Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia: Early Results of US Intergroup Trial C10403

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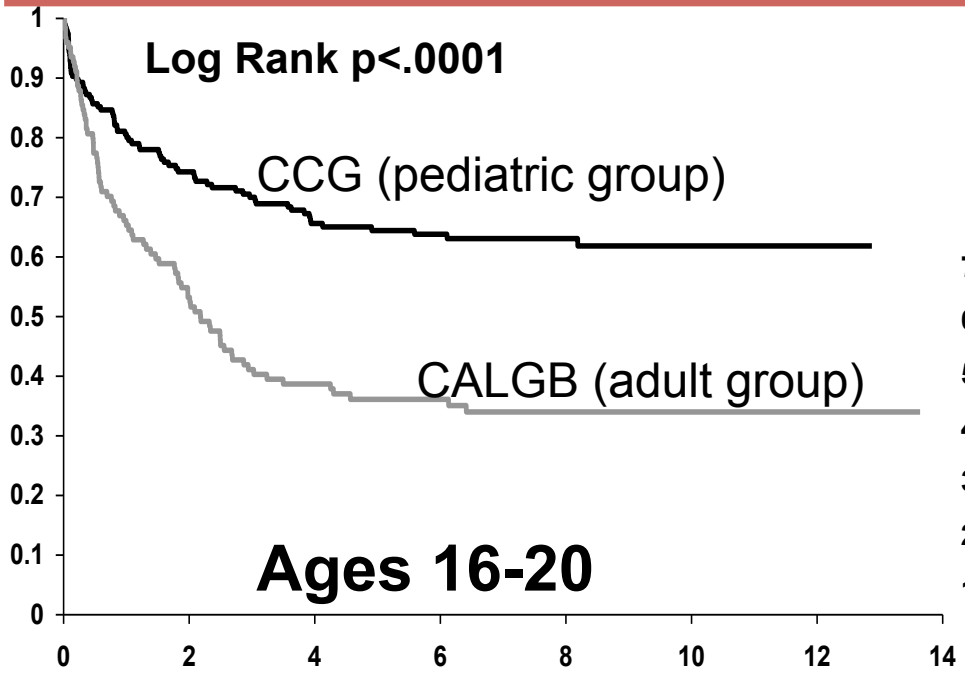
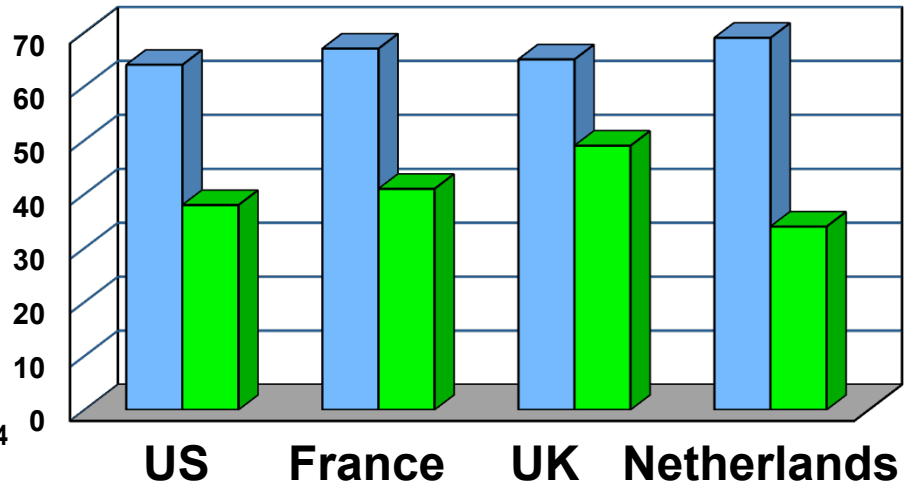
On Behalf of the Alliance for Clinical Trials, the Eastern Cooperative Oncology Group and the Southwest Oncology Group

Survival Differences in ALL are Dramatic: Depends on which "door" you enter





Blood 112:1646, 2008

Survival of Adolescents/Young Adults (AYA), Ages 16-20 years

Objectives

- To estimate feasibility and determine outcomes of AYAs with ALL up to age 40 when treated with a pediatric regimen by adult hematologists/ oncologists in the cooperative groups
- To describe toxicities and compare with similar patients treated on COG AALL0232
- To analyze outcomes by presenting biological features and MRD status
- To analyze patient and physician adherence
- To analyze outcomes based on psychosocial characteristics

US Intergroup study for AYAs 16- 39 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

C10403 Patient Population

- 318 patients entered on 10403;
  - 22 withdrew prior to Rx (exclusion of Ph+ ALL)
- 296 eligible patients enrolled from 11/07– 9/12
  - on schedule accrual
- Median age: 25 years
  - <20 years: 25%
  - 20-29 years: 49%
  - 30-39 years: 27%
- 75% Caucasian, 10% African American
  - Ethnicity: 16% Hispanic / Latino
- 61% Male; 39% Female

Patient/Disease Characteristics

Characteristic	Result (296 pts)
Immunophenotype	76% precursor B-cell 24% precursor T-cell
Performance Status: ECOG 0 or 1	91%
Body Mass Index (BMI)	Mean = 28 31% BMI $\geq$ 30 7% BMI $\geq$ 40
Initial WBC count	$\leq$30K: 74% >30K: 36%
CNS leukemia at presentation	7% with $\geq$ 5 blasts

Toxicity Comparison: Induction Only

- 2% induction mortality rate (identical to COG AALL0232)
- Grade 3-5 toxicities only

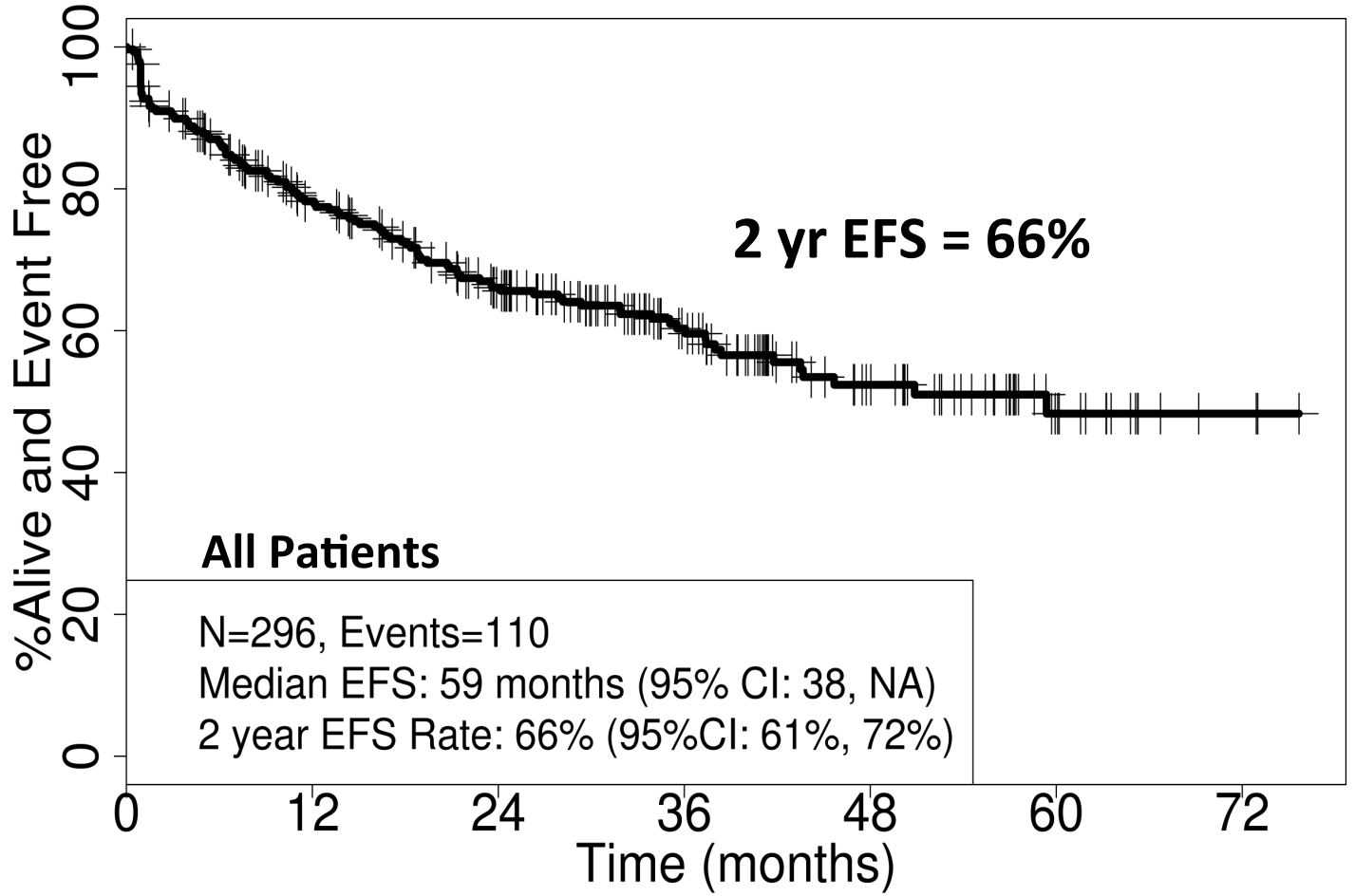
	C10403	COG 0232 16-29 yrs
Hyperglycemia	29.2%	22.0%
Bilirubin	16.4%	6.7%
AST/ALT	26.6%	N/A
Pancreatitis	1.1%	0.5%
Thrombosis/ CNS hemorrhage	3.0% 1.0%	1.5% N/A

Grade 3-5 Toxicities: All Treatment

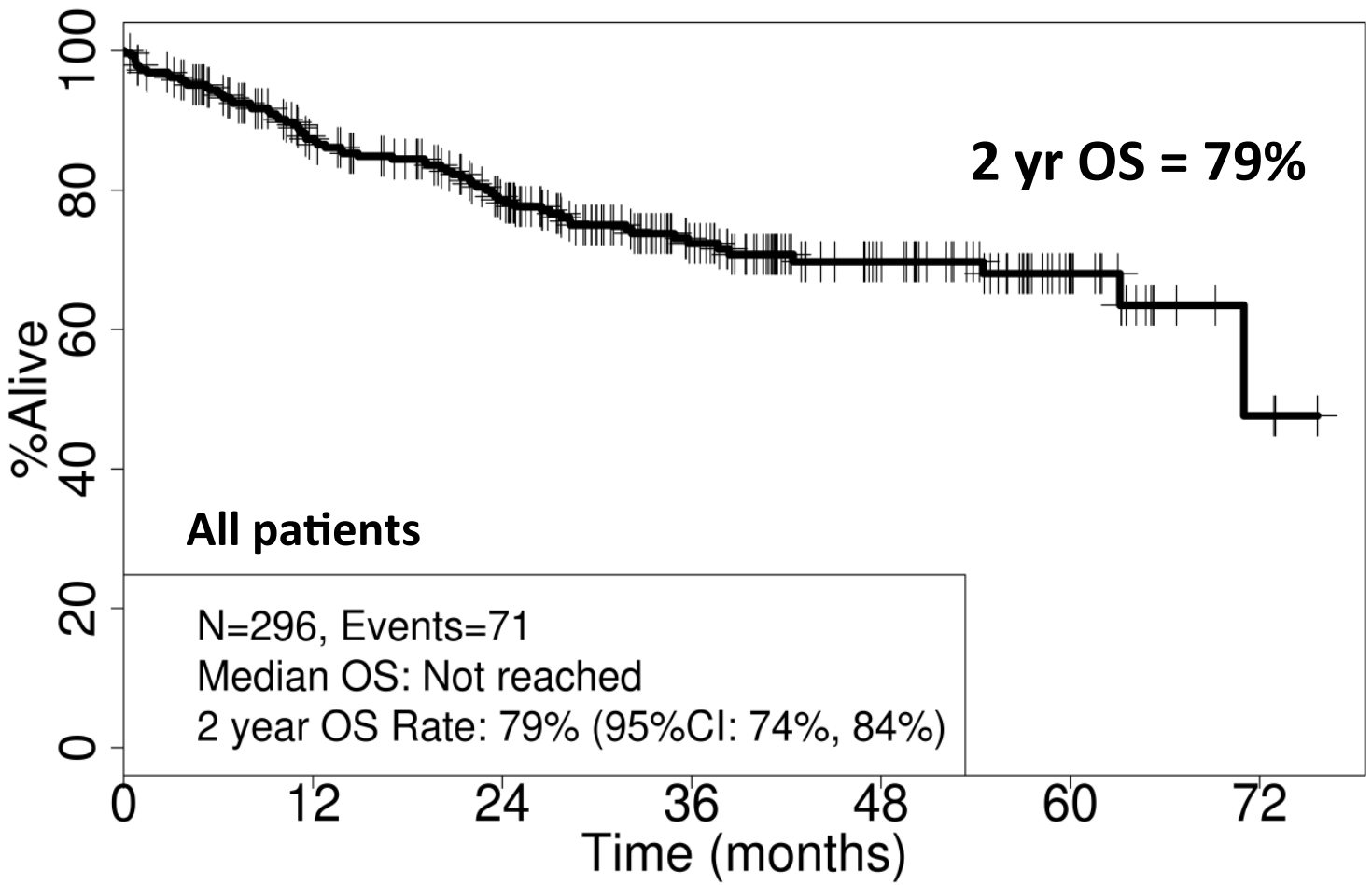
	10403	COG 0232 16-29 years
ALT/AST	54.3%	49%
Bilirubin	25.7%	25%
Pancreatitis	4.2%	3.8%
Neuropathy	15.7%	11.4%
Osteonecrosis	2.5%	3.2%
Hypersensitivity	9.6%	19%

Overall, treatment related mortality was 3%

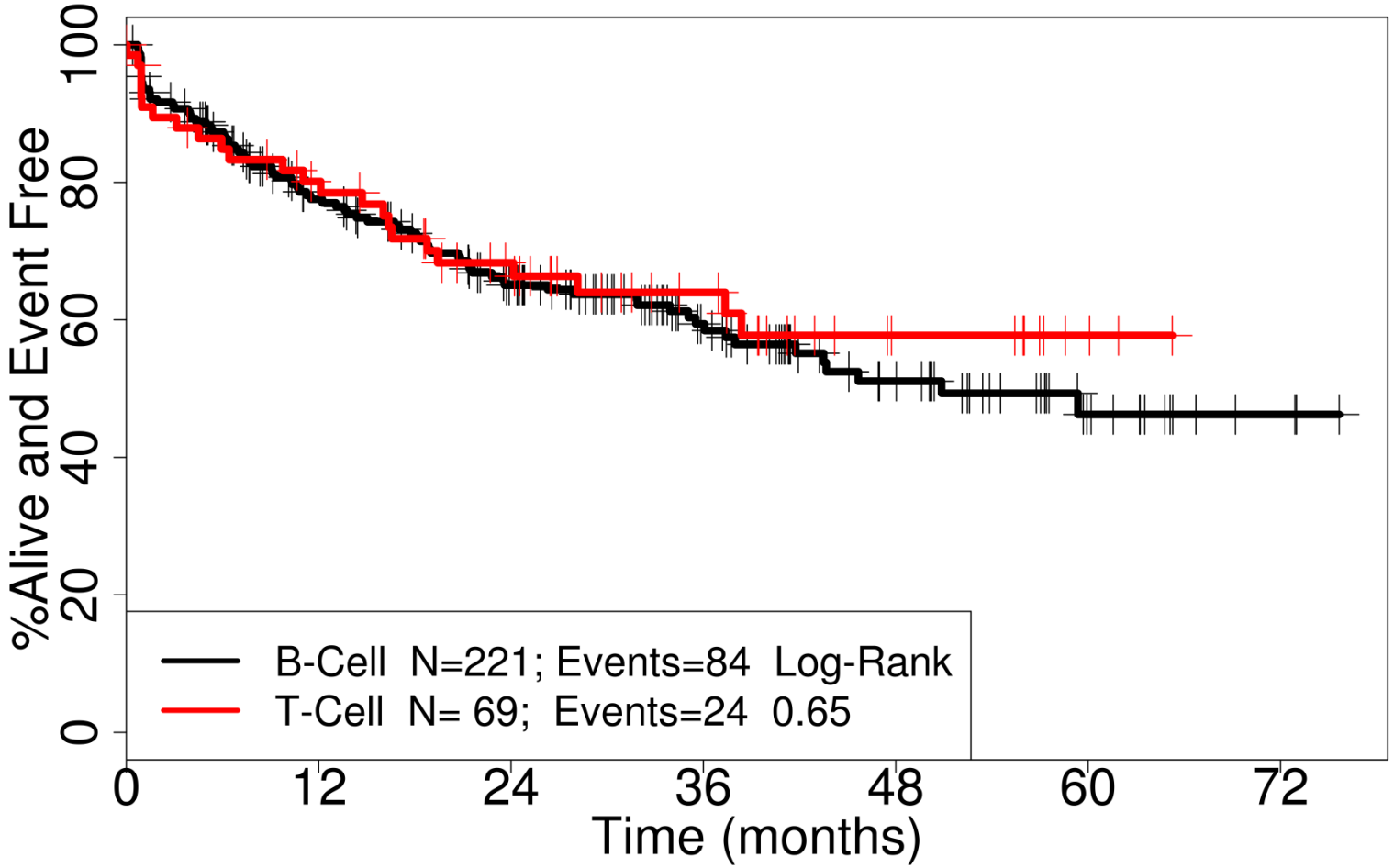
Event Free Survival



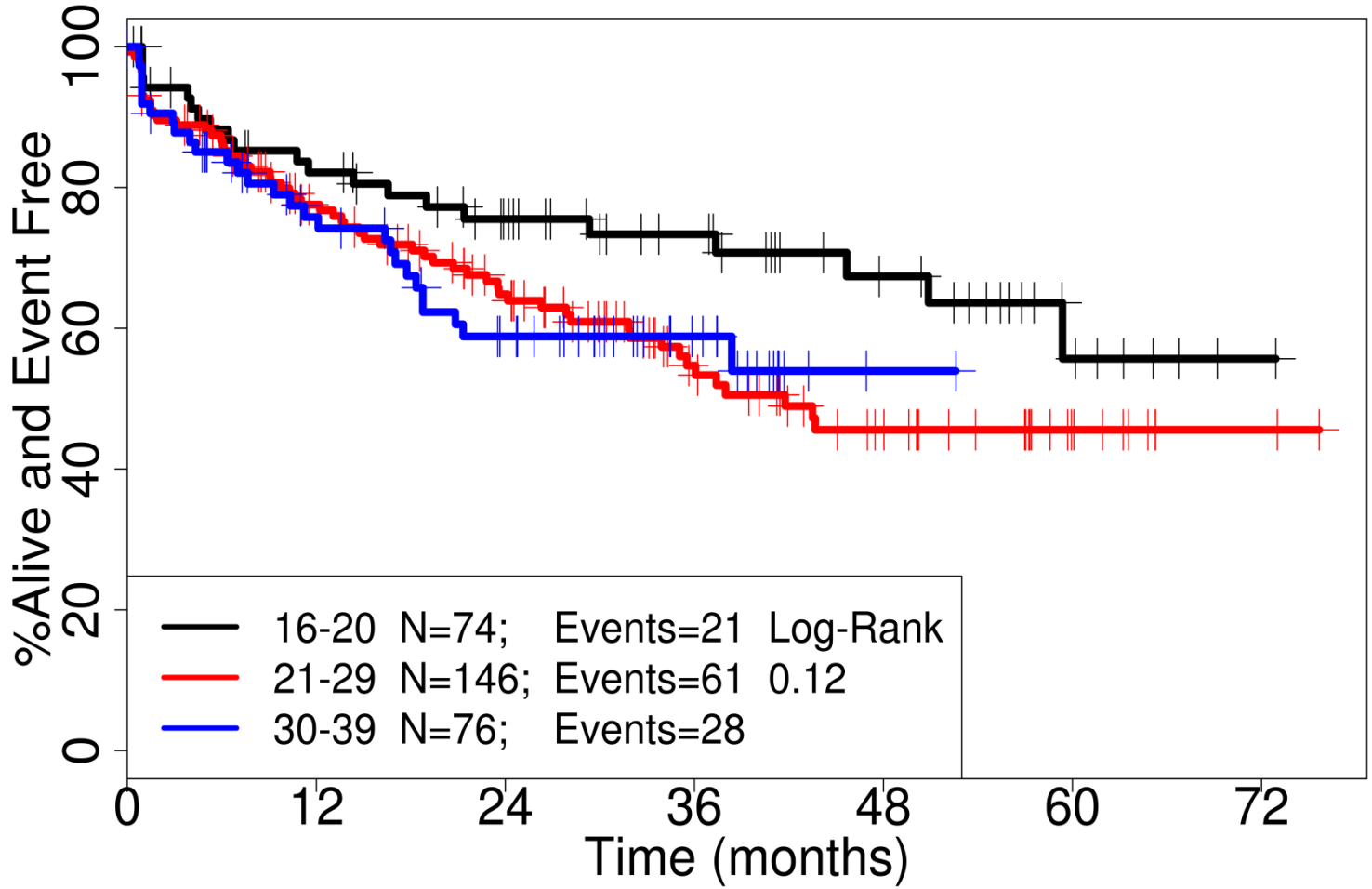
Overall Survival



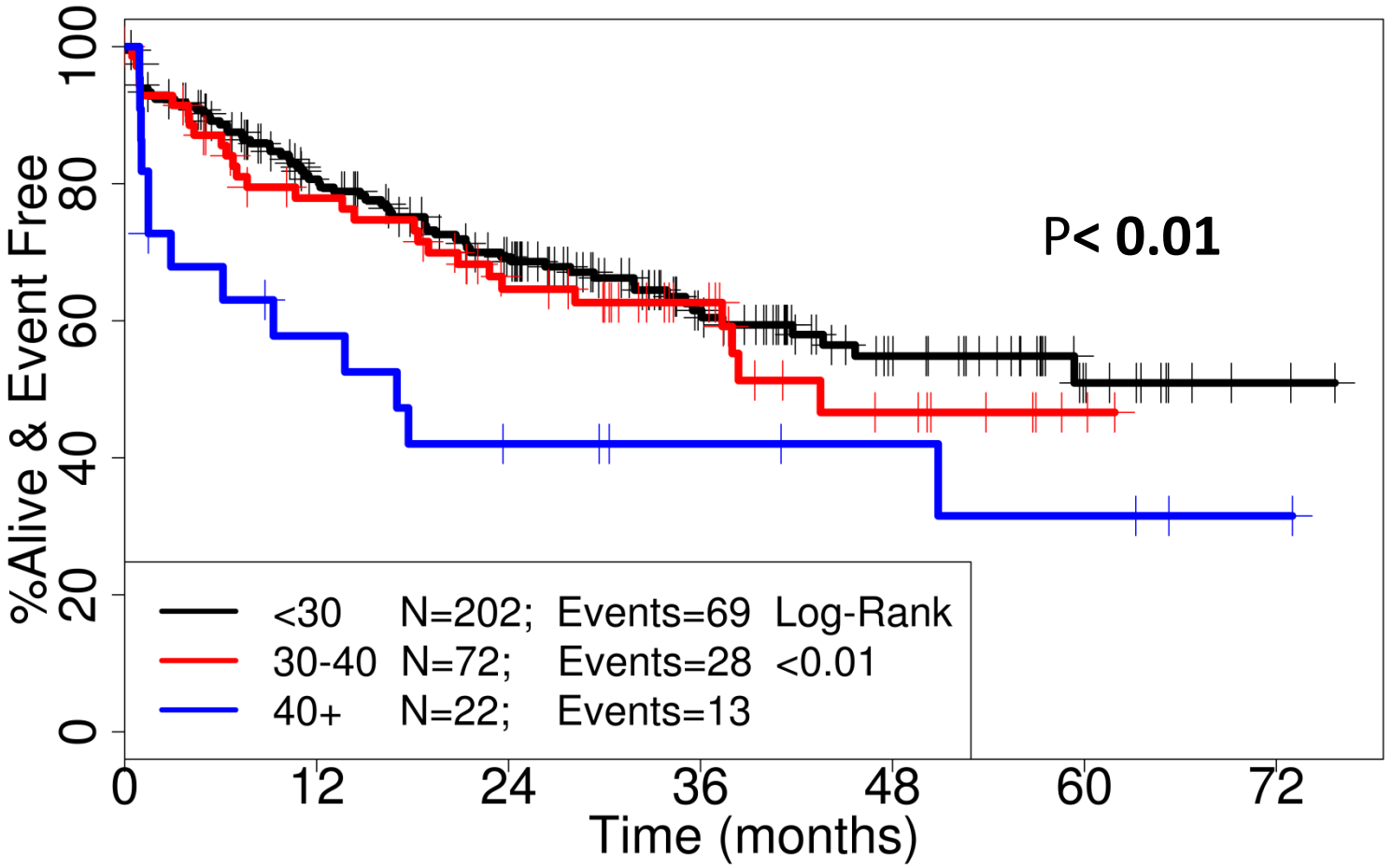
EFS Equivalent for B and T-Precursor ALL



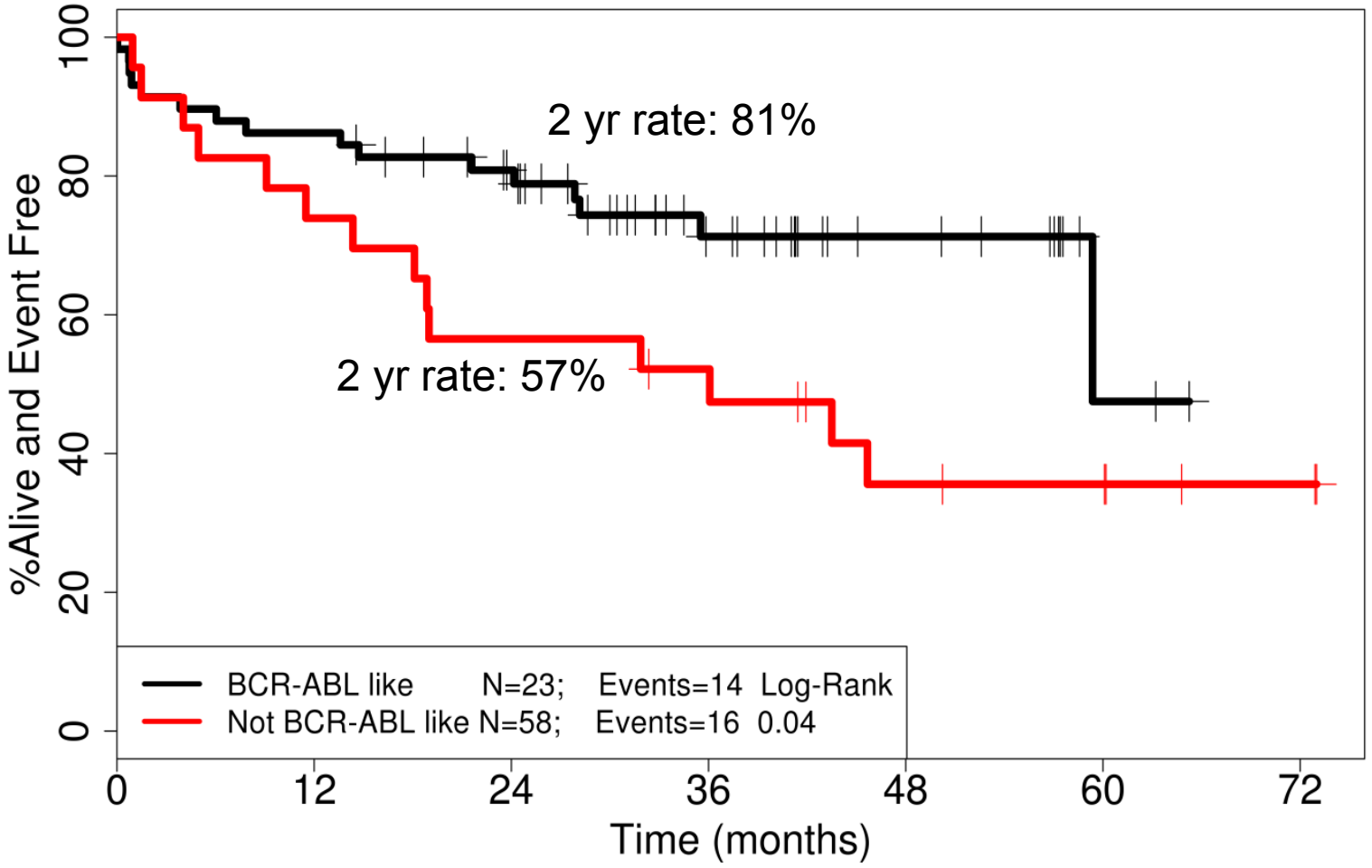
No difference in EFS by AYA age group



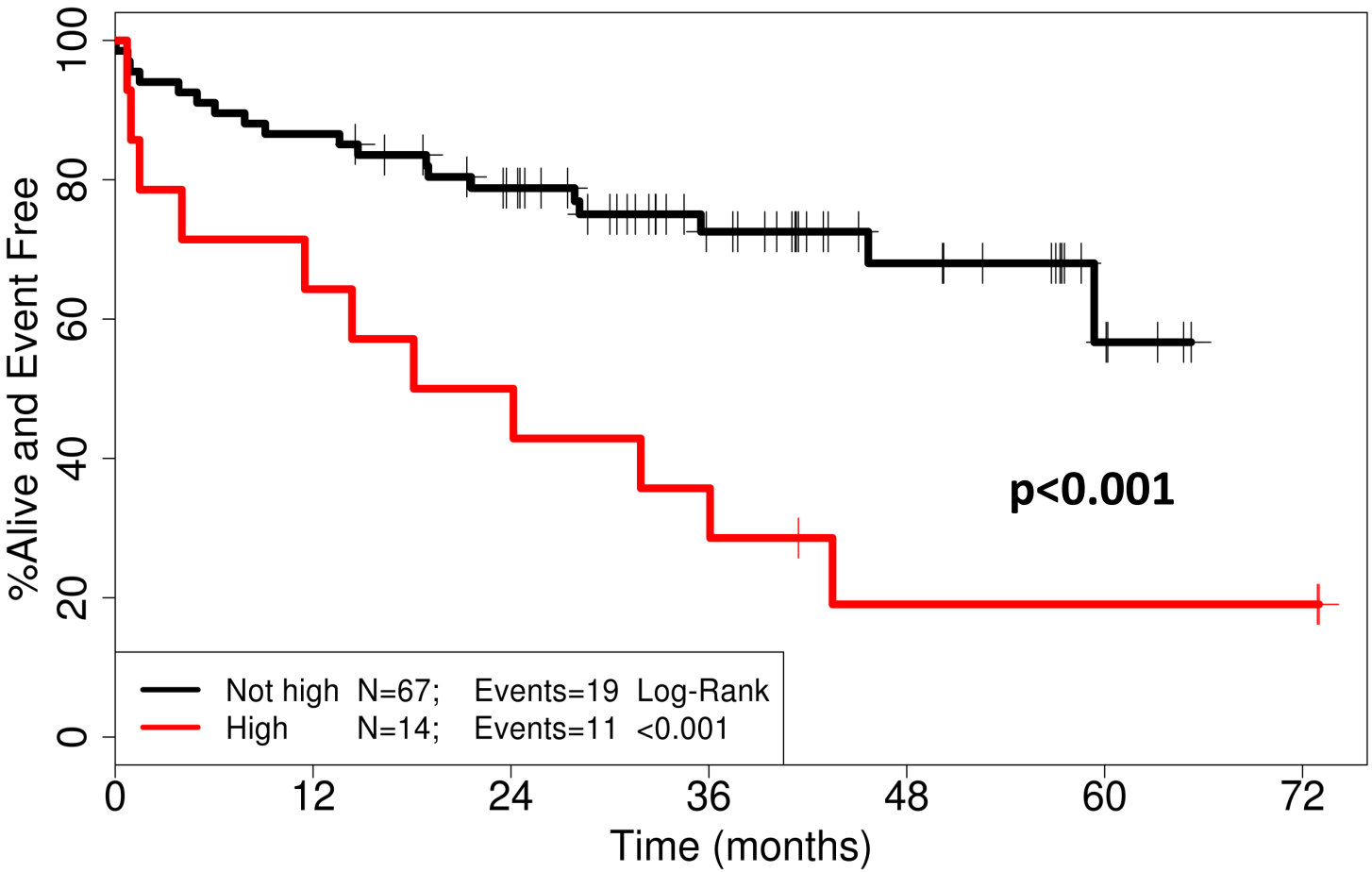
Morbid Obesity Associated with Poor EFS



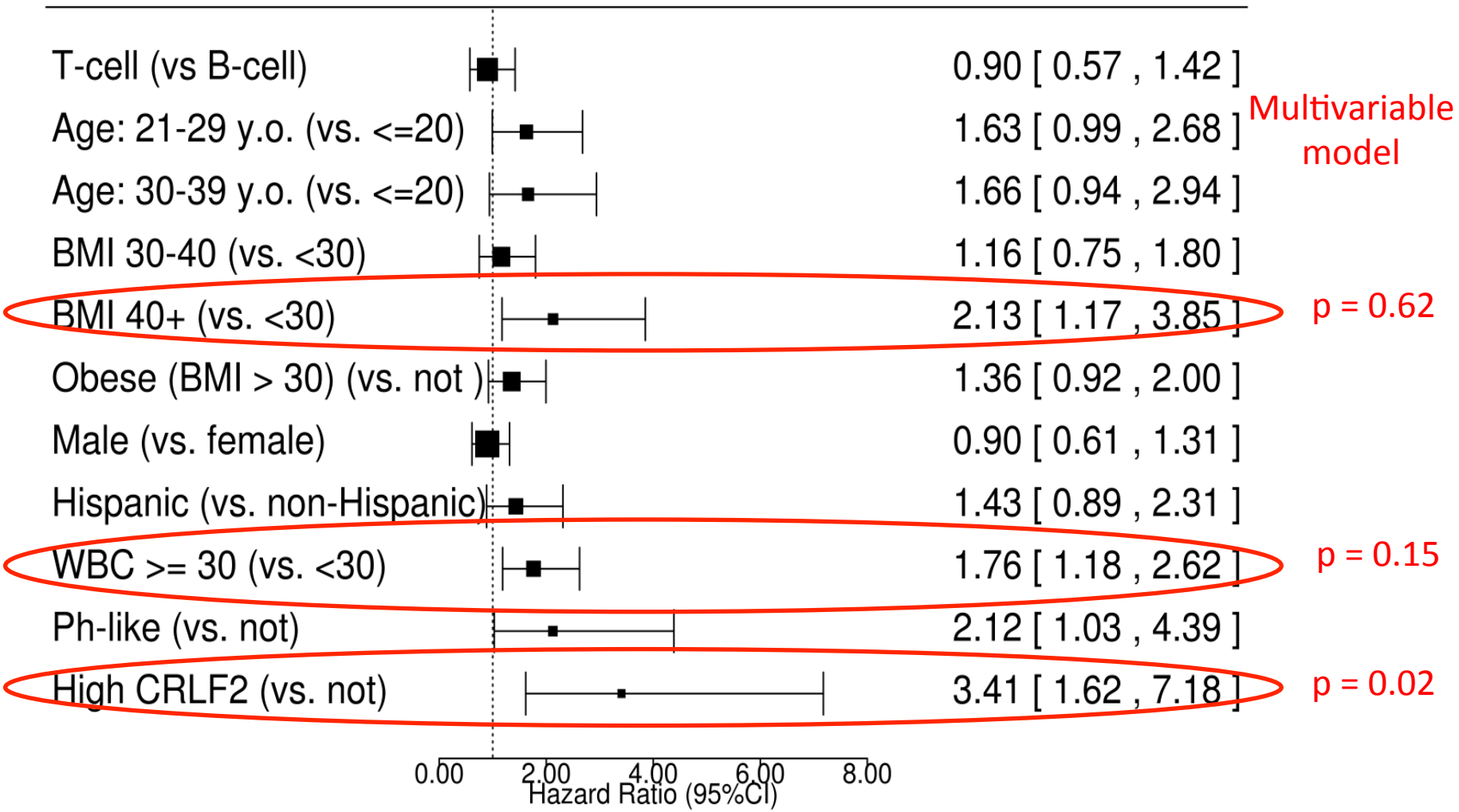
BCR-ABL1 like signature occurs in 28% of 10403 patients and is associated with poor EFS



Aberrant *CRLF2* Expression: Associated with Poor EFS



Univariate Analyses : Event Free Survival



Univariate Analyses: Overall Survival

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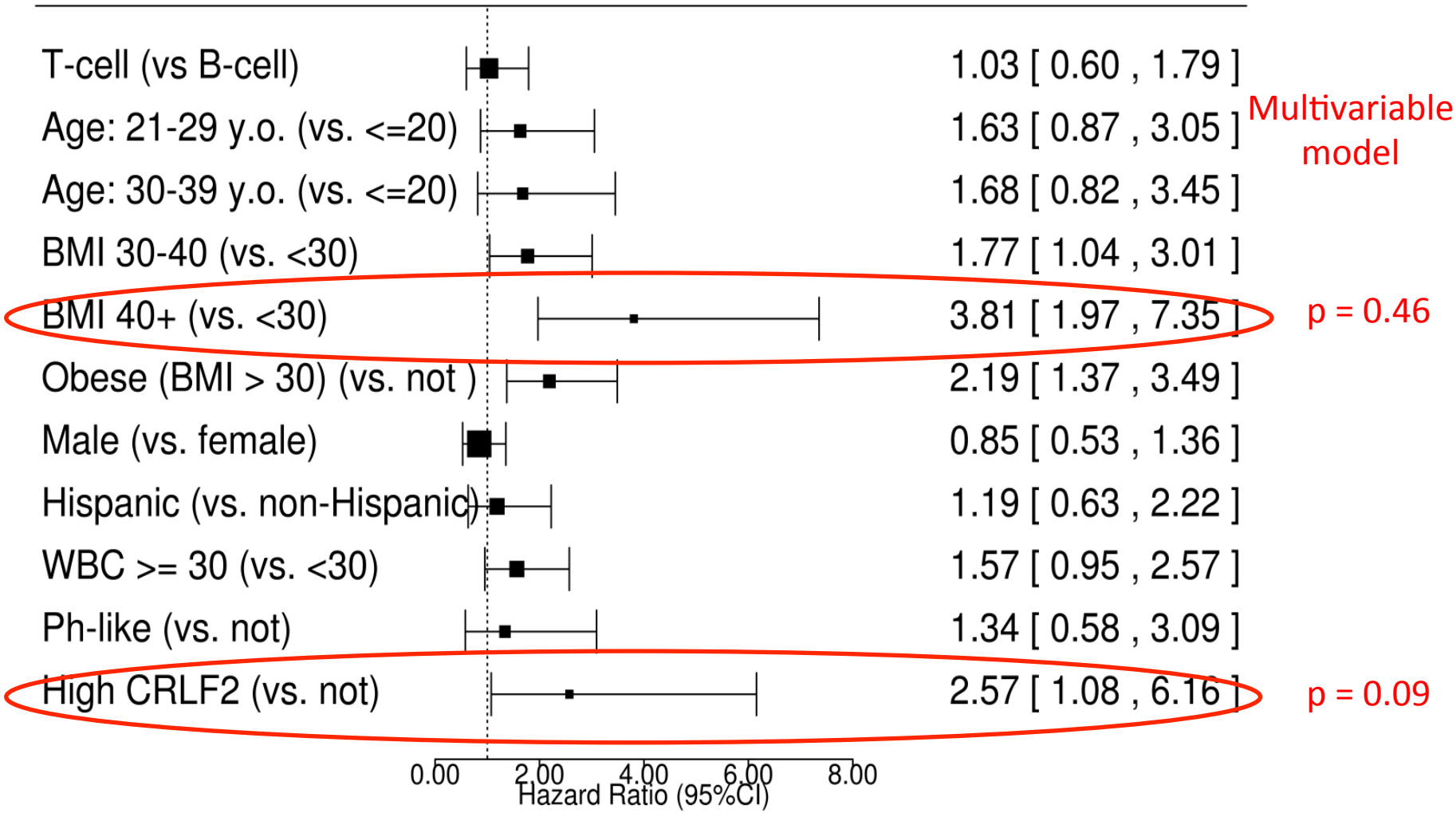
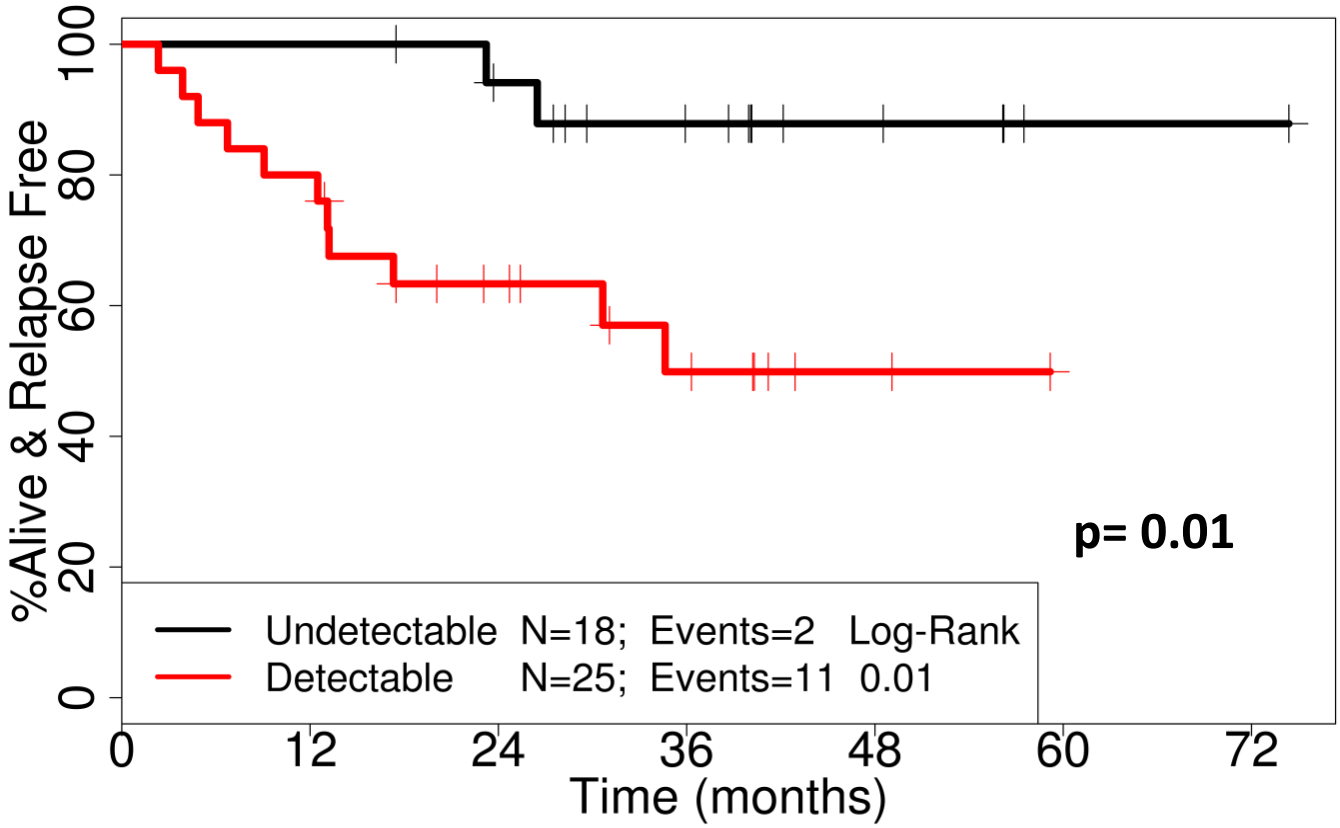


Absence of MRD using Q-PCR after Induction: Associated with Excellent DFS



Lessons Learned

- Intergroup collaboration highly successful
  - Bi-monthly calls for the duration of the study
- Low treatment related mortality; toxicities similar to COGAALL0232 AYAs (majority 16-21 years old)
- More work needed to optimize PEG-asp dosing in AYAs with ALL
  - Reduce dose but still achieve adequate depletion?
    - May be most important during induction cycle
    - Obesity issue?
  - Important insights will be obtained in the future from study of asparaginase levels
    - Now routinely available as CLIA/CAP approved test
    - Will also detect silent inactivation if it occurs

C10403: Conclusions

- Pediatric ALL regimen administered by adult hematologists/oncologists validated in large North American intergroup trial
- 2 year EFS of 66% and OS of 79% is a major improvement compared to 34% EFS historical controls in CALGB
  - Median EFS of 59 months allows for rejection of null hypothesis in this Phase II trial that true EFS is 32 mos
  - Longer follow-up to confirm the survival benefits
- Outcomes similar to other prospective international studies of pediatric regimen in AYAs
  - ***Ribera, J Clin Oncol 2008,26:1843; Huguet, J Clin Oncol 2009 27:911; Deangelo, Leukemia 2014 (epub); Gokbuget ASH 2013, abstract 839***

Conclusions

- In multivariable analysis, aberrant *CRLF2* was associated with both worse EFS and OS
- Presence *of BCR-ABL1* like signature (and *CRLF2* overexpression) is common and associated with significantly worse survival
  - Excellent EFS, OS if these features not present
- Absence of MRD following induction therapy associated with excellent DFS

Future Directions

- C10403 will serve as foundation for future studies in AYA ALL in US Intergroup
  - New Standard of Care

- Goal of future study: Incorporate new targeted antibodies, kinase inhibitors

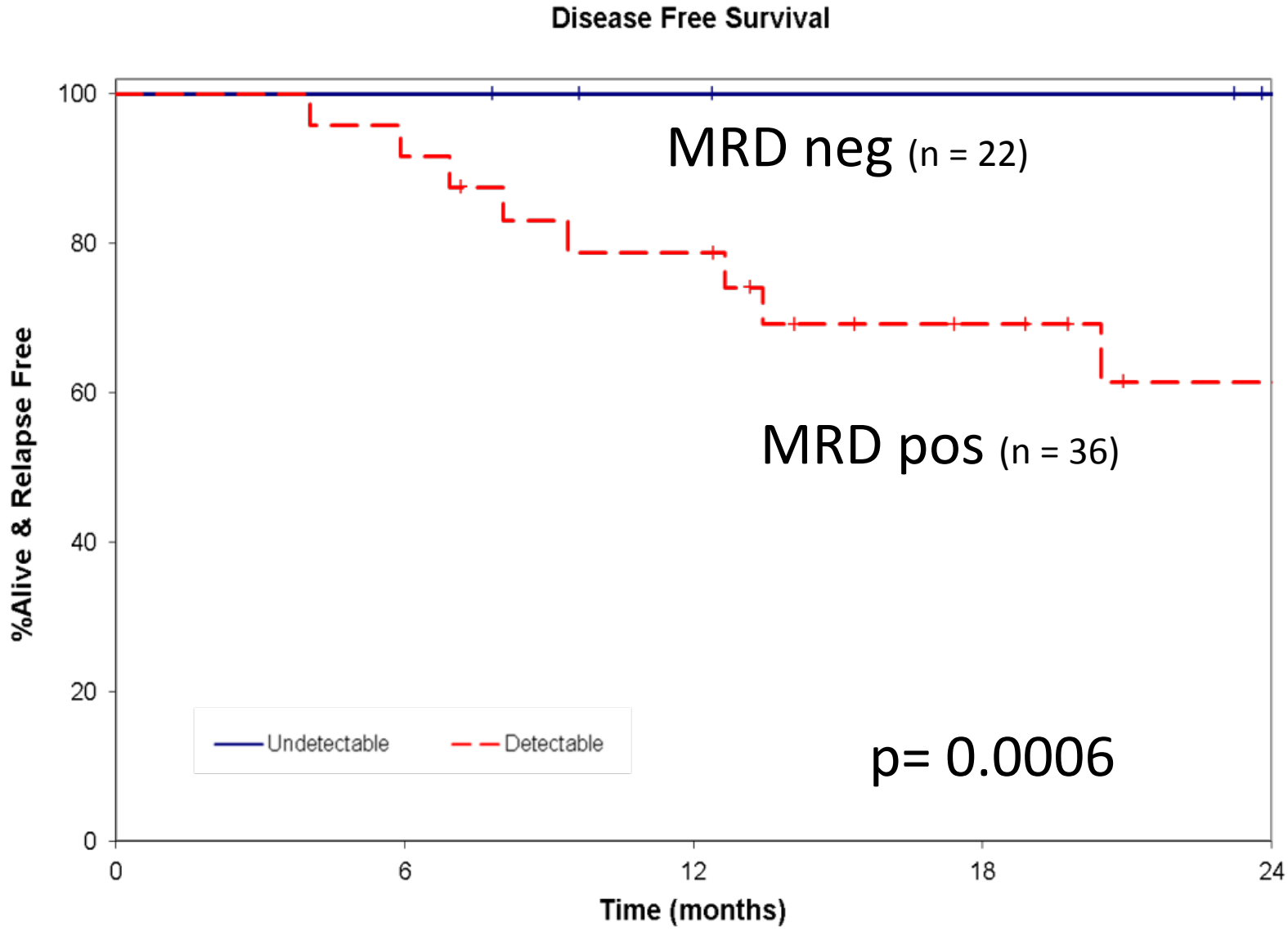
- Eradicate MRD and result in further improvements in survival for AYA ALL

Grateful Acknowledgements:

Patients and caregivers
Nurses and Practitioners
CRAs
Sigma Tau for correlative sciences support

Jim Nachman MD, 1948- 2011

Post-induction MRD in BM: Strong Predictor of DFS



Overall Survival Worse for Obese Patients