Management of ALL in Adolescents and Young Adults:

What have we learned and what are our challenges?

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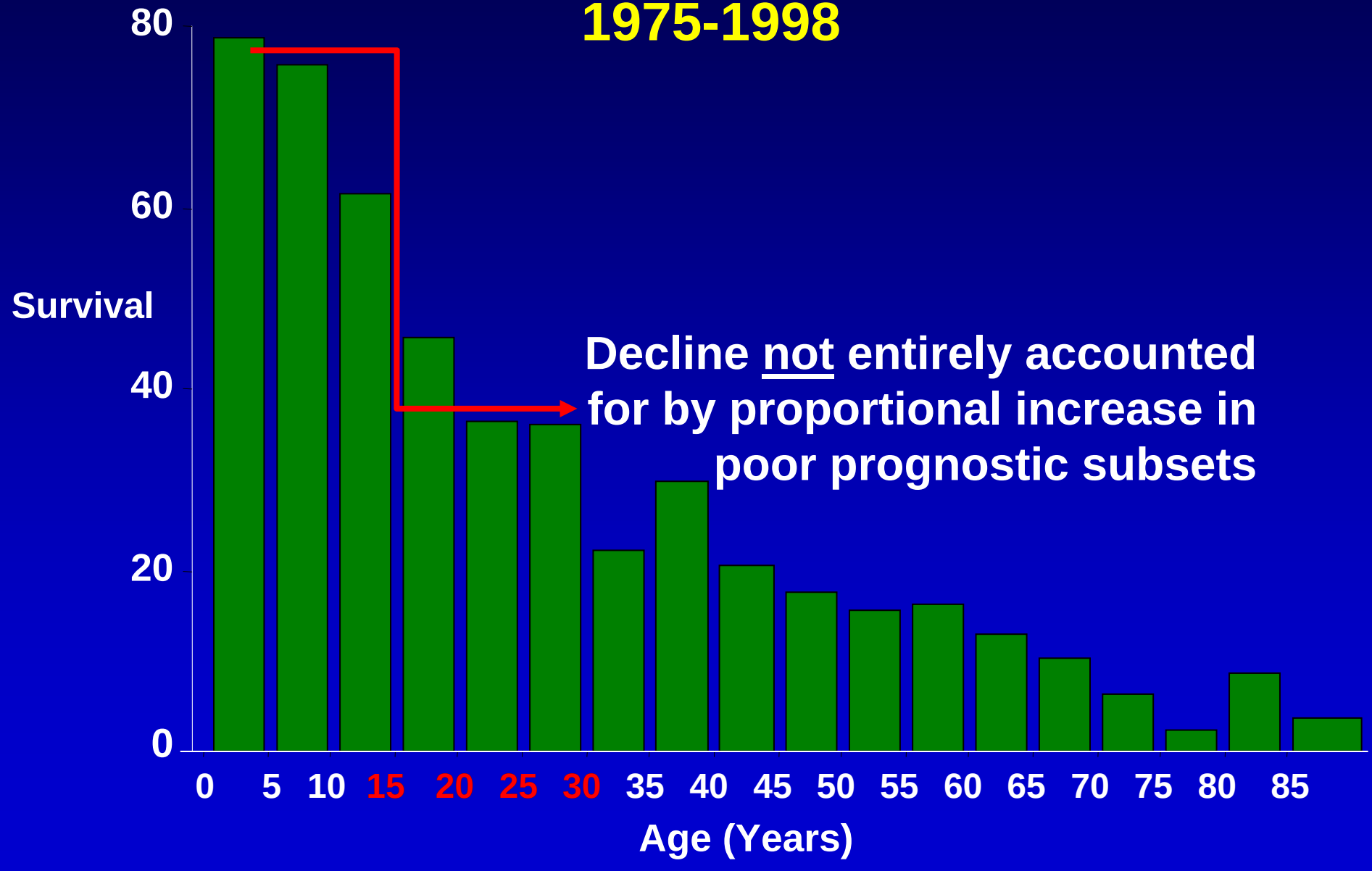
5-Year Survival
Acute Lymphoblastic Leukemia
1975-1998



ALL in Adolescents/Young Adults (AYA) What do we know now?

- **Survival rates correlate with level of participation in clinical trials**
- **AYAs are <u>least likely</u> population to participate in clinical trials (CTEP data)**
- **Problem compounded by lack of consistency in approach to treatment:**
  - **Adult vs pediatric hematologist/oncologist**
  - **Paucity of specific outcome data on AYAs**

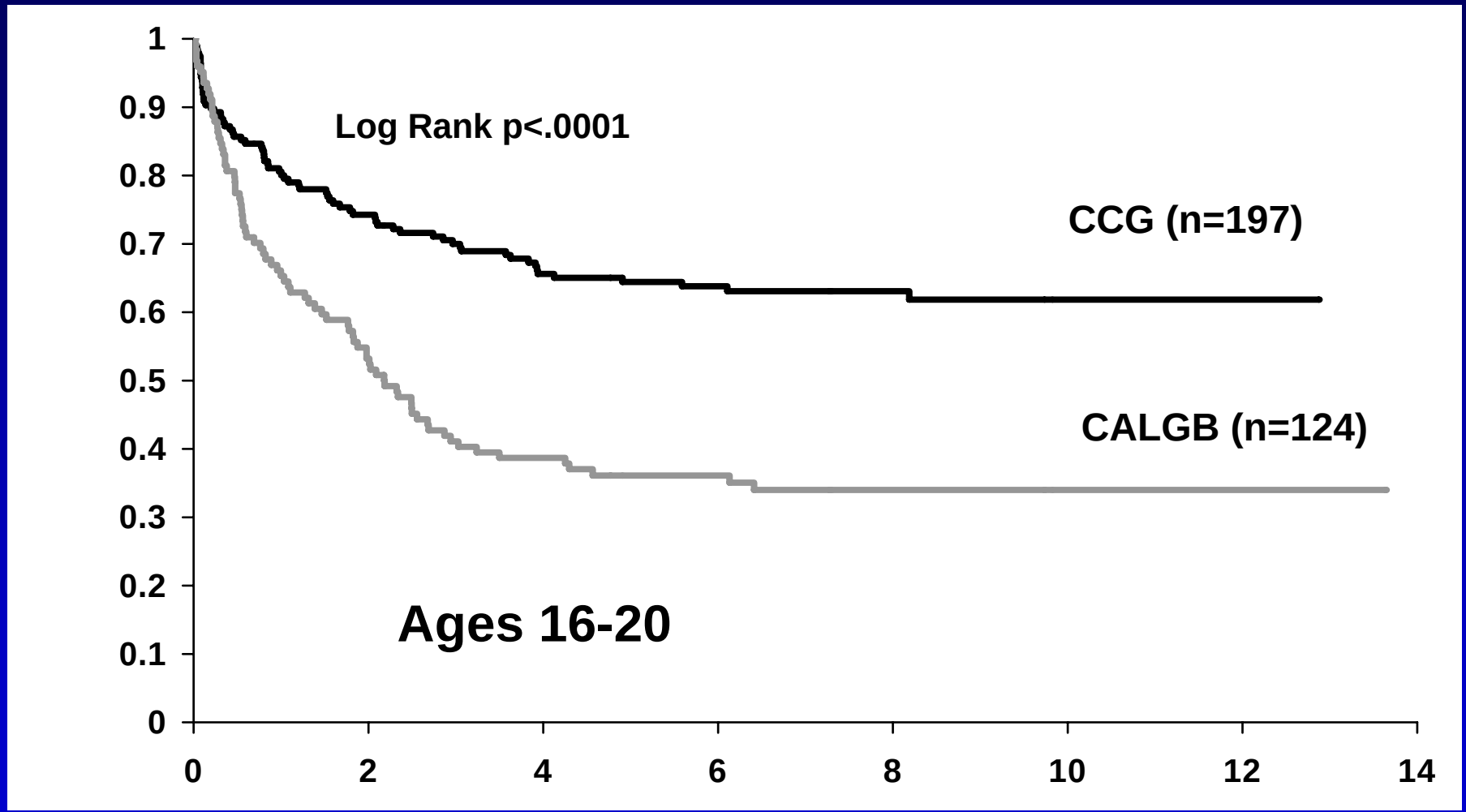
ALL in Young Adults: CCG and CALGB Studies Comparison of Outcomes from 1988-2003

	CCG Ages 16-20	CALGB Ages 16-20
Patients	197, (68% Male)	124, (69% Male)
Precursor T-cell	23%	27%
Precursor B-cell	77%	73%
Cytogenetics:		
Evaluable cases	61/197 (31%)	69/103 (56%)
t(9;22) or t(4;11)	4 (7%)	7 (10%)
WBC > 50 K	67 (25%)	27 (22%)

Summary of Results

	CCG	CALGB
Complete Remission	96%	93%
6 -year Event Free Survival (EFS)	65%**	38%
EFS by phenotype:		
B-lineage	56%	39%
T-lineage	74%	45%
EFS by WBC:		
<50 K	67%	41%
>50 K	58%	30%

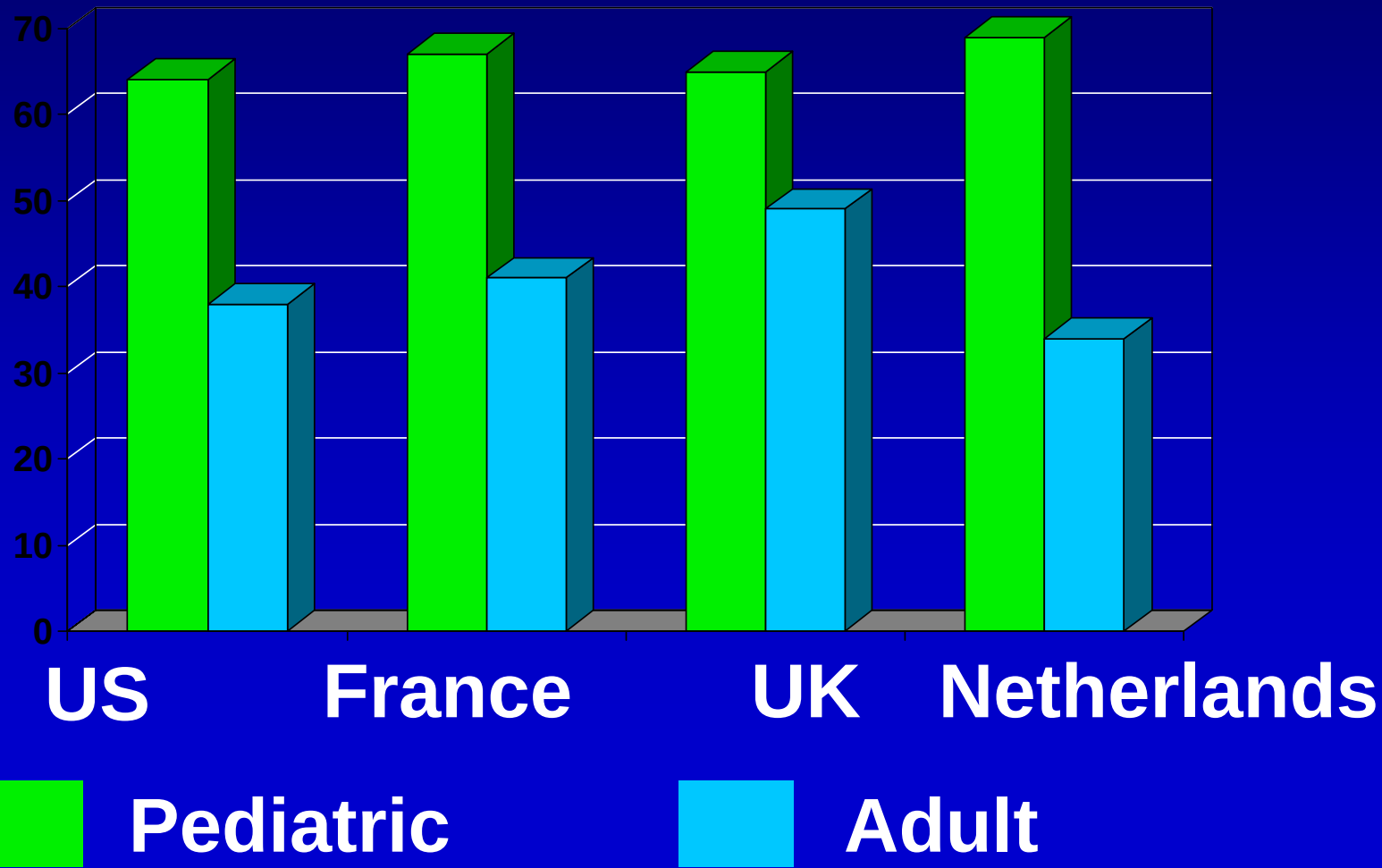
Event-Free Survival: CALGB vs CCG



Stock, W. et al. Blood 2008;112:1646-1654

Young Adults Treatment Outcome

Treating young adults on pediatric vs. adult protocols



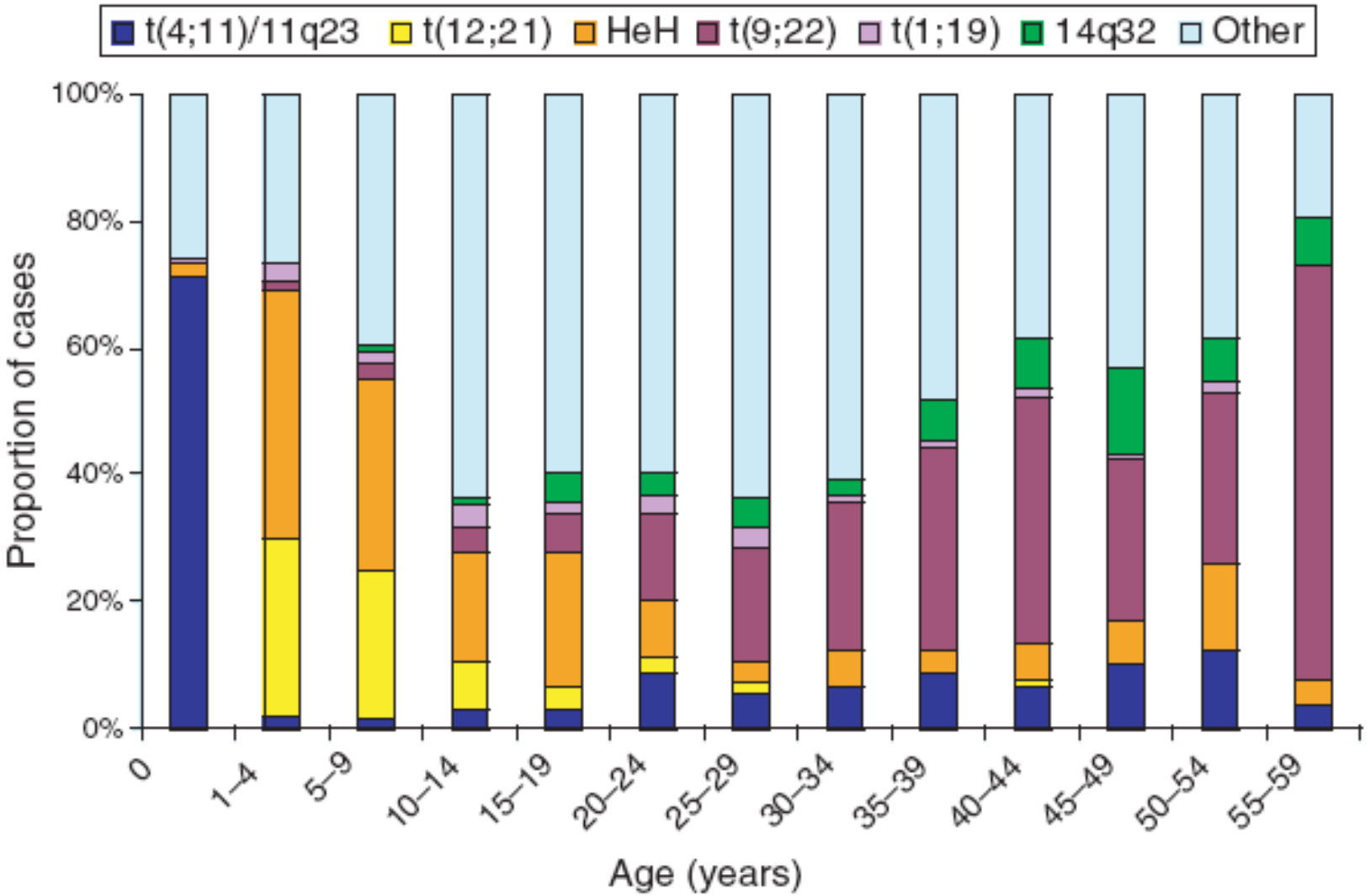
What Accounts for these Differences in Outcome?

Disease Biology?

Treatment ?

The People?

Cytogenetics of ALL as Function of Patient Age



Moorman et al, Brit J Haemat 10.1111,1365, 2008

Disease/Host Biology: Much to be done

- Focus on defining the incidence of new molecular genetic prognostic markers in AYA patients
  - *IKZF1*, *JAK2*
- Little known about potential differences in pharmacokinetic or pharmacogenomic regulation as patients age
  - Impact of puberty/hormonal changes?
  - Insights into drug toxicities, delays, omissions in treatment

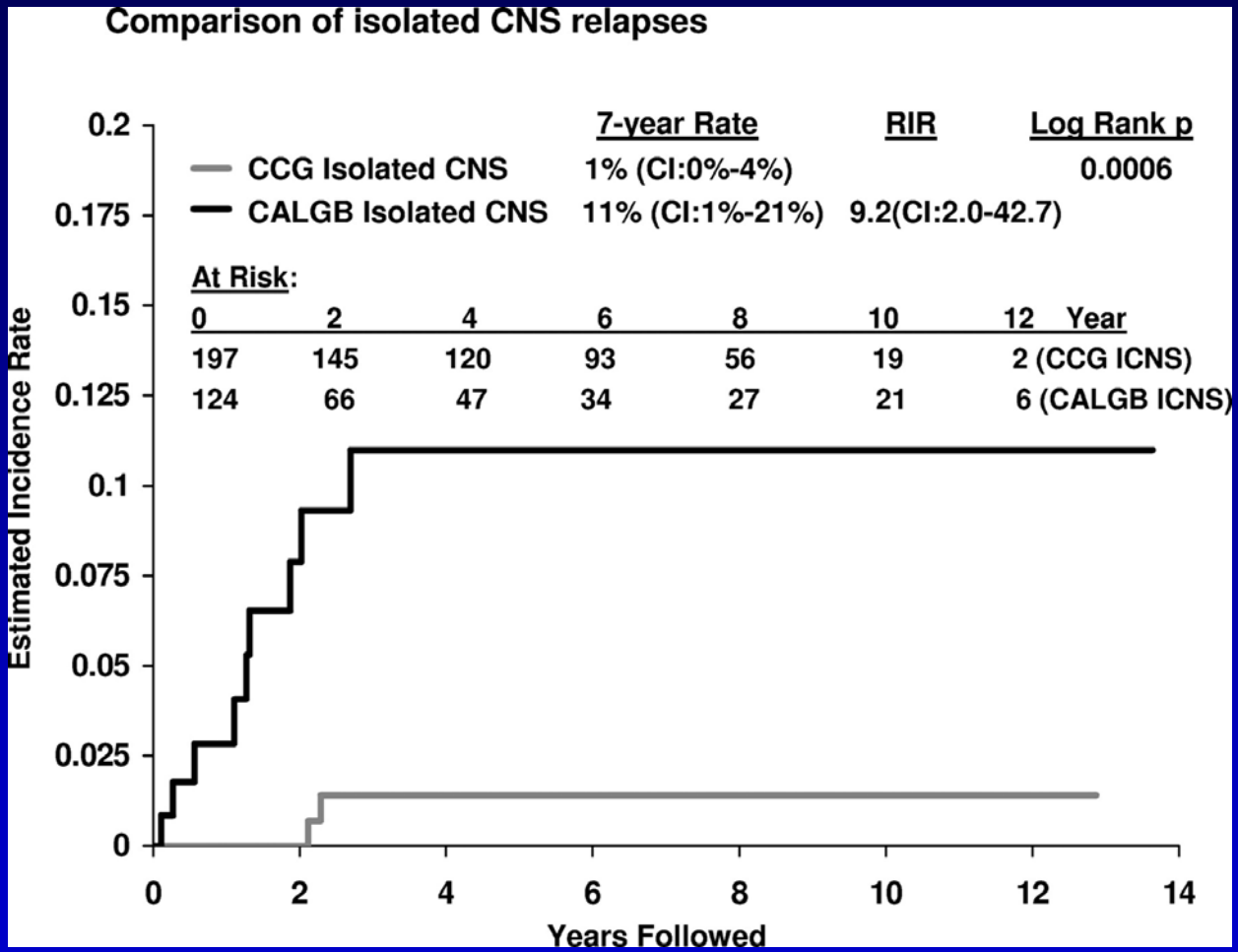
Treatment optimization: where are the differences in adult and pediatric regimens?

- Greater dose intensity of non-myelosuppressive drugs in pediatric regimens
  - vincristine, l-asparaginase, and steroid in CCG
- Earlier and more intensive CNS therapy
  - Given twice during induction therapy
  - Continues during long-term maintenance
- Longer duration of maintenance therapy in pediatric regimens

Comparison of Dose Intensity during Post-Remission Therapy

	CCG-BFM	CALGB
Dexamethasone	210 mg/m^2	140 mg/m^2
Vincristine	22.5 mg/m^2	14 mg
L-Asparaginase	90,000 u/m^2	48,000 u/m^2
Doxorubicin	75 mg/m^2	90 mg/m^2
Cyclophosphamide	3000 mg/m^2	3000 mg/m^2
IT-Methotrexate Cranial RT	132 mg + RT or 216 mg, no RT	105 mg 2400 cGy

Higher Rate of CNS relapses for CALGB patients

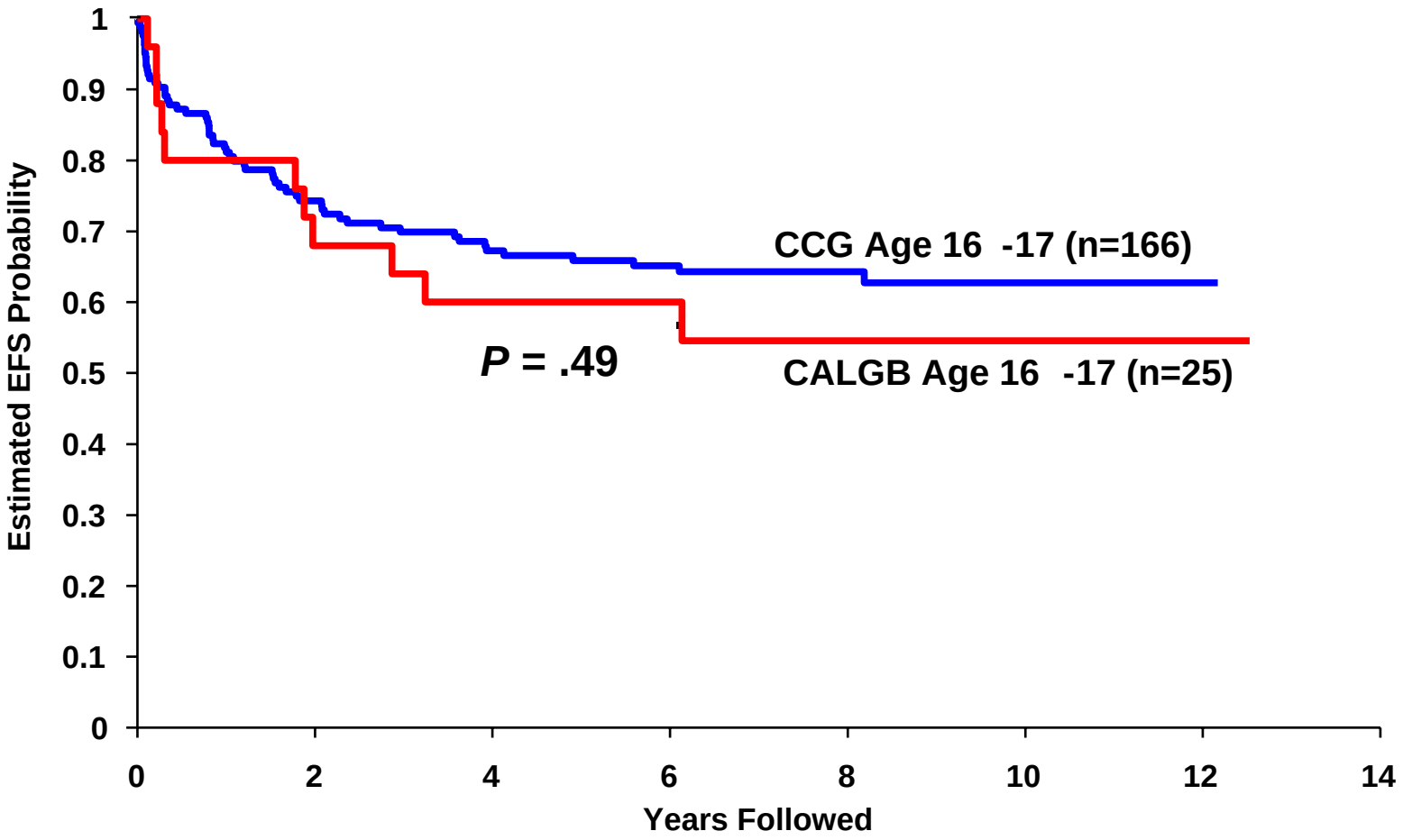


Stock, W. et al. Blood 2008;112:1646-1654

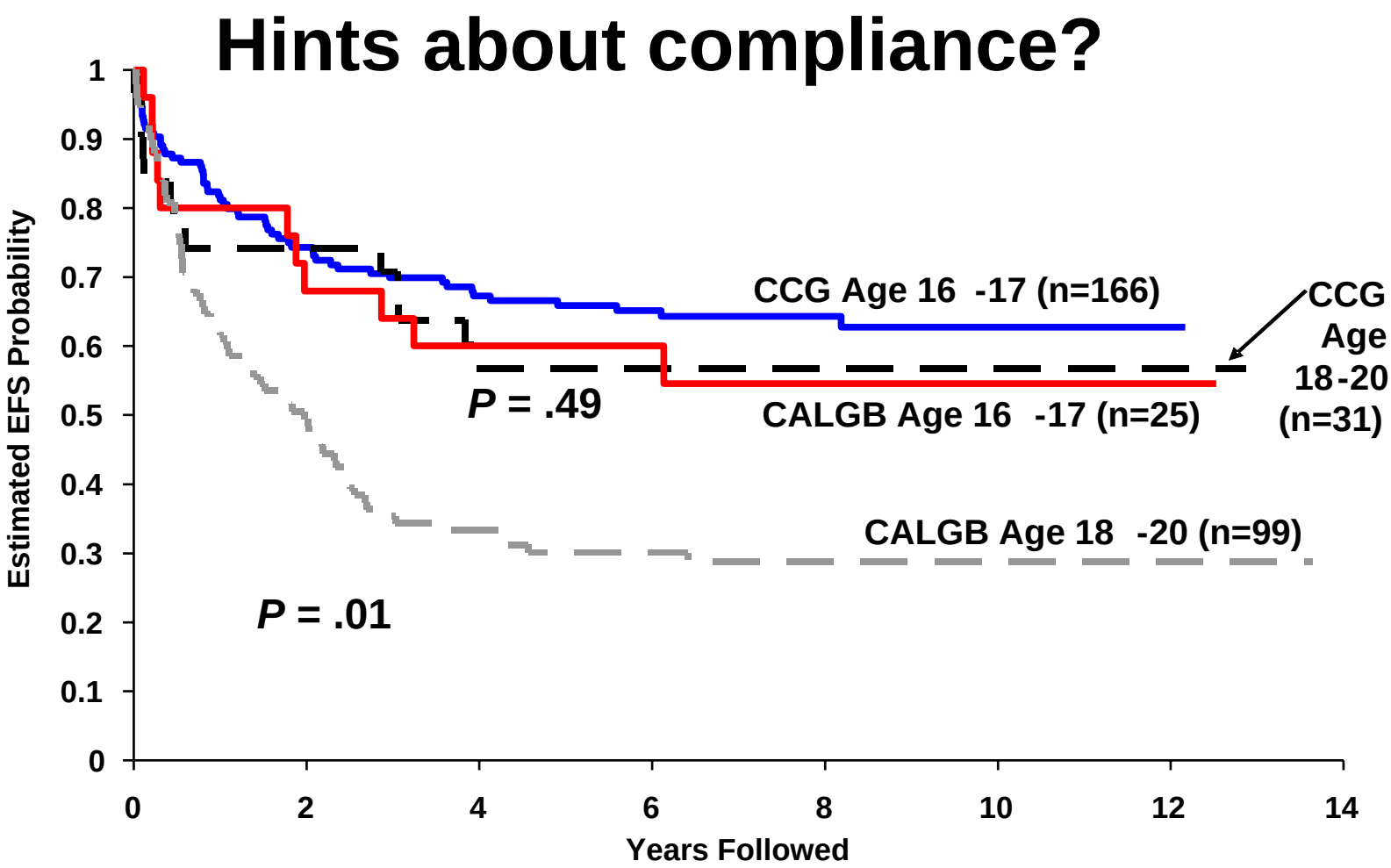
The Human Factor: Impact on outcome?

- Patient ?
  - "Emancipated adolescent" vs parental supervision
    - Insurance coverage for young adults
      - Loss of parental "umbrella"
    - Compliance issues – many oral medications
- Role of Treating Physician/Center?
  - Expertise and familiarity are relevant: Complicated regimens
    - Adherence to protocol by MD
    - ALL is "bread and butter" of pediatric heme/onc

Effect of Age on EFS



Effect of Age on EFS



Adherence to prescribed treatment: Did treatment delays impact outcome?

- Assessed time from initiation of induction therapy to the beginning of maintenance therapy by specified timeframe of the protocol
  - Only 75 (63%) CALGB and 126 (81%) CCG pts began maintenance therapy
    - Why no maintenance?: early relapses, treatment related deaths and toxicities, removal for allo-SCT, withdrawal of consent, lost to follow-up

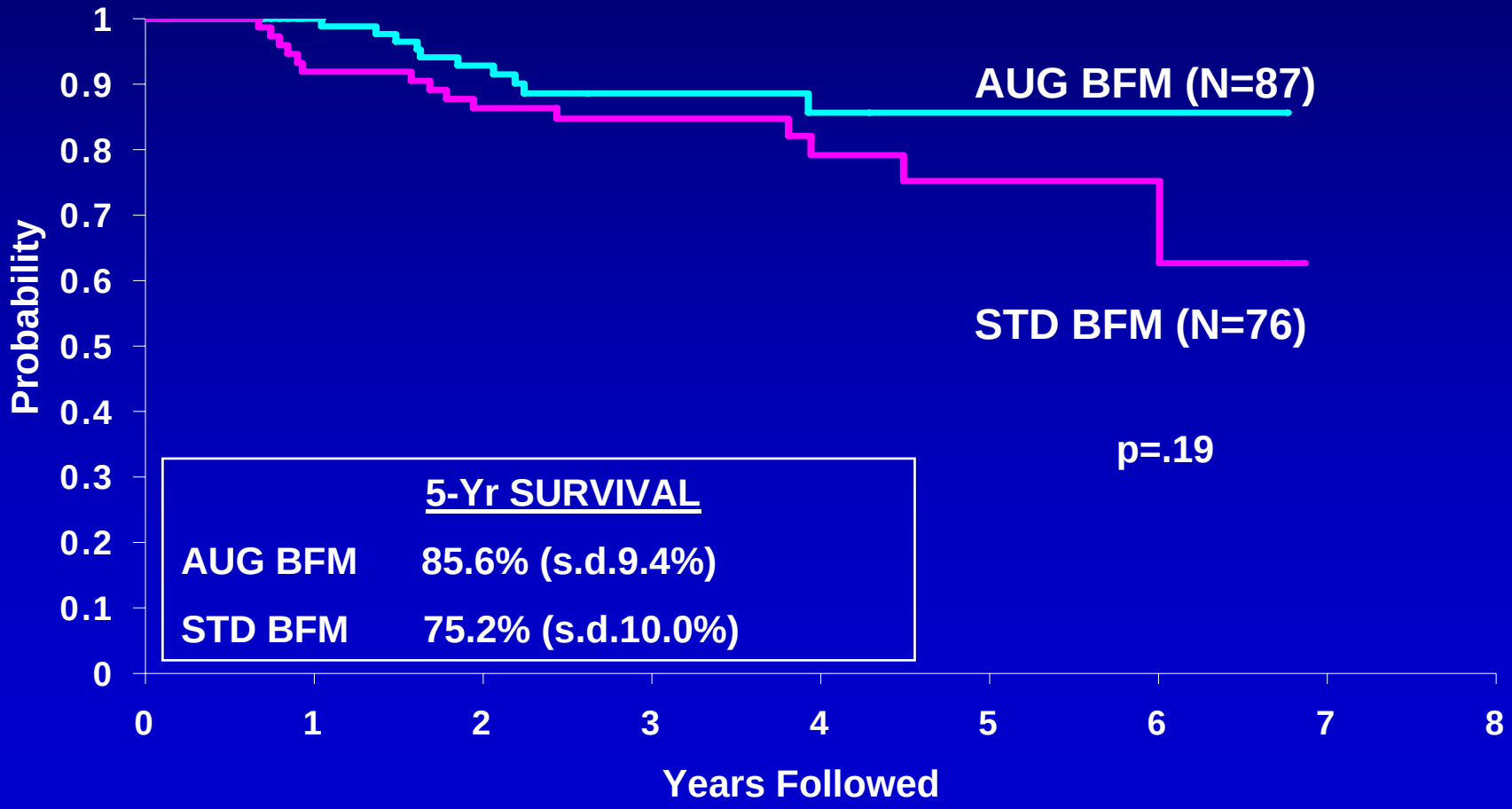
- However, no improvement in EFS noted for patients who began maintenance therapy within one-month of protocol specified timeframe compared to those who were delayed in time to beginning maintenance therapy
  - Could not address compliance with drug dosage in this retrospective analysis

US Intergroup study for AYA 16- 30 years old: C- 10403

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

T-ALL patients receive prophylactic RT after DI
Maintenance therapy continues for 2 (F) – 3 (M) years

CCG-1961 Augmented vs. Standard BFM Survival outcome (Age 16+ subset)

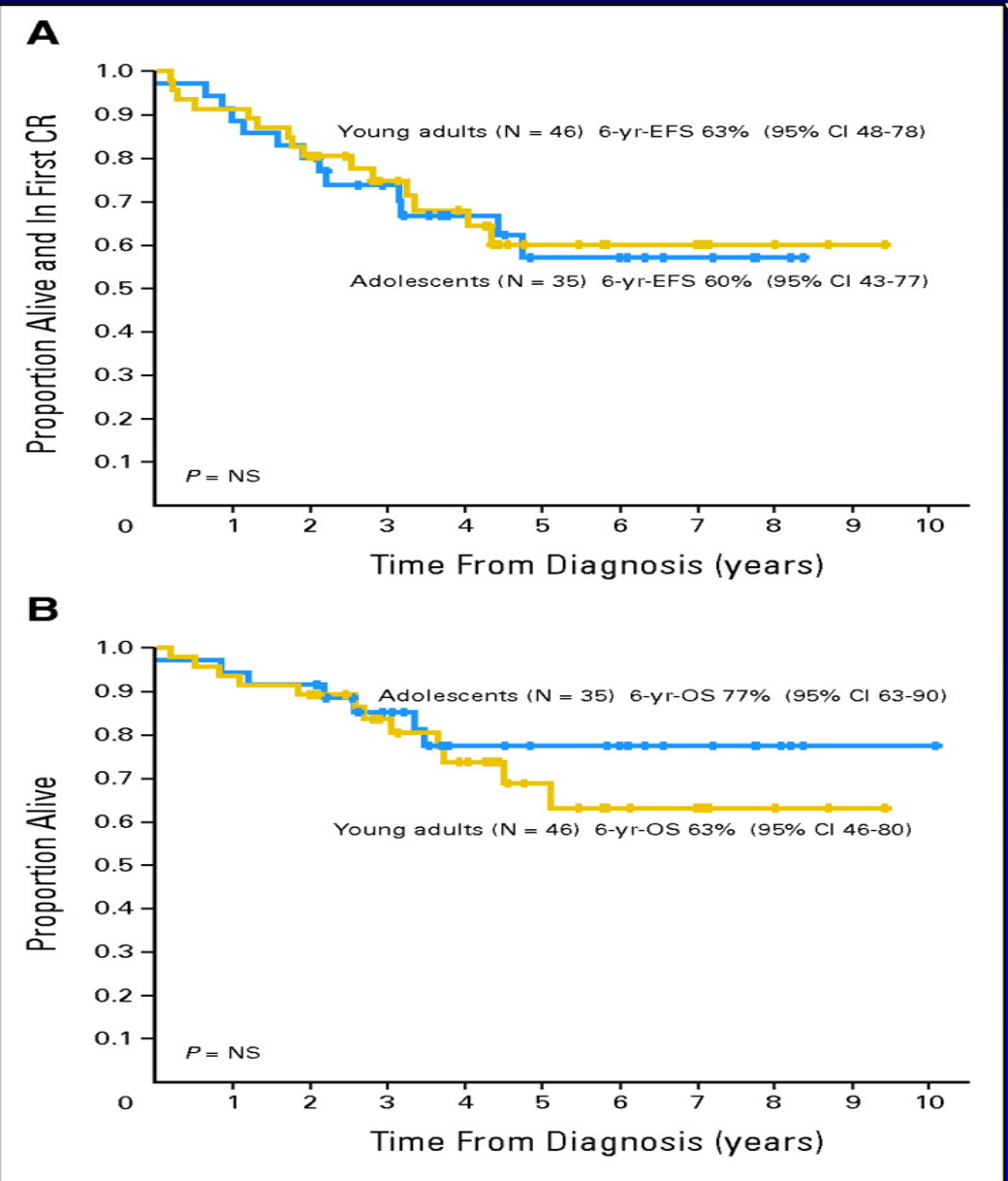


adapted by J Nachman from Seibel et al, Blood 111:2548, 2008

Goals of 10403 study

- To estimate feasibility and DFS using a successful COG regimen in adult cooperative group setting in USA
  - Flow sheets to evaluate compliance with doses/schedule of chemotherapy
- To obtain insights into age-specific molecular pathogenesis and to identify prognostic markers
  - Partnership with COG- Willman, Mullighan for GWAS studies
- To obtain insights into psycho-social and socio-economic issues
  - Patient survey at two treatment time-points

Extending the Pediatric Approach to Young Adults: An International "Sea Change": Similar EFS and OS



6-year EFS = 60%

6-year OS

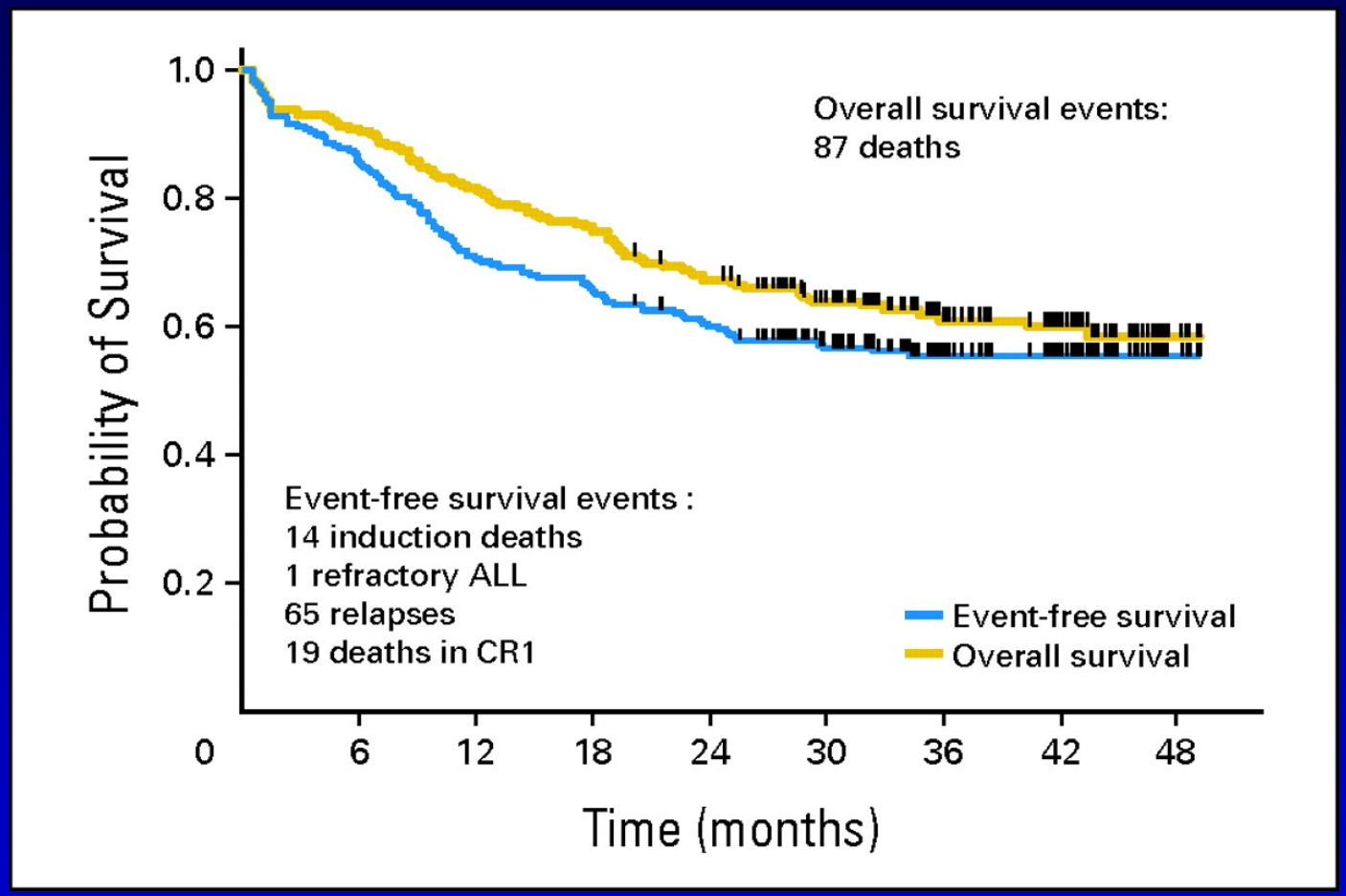
Adolescents (15- 18 yrs) = 77%

Young Adults (19 -30 yrs) = 63%

p = NS

Ribera et al, J Clin Oncol 26:2008

Improved Survival using a “Pediatric Inspired Approach”



Huguet, F. et al. J Clin Oncol; 27:911-918 2009

GRAAL- 2003: Can we extend this approach to older adults?

- Improvements in CR rates and EFS
  - EFS 55% overall
- However, less benefit for patients > age of 45
  - EFS: 46%
    - Higher cumulative incidence of treatment-related deaths (23% vs 5% for those< 45 years)

Huguet et al, J Clin Oncol 27:911, 2009

CALGB 10403: Early toxicities – more than expected?

- 39 patients enrolled as of 6/1/09
- Examined asparaginase toxicities via Adeers reports
  - 3 hypersensitivity reactions to IV Peg-ASP
    - during intensification therapy
  - 2 pancreatitis
  - 2 coagulopathy events
  - 1 Sinus thromobosis, 1 subarachnoid bleed during induction
    - Incidence of coagulopathies reported to increase in 11-16 year olds compared to younger children
      - » Appel et al, Thrombosis and Haemostasis 100 2: 330-37, 2008

Need to define / refine role of allo-SCT in CR1 for AYAs

Ph-Neg ALL – MRC UKALL XII / ECOG 2993:

Standard Risk	High Risk
None of :	Any of :
	Age ≥ 35 years
	WBC > 30,000/μL (*B Lineage*) > 100,000/μL (*T Lineage*)
	Time to CR > 4 weeks

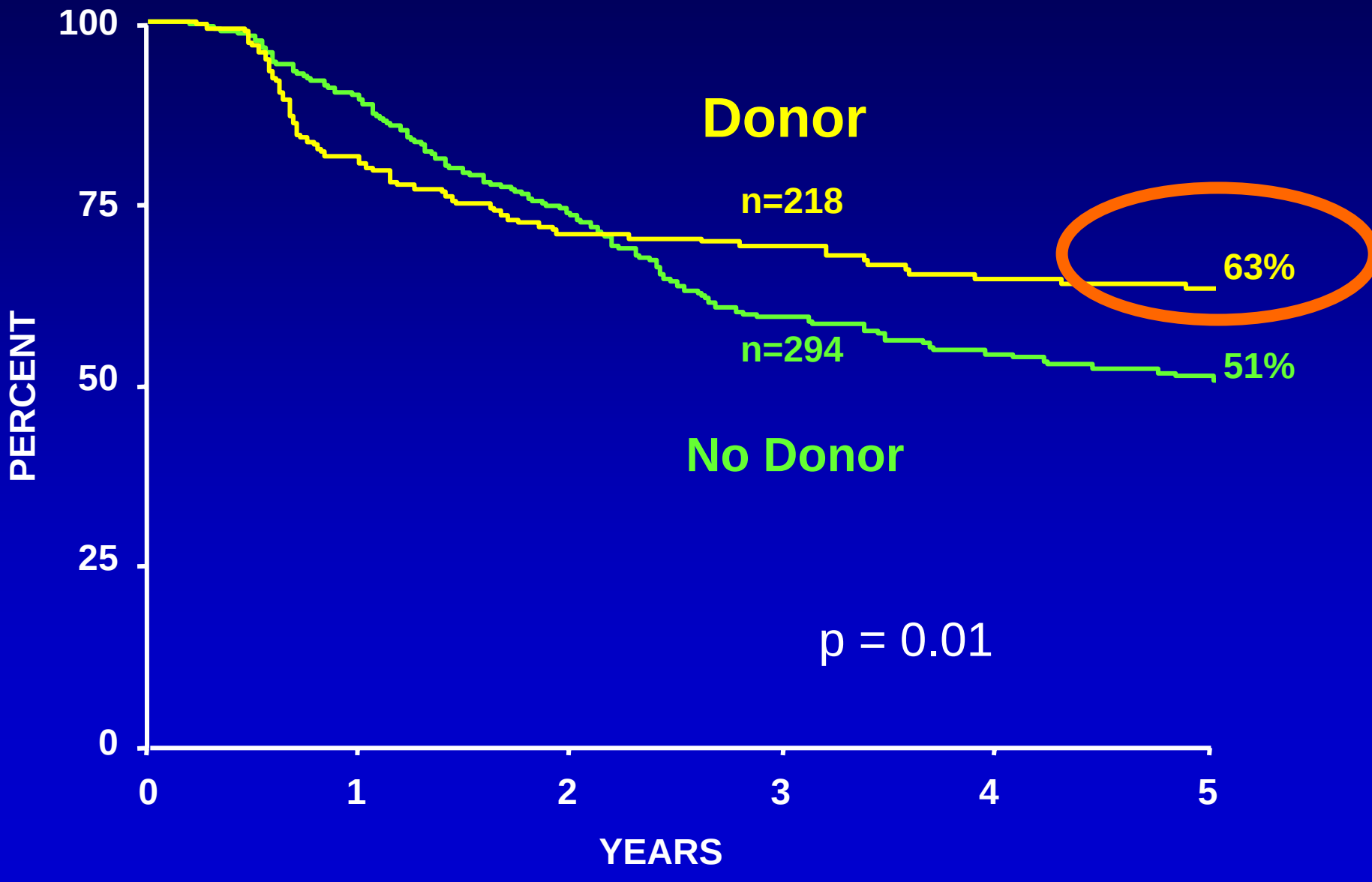
High-Risk Cytogenetics:

t(4;11), t(8;14), complex karyotype, low hypodiploidy, triploidy

Goldstone A et al, Blood 111:1827-1833, 2008

MRC UKALL XII / ECOG 2993 - OVERALL SURVIVAL

Standard Risk



AYAs and ALL: Where are we now?

- Promising developments: Intensive pediatric approaches appear to be improving EFS for the AYA patient
  - Clarify role of allo-SCT in CR1
- Successful ALL treatment (at any age) is not for the faint of heart!
  - Requires steady involvement of a knowledgable and dedicated medical and psychosocial support team and …..
  - Highly motivated and compliant patient with strong support from family, friends
  - Insurance issues: requirement for years of outpatient medication coverage

Clinical/Correlative Research Challenges

- Clinical issues:
  - Development of consensus guidelines: might be useful to manage/prevent toxicities and get more patients to be able to comply throughout treatment
    - Product support for coagulopathy
      - When to administer / when not?
    - Pre-medication for PEG-asparaginase?
    - Screening/monitoring/intervention for avascular necrosis/osteoporosis
  - Long-term survivorship issues
  - Medical insurance coverage for young adults

Research Challenges

- Ensuring adequate patient material and research support for GWAS studies
  - Cooperative groups must focus on provision of diagnosis, remission and relapse samples
  - Insights into molecular pathogenesis
    - already providing new prognostic markers
    - new targets for novel therapeutic strategies

- Better understanding of the pharmacokinetic and pharmacogenetic variations in AYAs that may impact treatment outcome
  - Interplay of host and environment

- Will result in refinement in care and better outcomes for AYAs: goal of “personalized medicine” for all patients