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Dear colleagues,

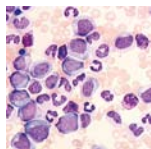
Since its constitution in 2004, the European LeukemiaNet (ELN) has made pioneering progress with collaborations across Europe in the field of Leukemia. In January this year the ELN held its 5th Annual Symposium in Heidelberg, Germany. More than 400 participants contributed with excellent scientific discussions and proposals to this special working conference. 2008, the infrastructure for this European network of Excellence in Leukemia can be considered established and operating in an efficient manner. Some highlights merit special mentioning:

- A network management (NMC) and an information center (ELIC) ensure collection, presentation and distribution of state of the art information through meetings, website and newsletters.
- 65 working meetings were held. An additional 25 scientific meetings were organised and/or supported by the ELN in 2007.
- An important activity within the ELN is the spread of excellence to colleagues and countries not yet participating in the network.
- In January 2008, 14 new institutions and four new countries were accepted by the General Assembly, resulting in a total number of 147 participants in 28 countries.
- European leukemia registries for CML, ALL, ET and MDS have been established to determine incidence and disease patterns with quality controlled outcomes across Europe, with far reaching implications for research and public health planning.
- Clinical trials on a European level have been promoted or activated. The establishment of an ELN Expert Committee on international investigator-initiated trials (IITs) was proposed and an information platform on international IITs was implemented (<http://www.leukemia-net.org>). Specific issues for IITs around the EU Clinical-Trials-Directive 2001/20/EC were addressed at an IIT workshop by about 100 ELN members from over 20 different countries in January 2008.
- Standardised and quality controlled diagnostics and therapies constitute the basis for improvements of clinical outcomes. Quality control rounds on an European or international level were performed for molecular monitoring in CML. Consensus recommendations were published for diagnosis, cytogenetic analysis and treatment of CLL and for morphological diagnosis of leukemias.
- Novel research approaches in molecular medicine, like the "Chromatin-Immuno Precipitation Chip" (ChIP-Chip) analysis or the "Gene Analysis Platform" (GAP) were applied to investigate leukemia pathogenesis or leukemia classification with the prospect of identifying so far unknown leukemia subtypes. GAP was specifically developed to process large-scale microarray datasets and to assure standardised data analysis workflow for gene profiling. A leukemia gene list web-server is currently under development and will facilitate a systematic comparison of gene expression data with published leukemia gene lists.
- The launch of public-private partnerships in the fields of CML and MDS constitutes another important step forward. EUTOS, the European Treatment and Outcome Study for CML, is unique in documenting outcome of leukemia on an European level. EUTOS comprises projects on an European CML registry, on standardized monitoring for quality-controlled outcomes, pharmacological monitoring and spread of excellence. Several meetings have taken place since contract signature and the infrastructure of the four subprojects is in place.
- Looking back to a successful educational event in Budapest in 2007, you are invited to the next ELN events: The 2nd International Symposium on Minimal Residual Disease in Hematological Malignancies in Kiel (Germany) from 18. - 20. September 2008 and the largest event this year entitled "Targeted CML Therapy: Innovating today for a better tomorrow" in Cannes (France) from 17. - 19. October 2008.

Five years ELN, that means five years hard work by many, achieving international progress in collaborative research and patient management, across Europe, breaking borders and spreading excellence. We thank all those who accomplished these goals and look forward to an exciting future.



Prof. Dr. Rüdiger Hehlmann  
Network Coordinator



## European Registry of chronic myelogenous leukemia patients in failure after imatinib therapy

**F. Guilhot**  
*Université de Poitiers, France*

Although imatinib is now the first line therapy for chronic myelogenous leukemia patients, experimental and clinical studies suggest that imatinib as a single drug might not be sufficient to eradicate Ph-positive stem cells. Moreover, a concern with any single agent administered chronically is that resistant clones may emerge. Molecular studies of resistant leukemia cells isolated from patients have implicated BCR-ABL kinase domain point mutation as the most common mechanism of resistance. However, other mechanisms of resistance such as drug efflux, drug metabolism, BCR-ABL amplification have also been described. Current knowledge of the efficacy of imatinib is based on the results of the large IRIS trial. In this trial the risk of progression after 5 years of therapy is near zero for patients who achieved a complete and sustained cytogenetic response. However, the true rate of failure patients treated with imatinib as a single agent is currently unknown. Knowledge on this subject is essential since no information is available concerning the true rate of failure outside clinical trials or unpublished studies.

Based on the considerations listed above, reasons for stopping imatinib could be multiple and the therapeutic decisions following imatinib failure are not well described.

Thus, the purpose of the imatinib failure patient (IFP) registry is to

1. collect data of imatinib failure CML patients in Europe,
2. document all subcategories of failure,
3. collect information on the treatment which was proposed and
4. collect information on the risk profile.

Therefore, the research questions are as followed:

- How many patients experience:
  - Lack of efficacy (failure) under imatinib therapy?
  - Toxicity leading to discontinuation of imatinib?
- What are the clinical and biological profiles of failure patients who experienced failure or toxicity?
- What was the dose and duration of treatment by imatinib until failure or toxicity was recorded?
- What was the medical decision after discontinuation of imatinib therapy?

Mechanisms of resistance are not detailed, and the different categories of mutations are not recorded in this registry. The IFP registry is organized as a sub-registry under the ELN-CML Registry (WP 4). IFP registry is supported by a grant from the 6<sup>th</sup> European Framework program and by Novartis Pharma. French authorities approved this study in accordance with the European Community and Helsinki protocol.

As of December 2007, 567 patients (M 55%; F 45%) were recorded (Fig. 1). Median age at diagnosis was 51 (range 12-80 years). Fifty seven percent were never included in prospective studies at the time of failure. Reason for registration was no or unsatisfactory response in 28% of cases, loss of responses and progression to accelerated phase or blast crisis (23%) or discontinuation because of toxicity (17%) (Tab. 1).

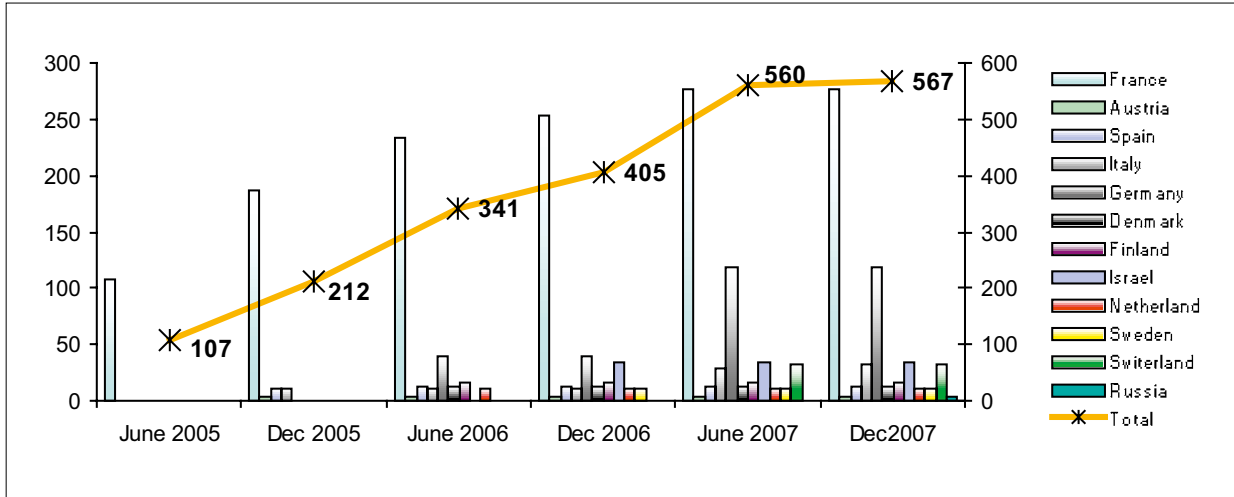


Fig. 1: Number of patients

<b>Reason for registration</b>	<b>[N]</b>	<b>%</b>
No CHR (after 3 months)	12	2
Not any CyR (after 6 months)	56	10
No MCyR (after 12 months)	90	16
Hematological relapse	42	7
Cytogenetic relapse or progression	65	11
Progression to accelerated phase or blast crisis	130	23
Toxicity (leading to discontinuation)	95	17
Miscellaneous	77	14
<b>Total</b>	<b>567</b>	<b>100</b>

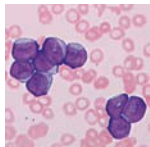
Tab. 1: Reason for registration (Form A); CHR: complete hematological response, CyR: cytogenetic response; MCyR: major cytogenetic response

End of 2007 the registry was activated in several participating centers of 12 European countries. The number of centers in Europe is constantly increasing and we are currently registering both new patients and the follow-up of patients with a target number of 1000 patients by the end of 2008.

## ChIP- chip microarrays to study the epigenome in leukemia

C. Müller-Tidow and M. Dugas

Department of Medicine A, Hematology and Oncology and Department of Medical Informatics and Biomathematics, University of Münster, Germany



### Microarrays to study leukemia

High throughput analyses have revolutionised research approaches in molecular biomedicine. The best known and established approach, the global analysis of mRNA-expression by microarrays, is now commonly used in leukemia research. Profiling of leukemia mRNA can also be used for diagnoses and classification. Recent developments in microarray technology and specimen-preparation have also led to the development of novel and complementary techniques. It is now possible to identify direct genomic binding sites of transcription factors as well as genome wide chromatin modifications by microarrays<sup>1,2</sup>. This is of special importance for leukemia, since transcription factor alterations are of crucial importance in the pathogenesis of several leukemia subtypes. For example, balanced translocations in acute myeloid leukemia (AML) involve transcription factors that are commonly associated with proliferation and /or myeloid differentiation. Identification of their direct genomic targets as well as the identification of genome-wide epigenetic alterations in AML might lead to better understanding of the disease and to novel therapeutic targets.

### Principle of ChIP-Chip

These novel microarray applications rely on different array platforms and usually originate from the specific immunoprecipitation of a protein-DNA complex (Fig. 1). They are thus called chromatin-IP-coupled with microarrays (ChIP-Chip analysis). First, proteins and DNA are cross-linked by formaldehyde in living cells *in vivo*. Subsequently, chromatin is sheared into smaller fragments with the transcription factors and the chromatin modifications still being in place. Sensitive and specific antibodies are utilized to significantly enrich specific protein-DNA-complexes from the total pool of chromatin. The immunoprecipitated DNA is purified. Finally, the DNA is amplified, labelled and hybridised onto genomic microarrays. The fluorescence intensity of the different genomic locations contained on the microarray can then be analysed and genomic binding sites can be correctly determined by appropriate bioinformatics analyses. In contrast to microarrays for expression profiling, genomic arrays most importantly contain promoter and enhancer as well as locus control regions, which are

relevant for transcription factor binding and regulation of gene expression. There are already several sources for specific genomic oligoarrays. Besides a few commercial suppliers, we have established a novel microarray-platform based on 50 mer oligonucleotides. These more than 33,000 independent genomic oligonucleotides are placed in the promoters and regulatory regions of more than 11,000 well characterised protein coding genes as well as more than 500 miRNAs. This microarray platform is very versatile given that novel sequences can easily be added. This is important since 2<sup>nd</sup> generation sequencing methods can be used after chromatin immunoprecipitation to identify transcription factor binding sites or chromatin alterations on a genome wide scale *in vivo*. The resulting spots (for example discovered in few samples in cell-lines) can then be used to complement the genomic oligoarray. Finally, the custom array can be used to query patient specimen with high throughput at relatively low cost.

### Applications for ChIP-Chip and genomic arrays

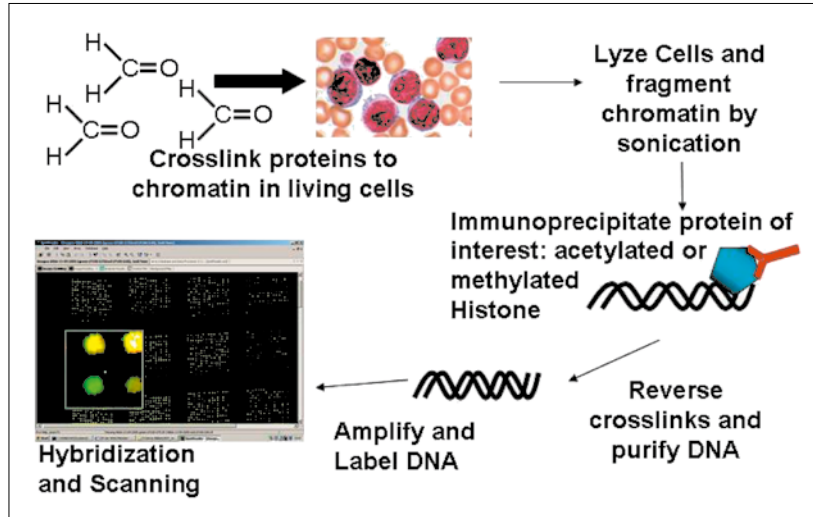
Regardless of the choice of array platform or even the use of 2<sup>nd</sup> generation sequencing to analyse the chromatin IPs<sup>3</sup>, three major arrays of application are emerging. First, transcription factor binding can be profiled with high sensitivity and specificity. Second, chromatin modifications such as posttranslational modifications of histones can be analysed. Histone modifications such as acetylation or methylation of amino acid residues are crucially important not only for chromatin structure but also for transcriptional regulation. Multiple histone modifications have been discovered and these are indicators of promoter activity and act as docking molecules for signalling. Finally, DNA-methylation can be analysed by immunoprecipitation of methylated DNA using anti-methylated-Cytosine antibodies. An alternative for the latter approach is the use of methyl-CpG binding proteins to identify methylated DNA-regions. Thus, genomic arrays can be used for a wide spectrum of *in vivo* analyses regarding transcriptional regulation and genome organization.

### Applications of ChIP-Chip in leukemia research

We have recently used ChIP-Chip to identify genomic binding sites of PML-RAR $\alpha$ , the chimeric oncogene produced by t(15;17) in acute promyelocytic leukemia (Fig. 2). More than 300 direct genomic *in vivo* targets of PML-RAR $\alpha$  could be identified<sup>4</sup>. This number far exceeds the only handful of already known direct PML-RAR $\alpha$  targets. The PML-RAR $\alpha$  targets can be broadly placed in genes regulating apoptosis, proliferation, transcription and myeloid differentiation. This is very well in accordance with the known biological functions of PML-RAR $\alpha$ . In addition to identifying PML-RAR $\alpha$  target genes, we also analysed the biological consequences of genomic PML-RAR $\alpha$  binding. We utilised the same ChIP-Chip-platform to analyse the binding of histone deacetylase 1 as well as the alteration of several histone modifications in PML-RAR $\alpha$  expressing versus non expressing cells. Interestingly, these data showed that PML-RAR $\alpha$  acts as universal repressor on almost all of its presumed direct targets. These findings highlight the special power of ChIP-Chip analyses for the identification of transcription factor targets *in vivo*. Recently, we have started to identify global alterations of important histone modifications in primary AML patients. In this currently ongoing project there are more than 170 patients with acute leukemia and control patients being analysed by ChIP-Chip for global histone acetylation and histone methylation pattern. Importantly, these analyses led to the generation of histone modification signatures that unambiguously allowed the identification of AML specimen versus normal hematopoietic progenitors and also allowed to distinguish between AML and ALL. In each case, between several hundreds and thousands of altered genomic locations could be identified by ChIP-Chip analyses. With the resulting data sets we can now analyse similarities and differences between individual leukemia subtypes and we are able to look for larger regions of epigenetic deregulation *in vivo*.

## Outlook

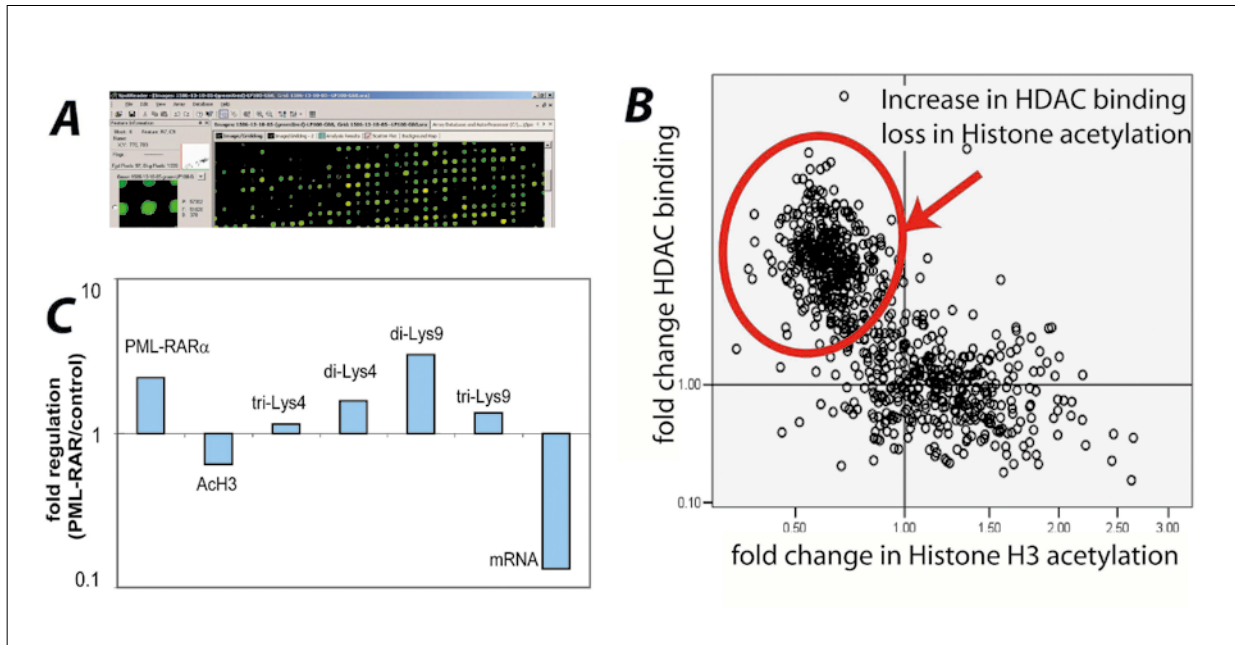
ChIP-Chip analyses have recently emerged as powerful tools for cell-culture-based analyses. Recent data from our laboratory also show that ChIP-Chip analyses can be successfully employed for the analyses of primary patient specimen. For *in vitro* as well as *in vivo* analyses, ChIP-Chip is increasingly used for the analysis of leukemia pathogenesis. Another prospect for the future could be to use ChIP-Chip for leukemia classification with the prospect of identifying so far unknown leukemia subtypes. In addition, the development of epigenetic drugs in AML, such as HDAC inhibitors and DNA methylation inhibitors, could be supported by ChIP-Chip analyses that identify response predictors *in vivo*. In the near future, the increasing availability of 2<sup>nd</sup> generation sequencing will complement ChIP-Chip analyses. These technologies will significantly increase our knowledge about leukemia pathogenesis in the near future and lead to novel therapeutic targets.



**Fig. 1: Principle of ChIP-Chip Arrays.** ChIP-Chip assays are used for microarray based analysis of global histone modification patterns (shown in Figure) or for transcription factor targets *in vivo*. Chromatin complexes containing DNA and protein are immunoprecipitated using specific antibodies. Subsequently, the DNA immunoprecipitated along the protein is purified and finally hybridized onto genomic microarrays.

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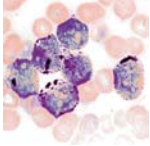


**Fig. 2: ChIP-Chip analysis to identify PML-RAR $\alpha$  target genes.**

A) We analyzed genome wide binding of PML-RAR $\alpha$  using ChIP-Chip. Example of an array.

B) Identified PML-RAR $\alpha$  target genes were analyzed for the resulting chromatin modifications. Each target gene is represented by one dot. Many target genes showed increased binding of histone deacetylase 1 (HDAC) and subsequent loss of histone acetylation.

C) The PML-RAR $\alpha$  target genes (here one example) showed a repressed chromatin configuration (increase in methylation of lysine 9 di-Lys9, tri-Lys 9 and loss of acetylated H3-acH3). As a consequence, mRNA expression is repressed.



*N. Gökbüget<sup>1</sup>, R. Bassan<sup>2</sup>, H. Dombret<sup>3</sup>, R. Foà<sup>4</sup>, J. Ribera<sup>5</sup>, R. Willemze<sup>6</sup>, D. Hoelzer<sup>7</sup>*  
<sup>1</sup>Universitätsklinikum Frankfurt, Germany; <sup>2</sup>Azienda Ospedaliera - Ospedali Riuniti di Bergamo, Italy; <sup>3</sup>Assistance Publique - Hôpitaux de Paris, France; <sup>4</sup>Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma "La Sapienza", Italy; <sup>5</sup>Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Spain; <sup>6</sup>Leiden University Medical Center, The Netherlands; <sup>7</sup>ONCOLOGIKUM, Frankfurt am Museumsufer, Germany

The European Working Group for Adult ALL was founded in 2002 as part of the European LeukemiaNet. Acute lymphoblastic leukemia (ALL) in adults is a rare disease with a variety of subtypes showing highly significant differences in terms of clinical manifestation, disease biology and outcome. Therefore most ongoing trials for de novo ALL are subtype adjusted and risk stratified. Diagnostic standardisation is therefore an essential pre-requisite for the achievement of major aims of the EWALL which are 1. comparative analysis and 2. joint clinical trials.

As a first step, the group defined under the leadership of R. Foà standards for diagnostic confirmation of ALL with a differentiation between 1. minimal pre-requisites which may also be applicable in developing countries and 2. optimal pre-requisites which should be the standard in the EWALL group. These definitions have been discussed with the workpackage on diagnostics (WP10) and are available through the ELN website.

In 2007 major decisions were made regarding the initiation of joint clinical trials. The first one was started in July 2007 in elderly Ph-positive ALLs with P. Rousselot as principal investigator. It is based on a chemotherapy backbone for treatment of elderly ALL which was designed by the EWALL based on French and German prospective trials for elderly ALL. Patients with Ph-positive ALL receive a low intensity induction chemotherapy with dasatinib in parallel. The initial phase is followed by sequential therapy with chemotherapy consolidation cycles and dasatinib cycles and finally a maintenance phase. The study is activated in France and upon activation in Italy, Spain and Poland.

Secondary endpoints of this trial are molecular response based on quantitative evaluation of BCR-ABL and the incidence and type of mutations which confer resistance to imatinib, dasatinib and other tyrosine kinase inhibitors. The analysis will be done in predefined central laboratories in each participating country. Clearly standards for the diagnostic procedure had to be defined, which were not available for analysis of m-BCR which is the most frequent BCR-ABL breakpoint in ALL. Under the leadership of H. Pfeifer the central laboratories exchanged information on applied methodologies. During a meeting at the EHA-10 in Vienna with representatives of the laboratories, the differences were discussed and the group agreed on common standards for quantitative BCR-ABL evaluation and for detection of mutations. Furthermore, there was an agreement to perform lab rounds in the EWALL laboratories in collaboration with the European Study Group on minimal residual disease detection in childhood acute lymphoblastic leukemia (ESG-MRD-ALL). The methodology for lab rounds was developed with support from the German CML Study Group (A. Hochhaus et al). The aim of this trial is to assess the variance of results obtained from different labs using different amplification platforms and different optimised protocols for cDNA synthesis and RT-QPCR conditions.

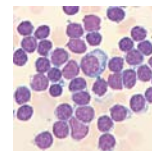
Two further EWALL trials in elderly ALL are planned for 2008 and 2009 in collaboration with Mundipharma. The aim is to evaluate the drug Forodesine in two different settings. Again, in this trial minimal residual disease (MRD) will be an entry criterium and also an endpoint. Two different methods are available for MRD-evaluation in ALL 1. based on PCR detection of individual rearrangements of TCR- and IgH-genes and 2. based on detection of leukemia-specific surface antigens by flow-cytometry. The EWALL decided to focus on the first method since elaborated standards have already been defined by the ESG-MRD-ALL (van der Velden 2007). The group agreed to adhere to these standards and the participating labs shall be involved in the lab rounds organised by the ESG-MRD-ALL.

The next step is the definition of response criteria based on MRD for BCR-ABL negative and positive ALL. This is in line with considerations of the regulatory authorities in the US and Europe regarding the acceptance of new endpoints for clinical trials.

The collaboration of EWALL and ESG-MRD-ALL will be intensified. During a meeting on MRD evaluation in Kiel (18.-20.9.2008) there will be a collaborative session dedicated to "ALL: Definition of remission and relapse in the era of flow and PCR".

# New aspects of the updated guidelines for the diagnosis and treatment of chronic lymphocytic leukemia

C. Schweighofer, M. Hallek  
Universität Köln, Germany



Since publication of the first two versions of guidelines on diagnosis and treatment of CLL in 1988 and 1996, notable progress has been made in CLL research with regard to prognostic and diagnostic parameters and new treatment options. Recently, the IWCLL (International workshop on CLL) -sponsored working group summarized these achievements in a new release of guidelines, which have been e-published in Blood in January 2008<sup>1</sup>. Members of the European Research Initiative on CLL (WP7) have been involved in their development, discussion and validation. The following article gives a short overview about the most important 5 new aspects of the up-dated IWCLL-guidelines in comparison to the 1996-version published by the National Cancer Institute Working Group (NCI-WG)<sup>2</sup>:

## Diagnosis of CLL versus MBL versus SLL

The requirement of  $\geq 5000/\mu\text{l}$  lymphocytes in peripheral blood for the diagnosis of CLL is still valid with more accentuation of the lymphocytes being identified as "B-lymphocytes" by immunophenotyping. The minimum duration of pathologic lymphocytosis is now defined at 3 months (former guidelines: 4 weeks). The presence of  $< 5000$  B-lymphocytes without further clinical pathologic signs and symptoms is separately named as "monoclonal B-lymphocytosis (MBL)" according to Marti et al.<sup>3</sup> with an increased risk of development of CLL. Notably, a heavy bone marrow infiltration with consecutive peripheral cytopenia annuls the criterion of 5000 B-cells in the peripheral blood. Then the diagnosis of CLL via bone-marrow is sufficient. The diagnosis of SLL (small lymphocytic lymphoma) has to be diagnosed via lymph node histology and is clinically defined by the presence of lymphadenopathy, less than 5000/ $\mu\text{l}$  peripheral B-lymphocytes and the absence of cytopenias caused by bone marrow infiltration. The criteria for the immunophenotypic definition of CLL have been similarly formulated to the 1996 criteria. In addition to the co-expression of CD5, CD19, CD20 and CD23, low surface immunoglobuline and kappa or lambda light chain expression, the low surface expression of CD79b on CLL cells is noted.

## Role of cytogenetics and FISH analysis

Molecular cytogenetic analysis via fluorescent in situ hybridization (FISH) for the

detection of unfavourable prognostic factors like deletions on chromosome 17p or 11q is recommended as a diagnostic procedure prior first-line treatment. The usage of unmutated VH status, VH 3.21 usage, ZAP70- and CD38 expression, serum markers like CD23, thymidine kinase and  $\beta 2$ -microglobuline for routine assessment is not advised. Further clinical trials are requested to standardize these prognostic markers and develop them to useful instruments in clinical practice.

## Indication for computed tomography (CT) scans

CT scans are recommended to assess lymphadenopathy in CLL patients only within clinical trials, in order to allow an optimal response assessment. Further clinical trials are demanded to investigate the necessity and efficiency of CT scans for response evaluation. Outside of clinical trials CT scans are considered not to be required, neither for initial staging nor for follow-up. Positron emission tomography (PET) scans are regarded as useful only in cases of Richter's syndrome.

## Definition of remission status and progressive disease

The criteria for the definition of a complete remission (CR) have been changed as follows: Staging examinations to assess the remission status after any therapy are recommended to be performed not earlier than 3 months (former criteria: 2 months) and not later than 6 months (in case of persistent cytopenias) after treatment completion. The absence of clonal lymphocytes in the peripheral blood is added as one of the major criteria. Pathologic lymphadenopathy is defined at a lymph node diameter of greater than 1.5 cm. For the confirmation of a complete remission after treatment within clinical trials a bone marrow biopsy is recommended, which should be additionally analyzed with flow cytometry or immunohistochemistry. In case of residual CLL cells by conventional flow or immunohistochemistry a partial remission has to be ascribed. The use of the definition "nodular PR" is no longer recommended. For patients with persistent cytopenias not caused by marrow infiltration and otherwise fulfilling all criteria for a CR, a new remission term is defined by "CR with incomplete bone marrow recovery (CRi)". The outcome of such patients in comparison to non-cytopenic CRs has to be assessed within future trials. The definition

of a partial remission has been changed as follows: The required 50% reduction of lymphadenopathy is now specified as a decrease in the "sum products of up to 6 lymph nodes" and extended by a complete lack of newly emerging or increasing lymph nodes. In case of a single enlarged lymph node the calculation with one diameter is allowed. The criteria for progressive disease have not been widely changed but are also outlined in more detail with regard to the required 50% increase in lymphadenopathy: e. g. small lymph nodes in the size of  $> 1$  cm to 1.5 cm must increase up to a size to at least 1.5 cm or by 50% to be clinically relevant. Lymph nodes with a diameter of  $> 1.5$  and  $< 2$  cm must increase to a size of  $> 2$  cm to be considered as significant. Importantly, it is advised that treatment related cytopenias must be excluded for the judgement of the CLL remission status.

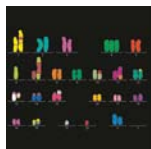
## Minimal residual disease (MRD) assessment

Due to its potential impact on long-term prognosis and survival of CLL patients, the assessment of MRD is highly recommended to be included into clinical trials, in order to further investigate the achievement of MRD eradication and duration of MRD negative complete remissions. As a current standard, four-colour flow cytometry (MRD flow) or allele-specific oligonucleotide PCR are considered as reliable techniques sensitive enough to track one single CLL cell in 10.000 leukocytes of peripheral blood or bone marrow<sup>4</sup>. In patients with peripheral cytopenia the latter has to be preferably assessed for MRD. In summary, the most important changes in the new CLL guidelines concern the following 5 aspects: 1. the approval of MBL as a subclinical disease entity with an increased risk of CLL development, 2. the recommendation of fish analysis prior first-line treatment to exclude chromosomal high-risk features, 3. the basic incorporation of MRD testing into clinical trials, 4. the referral of CT scan assessment solely within clinical trials and 5. the definition of a new remission status, the "complete remission with incomplete bone marrow recovery (CRi)". The new IWCLL-guidelines should be the basis for future scientific and clinical studies in CLL, but also deliver expert advice for daily clinical practice.

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# Gene Analysis Platform (GAP) for ELN



S. Merk<sup>1</sup>, H.-U. Klein<sup>2</sup>, M. Dugas<sup>3</sup>, T. Haferlach<sup>4</sup>

<sup>1,2,3</sup>Universitätsklinikum Münster, Germany; <sup>4</sup>MLL Münchner Leukämielabor GmbH, Germany

Gene Analysis Platform (GAP)<sup>1</sup> was developed to provide a system for convenient data exchange between various leukemia research groups, to process large-scale microarray datasets and to assure a standardized data analysis workflow for gene profiling. At present, GAP is used by twelve ELN-workgroups covering 65 analysis sets and about 1800 microarrays.

The technical core of GAP is a SQL database running on a multi-processor linux system. This database stores all occurring data including raw and normalized data as well as analysis results. A command line interface serves as back-end for data management and analysis. This back-end is implemented in R (a statistical programming language) and applies various packages of the Bioconductor project<sup>2</sup>. Exploration of data and results is provided by a web-based front-end which is implemented in PHP (a scripting language) and can be accessed via a standard web browser.

### Data exchange platform

Cooperating ELN-laboratories are spread over Europe, therefore a platform to exchange high-volume microarray data was implemented in GAP. The ELN file manager enables transfer of raw data, for instance Affymetrix cel-files, as well as files containing clinical/phenotype information.

### Data preprocessing and analysis

Microarray data preprocessing consists of several steps: parsing of raw data, normalization, quality assessment and filtering. Raw data can be imported by GAP in various formats, for example as Affymetrix cel-files or in tabular format. RMA, VSN and MAS5<sup>2</sup> are implemented for normalization of raw data. A comprehensive quality check includes assessing raw data chip images, differential chip images, 3'/5'-ratios of housekeeping genes like  $\beta$ -Actin or GAPDH, boxplots or density plots as well as Affymetrix specific quality parameters to identify chips with poor quality. Unspecific filtering helps to exclude genes that are likely to be non-expressed in the respective cells or tissue. It is also possible to filter out genes with low variance across all samples.

Several methods are implemented to reveal structure in the data without including class label information. Principal component analysis (PCA) is a standard technique to analyze multidimensional datasets. PCA can be visualized as 2D- or 3D-plots. Hierarchical clustering provides a partitioning of data into subsets according to their similarity. Clusters can be visualized with trees (dendrograms). Heatmaps with color-coded expression values can be generated to visualize microarray data.

A very common analysis method is identification of differentially expressed genes between different disease subgroups. The goal is to identify specifically up- or down-regulated genes. GAP provides methods like t-test for two-group comparisons as well as analysis of variance (ANOVA) for comparisons of more than two groups. Various statistical parameters can be calculated, such as fold change, false discovery rate (according to Benjamini & Hochberg or Storey & Tibshirani) and family-wise error rate according to Bonferroni (Fig. 1).

GAP also provides various methods for class prediction. Support vector machine algorithms can be applied to a training set to establish a prediction rule for an independent test set. These methods were applied to large leukemia microarray datasets<sup>3</sup>. A new feature of GAP are transcriptome correlation maps<sup>4</sup> which can be used to identify regions of adjacent genes showing correlated gene expression profiles.

From our experience, consistent biomedical interpretation of gene lists can be a challenging task, therefore we are developing the leukemia gene list web service (LGWS). It enables a systematic comparison of gene expression data with published leukemia gene lists. After input of gene expression data and a clinical variable of interest, these data are compared with published gene lists. Feedback from ELN members about relevant publications regarding leukemia gene lists to be included in LGWS is highly appreciated.

### Outlook

Currently we are working to provide methods for integrated analysis and visualization of gene profiling data with other chip platforms, in particular ChIP-chips, SNP chips and microRNA chips<sup>5</sup>. All ELN members are welcome to use GAP, which is available via workpackage 13 at <http://www.leukemia-net.org>. For more information or a demo account please contact:

[dugas@uni-muenster.de](mailto:dugas@uni-muenster.de).

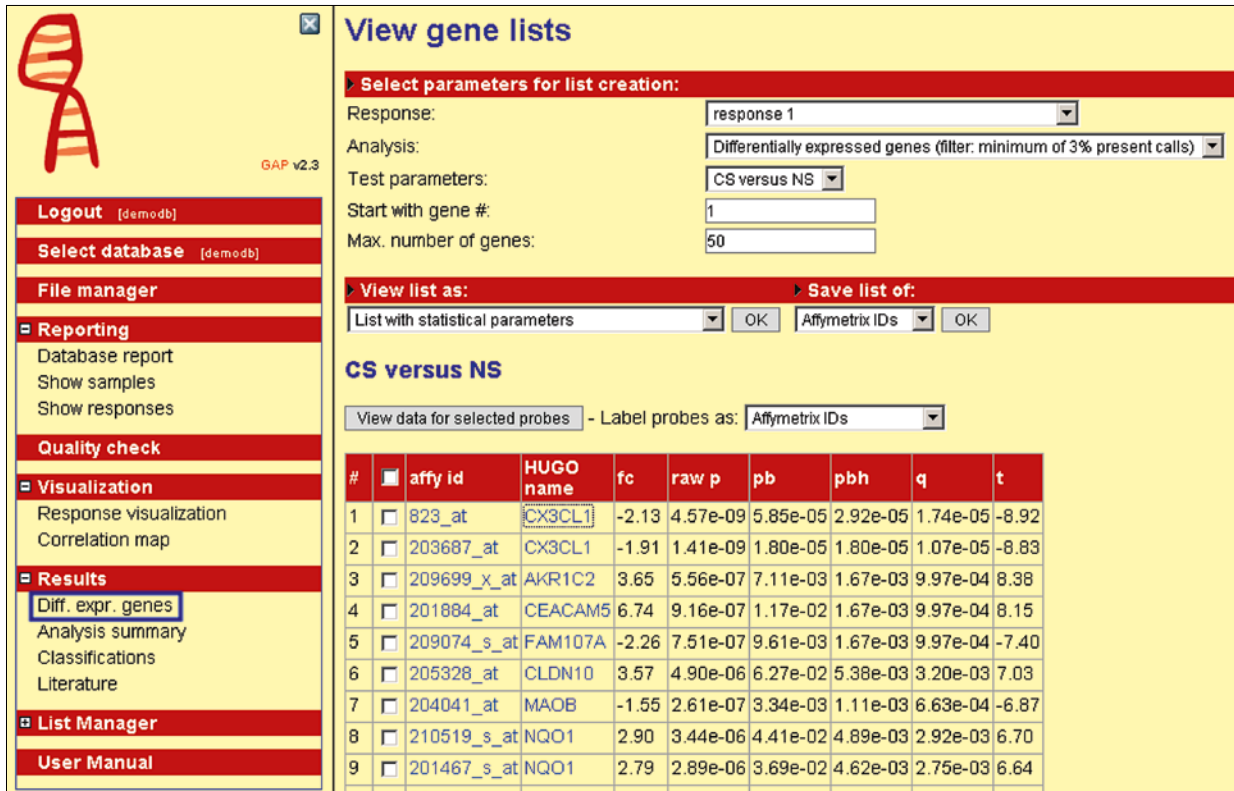


Fig. 1: A screenshot of GAP, showing results of differentially expressed genes.

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N. Gökbuget, K. Ihrig  
Universitätsklinikum Frankfurt, Germany

**Present regulative status**

Intentionally the EU Clinical Trials-Directive 2001/20/EC planned to harmonize good clinical practices for clinical trials in any member state of the European Community. The directive assigned all member states to implement the regulatory requirements into national law until end of 2004. 7 years after its setting, it turns out, that

- member states needed about 6 years to amend their national law
- they did so in many different ways and harmonization is not achieved in a lot of aspects.
- Clinicians and study centers are still in process to adapt to the new regulatory requirements and finally
- this implementation made the situation of Investigator-initiated-trials (IITs) more difficult, not only on an European but also on a national level. Although IITs are recognized as a specific kind of a clinical trial with a specifically valuable impact for patients and research, the new time- and cost-consuming organizational demands escalated tremendously as elucidated by several publications<sup>1,2</sup>.

**Workshop on IITs at the 5<sup>th</sup> ELN Symposium**

In order to address these specific difficulties for international IITs, a workshop was organized by ELIC, on the day before the 5<sup>th</sup> ELN symposium. The workshop bundled experience in initiation and conduct of IITs on a multinational level from both ELN internal working groups and other international European working groups as ECRIN (Dr. Kubiak, European Clinical Research Infrastructure Network), EORTC (Dr. Lambert, European Organisation on Research and Treatment of Cancer), EBMT (Prof. Dr. Apperly, European Group for Blood and Marrow Transplantation) and KPOH (Dr. Mauz-Körholz, Competence Network on Pediatric Oncology and Hematology). It attracted about 100 people from about 20 different countries and was evaluated afterwards.

**Summary**

All groups shared the same experience, as the initiation and conduct of international IITs is much harder than before EU directive 2001/20/EC. Furthermore, there is no harmonisation of approaches in the different European countries and nobody has a real overview. There is also a lack of information on available support (e.g. as offered by the ECRIN). Real alternatives to clinical trials e. g. registries are not available since they are subject to detailed regulations as well. On the other hand there are a lot of different approaches to deal with the situation and to find ways to initiate IITs. There are also few examples of international IITs (WP6, WP8) in the frame of the ELN which have started or are starting with great difficulties. Not surprisingly the costs have been exploded.

**Next steps**

Some WPs had started international IITs, and most of them plan to do so in the near future since this is a major goal of the network. The relevance of the topic was reflected by the large audience and the feedback from participants; the overall grading of the workshop in the evaluation was very good. Taking all that into account the suggestion of ELIC to set up an "ELN Expert Committee on International IITs" was highly welcomed. ELIC implemented as a first practical result another substructure into the ELN website (<http://www.leukemia-net.org>: ELN>Network Services>Infocenter>International IITs).

ELIC wants to thank all speakers for their contribution: B. Simonsson, T. Büchner, P. Rousselot, N. Gökbuget, A. Westermann, E. Hellström-Lindberg, T. Barbui, Z. Doran, J. Hasford, K. Ihrig; C. Kubiak, F. Lambert, C. Mauz-Körholz. At the website you will find the presentations of the workshop and further information for investigators. All those who are interested in the ELN Expert Committee are invited to contact ELIC (ihrig@med.uni-frankfurt.de).

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**A. Hellenbrecht**  
**Universitätsklinikum Frankfurt, Germany**

It is well known, that the International Committee of Medical Journal Editors (ICMJE) accepts only WHO-registered trials for potential publication. According to the statements of the ICMJE and WHO from 2004 and 2005<sup>1, 2, 3</sup>, all ongoing studies are accepted, that are registered before September 13, 2005. All studies – initiated after this date - must be registered before the enrollment of the first patient.

In the beginning in 2004, the study-registration was limited to so called "interventional studies". Now, the ICMJE will begin to implement the WHO definition of clinical trials for all trials that begin enrolment on or after July 1, 2008. This definition states that a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."

The WHO/ICMJE rules for registration and the definitions of what a proper trial registry is, changed arbitrarily in the last years. The latest information from WHO/ICMJE confirmed, that only one trial registry per country (National Registry) would be accepted. You will find a list of actually WHO-accepted registries at: [http://www.who.int/ictpr/network/list\\_registers/en/index.html](http://www.who.int/ictpr/network/list_registers/en/index.html)

The majority of the European countries have no national registries at the moment. So it's currently recommended to register all trials with one of the WHO-listed primary registries. Most probably the NIH registry [clinicaltrials.gov](http://www.clinicaltrials.gov) is also accepted although it is deleted from the list of primary registries at the moment.

Beyond the mentioned duties, the European Leukemia Trial Registry (ELTR) has the genuine aim to inform physicians and patients in Europe about ongoing trials. We would like to encourage all physicians and researchers to register their trials furthermore also in the ELTR.

The short protocol template which is found at <http://www.leukemia-net.org> >Leukemias> Trial Registry can be sent to the Information Center. This is sufficient to register the trial in the ELTR. Even more easily you may provide us your registration number in one of the other registries.

For further information please refer to the website <http://www.leukemia-net.org> or contact the European Leukemia Information Center: [elic@em.uni-frankfurt.de](mailto:elic@em.uni-frankfurt.de)

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## A novel collaboration between academia and industry to improve treatment in CML

F. Pane<sup>1</sup>, F. Cervantes<sup>2</sup>

<sup>1</sup>CEINGE Biotecnologie avanzate s.c.a.r.l., Italy; <sup>2</sup>Hospital Clinic Provincial de Barcelona, Spain

The European Treatment and Outcome Study (EUTOS) for chronic myeloid leukemia (CML) represents a unique collaboration between the European LeukemiaNet (ELN) and Novartis. The EUTOS for CML project:

- was launched in June 2007
- is underpinned by a contract between the University of Heidelberg (legal representative of the ELN-CML group) and Novartis
- is a collaboration that will run for three years, with an option to extend the contract beyond 2010
- is an excellent example of a novel public-private partnership for translational research.

The objectives of the collaboration are to enhance understanding of the nature and management of CML, to improve standardized evaluation and monitoring, and to optimize diagnosis and treatment of CML across Europe.

EUTOS for CML comprises four subprojects: 1. an expanded CML Registry with quality controlled outcome, 2. standardized Molecular Monitoring, 3. Pharmacological Monitoring and 4. Spread of Excellence. Each subproject is overseen by a Working Group consisting of ELN members and Novartis representatives. An Executive Board periodically verifies direction and meets results, the next time in a year from now. Significant progress has been made since inception (see Tab. 1 for key achievements so far), and physicians and patients from across Europe have engaged positively with the project.

### CML Registry

The purpose of this subproject is to expand the already existing ELN-CML registry to cover a significant proportion of CML patients in European countries. The additional funding through EUTOS for CML is enabling the ELN to extend the registry to patients not enrolled in clinical trials, and to centers and countries that have not previously partici-

pated in the ELN. It is expected that by 2010 around 5,000 patients will be included in total, comprising patients already enrolled in clinical trials ('in study' group), patients already registered in existing databases of national/regional study groups or reference centers ('out study' group), and newly diagnosed patients on a population basis ('prospective' group).

A core data set has been established for the collection of retrospective data from patients in existing studies or national/regional databases across Europe, and discussions are now underway on the inclusion of prospective data from patients newly diagnosed with CML in 2008 and 2009. Scientific committees have been set up to define key questions that may be addressed with registry data.

### Molecular Monitoring

The Molecular Monitoring subproject will facilitate the spread of internationally standardized PCR analysis for the quantification of BCR-ABL mRNA levels and the detection of BCR-ABL mutations. The goal is to standardize the methodology and results of residual-disease monitoring in 50 centers, with at least one per participating country/region, which will then serve as a national reference laboratory to further standardize other laboratories in that country. Dilutions of cell lysates have already been sent out to around half of these centers. Results from the analysis of these samples can then be used to calculate laboratory-specific conversion factors, which allow for the representation of all results on a common international scale.

### Pharmacological Monitoring

Recent publications (Picard et al. *Blood* 2007;109:3496-9; Larson et al. *Blood* 2008;111:4022-8) provide evidence that low trough plasma levels of imatinib may result in inferior treatment outcomes in CML, suggesting that adequate

blood levels of imatinib are important for good clinical response. However, until now, the availability of plasma level testing for clinical centers has been limited. The aims of the EUTOS for CML Pharmacological Monitoring subproject are to expand the availability of imatinib monitoring to a European level, and to construct a dosing database to define therapeutic threshold and toxic dose.

Under the terms of the EUTOS for CML contract, a central facility at the Bordeaux University Hospital in France is now available to analyze samples from all over Europe free of charge. In addition, the Bordeaux laboratory is assisting in the establishment of monitoring facilities in European countries, using a standardized, quality-controlled monitoring protocol. The project covers 3000 free tests over two years. In addition, a laboratory kit has been developed to facilitate sample submission by physicians, and to ensure that samples arrive intact and on time.

### Spread of Excellence

The Spread of Excellence subproject was created to raise awareness of EUTOS for CML, and to foster ELN activities. It supports all activities that promote realization of the Registry, Molecular Monitoring, and Pharmacological Monitoring subprojects.

A successful EUTOS for CML launch event was held in Budapest in October 2007, with more than 200 press representatives attending or viewing the webcast. In addition, a EUTOS for CML website has been constructed ([www.eutos.org](http://www.eutos.org)), and supportive materials have been developed to explain and promote the other three subprojects. EUTOS for CML is also featured in the ELN exhibition booth for major national and international congresses (Fig. 1), and there will be dedicated EUTOS for CML sessions at upcoming ELN CML events.

### Registry

- A research plan and core data set have been agreed for in-study and out-study patients
- About 3,000 in-study patients are already registered
- Discussion of the prospective patient group has been initiated
- Scientific committees have been formed
- Registry Working Group meetings have been held in Munich (April 2008), Copenhagen (June 2008) and Heidelberg (July 2008)

### Molecular monitoring

- Harmonization of methods and implementation of the international scale is on schedule
- Standardized results are available in about 40 laboratories in 10 countries

### Pharmacological monitoring

- The central facility in Bordeaux is ready to accept samples
- Local facilities across Europe are undergoing standardization

### Spread of excellence

- Supportive materials and information packs for the other subprojects have been created and distributed
- An ELN recommendations pocket card and an ELN/EUTOS exhibition booth have been completed
- The EUTOS for CML website has gone live
- EUTOS for CML sessions are planned at upcoming ELN CML events

**ESH International Conference  
CHRONIC MYELOID LEUKEMIA -  
Biological Basis of Therapy**  
5. - 7. September 2008, Boston, US

**ESH Conference  
Myeloproliferative disorders**  
18. - 20. September 2008, Athens, GR

**2nd International Symposium  
on Minimal Residual Disease in  
Hematological Malignancies**  
18. - 20. September 2008, Kiel, DE

**ESH - EHA Scientific Workshop on  
Molecular Prognostic Markers  
in Acute Myeloid Leukemia**  
3. - 5. October 2008, Mandelieu, FR

**Joint Meeting of the German and  
Austrian Societies of Hematology  
and Oncology and the Swiss Society  
of Medical Oncology -  
DGHO, ÖGHO and SGMO**  
10. - 14. October 2008, Wien, AT

**ELN Frontiers Meeting 2008  
Targeted CML therapy:  
innovating today for a better tomorrow**  
17. - 19. October 2008, Cannes, FR

**50th Annual Meeting of the  
American Society of Hematology  
(ASH)**  
6. - 12. December 2008, San Francisco, US  
Abstracts until 21.08.2008

**ELN Brekfast Meeting  
during ASH**  
7. December 2008, San Francisco, US

**10th Annual Symposium of the German  
Competence Network "Acute and  
chronic Leukemias" and  
6th Annual Symposium of  
the European LeukemiaNet**  
2. - 5. February 2009,  
Rosengarten Mannheim, DE

Tab. 1. Key achievements of the EUTOS for CML project (up to July 2008)



Fig. 1. The ELN exhibition booth, featuring the EUTOS for CML project

### Ongoing studies of the European LeukemiaNet (European Leukemia Trial Registry)

The European Leukemia Trial Register (ELTR) includes active clinical trials administered by study groups of the ELN. Currently over 70 European leukemia studies are listed. Detailed study information and short-protocols are available for free download from the website ([www.leukemia-net.org](http://www.leukemia-net.org)).

The ELTR is the first international leukemia register with expert service and an interface adapted to WHO criteria and is constantly expanding. If you need more information, contact the European Leukemia Information Center ELIC ([Elic@em.uni-frankfurt.de](mailto:Elic@em.uni-frankfurt.de)).

#### ALL: Acute lymphatic leukemia

##### All subtypes:

##### De novo/non-treated

- ALL GIMEMA 0904: Treatment of high-risk ALL and MRD-monitoring
- ALL GRAALL 02/2005: HyperC vs. standard induction and late intensification in Ph neg. ALL
- ALL NILG 09/00: Postremission programme according to MRD
- ALL PALG 4-2002 MRD: MRD as prognostic value for long-term outcome
- ALL PETHEMA LAL-AR-03: Therapy of high-risk ALL
- ALL GMALL 07/2003: Therapy optimization by MRD-evaluation

##### relapsed/refractory

- ALL GMALL Marqibo: Therapy optimization by MRD-evaluation

##### B-Precursor ALL:

##### novo/non-treated

- ALL GMALL 07/2003 with Rituximab: Therapy optimization with Rituximab in ALL Standard-risk (concomitant study to GMALL 07/2003)
- ALL GRAALL 02/2005-R: Mabthera + induction, consolidation and late intensification in Ph neg., CD20+ ALL

##### relapsed/refractory

- Nelarabine T-ALL/ NHL: Phase II-Study with Nelarabine in patients with refractory or relapsed T-ALL or T-lymphoblastic lymphoma

##### PH+ALL/BCR-ABL:

##### De novo/non-treated

- ALL GIMEMA 0201: Imatinib in Ph+ and/or BCR/ABL ALL
- ALL GRAAPH 02/2005: Imatinib-based vs. standard imatinib containing Hyper CVAD induction in de novo Ph+ ALL
- ALL NILG 09/00/Ph+: Intermittent Imatinib programme in Ph+ ALL and CML blast crisis
- EWALL Ph-01: An open label phase II study to evaluate the efficacy and safety of induction and consolidation therapy with dasatinib in combination with chemotherapy in patients aged 55 yrs or over with Philadelphia Chromosome positive (Ph+ or BCR-ABL +) acute lymphoblastic leucemia (ALL)

##### all stages/not specified

- ALL PALG Imatinib in Ph+ ALL: Imatinib as maintenance treatment after consolidation +/- auto SCT in Ph+ ALL

##### Mature B-ALL / Burkitt's Lymphoma

- GMALL B-ALL/NHL 2002: Multicentre Study to Optimize Therapy of B-ALL and High-grade Non-Hodgkin's Lymphoma in Adults (GMALL-B-ALL/NHL 2002)

#### AML: Acute myeloid leukemia

##### AML all subtypes without FAB M3:

##### De novo/non-treated

- AML Low-dose-Deцитabine II (Elderly) (Pending)
- AML Sorafenib (Elderly): Efficacy of Sorafenib added to standard primary therapy in elderly patients with newly diagnosed acute myeloid Leukemia
- AML AZD1152: Safety, Tolerability, PK and Efficacy of AZD1152 in Patients With Relapsed Acute Myeloid Leukemia
- AML AraC-IL2: Combination Chemotherapy, Interleukin-2 and Peripheral Stem Cell Transplant in Treating Patients With Acute Myeloid Leukemia
- AML CP4055: A Phase I/II Study of CP-4055 in Patients With Refractory/Relapsed Hematologic Malignancies
- AML Systematic Vs. Response: Timed-Sequential Induction in CBF-AML

##### all stages/not specified

- AML HOVON / SAKK - 42A (Active): G-CSF priming in adult patients with acute myelocytic leukemia (AML) or refractory anemia
- AML HOVON SAKK 42: Randomized induction + post induction in AML/RAEB/RAEB-T
- AML-Intergroup: Therapy optimization and prognostic research in AML and MDS
- AMLCG-2000: Biology and therapy strategy of AML and its subgroups
- AML VION CLI-033: Phase II Study of VNP40101M in Patients With Acute Myelogenous Leukemia or High-Risk Myelodysplasia
- AML 5-azacitidine (Vidaza®): Treatment of imminent haematological relapse in patients with AML and MDS following allogeneic stem cell transplantation with 5-azacitidine (Vidaza®) "RELAZA - S t u d y"
- AML RICMAC/MDSSAML : Dose reduced vs. standard conditioning + SCT in MDS or sAML
- AML Allo SCT after treosulfan fludarabine: Allogeneic stem cell transplantation after toxicity-reduced conditioning regimen with treosulfan and fludarabine for patients with myelodysplastic syndrome (MDS) or secondary acute myeloid leukaemia (sAML) who were not eligible for a standard conditioning regimen: A phase II-study

##### AML with FAB M3 (APL):

##### De novo/non-treated

- APL Arsenic Trioxide/ATRA: Acute Promyelocytic Leukemia 2006 (APL)

#### CLL: Chronic lymphatic leukemia

##### All subtypes:

- CLL2I: Patients with chronic lymphocytic leukemia who are in complete or partial 2nd remission
- CLL2M: CLL2M – BR for previously untreated or relapsed CLL
- CLL 7: CLL7 Study for previously untreated patients in early stage
- CLL X2: CLL Unrelated and Related Allogeneic Transplantation In Very-high-risk disease for leukemia Eradication (CURATIVE) Trial
- CLL 2L: CLL 2L protocol of the German CLL-Study Group (GCLLSG)
- CLL 20: CLL 20 protocol of the German CLL-Study Group (GCLLSG)
- CLL 10: CLL10 Study – FCR vs. BR in first line therapy of CLL

## **CML: Chronic myeloid leukemia**

### **Chronic Phase:**

#### **De novo/non-treated**

- CML-IV: Standard-Dose Imatinib (400 mg) with or without Interferon alpha Compared to High-Dose Imatinib (800 mg) Followed by Donor Stem Cell Transplant in Treating Patients with Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia (Protocol version 10. May 2005)
- CML Imatinib+Zoledronic Acid: Imatinib Mesylate and Zoledronic Acid in Patients With Chronic Myeloid Leukaemia in Cytogenetic Response Without Molecular Response
- Imatinib vs. Nilotinib (AMN-107-2303): Imatinib Versus Nilotinib in Adult Patients With Newly Diagnosed Philadelphia Chromosome Positive (Ph+)
- CML Dasatinib Vs. High Dose Imatinib: Study of Dasatinib in Patients With Chronic Myeloid Leukemia (CML) and a Suboptimal Response to Imatinib
- CML SKI606: Study Evaluating SKI-606 in Philadelphia Chromosome Positive Leukemias
- CML STI571 Spirit: High-dose of Imatinib (STI571) vs. low-dose Imatinib in combination with cytostatics vs. reference-dose of Imatinib (SPIRIT-study)
- CML Imatinib vs. Dasatinib: A Phase III Study of Dasatinib vs. Imatinib in Patients With Newly Diagnosed Chronic Phase CML
- CML Imatinib vs. Bosutinib: Compare Bosutinib To Imatinib In Subjects With Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive CML

#### **Imatinib resistance - intolerance/Dies:**

- CML Homoharringtonine (Active): Homoharringtonine in Treating Patients With Chronic Myeloid Leukemia (CML) With the T315I BCR-ABL Gene Mutation

#### **Lymphatic blast crisis:**

- CML NILG 09/00/Ph+ : Intermittent Imatinib programme in Ph+ ALL and CML blast crisis

## **CMPD: Chronic myeloproliferative disease**

### **Polycythemia vera:**

#### **all stages/not specified**

- CMPD PV Venesection: Symptoms of iron deficiency in patients with polycythemia vera treated with venesection
- CMPD CYTO-PV: A large-scale trial testing the intensity of CYTOreductive therapy to prevent cardiovascular events in patients with polycythemia vera

## **MDS: Myelodysplastic Syndrome**

### **All subtypes:**

#### **De novo/non-treated**

- MDS Lenalidomide II: A phase II study of the efficacy and safety of Lenalidomide in adult subjects with intermediate-2-or high risk myelodysplastic syndromes (MDS) associated with a deletion (del) 5q[31]
- MDS Thymoglobulin: Thymoglobulin in MDS
- MDS Velcade Zarnestra: A phase I Clinical Trial to study the safety of treatment with Tipifarnib (ZARNESTRA) combined with Bortezomib (VELCADE) in patients with myelodysplastic syndrome (MDS)

#### **Relapsed/refractory**

- MDS VION CLI-033: Phase II Study of VNP40101M in Patients With Acute Myelogenous Leukemia or High-Risk Myelodysplasia
- MDS 5-azacitidine (Vidaza®): Treatment of imminent haematological relapse in patients with AML and MDS following allogeneic stem cell transplantation with 5-azacitidine (Vidaza®) "RELAZA - S t u d y"

#### **All stages/not specified**

- MDS Revlimid: The efficacy and safety of cc-5013 (Revlimid®) monotherapy in red blood cell transfusion dependent subjects with myelodysplastic syndrome associated with a del (5q) cytogenetic abnormality
- MDS 5-Azacitidine II: A phase II study of maintenance with Azacitidine in MDS patients achieving complete or partial remission (CR or PR) after intensive chemotherapy
- MDS AMG531: An open label, sequential cohort, dose escalation study to evaluate the safety and efficacy of AMG 531 in thrombocytopenic subjects with low or intermediate-1 risk myelodysplastic syndrome (MDS)
- MDS Darbepoetin-Filgrastim :A randomised controlled trial of prolonged treatment with darbepoetin alpha and recombinant human granulocyte colony stimulating factor (G-CSF) versus best supportive care in patients with low-risk myelodysplastic syndromes.
- MDS Darbepoietin alpha: A phase II study of Darbepoietin alpha in MDS with low or intermediate 1 risk according to IPSS, with significant anemia (transfusion dependant or not)"
- MDS Deferasirox: Deferasirox (ICL670) in transfusion dependent iron overload
- MDS Aranesp®: A phase II clinical trial to evaluate the efficacy and feasibility of treatment of anemia with erythropoiesis stimulating protein (Aranesp) in patients with myelodysplastic syndrome (MDS)
- MDS NMDSG03A: Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- MDS Velcade: A phase II study of PS341 (Velcade) in patients with myelodysplastic syndromes. GIMEMA MDS0104
- AML-Intergroup: Therapy optimization and prognostic research in AML and MDS
- MDS Bortezomib/Cytarabine: Adult subjects with Myelodysplastic Syndromes (MDS) will receive Bortezomib and Low Dose Cytarabine
- MDS EBMT allo 2x2 (pending): A prospective 2x2 randomized study evaluating the role of remission induction and consolidation chemotherapy prior to allogeneic stem cell transplantation and mobilised peripheral blood stem cells versus bone marrow stem cells using hla-identical siblings in patients less than 50 years of age with myelodysplastic syndromes and 5% to 20% bone marrow blasts
- MDS RICMAC/MDSsAML : Dose reduced vs. standard conditioning + SCT in MDS or sAML
- MDS Allo SCT after treosulfan fludarabine: Allogeneic stem cell transplantation after toxicity-reduced conditioning regimen with treosulfan and fludarabine for patients with myelodysplastic syndrome (MDS) or secondary acute myeloid leukaemia (sAML) who were not eligible for a standard conditioning regimen: A phase II-study

## **SCT: Stem cell transplantation**

### **all stages/not specified**

- SZT Allo SCT with red. conditioning : Allografting as Consolidative Immunotherapy for Older Patients with AML in Complete Remission Using Low Dose TBI, PBSC Infusion And Post- Transplant Immunosuppression With Cyclosporine And Mycophenolate Mofetil

## **Supportive: Supportive care**

To this moment no studies are included in the registry.



5<sup>th</sup> Annual Symposium of the "European LeukemiaNet" and 9<sup>th</sup> Annual Symposium of the German Competence Network "Acute and chronic Leukemias" Heidelberg, January 29-31, 2008

## New colleagues in the Network Management Center in Mannheim, Germany



Dr. Petra Schrotz-King

Since the beginning of 2008 three new employees support the Network Management Center.

**Dr. Petra Schrotz-King** started in March 2008. She is Assistant Managing Director and oversees the European LeukemiaNet (ELN), EUTOS, the German Competence Network „Acute and Chronic Leukemias“ and the German „Stiftung Leukämie.“

She joined us directly from a Chief Scientific Officer (CSO) position of a company, developing human vaccines, in Denmark, where she had also worked as Assistant Professor in Proteomics.

**Dr. Catherine Sodan-Boyer** has joined in February. With a Ph.D. in Physics, she enjoys working with numbers and

formulas and takes care of all the finance issues regarding grants, collaborations and projects. As a French National, she is the contact person in the Management Center to our direct neighbours in France.

**Dr. Ute Kossak** is part of the Network Management Center since January 2008. Dr. Kossak is responsible for questions regarding the German Competence Network and the collaboration with the José Carreras Foundation. Furthermore she is the major contact person concerning the online registration of our Member-Database. Dr. Kossak was until December 2007 Scientific Coordinator at the Institute of Marine Sciences (IFM-GEOMAR), in Kiel, Germany.



Dr. Catherine Sodan-Boyer



Dr. Ute Kossak

## IMPRESSUM

### Publisher:

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### Coordinator:

Prof. R. Hehlmann

### Scientific Manager:

Dr. S. SauBele

### Editor-in-Chief:

Dr. N. Gökbuget, Prof. D. Hoelzer

### Authors contributed to this issue:

Prof. R. Bassan

Prof. F. Cervantes

Prof. H. Dombret

Prof. M. Dugas

Prof. R. Foà

Dr. N. Gökbuget

Prof. F. Guilhot

Prof. M. Hallek

Prof. T. Haferlach

Prof. R. Hehlmann

A. Hellenbrecht

Prof. D. Hoelzer

K. Ithrig

H.-U. Klein

Dr. S. Merk

Prof. C. Müller-Tidow

Prof. F. Pane

Prof. R. Ribera

Dr. C. Schweighofer

Prof. R. Willemze

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available online at

[www.leukemianet.eu](http://www.leukemianet.eu)

### Network Management Center:

Dr. S. SauBele

Dr. P. Schrotz-King (Deputy)

III. Medizinische Universitätsklinik

Wiesbadener Straße 7-11

D-68305 Mannheim (Germany)

Phone: ++49 (0)621 383 4188

Fax: ++49 (0)621 383 4239

eMail: [nmc@leukemia-net.org](mailto:nmc@leukemia-net.org)

### Information Center:

Dr. N. Gökbuget

Medizinische Universitätsklinik II

Theodor-Stern-Kai 7

D-60590 Frankfurt (Germany)

Phone: ++49 (0)69 6301 6365

Fax: ++49 (0)69 6301 7463

eMail: [elic@leukemia-net.org](mailto:elic@leukemia-net.org)

### Homepage:

[www.leukemianet.eu](http://www.leukemianet.eu)

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