European LeukemiaNet

Developing stratified diagnostic and treatment approaches

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Chicago

(Update May 08, 2013)

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Short introduction on ELN

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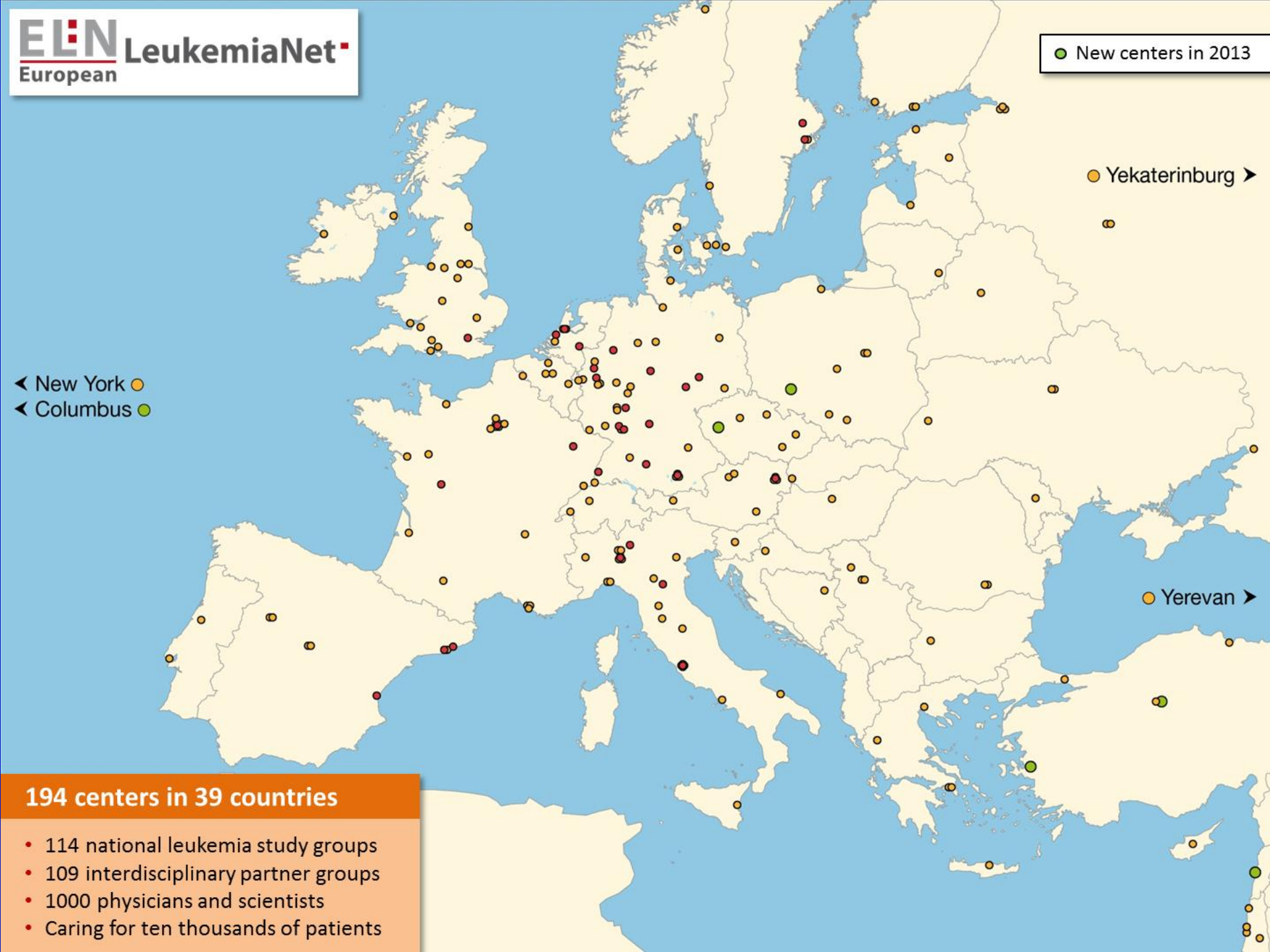
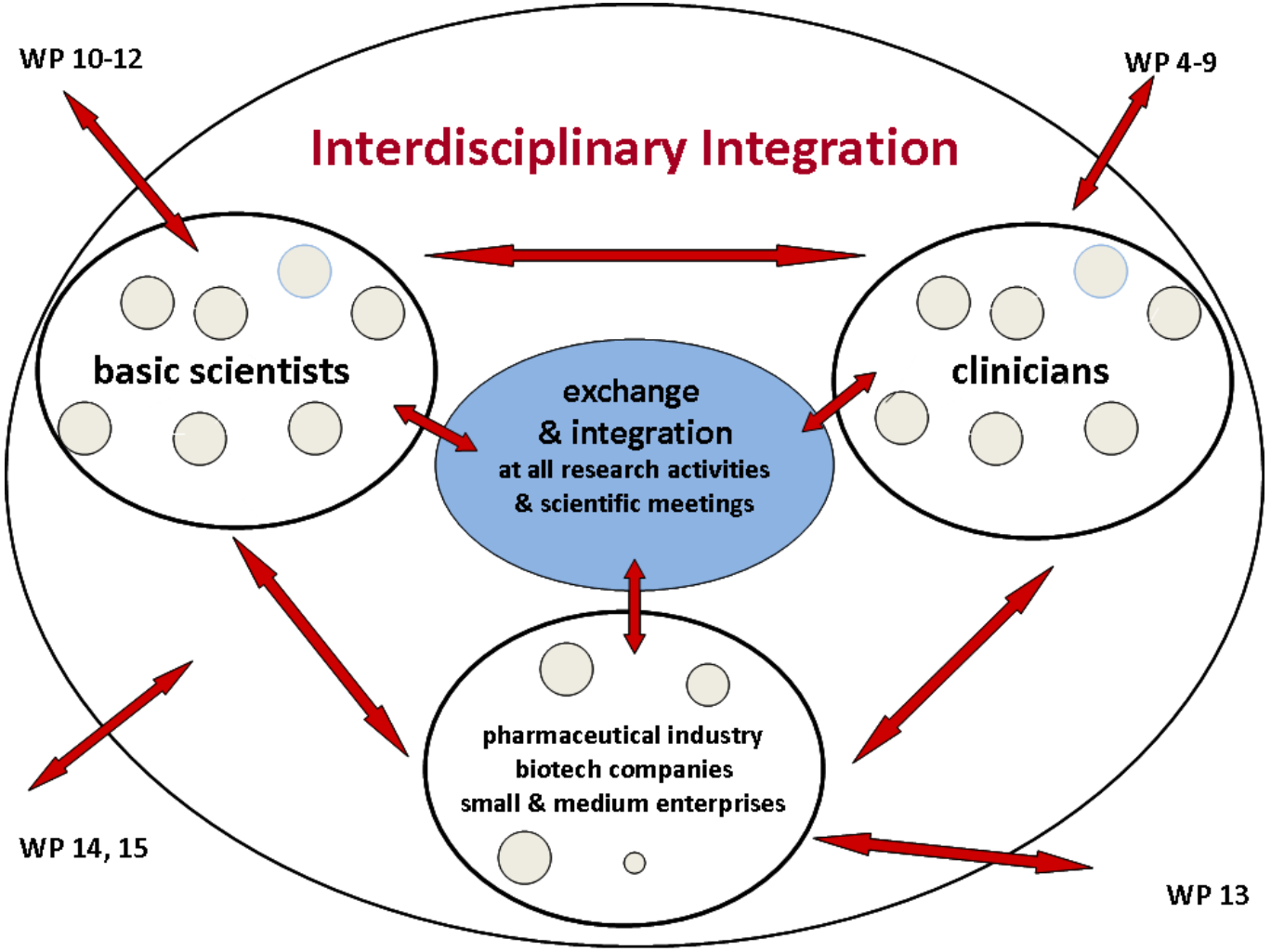

ELN European LeukemiaNet
New centers in 2013
Yekaterinburg
New York
Columbus
Yerevan
194 centers in 39 countries
• 114 national leukemia study groups
• 109 interdisciplinary partner groups
• 1000 physicians and scientists
• Caring for ten thousands of patients

European LeukemiaNet

concerns: all leukemias with
all interdisciplinary partner groups



Hehlmann R et al. Haematologica 2011;96:156-162 [1]

Management Recommendations in CML

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JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet

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ABSTRACT

Purpose
To review and update the European LeukemiaNet (ELN) recommendations for the management of chronic myeloid leukemia with imatinib and second-generation tyrosine kinase inhibitors (TKIs), including monitoring, response definition, and first- and second-line therapy.

Methods
These recommendations are based on a critical and comprehensive review of the relevant papers up to February 2009 and the results of four consensus conferences held by the panel of experts appointed by ELN in 2008.

Results
Cytogenetic monitoring was required at 3, 6, 12, and 18 months. Molecular monitoring was required every 3 months. On the basis of the degree and the timing of hematologic, cytogenetic, and molecular results, the response to first-line imatinib was defined as optimal, suboptimal, or failure, and the response to second-generation TKIs was defined as suboptimal or failure.

Conclusion
Initial treatment was confirmed as imatinib 400 mg daily. Imatinib should be continued indefinitely in optimal responders. Suboptimal responders may continue on imatinib, at the same or higher dose, or may be eligible for investigational therapy with second-generation TKIs. In instances of imatinib failure, second-generation TKIs are recommended, followed by allogeneic hematopoietic stem-cell transplantation only in instances of failure and, sometimes, suboptimal response, depending on transplantation risk.

J Clin Oncol 27:6041-6051. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Nearly a decade has passed since the introduction into clinical practice of the first tyrosine-kinase inhibitor (TKI), imatinib mesylate, (Gleevec, Glivec; Novartis, Basel, Switzerland).[1,2] Before imatinib, the therapy of Philadelphia-positive (Ph+) chronic myeloid leukemia (CML) included hydroxyurea, interferon alfa (IFN-α), and allogeneic hematopoietic stem-cell transplantation (alloHSCT).[3] The advent of imatinib, which specifically targeted the TK activity of the oncogenic proteins encoded by *BCR/ABL1*,[4] rapidly and dramatically modified the treatment of CML and led to important changes in management.[5] Subsequently, more information became available about imatinib therapy as a result of experience with more patients, longer follow-up, and better understanding of the causes and mechanisms of resistance to imatinib.[6-14] At the same time, other drugs, most of them also classifiable as TKIs, were developed.[15-20] Some have been tested in clinical trials, and two of them, dasatinib (Sprycel; Bristol-Myers Squibb, New York, NY) and nilotinib (Tasigna; Novartis), have been registered worldwide for the treatment of patients with imatinib-intolerant and imatinib-resistant disease.[21-29] The confirmation of the high efficacy of imatinib, the observation that the response to imatinib is durable, and the availability of two potent new agents have raised the level of satisfaction and expectation for the outcome of therapy of CML, so that the goal of therapy has become more ambitious—an aim for 100% survival and a normal quality of life. For these reasons, the European LeukemiaNet (ELN) decided to review recent results of therapy, standard monitoring procedures, and definitions of responses and to update the published recommendations, with the aim of contributing to optimize and standardize the management of CML.

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ELN European LeukemiaNet

UPDATE 2010

Recommendations from the European LeukemiaNet for the Management of chronic myeloid leukemia (CML)

Definitions of optimal response, suboptimal response, failure and warnings for previously untreated patients with early chronic phase CML who are treated with Imatinib 400 mg daily.

New recommendations are marked in yellow.

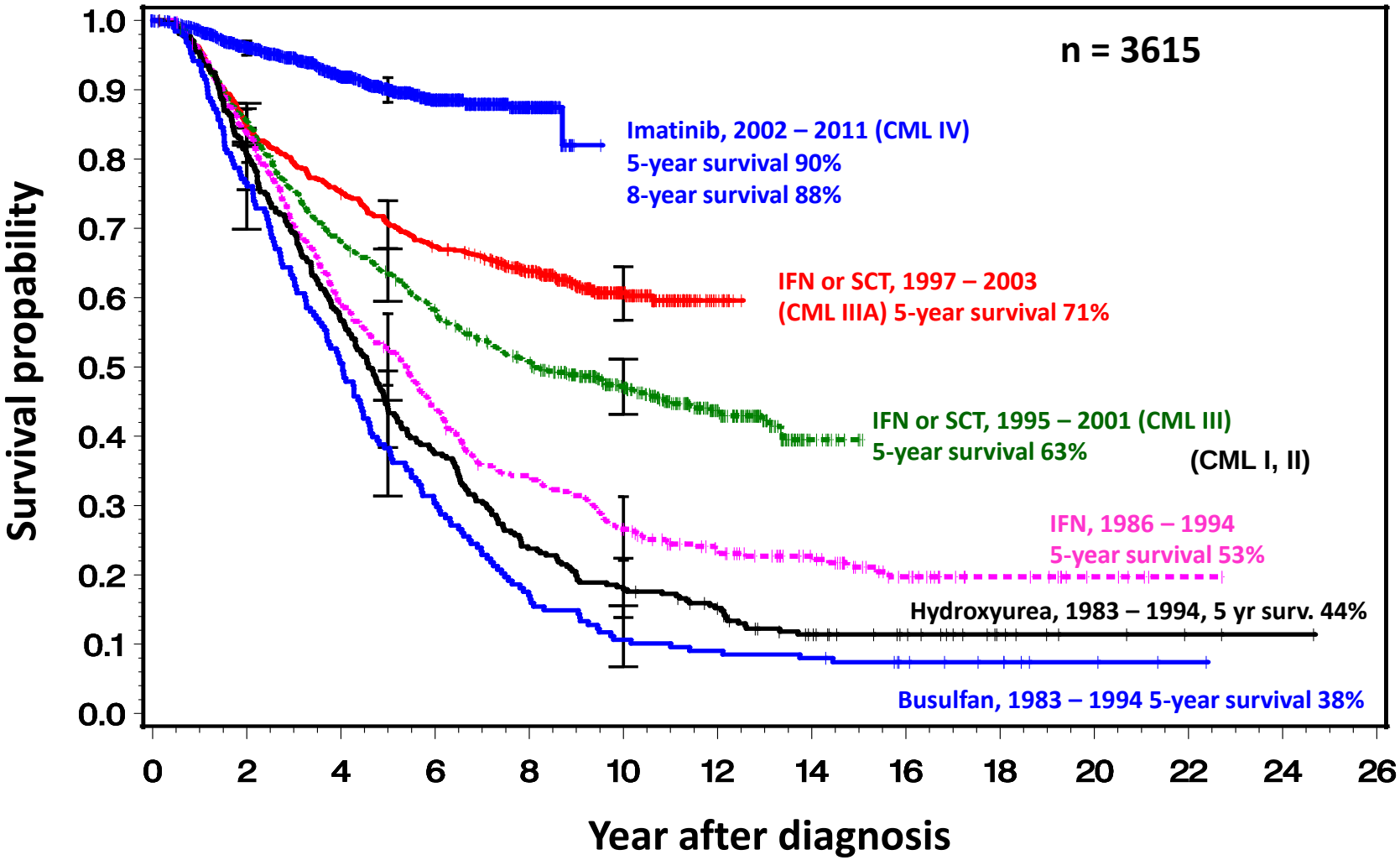
Time	Optimal response	Suboptimal response	Failure	Warnings
Diagnosis	N/A	N/A	N/A	High Risk CCA/Ph+[3]
3 mon.	CHR, at least Minor CgR	No CgR	Less than CHR	N/A
6 mon.	At least PCgR	Less than PCgR	No CgR	N/A
12 mon.	CCgR	PCgR	Less than PCgR	Less than MMR
18 mon.	MMR	Less than MMR	Less than CCgR	N/A
Any time (during treatment)	Stable or improving MMR	Loss of MMR Mutations[1]	Loss of CHR, Loss of CCgR, Mutations[2] CCA/Ph+[3]	Increase in transcript levels CCA/Ph-

mon.: Months after diagnosis **N/A:** Not applicable **CCA:** Clonal chromosome abnormalities

[1] BCR-ABL1 kinase domain mutations still sensitive to imatinib, [2] BCR-ABL1 kinase domain mutations poorly sensitive to imatinib or other TKIs, [3] CCA/Ph+ is a "warning" factor at diagnosis, although its occurrence during treatment (i.e., clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least two Ph+ cells.

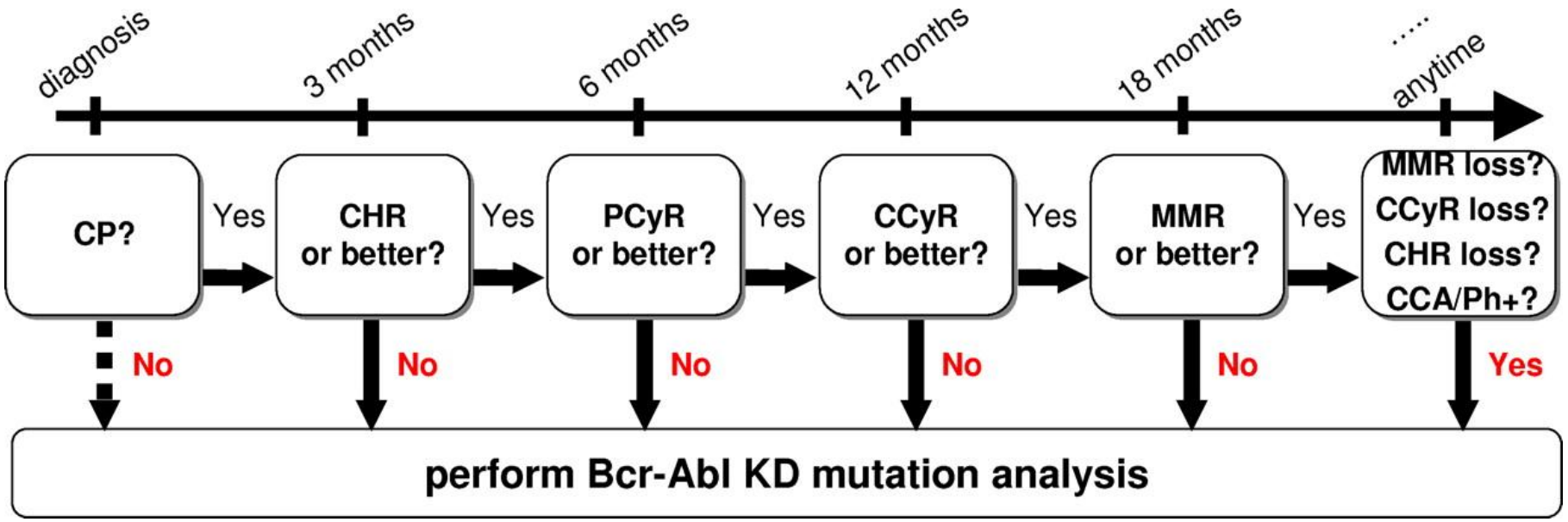
- One of the 50 most cited papers of JCO
- 20.000 pocket cards distributed

Improvement of survival of CML by therapy 1983 – 2011



German CML Study Group

BCR-ABL kinase domain mutation analysis in CML patients treated with TKI: recommendations from an expert panel of ELN



Soverini S et al., Blood. 2011 Aug 4;118(5):1208-15. [17]

Multicentre validation of a reproducible flow cytometric score for the diagnosis of low-risk MDS

Table 3. Calculation of the flow cytometric score (FCM-score) for the diagnosis of low-risk MDS.

Cytometric Parameter	*Cut-off values*	*Regression coefficient*	*Variable weighted score* #
Myeloblast-related cluster size (%)*	≥2	2.59	1
B-progenitor-related cluster size (%)**	≤5	1.87	1
Lympocytes to myeloblasts CD45 ratio	≤4 or ≥7.5	1.76	1
Granulocytes to lymphocytes SSC ratio	≤6	2.31	1

* in all nucleated cells; **in all CD34+ cells; #a diagnosis of MDS is formulated in presence of a FCM-score value ≥2.

This score may help establish MDS diagnosis especially when morphology and cytogenetics are indeterminate

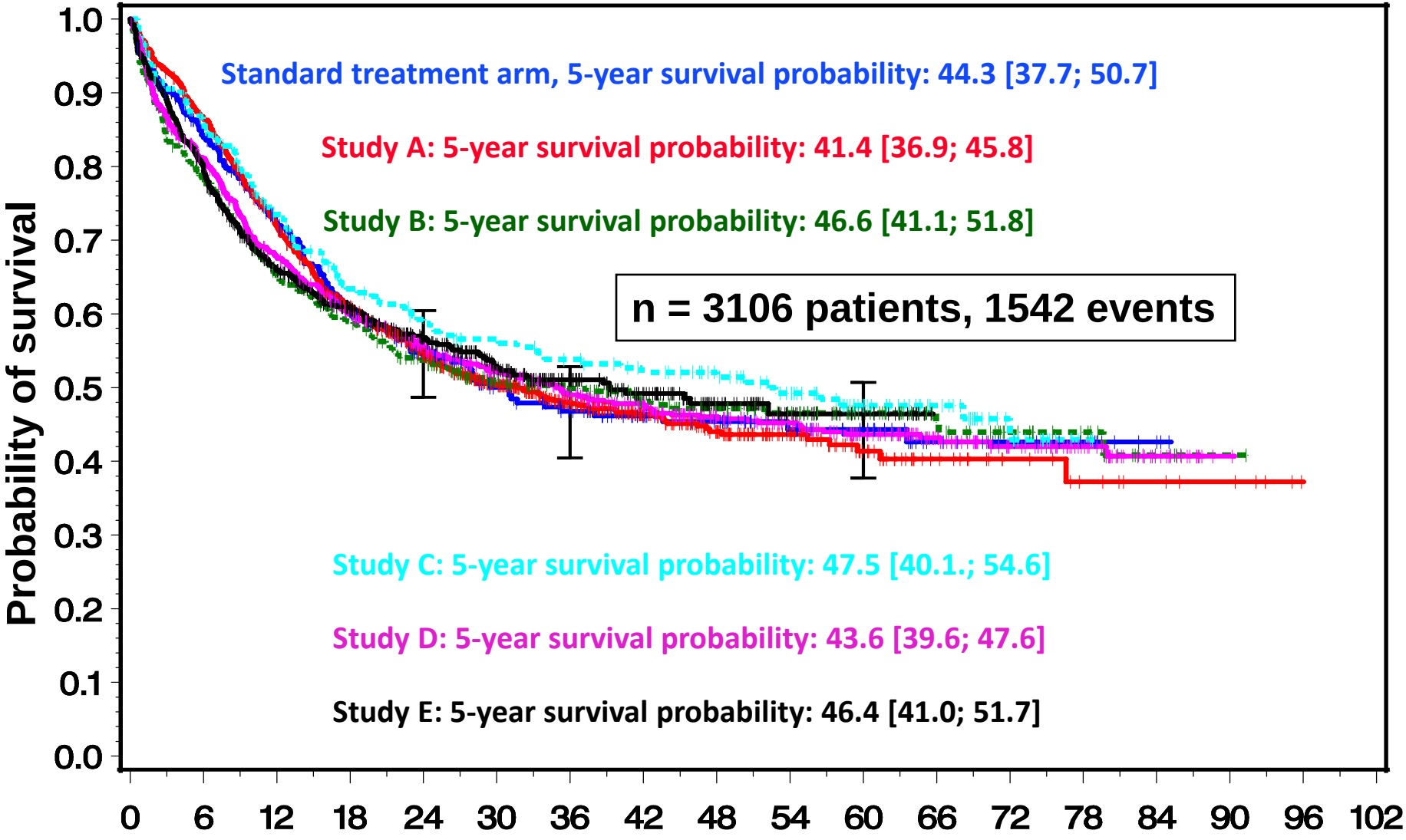
Della Porta MG et al., Haematologica. 2012 Feb 7. [Epub ahead of print] [19]

Recommended minimal requirements to assess dysplasia in MDS by FC

Bone marrow subset	*Recommended analyses*	*Aberrancy*
Immature myeloid and monocytic progenitors	Percentage of cells in nucleated cell fraction[a]	Increased percentage
	Expression of CD45	Lack of/decreased/increased
	Expression of CD34	Lack of/decreased/increased
	Expression of CD117	Homogenous under/overexpression
	Expression of HLA-DR	Lack of/increased expression
	Expression of CD13 and CD33	Lack of/decreased/increased
	Asynchronous expression of CD11b, CD15	Presence of mature markers
	Expression of CD5, CD7, CD19, CD56[b]	Presence of lineage infidelity markers
Maturing neutrophils	Percentage of cells as ratio to lymphocytes	Decreased
	SSC as ratio vs SSC of lymphocytes	Decreased
	Relationship of CD13 and CD11b	Altered pattern[c]
	Relationship of CD13 and CD16	Altered pattern[c]
	Relationship of CD15 and CD10	Altered pattern[c]; for example, lack of CD10 on mature neutrophils
Monocytes	Percentage of cells	Decreased/increased
	Distribution of maturation stages	Shift towards immature
	Relationship of HLA-DR and CD11b	Altered pattern[c]
	Relationship of CD36 and CD14	Altered pattern[c]
	Expression of CD13 and CD33	(Homogenous) under/overexpression
	Expression of CD56[b]	Presence of lineage infidelity marker
Progenitor B cells	Enumeration as fraction of total CD34+ based on CD45/CD34/SSC in combination with CD10 or CD19	Decreased or absent
Erythroid compartment[d]	Percentage of nucleated erythroid cells	Increased
	Relationship CD71 and CD235a	Altered pattern[c]
	Expression of CD71	Decreased
	Expression of CD36	Decreased
	Percentage of CD117-positive precursors	Increased

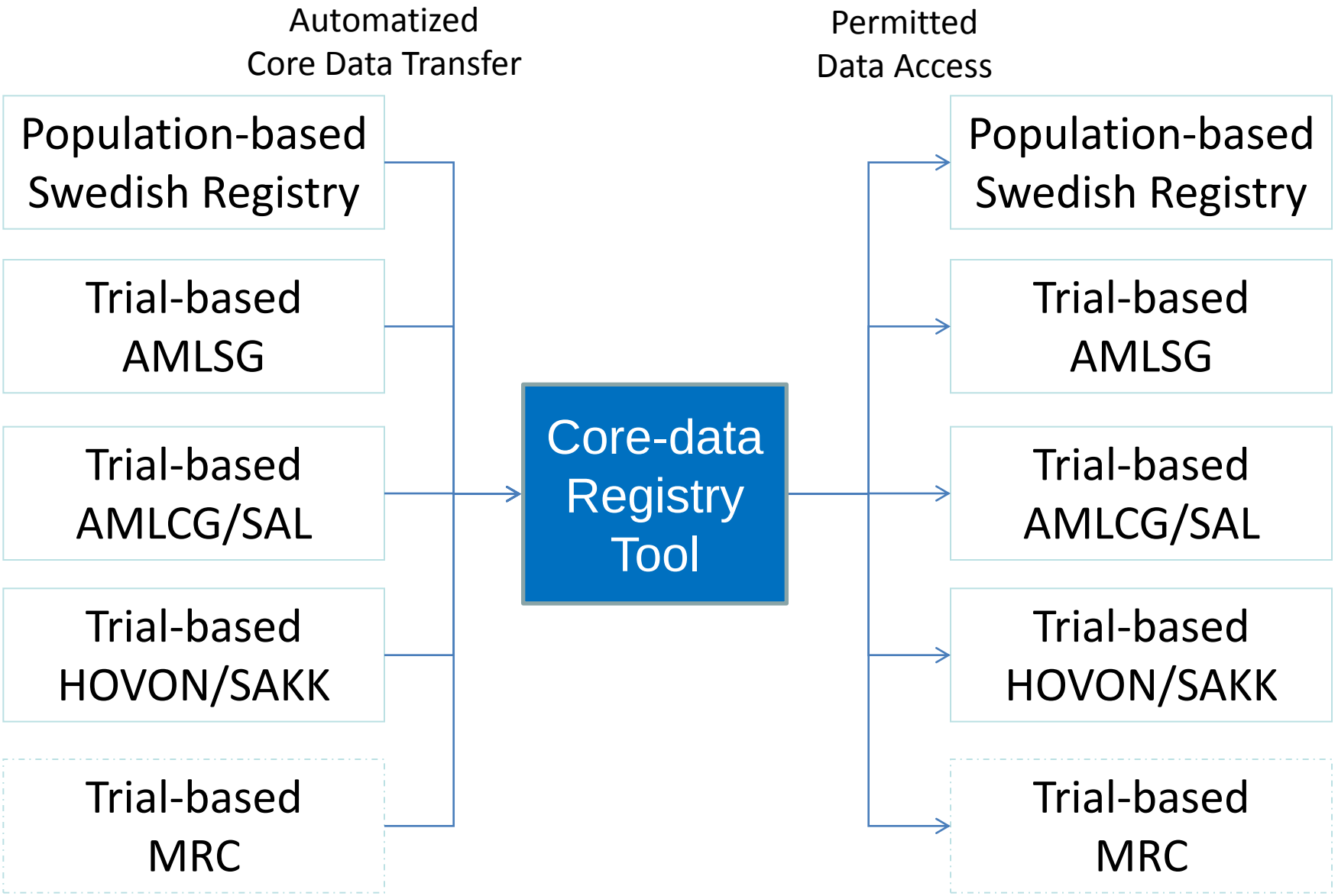
Westers TM, et al., Leukemia. 2012 Feb 6. [Epub ahead of print] [20]

AML Intergroup study - Overall survival (n = 3106)

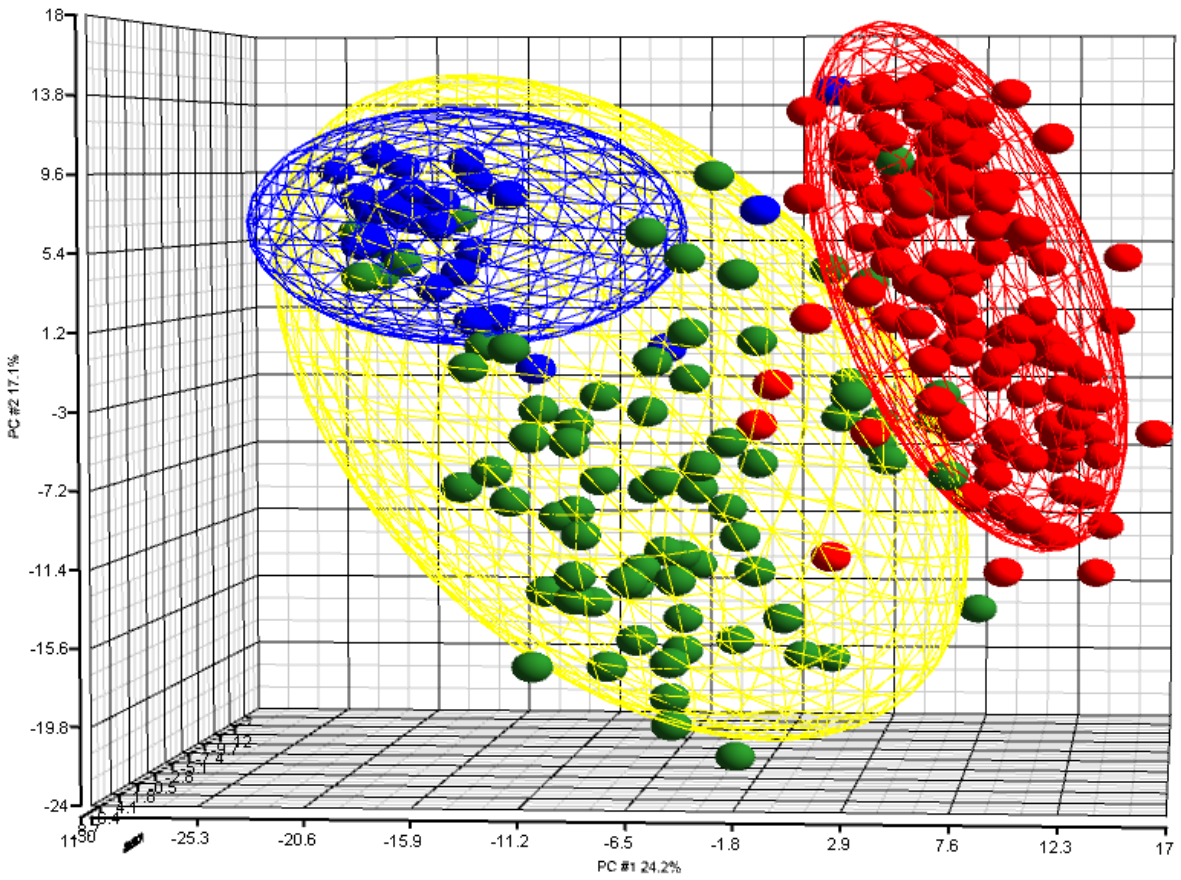


ELN European LeukemiaNet

Model for interconnecting AML registries



Signatures and molecular markers in AML-NK



Marker

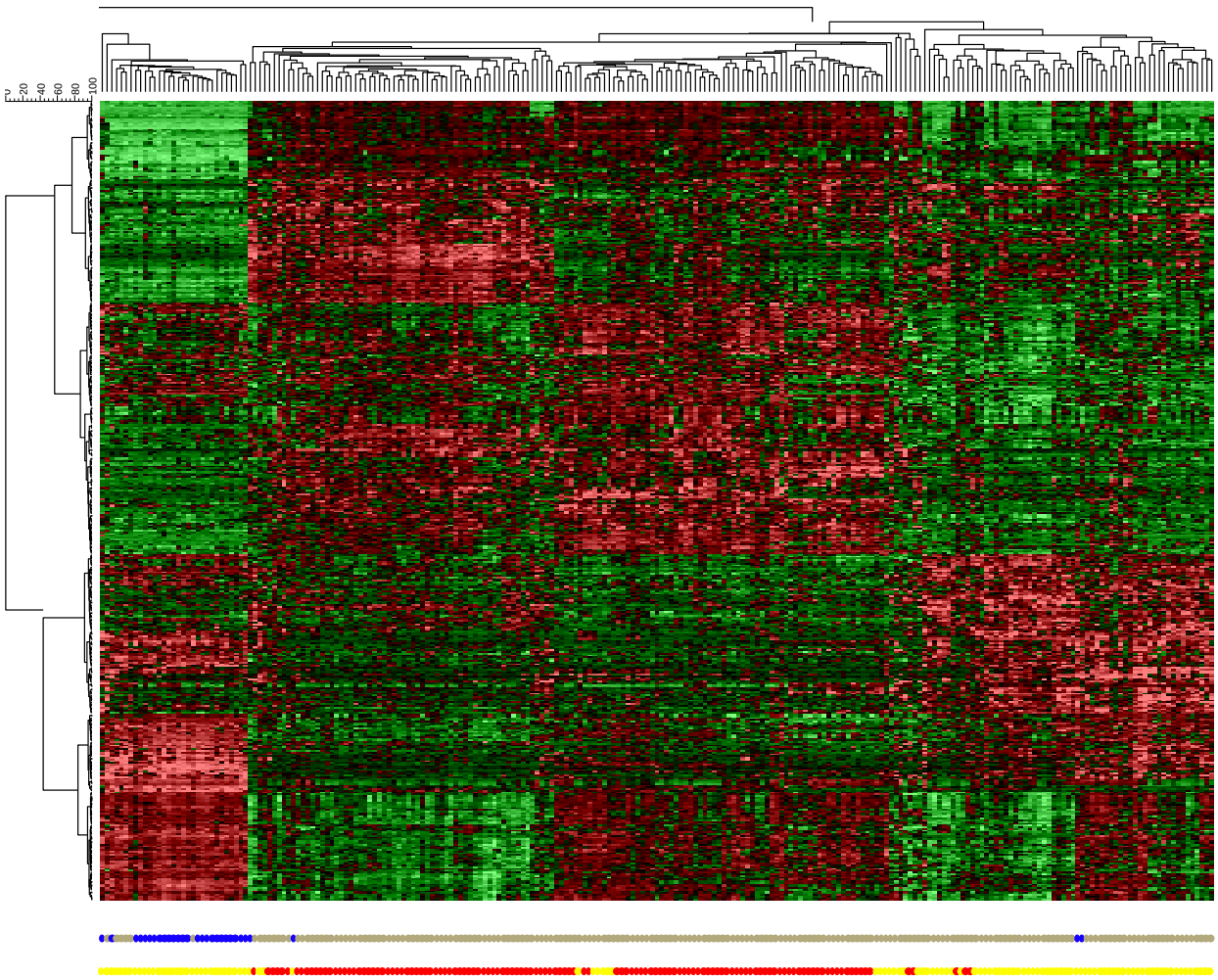
- *NPM1+, CEBPAwt*
- *NPM1wt, CEBPA+*
- *NPM1wt, CEBPAwt*

Ellipsoid

- *NPM1 wild type*
- *NPM1 mutated*
- *CEBPA mutated*

Kohlmann et al., Leukemia; 24(6):1216-20, 2010 [29]

Signatures and molecular markers in AML-NK



NPM1

- wild type
- mutated

CEBPA

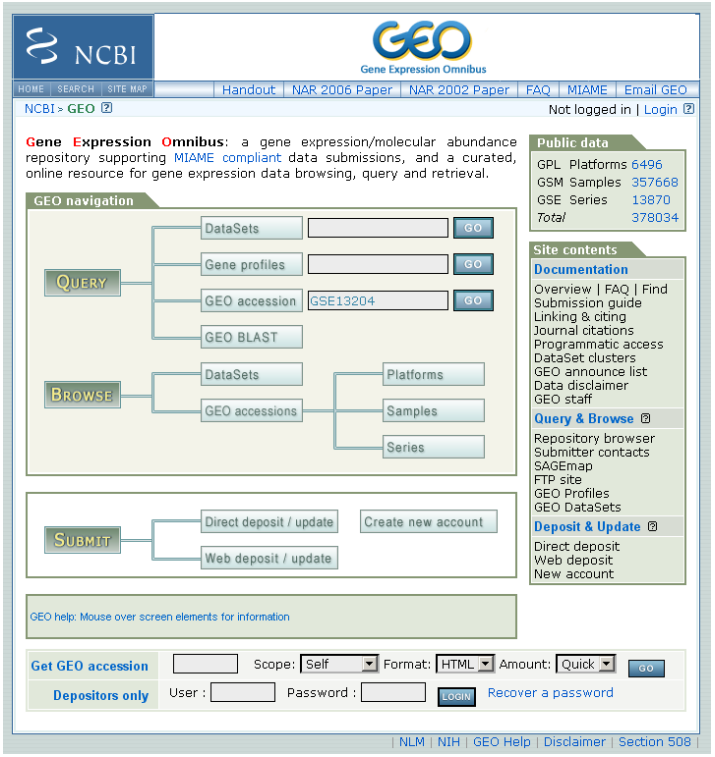
- wild type
- mutated

cases: n=233
genes: n=461

MILE Study: Data set

Complete study database uploaded to GEO repository

All CEL files available (n = 3248)



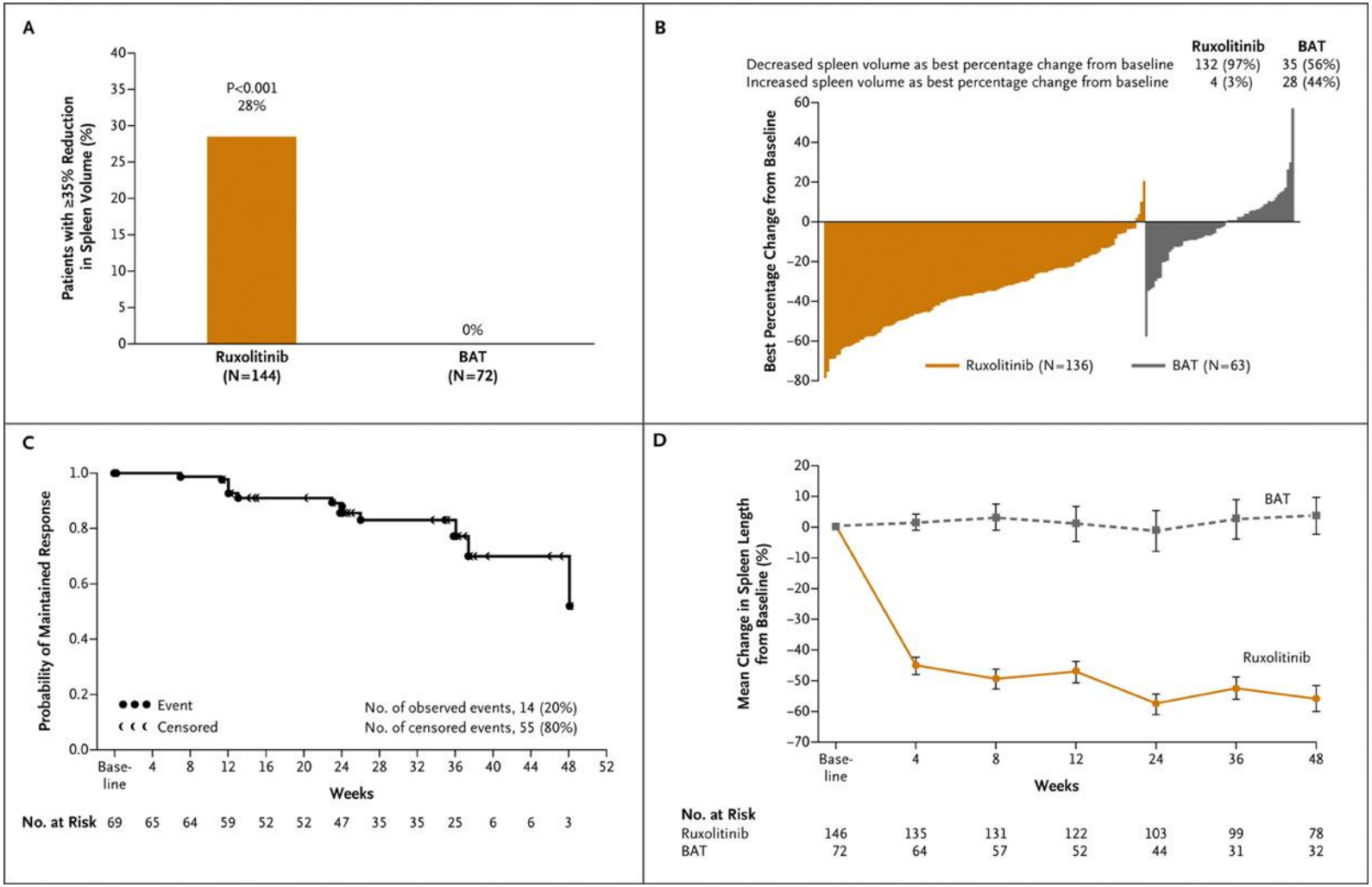
GSE13204

Individual rows of gene expression values:

114,888,960

Myelofibrosis

JAK Inhibition with Ruxolitinib versus Best Available Therapy - Changes in Spleen Volume



Harrison C et al. N Engl J Med 2012;366:787-798 [42].

Figure 1. Changes in Spleen Volume and Spleen Length, According to Treatment Group. Panel A shows the percentage of patients in the efficacy-analysis population (all patients who underwent randomization and had both a baseline measurement and at least one subsequent assessment) who had a reduction in spleen volume of at least 35% from the baseline volume, as assessed by magnetic resonance imaging (MRI) or computed tomography (CT) at 48 weeks. Panel B shows the best percentage change from baseline in spleen volume, as assessed by MRI or CT, at any time within the first 48 weeks of treatment, among patients with a baseline assessment and at least one subsequent assessment. Data are shown for individual patients. Panel C shows the median length of time that a reduction of at least 35% in spleen volume, as assessed by MRI or CT, was maintained, among patients who were continuously receiving ruxolitinib. Patients were considered to have had a loss of response (event) if the spleen volume was no longer reduced by at least 35% from the baseline volume and was increased by 25% or more from the nadir. Data from patients who did not have an assessment subsequent to the baseline assessment, or who were still having a response at the time of cutoff of the data, were censored. Panel D shows the mean percentage change from baseline in palpable spleen length over time. I bars represent standard errors. BAT denotes best available therapy.

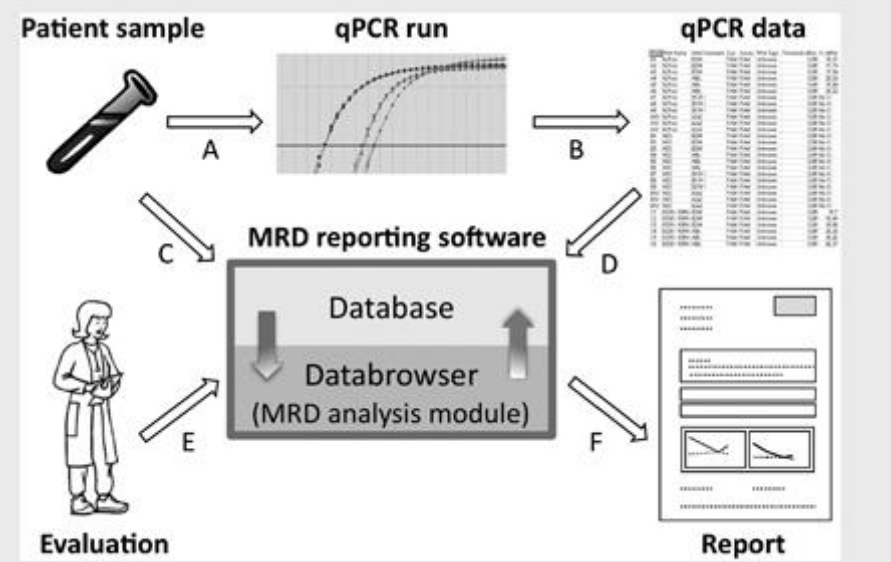
Critical concepts and management recommendations on Philadelphia-negative classical MPNs

Continuous ruxolitinib therapy, as compared with the best available therapy, was associated with marked and durable reductions in splenomegaly and disease-related symptoms, improvements in role functioning and quality of life, and modest toxic effects. An influence on overall survival has not yet been shown.

- With the introduction of JAK2 inhibitors study design with relevant endpoints is critical
- The WP works on outcome definition and related issues

Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Hehlmann R, Hoffman R, Kiladjian JJ, Kröger N, Mesa R, McMullin MF, Pardanani A, Passamonti F, Vannucchi AM, Reiter A, Silver RT, Verstovsek S, Tefferi A; European LeukemiaNet. J Clin Oncol. 2011 Feb 20;29(6):761-70. [23]

Development of standardized approaches to reporting of MRD data using a reporting software package



- Differences in data analysis and presentation complicate multicenter clinical trials
- A highly flexible MRD-reporting software program was designed
- Data from various qPCR platforms can be imported, processed, and presented in a uniform manner The software was tested in a two-step quality control study

Østergaard M, Nyvold CG, Jovanovic JV, Andersen MT, Kairisto V, Morgan YG, Tobal K, Pallisgaard N, Ozbek U, Pfeifer H, Schnittger S, Grubach L, Larsen JK, Grimwade D, Hokland P. Leukemia. 2011 Jul;25(7):1168-73 [24]

Summary

- The ELN combines 108 national leukemia study groups and 105 partner groups within 38 countries buidling a network of more than 1000 scientists and physicians
- 184 studies are listed within the ELTR of which 93 are active
- More than 40 guidelines and treatment recommendations have been published with major impact on diagnostics and treatment of leukemia patients
- Multiple projects of this network received additional funding (e.g. EUTOS, ESF support, COST program); in total >40 Mio Euro