LE NEOPLASIE IN EMATOLOGIA: VERSO TERAPIE SEMPRE PIU' MIRATE E PERSONALIZZATE

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EXAMPLES OF RADICAL CHANGES IN MANAGEMENT. II

- ALL in childhood
- L3 ALL
- APL ⇨ *ATRA (1st example of targeted therapy)*
- Hairy cell leukemia ⇨ *IFN, CDA, DCF,…*
- CML ⇨ *TK inhibitors (1st, 2nd & 3rd generation)*
- Ph+ ALL ⇨ *TK inhibitors*
- NHL-CLL ⇨ Chemo-immunotherapy
- Progressive clinical use of MoAb
- Progressive personalization of treatment based on MRD monitoring

EXAMPLES OF RADICAL CHANGES IN MANAGEMENT. II

- PNH ⇨ *AcMo*
- Role of growth factors
- Extension of transplant procedures for malignant and non-malignant conditions
- Role of maintenance outside acute leukemias (disease chronicization)
- New approaches and new drugs for MM, CLL, MDS
- *Progressive development and use of non-chemo agents/strategies*

Objectives of a Broad and Integrated Characterization at Diagnosis ⇨ *at all ages, including the elderly*

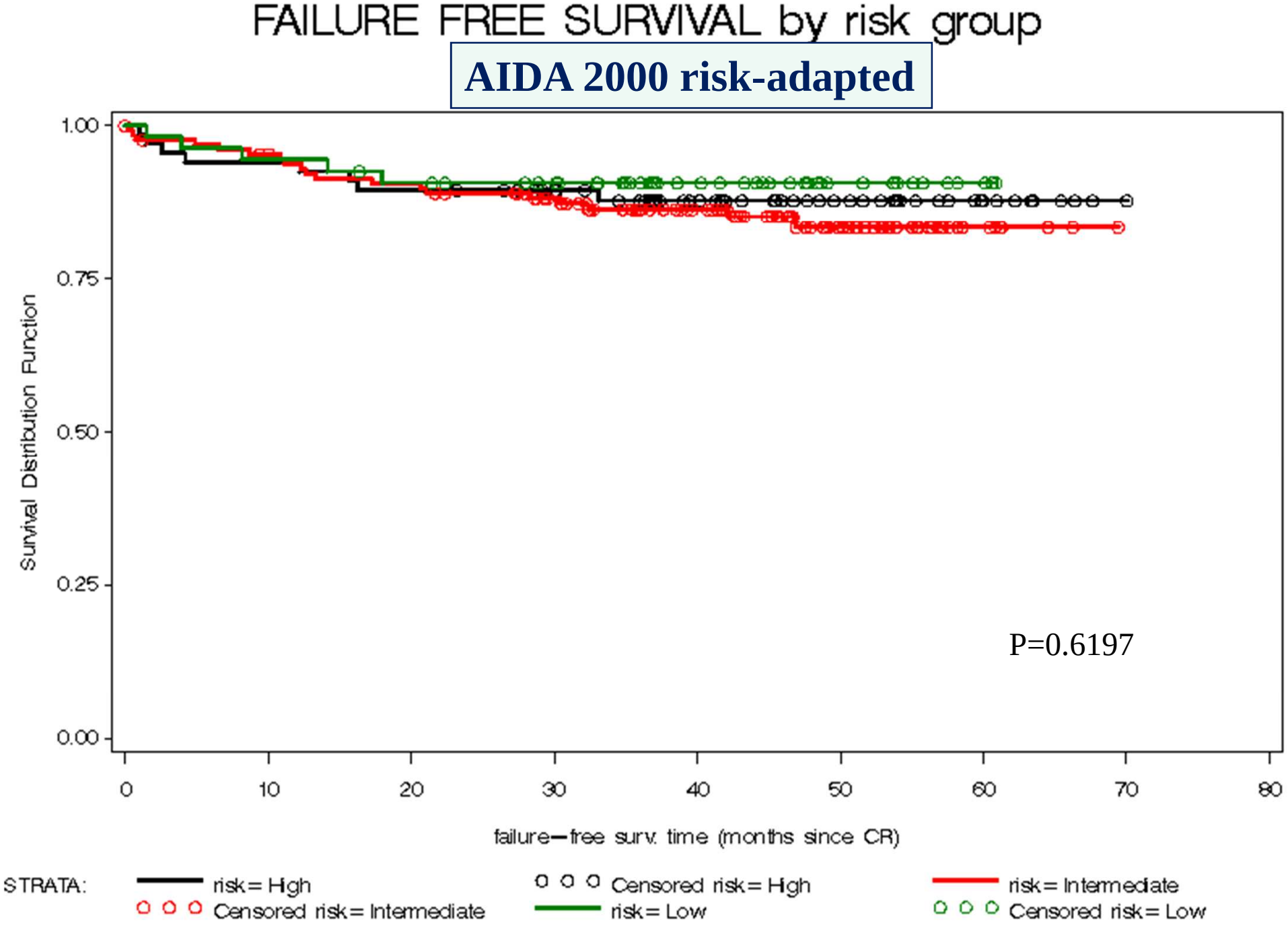
- Accurate *diagnostic work-up*
- Precise definition of disease *subentities*
- Biologically-based *prognostic stratification*
- Definition of markers for MRD monitoring
- *MRD monitoring*
- *Targeted therapies*
- Identification of targets for potential new *targeted therapies*

⇨ ***Requirement of a central processing, recognized laboratories and standardized methodologies***

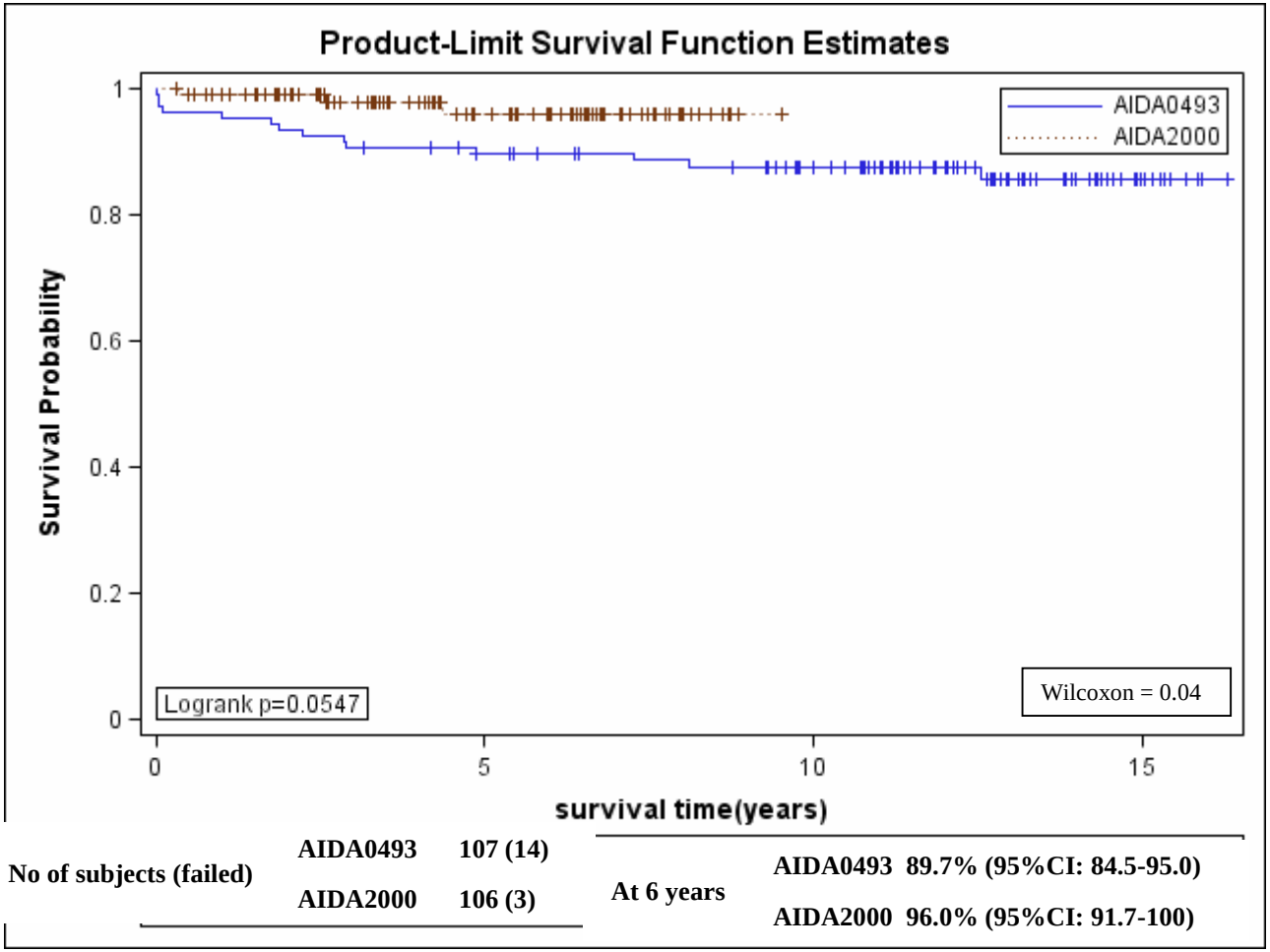
ACUTE PROMYELOCYTIC LEUKEMIA (APL)

- APL is characterized by a non-random specific translocation t(15;17)
- t(15;17) involves the retinoic acid receptor gene RAR-alpha on chromosome 17 and the PML gene, a putative transcription factor, on chromosome 15, generating the PML-RAR-alpha chimeric gene

- ***The resulting PML/RAR-alpha chimeric protein is crucial to the pathogenesis of APL***


FAILURE FREE SURVIVAL by risk group
AIDA 2000 risk-adapted
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
80
failure–free surv. time (months since CR)
P=0.6197
STRATA:
risk= High
Censored risk= Intermediate
Censored risk= High
risk= Low
risk= Intermediate
Censored risk= Low

Childhood APL. Overall Survival AIDA-0493 vs AIDA-2000 (all risks)



No of subjects (failed)	**AIDA0493**	**107 (14)**
	AIDA2000	**106 (3)**

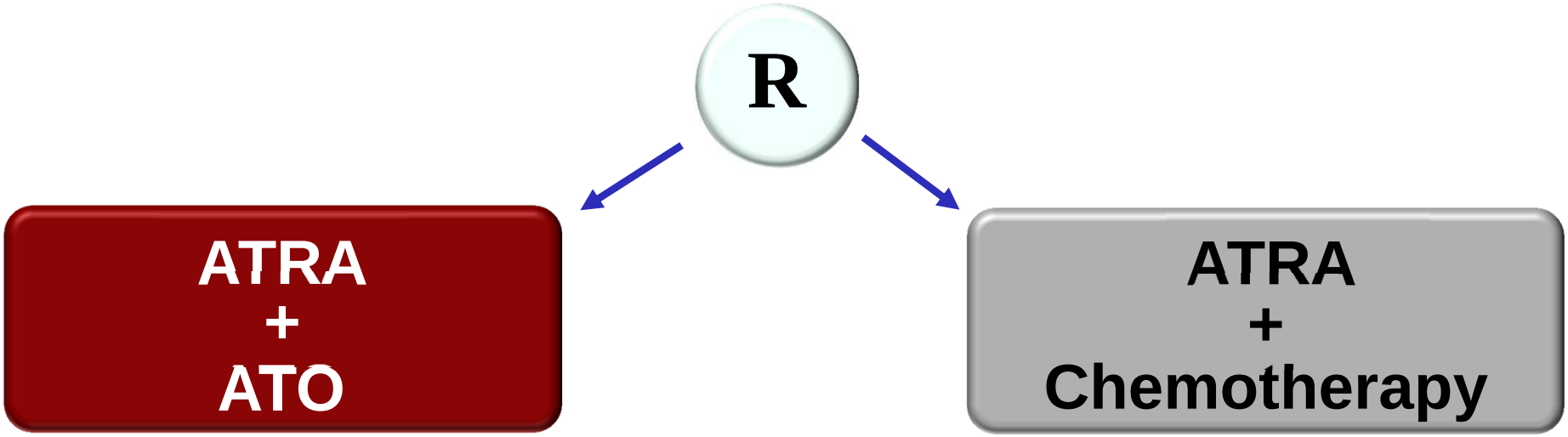
At 6 years	**AIDA0493**	**89.7% (95%CI: 84.5-95.0)**
	AIDA2000	**96.0% (95%CI: 91.7-100)**

APL 0406 Study

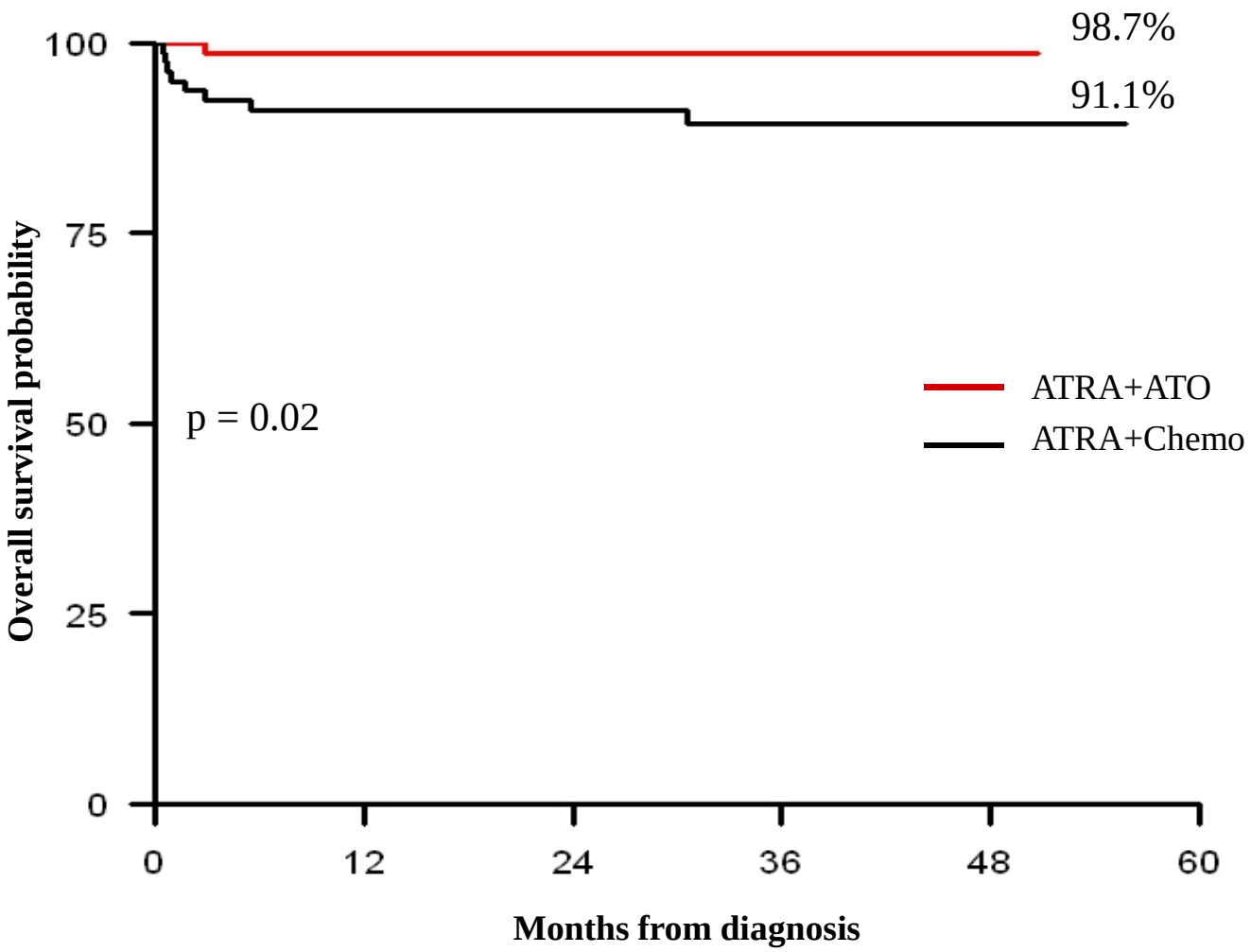
Acute Promyelocytic Leukemia

Low/intermediate risk patients

(WBC $\leq 10 \times 10^9$/L)



Overall Survival



Conclusions

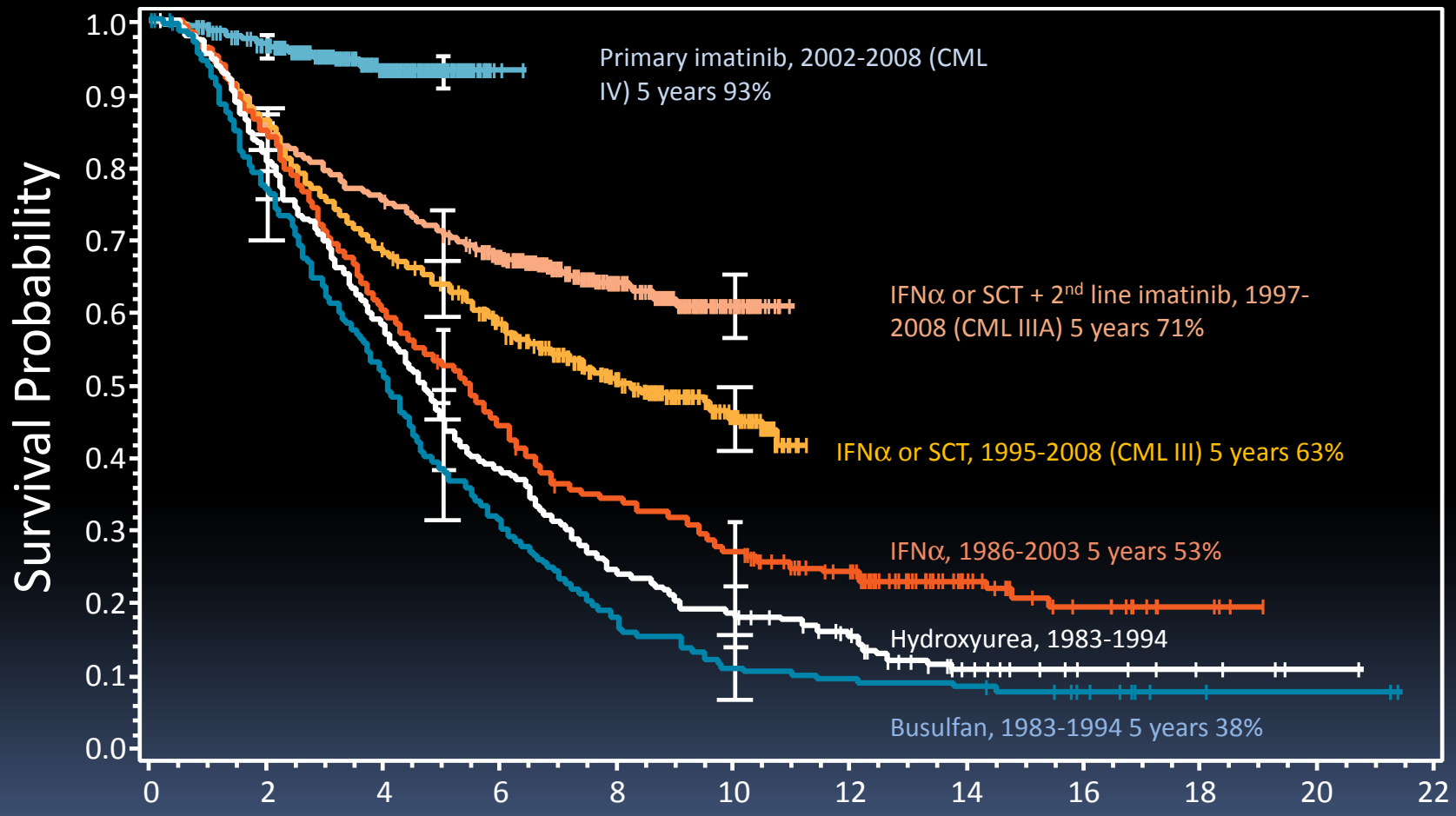
ATO + ATRA is at least not inferior to ATRA + chemo for 2-yr EFS in low/intermediate risk APL

ATO + ATRA is associated with less hematologic toxicity and more, yet manageable, hepatic toxicity and QTc prolongation

This regimen may emerge as the new standard of care for low/intermediate risk APL

Lo Coco et al, NEJM 2013

The Concept of Targeted Therapy Helped Improve Survival for Patients With CML



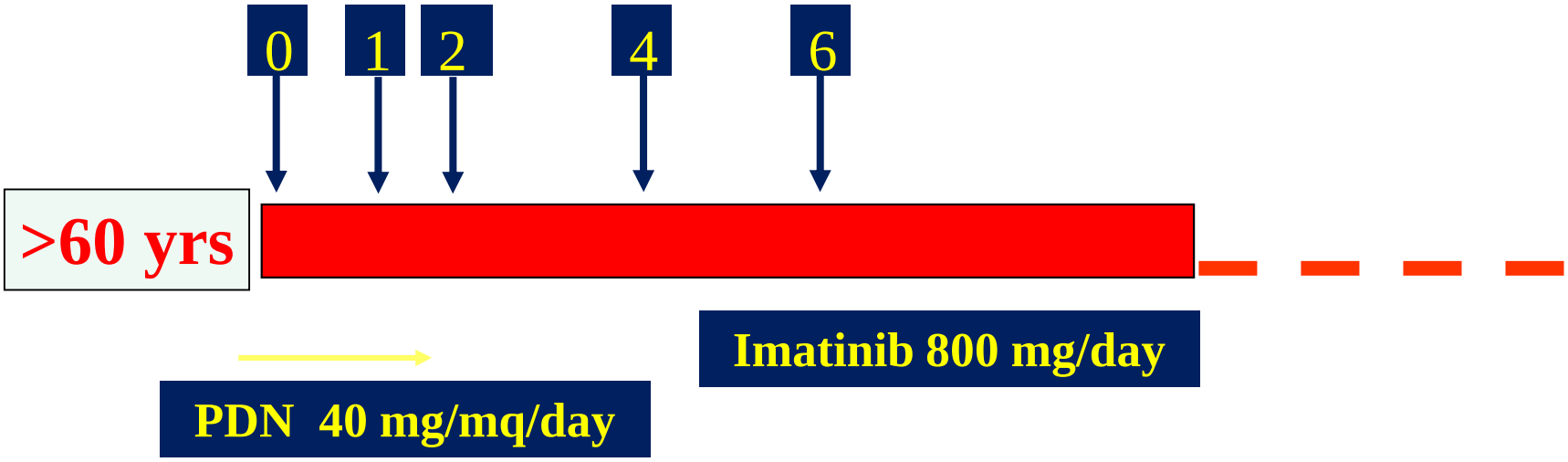
stem-cell transplantation.

ed from R. Hehlmann, German CML Study Group.

Ph+ ALL

- Important prevalence in adults (20 – 60% ? of cases) ⇨ *increases with age*
- Unfavorable prognosis in both children and adults
- Conventional chemotherapy unsatisfactory
- Impact of tyrosine kinase inhibitors (TKI)

Imatinib in Adult Ph+ ALL: GIMEMA LAL 0201B Study



Enrolled: 45 patients

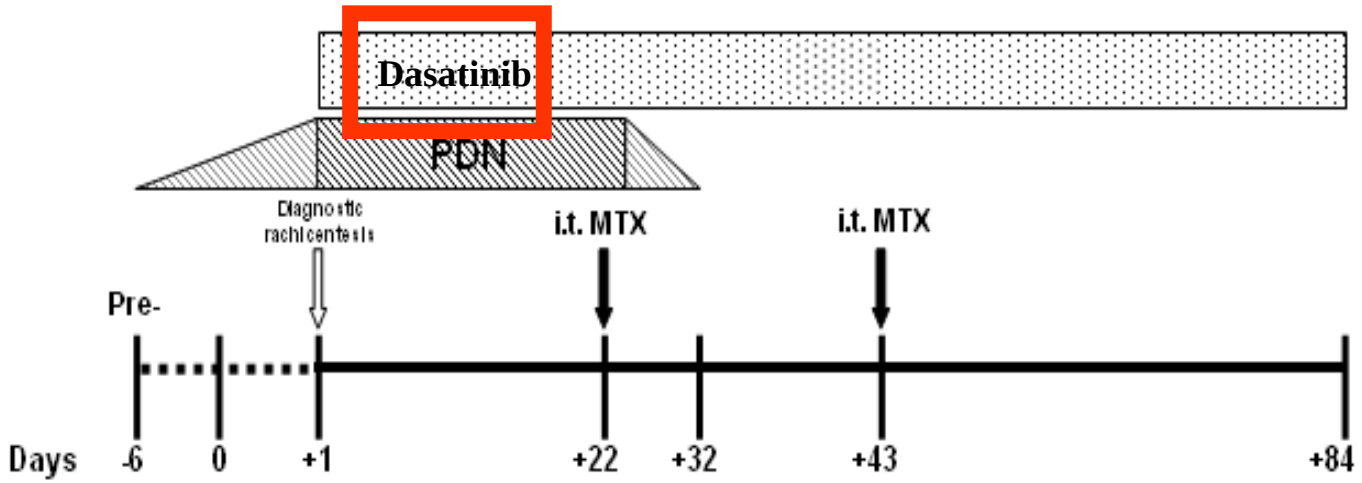
Median age 68; range 61 – 89

Evaluable: 37 patients

Hematologic CR 100%

Vignetti et al. Blood 2007;109:3676–3678

GIMEMA LAL1205
Protocol: Ph+ ALL >18 yrs



Dasatinib 70 mg twice a day (total planned treatment is 12 weeks, i.e. 84 days)

★ Diagnostic work-up (within 7 d) and immunophenotypic & molecular monitoring of MRD carried out centrally in Rome

Ph+ ALL TODAY

- Putting together the data of the two GIMEMA protocols based on the use of Imatinib and Dasatinib alone as 1st line treatment, with no upper age limit, c100 Ph+ ALL so far treated (overall median age 62.7 yrs, range 24-89)
  ⇨ *100% CHR no deaths in induction*
- ***Is there a role for chemotherapy in the remission induction of Ph+ ALL??***
- Post-HCR treatment is today the ***most relevant open question***

A 91 YEAR OLD ALL PATIENT…

*PC, diagnosed with **Ph+ ALL** in September 2007 at the age of 89. Treated with Imatinib alone (partly at home…). Obtained a CHR, MRD-, and turned 90...*

Drived a car and occasionally helped in the family garage…

Relapse in June 2009. IInd CR with Dasatinib. Relapse in February 2010, responded to VCR. Died March of heart failure, at 91, 2½ years from diagnosis.

Courtesy of Prof. G. Pizzolo

MoAb in the Management of Hematologic Malignancies

- Anti-CD20 (first, second and third generation)
- Anti-CD19
- Anti-CD22
- Anti-CD52
- Anti-CD33
- Anti-CD30
- Bispecific anti-CD19/anti-CD3

⇨ *Positivity and degree of antigen expression in the various ages not well defined (e.g. elderly)*

Bispecific anti-CD19/anti-CD3

- **Blinatumomab (MT-103), BiTE**
- A bispecific single-chain antibody derivative designed to link B cells and T cells resulting in T-cell activation and a cytotoxic T-cell response against CD19 expressing cells.
- Promising results in phase I studies, particularly on MRD clearance.
- A multicenter, multinational protocol aimed at treating MRD in ALL ongoing started.
- Study ongoing also for relapsed/refractory ALL

HAIRY CELL LEUKEMIA. BRAF

1. *Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, Pucciarini A, Bigerna B, Pacini R, Wells VA, Sportoletti P, Pettirossi V, Mannucci R, Elliott O, Liso A, Ambrosetti A, Pulsoni A, Forconi F, Trentin L, Semenzato G, Inghirami G, Capponi M, Di Raimondo F, Patti C, Arcaini L, Musto P, Pileri S, Haferlach C, Schnittger S, Pizzolo G, Foà R, Farinelli L, Haferlach T, Pasqualucci L, Rabadan R, Falini B.*

BRAF mutations in hairy-cell leukemia.

N Engl J Med. 364:2305-15, 2011.

2. *Tiacci E, Schiavoni G, Forconi F, Santi A, Trentin L, Ambrosetti A, Cecchini D, Sozzi E, Francia di Celle P, Di Bello C, Pulsoni A, Foà, Inghirami G, Falini B.*

Molecular diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation.

Blood, 119:192-5, 2012.

⇨ ***DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS***

Phase II multicenter, open-label trial on Vemurafenib in HCL (No profit study, Principal investigator: B. Falini)

Inclusion criteria:

1) HCL patients refractory to purine analogs
2) HCL patients relapsed after purine analogs therapy (≤ 2ys CR/PR after the 1st cycle or ≤ 4ys CR/PR after 2nd or more cycles)
3) HCL patients with residual disease in BM (>30%) after multiple courses of therapy
4) HCL patients with severe side effects during/after previous purine analog therapy

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Drug supplied by Roche. Total number of HCL patients to be enrolled N° 25 (recruitment started on May 2011, now completed. Additional 3 patients included).

Primary endpoints: assess the efficacy (at least 30% CR) and safety of Vemurafenib in refractory and relapsed HCL.

‘*Genetics-driven targeted management of lymphoid malignancies*’

AIRC 5 x 1000 Molecular Clinical Oncology program

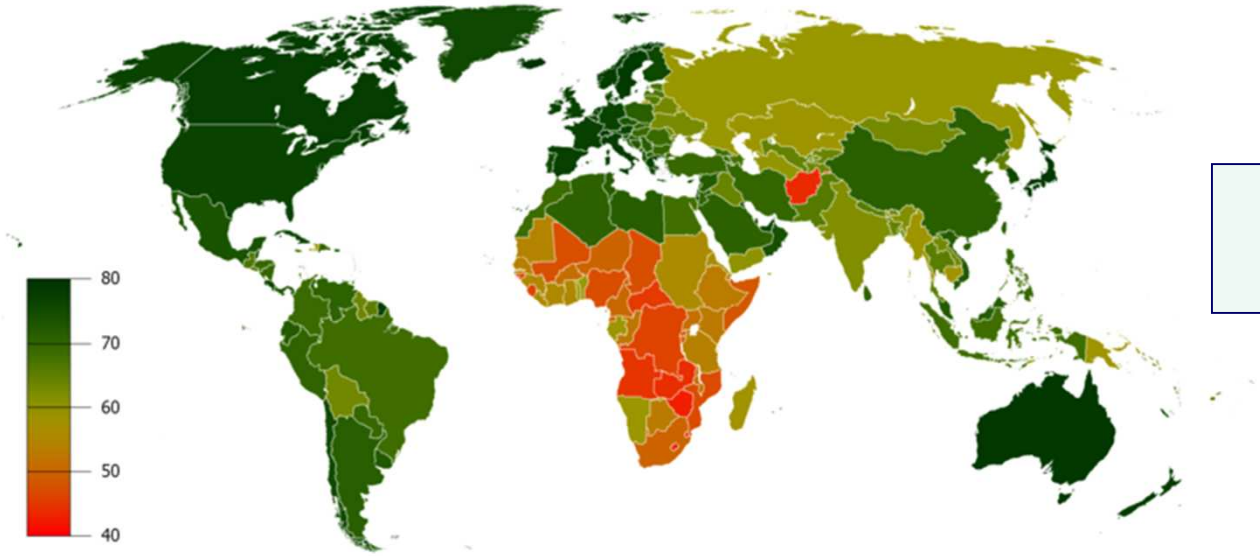
FINAL CONSIDERATIONS. I

- The management of patients with hematologic disorders is today progressively more guided by the laboratory and by always evolving technologies
- In terms of diagnosis, prognosis, monitoring and treatment
- Targeted treatment is a reality
- Many diseases are being chronicized ⇨ *maintenance*
- Always grower impact of non-chemo approaches
  ⇨ *MoAb, inhibitors, small molecules, etc*
- Algorithms of treatment and are a reality
- Personalized management no longer a dream

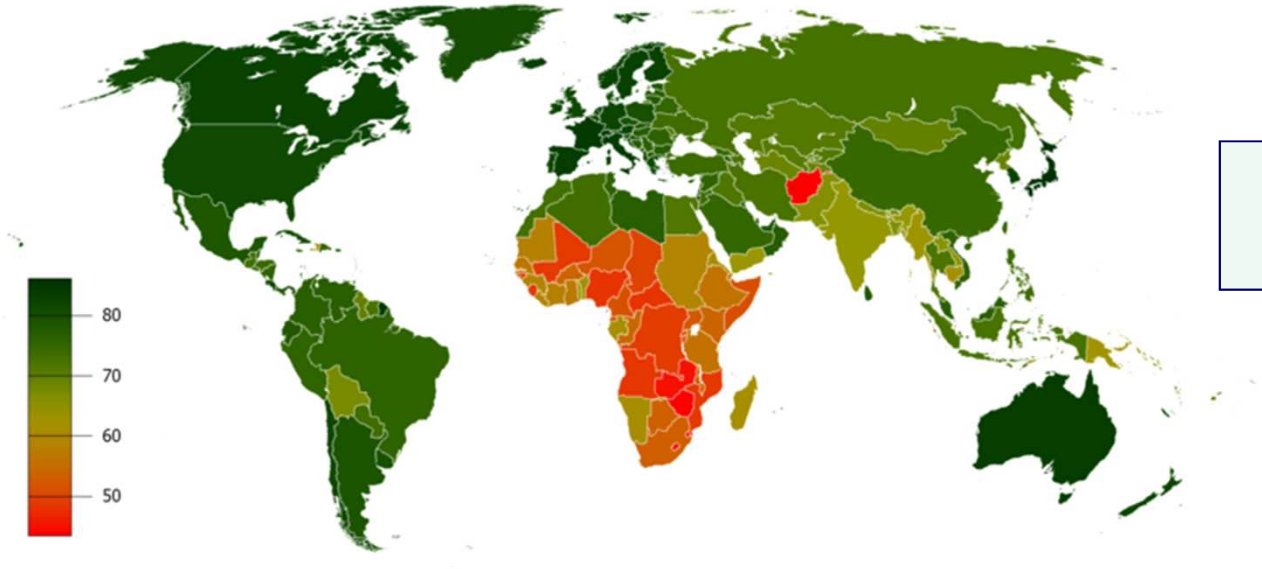
FINAL CONSIDERATIONS. II

- Based on the above considerations, the number of rare tumors in hematology is increasing, as we are progressively identifying subgroups of patients with well defined features who require specific treatments.

LIFE EXPECTANCY BY THE UNITED NATIONS (2005-2010)



Male life expectancy



Female life expectancy