

Biometrische Aspekte der Studien zur akuten myeloischen Leukämie: Sequentielle Verfahren und Evaluation prognostischer Faktoren

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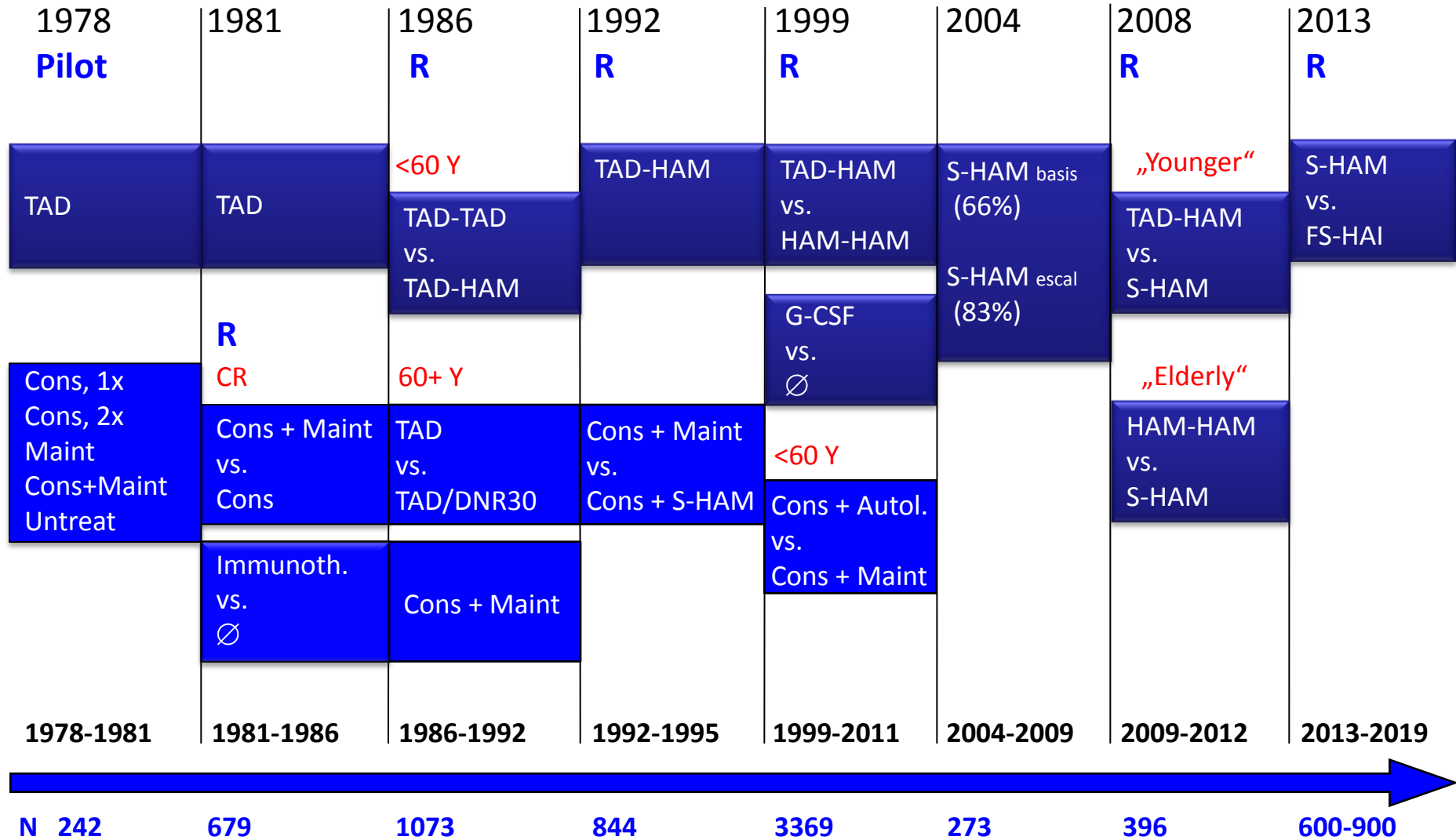
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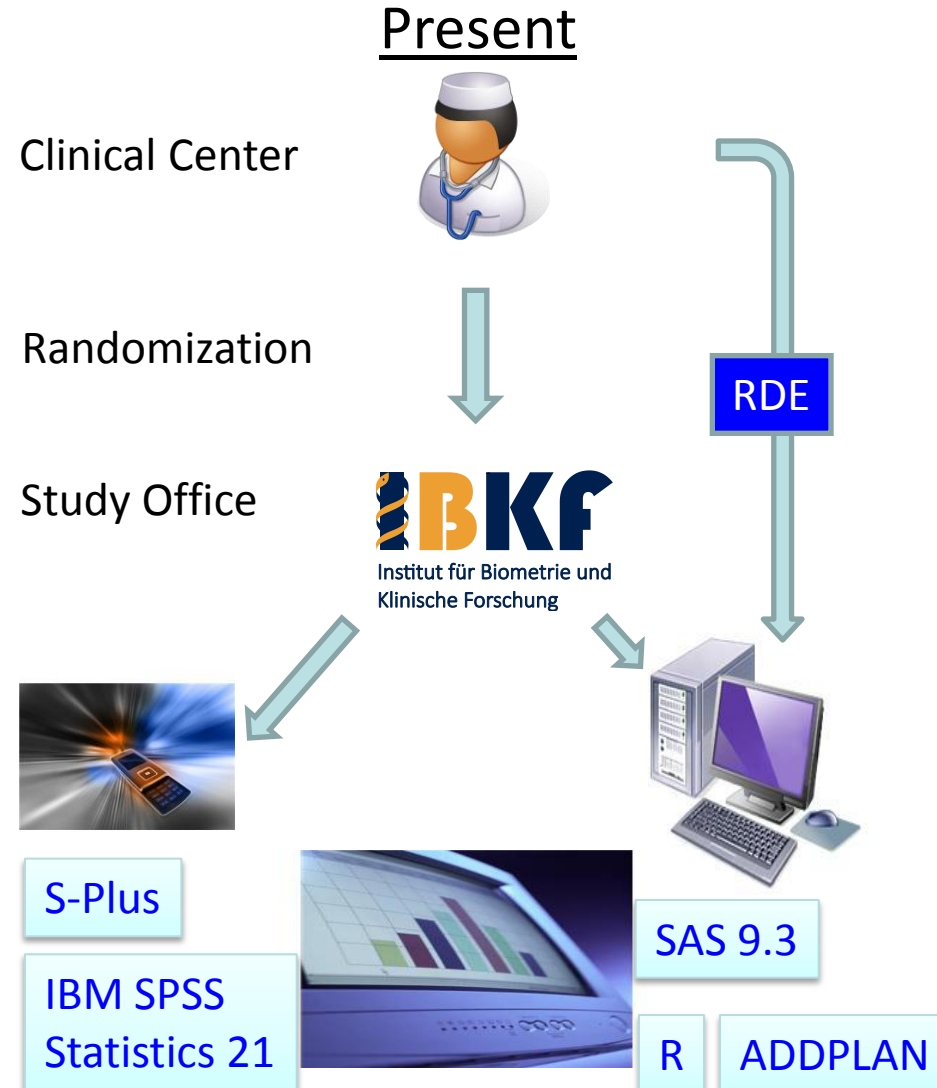
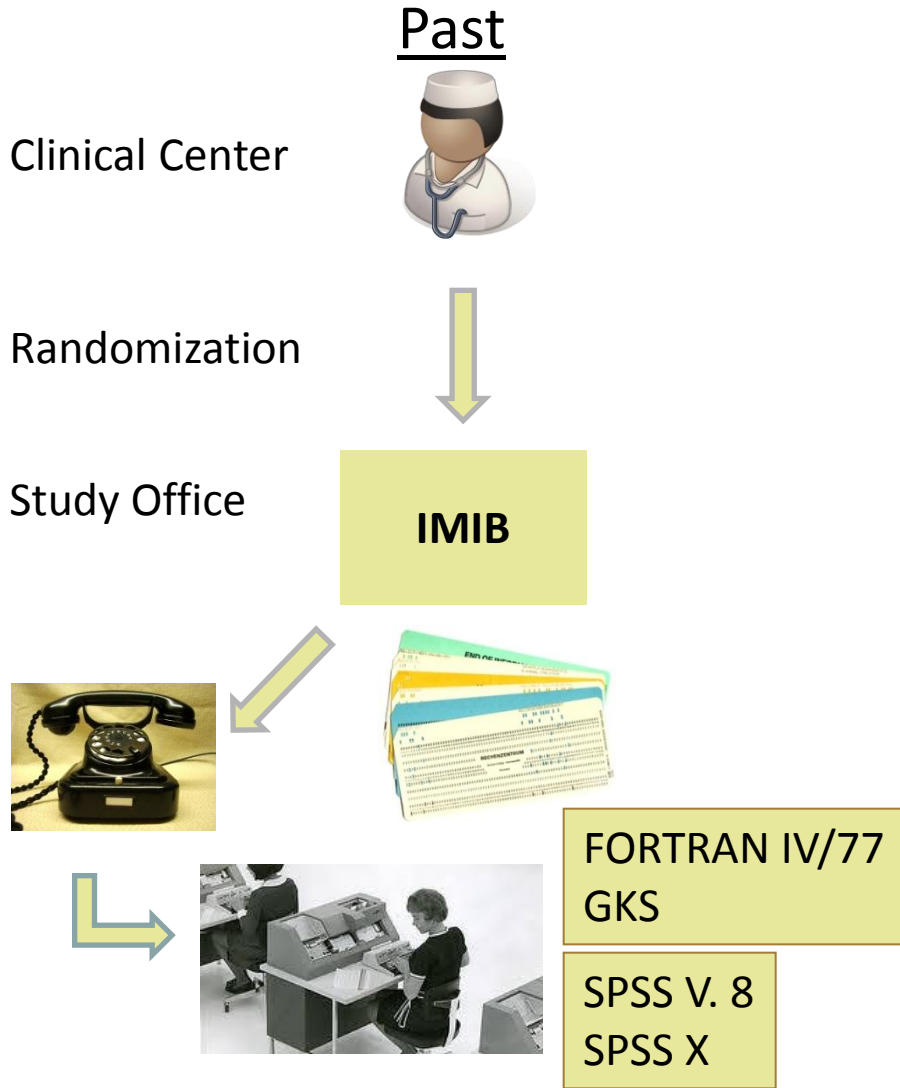
1. AMLCG Trials since 1981
2. Randomization: Past and Present
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4. Identification of Prognostic Factors (AMLCG 81-92)
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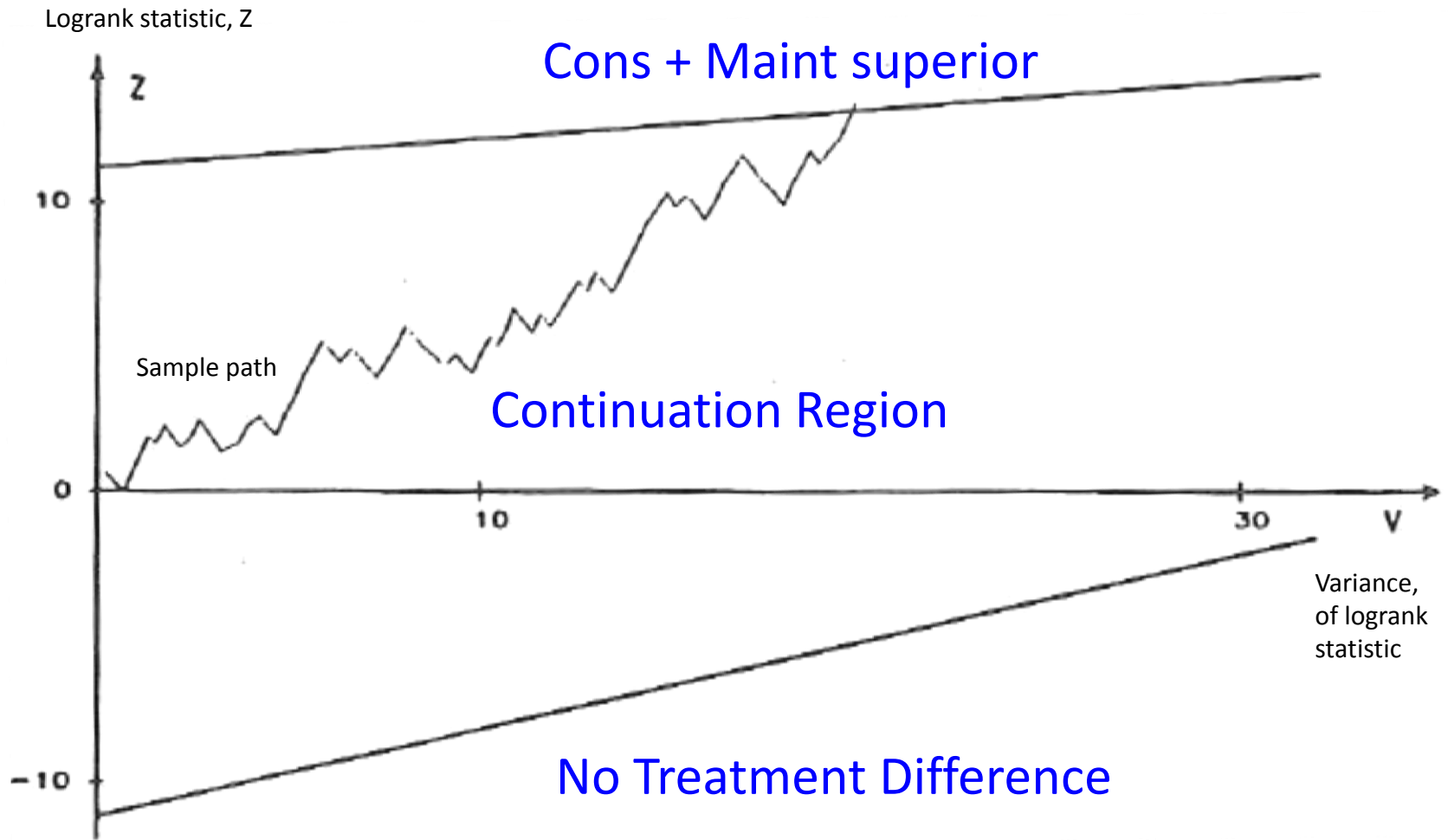
AMLCG Trials since 1981



Randomization: Past and Present



AMLCG 81 – A Sequential Test



Heinecke et al., Haematol Blood Transfus 1990;33:285-9

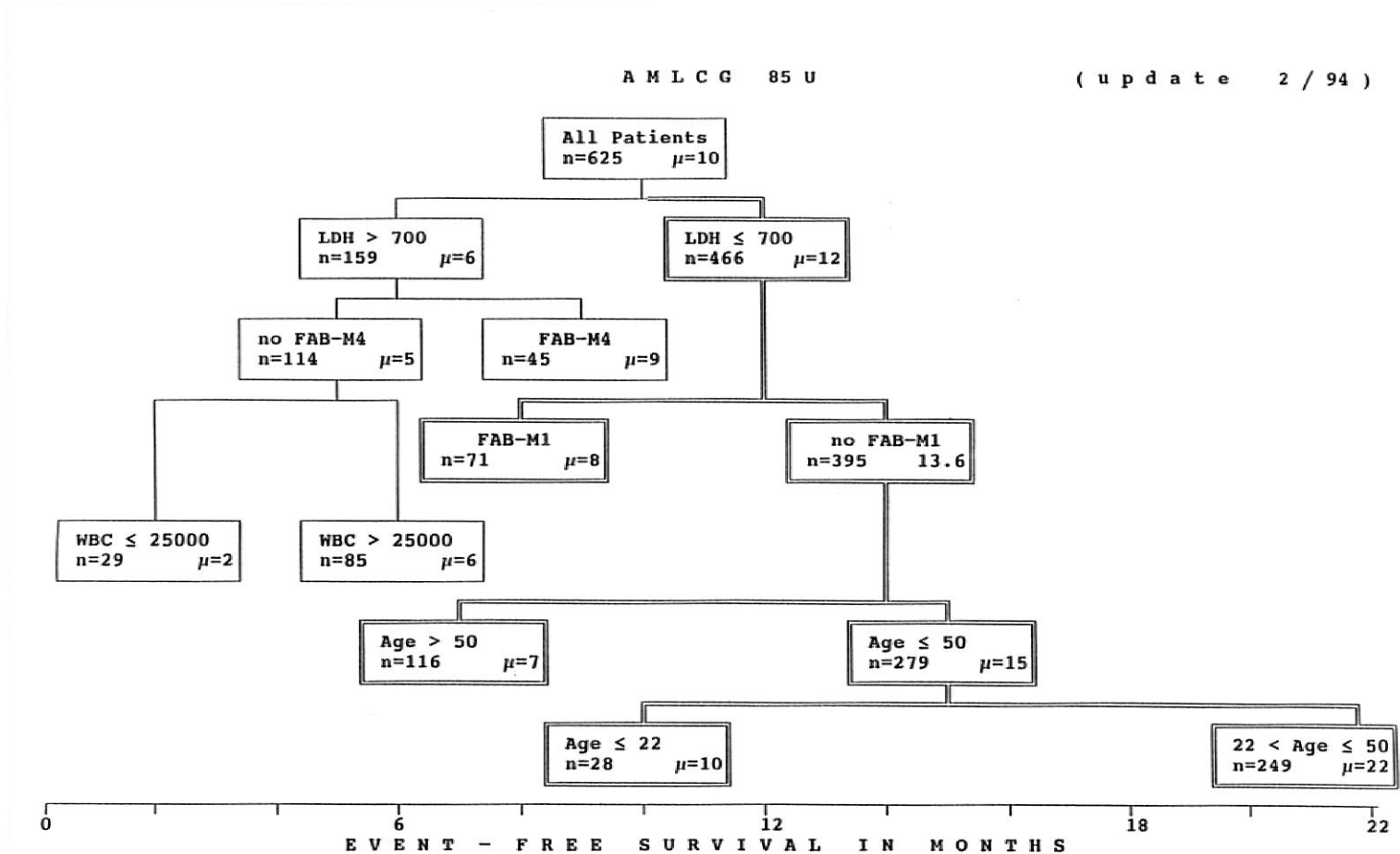


A test with the same α (0.05) and $1-\beta$ (0.95) but **fixed sample size** would have required at least **200** patients. 100 for each therapy. So, in this case the use of the **sequential procedure saved** about **40** randomizations.

Heinecke et al., Haematol Blood Transfus 1990;33:285-9

Identification of Prognostic Factors (AML CG 81-92) ⁷

- CART (Classification And Regression Trees)



Heinecke et al., Blood 1994;1:A310

Regression analysis – Findings

- **Age** at start of therapy
- Performance status at diagnosis (**ECOG**)
- Morphological classification (**FAB**)
- Initial serum concentration of lactate dehydrogenase (**LDH**)
- Initial leucocytes (**WBC**)
- Adequate marrow blast reduction (**BM blasts reduction**)
- **Karyotype** (cytogenetic analysis)
- **ELN Risk** (cytogenetic and molecular analysis)

Background

- Prediction of Complete Remission (CR) and risk of Early Death (ED) after intensive induction chemotherapy in pts. age ≥ 60 Y with acute myeloid leukaemia

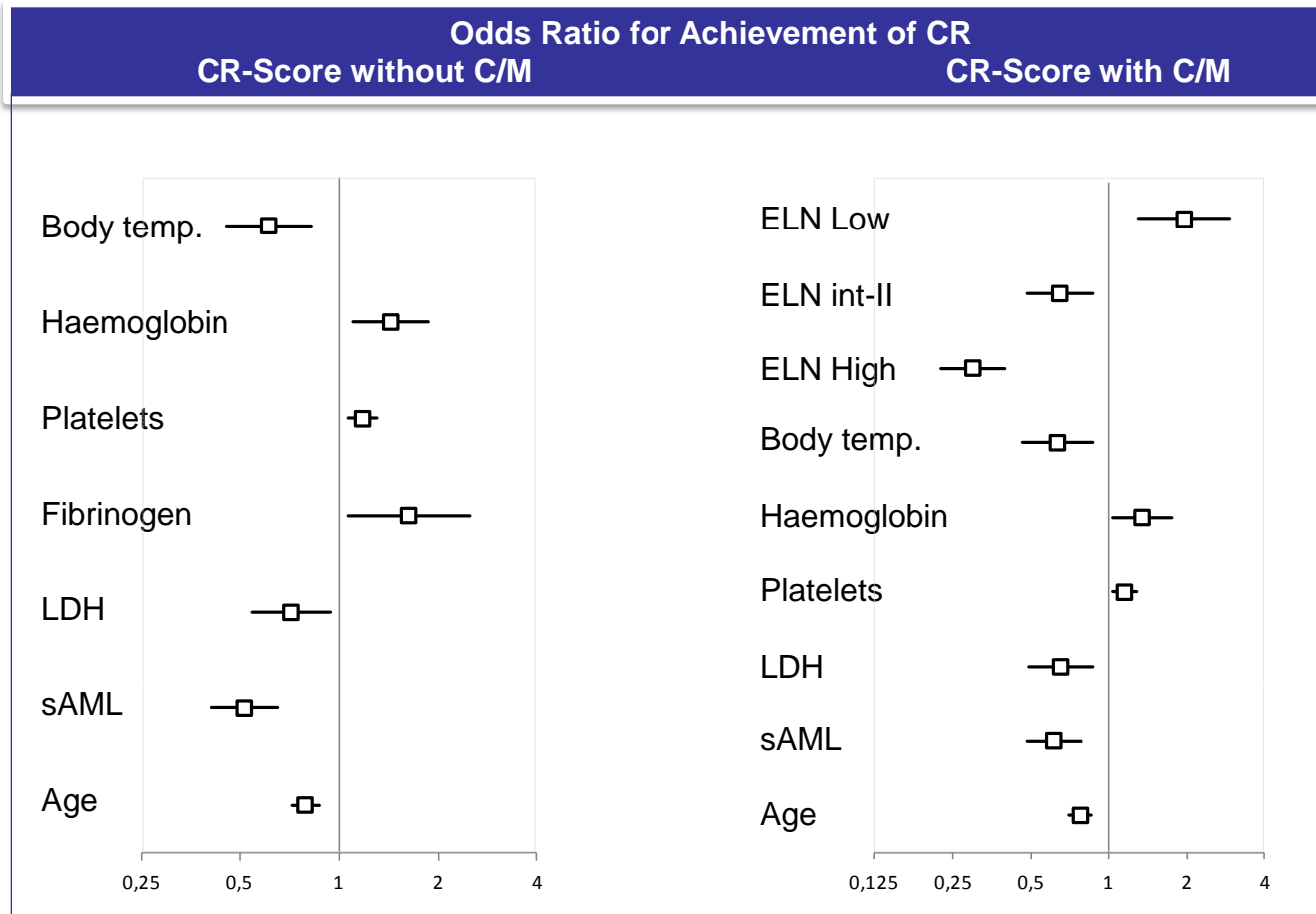
Methods

- Cohort of 1406 pts. (aged ≥ 60 y) treated in AMLCG 99 Trial
- Web-based application
- External validation in 801 pts. (aged > 60 y) in AML 96 Trial (SAL)

Statistical Analysis

- Logistic regression with stepwise selection independently for CR and ED, without and with knowledge of cytogenetic and molecular risk

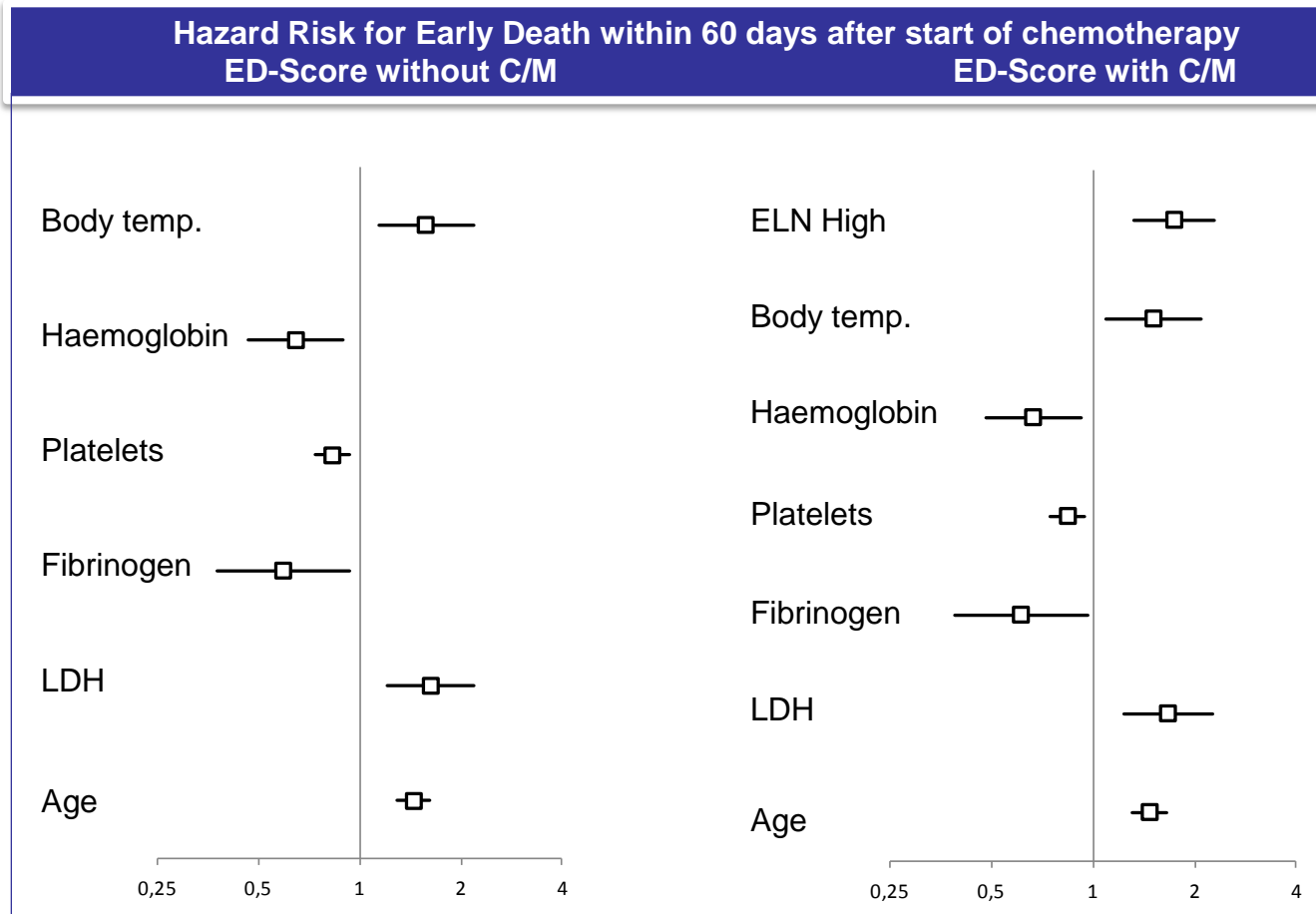
- CR-Score



mod. acc. to Krug U et al., Lancet 2010;376:2000-8

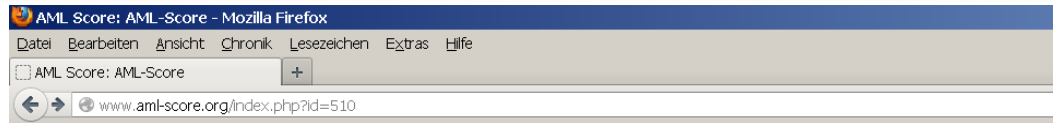


- ED-Score



mod. acc. to Krug U et al., Lancet 2010;376:2000-8





AML-SCORE for estimating the chance of a complete remission and the risk of an early death in elderly patients with acute myeloid leukemia (AML) after intensive induction therapy.



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AML-Score

Please select the following pretherapeutic parameters for the AML risk score prediction.
[Click here for more information about AML risk prediction](#)

Parameter	Unit	
Body temperature	<input checked="" type="radio"/> Celsius	>38°C
	<input type="radio"/> Fahrenheit	≤100.4°F
	<input type="radio"/> unknown	
Hemoglobin (before blood transfusion)	<input checked="" type="radio"/> g/dl	≤10.3
	<input type="radio"/> mmol/l	≤6.4
	<input type="radio"/> unknown	
Platelets (before platelet transfusion)	<input type="radio"/> G/l	≤28
	<input checked="" type="radio"/> per μ l	>104,000
	<input type="radio"/> unknown	
Fibrinogen	<input checked="" type="radio"/> mg/dl	>150
	<input type="radio"/> g/dl	≤0.15
	<input type="radio"/> g/l	≤1.5
	<input type="radio"/> μ mol/l	≤4.41



AML Score: AML-Score - Mozilla Firefox

AML Score: AML-Score

www.aml-score.org/index.php?id=510

UKM
Universitätsklinikum
Münster

SAL
Study Alliance
Leukemia
AML CG

AML-SCORE for estimating the chance of a complete remission and the risk of an early death in elderly patients with acute myeloid leukemia (AML) after intensive induction therapy.

AML-Score

You selected the following input parameter:

Body temperature:	>38°C
Hemoglobin:	≤10.3 g/dl
Platelets:	>104,000 per µl
Fibrinogen:	>150 mg/dl
LDH:	≤700 U/l
Age:	65-67 years
Type:	de novo
Cytogenetic / molecular risk:	intermediate normal (NPM1 unknown; FIt3 unknown)

Based on these input parameters, the following scores were calculated:

The chance for the achievement of a complete remission after intensive induction therapy is	
Complete remission [%]	64.1
The risk of an early death within 60 days after start of an intensive induction therapy is	
Early death [%]	17.8

Primary Objective

- ORR (Overall Response Rate)
- 15% increase in the CR/CR_i rate by S-HAM versus TAD – HAM for younger patients / HAM (– HAM) for elderly patients
- One-sided Sequential Truncated Probability Ratio Test (Whitehead)

Hypothesis

$$H_0 : ORR(Standard) \geq ORR(S - HAM)$$

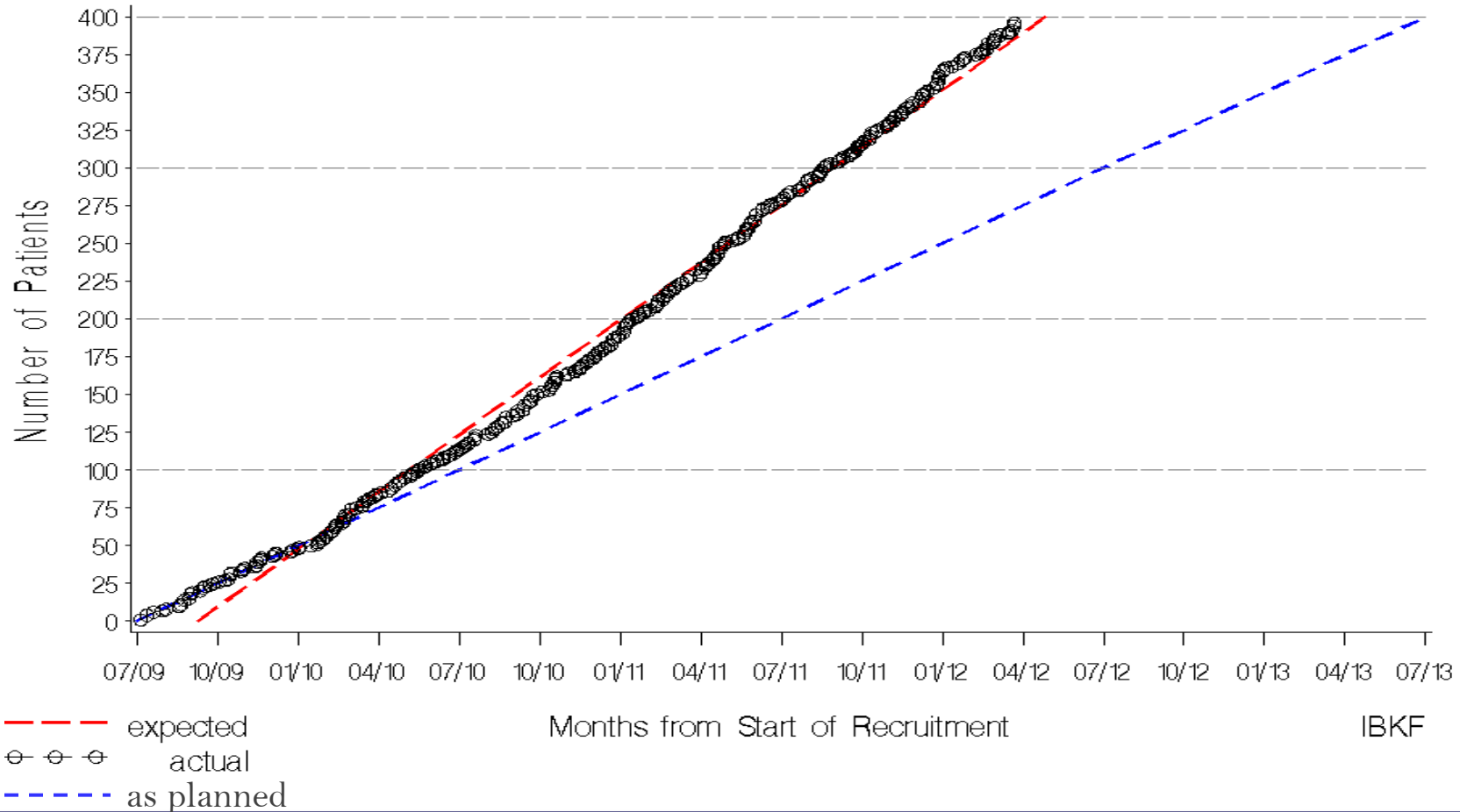
$$H_1 : ORR(Standard) < ORR(S - HAM)$$

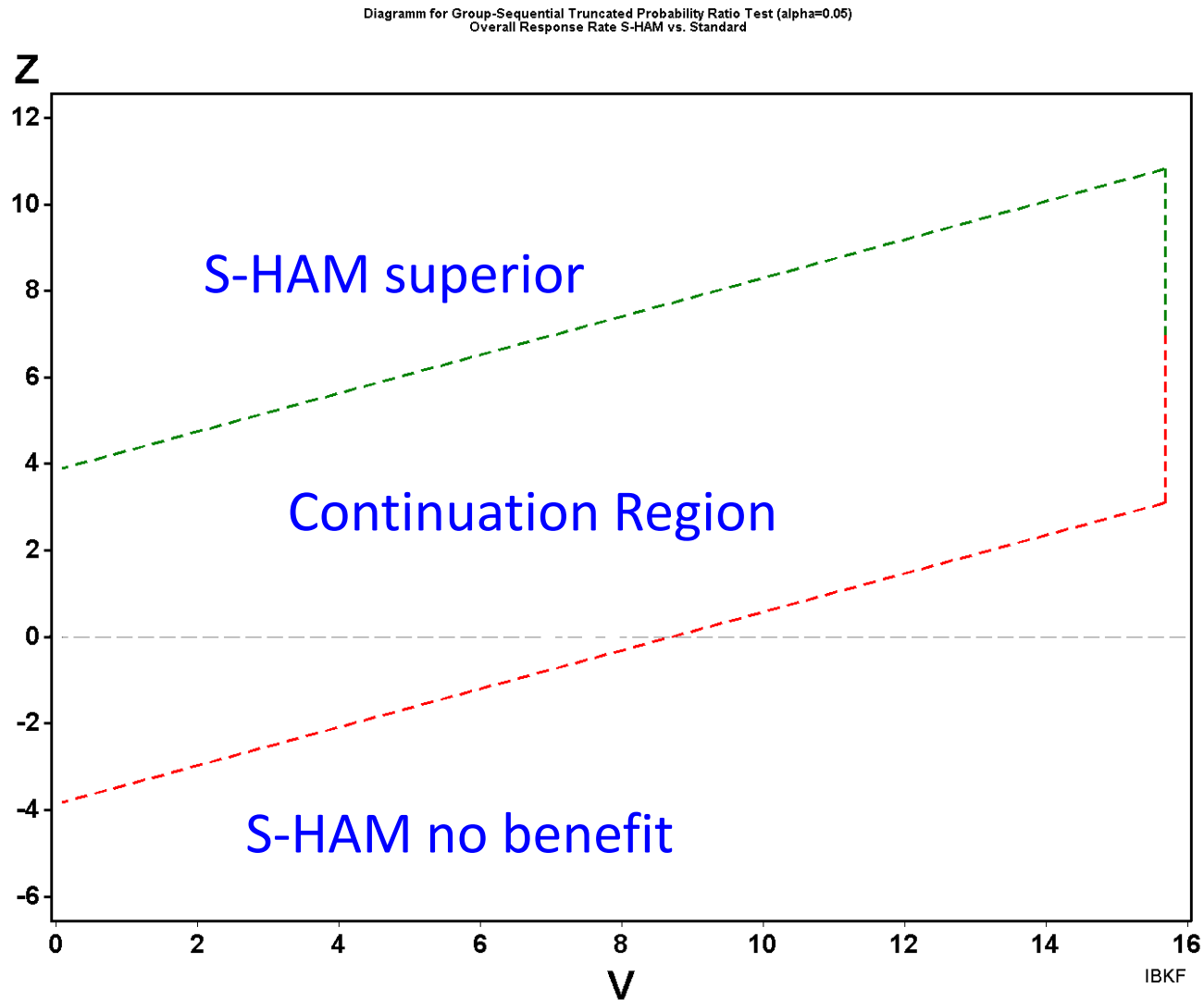
Sample Size

- ORR: Standard (70%) vs. S-HAM (85%)
- $1 - \beta = 0.95$ $\alpha = 0.05$
- N = 400 pts. (200 per arm)

AML–CG–2008

Randomized Patients, Expected Randomizations





- Up to now, the **most important prognostic factors** were patient's **age at diagnosis** and the **cytogenetic risk**
- Suitable **scoring systems** can be used to reliably estimate the **prognosis** for patients with acute myeloid leukemia
- **Group sequential designs** allowing the decision to **stop** the trial (futility/benefit) or **continue**, but with **restriction** of determining the required sample size **before** start of study
- **Solution: flexibility of adaptive designs** in ongoing survival trials
Adaptation of the **sample size, study design, study objective**
⇒ **AMLCG 2013 Trial**

- Büchner T, Urbanitz D, Hiddemann W et al (1985): Intensified Induction and Consolidation With or Without Maintenance Chemotherapy for Acute Myeloid Leukemia (AML): Two Multicenter Studies of the German AML Cooperative Group. *Journal of Clinical Oncology, Vol 3, No 12, 1583-1589.*
- Büchner T, Hiddemann W, Berdel W, Wörmann B et al (2003). 6-Thioguanine, Cytarabine, and Daunorubicin (TAD) and High-Dose Cytarabine and Mitoxantrone (HAM) for Induction, TAD for Consolidation, and Either Prolonged Maintenance by Reduced Monthly TAD or TAD-HAM-TAD and One Course of Intensive Consolidation by Sequential HAM in Adult Patients at All Ages With De Novo Acute Myeloid Leukemia (AML): A Randomized Trial of the German AML Cooperative Group. *J Clin Oncol. 15;21(24): 4496-504.*
- Büchner T, Hiddemann W, Blasius S, Koch P, Maschmeyer G et al. (1990). Adult AML: The Role of Chemotherapy Intensity and Duration. Two Studies of the AML Cooperative Group. *Haematol Blood Transf. 33: 261-6.*
- Büchner T, Hiddemann W, Wörmann B et al. (1999). Double Induction Strategy for Acute Myeloid Leukemia: The Effect of High-Dose Cytarabine with Mitoxantrone Instead of Standard-Dose Cytarabine with Daunorubicin and 6-Thioguanine: A Randomized Trial by the German AML Cooperative Group. *Blood, Vol 93, No 12 (June 15) 4116-4124.*
- Büchner T, Berdel WE, Haferlach C, et al. (2009). Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol; 27: 61-69.*
- Büchner T, Berdel WE, Schoch C, et al. (2006). Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia *J Clin Oncol; 24: 2480-89.*
- Cox DR (1972). Regression models and life tables. *J R Stat Soc (B) 34: 187-220.*

- Heinecke A, Sauerland MC, Büchner T (1990). Predictive Models for Achievement of Complete Remission and Duration of First Remission in Adult Acute Myeloid Leukemia. *Haematology and Blood Transfusion 33, Acute Leukemias II*, 285-289
- Heinecke A, Sauerland MC, Büchner T (1990). Sequential decision strategy of the AML Cooperative Group studies. *Haematol Blood Transf. 1990;33:290-4*.
- Heinecke A, Sauerland MC, Büchner T (1994). CART – A Method to detect prognostic subgroups in AML. *Blood 84 Suppl. 1, A310-A310*
- Jones D.R., Newman CE, Whitehead J. (1982). The Design of a sequential clinical trial for the comparison of two lung cancer treatments. *Statistics in Medicine, Vol.1, 73-82*.
- Kaplan EL, Meier P (1958). Non-parametric estimation from incomplete observations. *J Am Stat. Assoc 53:457*.
- Krug U, Röllig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, Thiede C, Kramer M, Braess J, Spiekerman K, Haferlach T, Haferlach C, Koschmieder S, Rohde C, Serve H, Wörmann B, Hiddemann W, Ehninger G, Berdel WE, Büchner T, Müller-Tidow C; German Acute Myeloid Leukaemia Cooperative Group (2010). Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet 376:2000-8*.
- Peto R, Pike MC, Armitage P, Breslow NE, Cox DR et al. (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. *Analysis and example. Br J Cancer 35:1*.
- Röllig C, Aulitzky WE, Bodenstein H, et al. (2009). Risk stratification and prognostic factors in elderly AML patients- updated results of 909 patients entered into the prospective AML96 trial. *Blood; 114: 329 (abstr)*.
- Whitehead J (1983). The design and analysis of sequential clinical trials. *Horwood, Chichester*

THANK YOU
for your attention!