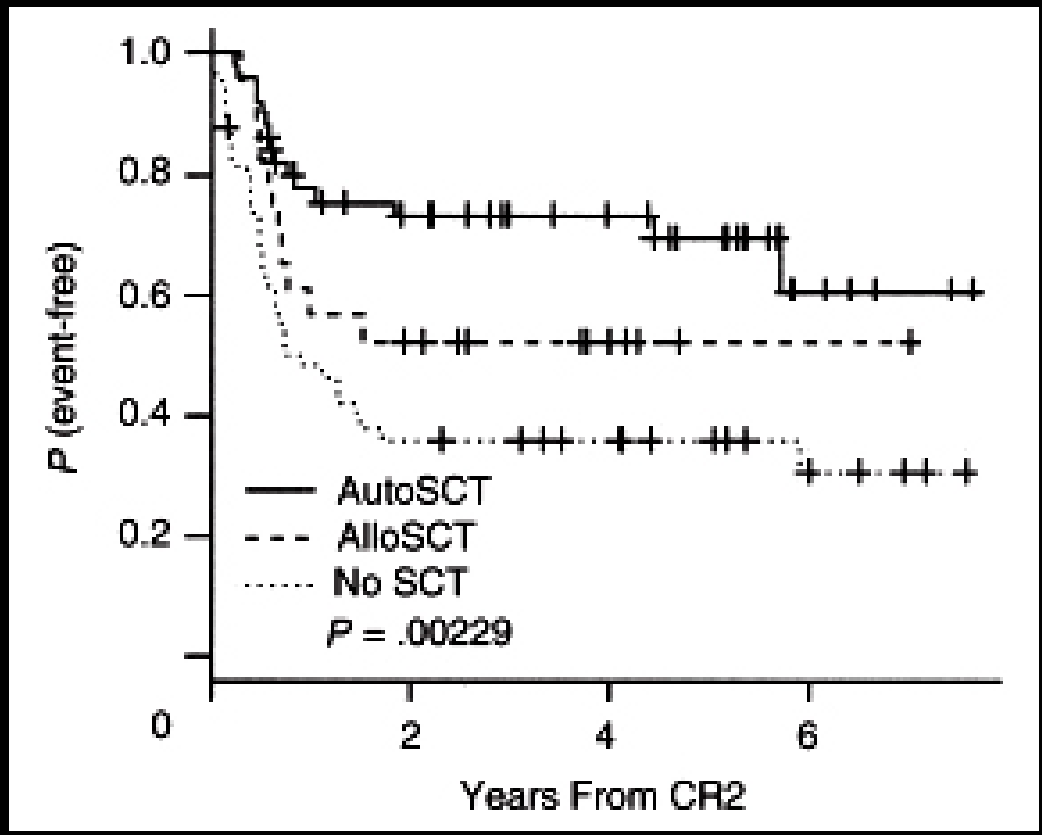
De Bottom et al., JCO, 23: 120; 2005



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Disease Status by RT-PCR

Before Auto-HSCT	Relapsed		RFS	EFS	OS
28 Negative	3		87.3%	76.5%	75.3%
2 Positive	1				
20 Not accessed	6		69.8%	49.2%	51.1%
		p	0.11	0.07	0.2

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Disease status at the time of HSCT is critical for autologous HSCT in APL

Meloni et al., Blood, 90:1321; 1997

	Relapsed <14 mo	CCR* >14 mo	
Pre-ABMT PCR +ve	7	0	$P < .001$†
Pre-ABMT PCR −ve	1	7	

* Continuous clinical and molecular remission of APL, thus including patient no. 12 who developed a secondary leukemia.

† By Fisher's exact test.

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Conclusions & Recommendations

1) Clinical Benefit as a criteria for approval should be central and predominant factor but balanced by toxicity considerations

2) Achieving a CR or MRD bone marrow status following relapse of leukemia impacts outcome following HSCT

3) Achieving a CR or MRD bone marrow status following relapse of leukemia impacts on whether a patient is considered eligible for HSCT

    a) Especially important for Reduced Intensity HSCT

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Conclusions & Recommendations

4) For HSCT involving unrelated donors, achieving CR or MRD status may provide necessary time to identify and activate appropriate donor

5) A combination of criteria should be used for approval such as Bridge to HSCT with acceptable or reduced toxicity than conventional therapy

6) Subgroups of patients will obligate the use of studies enrolling smaller numbers of patients upon which to determine clinical benefit

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Conclusions & Recommendations

7) If the goal is cure, not just duration of remission, then goal should be HSCT. If the goal is HSCT, then improved disease and patient status prior to HSCT should be goals.

8) Drug development should not end with approval, but really begin a new phase.