Dear Colleagues,

"The only way to cure leukemia is by cooperative research". This is the introductory sentence of the article "The European LeukemiaNet: Achievements and Perspectives", published in Haematologica in January 2011 and this is the key to the success of ELN, grown together, built on trust, for more than 8 years. ELN stands for cooperative research, a network of excellence, including over 1000 leukemia specialists from 175 institutions in 33 countries across Europe. ELN has become a landmark in the medical history of leukemia.

2011 is the last year of EU funding within the 6th framework programme, but not the last year of ELN. Funding will continue through the European Science Foundation (ESF), which can secure the ELN Symposia until 2015 (page 20, this infoletter). Furthermore the ELN Foundation will support goals and activities of ELN through donations for ELN research activities (www.eln-foundation.org). In 2011, ELN may assume a new identity, developing from an EU NoE-project to an organisation with legal status. The ELN Steering Committee will take decisions during the ELN symposium in February 2011 in Mannheim. New collaborations and research goals will be started between partners, new participants will continue to join.

Looking back the ELN has published over 35 guidelines and management recommendations on leukemia diagnosis and therapy. These are the basis for high quality patient care in leukemia across Europe. In chronic myeloid leukemia the survival time increased almost 10 fold, from 3-4 years in 1982 to over 25 years in 2011. More leukemia patients survive longer times. Will curing the disease be possible in the near future? To evaluate this, EUROS for CML (European treatment and outcome study), a public-private partnership between the ELN and Novartis was recently updated and extended until 2012. A brochure on the EUROS achievements 2007-2010 is available through the ELN Management center, or at the Annual Symposium 2011 in Mannheim. Achievements of the subproject "Registries" are summarised on page 8 in this infoletter.

The articles published in this issue present state of the art ELN research and networking activities, where we stand in leukemia diagnosis and treatment today. You will find results of 8 years collaborative research of ELN:

- WP1 informs on the ESF-ELN Research Networking Programme (2010-2015), which will support the annual ELN Symposia until 2015.
- WP4 gives an update on the activities around the EU Clinical Trial Directive.
- WP4 reflects on the challenge to stop imatinib, and on the achievements of the EUROS collaboration 2007-2010.
- WP5 elaborates on its experience with prospective comparison of different treatments with a common standard treatment in AML. It furthermore introduces the EBM/ELN study in AML, the first randomised study in hematopoietic cell transplantation. In addition WP 5 summarises the results of the AML HD98A study and points to the role of TET2 mutations.
- WP 6 elaborates on the use of the "Bispecific single-chain T-cell Engaging" (BiTE) antibody construct, Blinatumomab.
- WP 6 resolves interesting data of MPN evolving to sAML through the use of SNP-Arrays and presents critical concepts and ELN Management recommendations in Ph- classical MPNs.
- WP10 explains the achievement on a European report on blood cell differentiation, the combination of the consensual ELN Blood Cell Glossary (EBCG) and the corresponding image library available on the ELN and EHA website.
- WP 11 highlights whole genome sequencing with next-generation technology for identifying a wide spectrum of genetic alterations in leukemia patients. Last but not least.
- WP12 exemplifies how reporting software allows harmonisation of data across laboratories.

For this coming year I wish you many new ideas and good partnerships within the cooperative research of ELN evolving identity.

Prof. Dr. Rüdiger Hehlmann
Network Coordinator
Dear colleagues,

since 2005 we are preparing the ELN Information Letter in collaboration with the Network Management Center and hope to present you interesting topics and innovations concerning the treatment of leukemias. Furthermore the Information Letter gives you interesting insights into the work of the ELN.

The WP leaders of the ELN were requested to hand in absorbing articles on their fields of research and to have the continuing ability to present all active trials online. The European Leukemia Trial Registry (ELTR) has been restructured updated on enquiry.

All in all we hope that this publication is conducive to the importance of academic clinical trials for promoters, sponsors, administration and politics. We ask all ELN members to hand in interesting contributions representing their field of research and expect absorbing articles for the ELN Information Letter.

With best regards,

Information Center

Dr. Nicola Gökteugut Dr. Silvia Schäfer Kristina Ihrig

WP 2 - ELIC

ELIC Editorial

To stop treatment with Tyrosine Kinase Inhibitors in Chronic Myelogenous Leukemia

F.-X. Mahon, CHU de Bordeaux, Laboratoire d'hématologie, Université Bordeaux Segalen, INSERM U876, 146 Rue Léo Saignat, 33076 Bordeaux, France

Chronic myeloid leukemia (CML) is the first malignant disease of hematopoietic stem cells (HSC) with the identification of an acquired chromosomal abnormality discovered 50 years ago in Philadelphia (Ph). Hence entitled, the Ph chromosome results from a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11). The molecular consequence of this translocation is a novel fusion gene, BCR-ABL. Expression of this fusion gene results in the oncoprotein BCR-ABL whose tyrosine kinase activity deregulates many intracellular molecular substrates within hematopoietic cells. The BCR-ABL tyrosine kinase activity represents the primum movens in CML, proved in vitro and in animal models. The discovery of imatinib, the first orally applicable BCR-ABL tyrosine kinase inhibitor (TKI), led to a kind of revolution in the treatment of CML. In vitro, imatinib inhibits specific growth and induces apoptosis of BCR-ABL positive cells and CML primary cells. We have to thank to Professor Brian Druker’s perseverance for the development of this drug which was impressive. Imatinib proved its efficacy on interferon (IFN)-resistant CML in phase I and phase II clinical trials. The phase III multicenter trial IRIS (International Randomized Study of Interferon versus STI571) studied 1106 patients who were randomized between imatinib versus IFN-alpha + AraC. The superiority of imatinib over IFN-alpha + AraC was proved after 19 months median follow-up. At 60 months, the estimated overall survival (OS) rate was 89% for the imatinib arm the follow up of IFN arm being no possible any more since IFN treated patients concern a very low number. Importantly, only an estimated 6% of all patients progressed to accelerated phase (AP) or blast crisis (BP) [1]. The updated overall survival at 8 years is now 85 % (93% when only CML-related deaths and those prior to stem cell transplantation) which illustrate the fantastic efficacy of imatinib as first line treatment in CML. However, current practice has been for patients to continue treatment indefinitely, and the ability of imatinib to eradicate the CML clone is uncertain. The major molecular response (MMR) rate, defined as the 3-log reduction of leukemic cells, and the depth of molecular response increase over time. The undetectable residual disease using QRT-PCR is designated complete molecular remission (CMR). In a pilot study of patients achieving CMR and sustained during at least two following years who stopped imatinib, a molecular relapse rate of 50% was observed. All patients had previously been treated with IFN prior to imatinib. Then, we performed a prospective new multicentre study “Stop Imatinib” (STIM), including also newly-diagnosed patients, initiated in July 2007 to evaluate the persistence of CMR after discontinuation of the drug, and to determine the factors that could be associated with CMR persistence [2]. The research team enrolled 100 patients with chronic or accelerated phase CML with a sustained complete molecular response (CMR), defined as a 5 log reduction in BCR-ABL and ABL levels as well as undetectable transcripts on RT-PCR, for at least two years. Fifty-one patients were previously treated with interferon. After stopping imatinib, molecular relapse was seen in 54 patients after a median follow-up of 17 months. The remaining forty-six pa-
Patients remained in CMR at a median follow-up of 14 months, with the overall probability of maintaining a CMR at 12 months of 43%. In the subset of 69 patients with follow-up over one year (median 24 months), molecular relapse occurred in 42, usually within 6 months. Molecular relapse free survival in this group was 41% at one year and 38% at 2 years. Patients treated with interferon before imatinib showed no differences in relapse rates than those treated with imatinib first. Molecular relapse at or before 18 months occurred in 70% of men and 46% of women. Among patients with high, intermediate, and low Sokal risk scores (calculated based on patient age, spleen size, platelet count, and percentage of peripheral blood myeloblasts), molecular relapses were detected in 88%, 65%, and 49%, respectively. Further, patients with a duration of imatinib therapy of at least 50 months had a 53% likelihood of molecular relapse, whereas 78% of patients with shorter duration of treatment relapsed. When these three factors, gender, Sokal group, and duration of treatment, were entered into a Cox regression model, they all significantly and independently predicted likelihood of molecular relapse. All patients who relapsed were retreated with imatinib and all patients remained sensitive. No loss of hematologic response (or progression to advanced phase) was seen. Of the 42 who relapsed, 26 achieved a CMR with imatinib retreatment at the time of the analysis. The identification of patients who would benefit most from discontinuation of imatinib remains a key issue.

In a goal to override the resistance or improve the response to imatinib, second-generation TKIs have been developed by pharmaceutical companies. Dasatinib is a multi-targeted kinase inhibitor which has significant activity in imatinib-resistant or intolerant patients. Dasatinib is currently approved by the FDA for the treatment of imatinib-resistant or intolerant patients who are in CP, AP, or BP. Dasatinib has been studied in the frontline setting, both in a Phase II study and in a prospective randomized study versus imatinib therapy. In the latter, after a minimum follow-up of 12 months, the rate of confirmed complete cytogenetic response was higher with dasatinib than with imatinib (77% vs. 66%, P = 0.007), as was the rate of complete cytogenetic response observed on at least one assessment (83% vs. 72%, P = 0.001). The rate of major molecular response was higher with dasatinib than with imatinib (46% vs. 28%, P<0.0001), and responses were achieved in a shorter time with dasatinib (P<0.0001) [3]. Nilotinib is also a more potent BCR-ABL1 inhibitior than imatinib has significant efficacy in patients with CML in chronic (CP), accelerated (AP), and blastic phase (BP), following imatinib failure. Nilotinib has been reported to be effective and safe in two phase II studies conducted in patients with newly diagnosed CML. In the ENEStnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) study, the MMR rate at 12 months was superior for nilotinib 300 mg BID (44%, P<0.0001) and 400 mg BID (43%, P<0.0001) vs imatinib (22%). The rate of complete cytogenetic response by 12 months was significantly higher for nilotinib 300 mg BID (80%, P<0.0001) and 400 mg (78%, P=0.0005) BID vs imatinib (65%). Both doses of nilotinib showed significantly improved time to progression to advanced phase or blast crisis (AP/BC) compared to imatinib (P=0.0095, P=0.0037) [4]. Recent FDA approval was based on the results of this ENEStnd study. So, based on the results of the STIM study we know that a proportion of patients who achieve CMR on imatinib therapy remain in CMR for variable periods after cessation of imatinib therapy. Because these second-generation tyrosine kinase inhibitors confer a much higher rate of CMR than imatinib, we may speculate that the number of patients who will reach molecular criteria as those defined in the STIM study will be more important. In addition, the solution to cure CML would maybe come also from the combinations of drug such as TKI and IFN. Indeed, it was the first biologic agent to significantly improve the prognosis of patients with CML before imatinib era. It may still have a room among the different therapeutic weapons since it has been recently reported by the French SPIRIT Study a higher rate of molecular response by combining IFN with imatinib than imatinib alone [5].

All of those studies allow thinking about the next endpoint of the future clinical trials should be the sustained CMR in the aim to increase the potential number of patient who will be proposed to stop the treatment and who would be cured. That is the challenge of the next decade.

REFERENCES
In 2005, detection of acquired uniparental disomy (UPD) in chromosome 9p using microsatellite mapping was one strategy to identify the gain-of-function mutation V617F in JAK2 in myeloproliferative neoplasms (MPN) [1]. More recently, use of single-nucleotide polymorphism-(SNP-) arrays facilitated the identification of an increasing number of gene mutations such as TET2 polymorphism-(SNP-) arrays facilitated the recent genetic profiling of 224 chronic- or blast-asso ciated diseases (0.1-5.9 Mb) harboring 1-45 cande date genes were mainly detected in large CNAs were aberrations relatively rare in ET (4%) and PV (10%). In accordance, informative micro-deletions (0.1-5.9 Mb) harboring 1-45 candidate genes were mainly detected in MF (n=18; 22%) and SAML cases (n=13; 32%). Of these, the following three chromosomal regions were recurrently deleted: 12q24.31 (MF, n=1; SAML, n=1), 17q23.2 (SAML, n=2), and 17q11.2 (MF, n=3; SAML, n=2); the latter one is encompassing the tumor suppressor gene Neurofibromatosis-1 (NF1).

NF1 is associated with the hereditary Von Recklinghausen’s neurofibromatosis. It has been shown that these patients have an increased risk for the development of various tumors including myeloid leukemias [5]. NF1 functions as a negative regulator of the RAS signal transduction pathway, and loss of NF1 can lead to a progressive myeloproliferative disorder [6]. Cases with cryptic deletions in 17q11 encompassing NF1 have been identified in several recent studies on adult and childhood acute myeloid and T-lymphoblastic leukemia patients as well as in primary MF patients [7-10]. In addition, truncating mutations in the remaining allele have been identified in one of these studies in three out of four childhood leukemia patients with monallelic NF1 deletions, that resulted in biallelic inactivation of the gene [9].

To validate our finding of cryptic NF1 loss ranging from 1.2 to 5.9 Mb, a matched-pair analysis using dermal cells and tumor material was performed in one secondary MF case with a 1.6 Mb deletion in 17q11.2. The SNP-profile clearly confirmed the tumor-specific origin of cryptic deletion in 17q11.2 (Figure 1). Furthermore, fluorescence-in-situ-hybridization (FISH) showed monallelic NF1 deletion in nearly 100% of the metaphase and interphase cells. Mutation analysis of the remaining allele revealed a single base pair deletion in exon 5 leading to a stop codon. Of note, this patient with biallelic NF1 mutation was already detectable. This finding demonstrates that the TP53 mutation was acquired during disease progression. Interestingly, an association between NF1 and TP53 alterations was also observed in both SAML cases showing NF1 micro-deletions. In these two cases, TP53 was completely inactivated due to genomic loss of one and mutation of the remaining allele. Thus, we conclude from these data that combined inactivation of NF1/TP53 may represent one important mechanism in MPN to evolve SAML.
In summary, our study on a large MPN cohort confirmed that SNP-array analysis is robust and suitable for detailed genomic characterization. Furthermore, SNP-array profiling revealed a high frequency of genomic lesions in MF and sAML reflecting the genomic instability of these disease entities. In contrast, the use of SNP-arrays was limited to uncover novel genomic aberrations in ET, while the high number of 9p upPDs associated with JAK2 V617F underlines the importance of the gain-of-function mutation in PV. upPDs affecting other chromosomal regions were relatively rare. Nevertheless, as shown for TET2, EZH2, and CBL these genomic lesions might pinpoint to genes that are of relevance in MPN pathogenesis. Moreover, our study revealed a significant number of novel micro-deletions in MF and sAML that likely harbor disease-relevant genes. Of these, combined NF1/TP53 inactivation emerged as one possible mechanism to trigger leukemic transformation in MPN.

Data partially presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) 2010 in Orlando/USA

References
Driven by technological advances, recent years have witnessed a deluge of new methods for interrogating different properties of a cell on a genome-wide scale. Each technology offers a unique, although complementary, view of genome organization and cellular function and therefore allows the identification of specific molecular alterations of tumor cells, such as aberrant gene expression profile signatures, “driver” mutations, novel gene fusions and novel methylation patterns. Single nucleotide polymorphisms (SNPs) array technology allows the identification of copy number abnormalities but fails to characterize the full spectrum of mutations and structural genomic rearrangements. Moreover, high resolution array-based approaches for detailed transcriptome expression analysis require large amounts of RNA and still present limitations inherent to normalization procedures, detection of low-abundance transcripts, background noise and artifacts [1]. On the contrary, high throughput “Next Generation Sequencing Technologies”, overcoming the limited scalability of traditional Sanger sequencing, are revolutionizing genomics and transcriptomics by providing a cost-efficient and single base resolution tool for a unified deep analysis of the leukemia complexity.

There is a vast diversity to next-generation technologies, but these sequencing approaches generally use massively parallel amplification and detection strategies. A sheared DNA sample is amplified evenly through the use of emulsions (Roche 454, Life SOLID, Polonator G.007) and substrates (Illumina Genome Analyzer) to segregate amplicons from each other. The amplified DNA is then arrayed in the sequencing device to enable parallel optical detection of the fluorescence based sequencing process. In all second-generation sequencing approaches, an enzyme such as polymerase or ligase is used to replicate the separated clusters of amplicons and provide nucleotide specificity. As a result of the sequential addition of nucleotides or dinucleotides, a fluorescence signal is generated and recorded at each amplicon location. The large-scale parallelization results in billions of sequence reads that are then computationally assembled [2]. Bioinformatic analysis results in the identification of somatic base pair and in-del mutations, balanced and unbalanced rearrangements, and copy number changes in a single experiment. Apart from sequencing whole genomes, massively parallel sequencing can be coupled with DNA capturing methods for focused analysis of specific genomic regions, specific genes or the whole exome [3]. Moreover, in addition to the ability to sequence DNA, it can be applied to sequencing RNA. Four main applications have already been developed, including digital gene expression, RNA sequencing, paired end RNA sequencing, and small and noncoding RNA sequencing.

The first whole cancer genome sequence was reported in 2008 with the description of the nucleotide sequence of DNA from an acute myeloid leukemia (AML) compared with DNA from normal skin from the same patient [4]. Since then, six more complete sequences of cancer genomes together with matched normal genomes have been reported and this number is rapidly growing. Recently, our group identified an isocitrate dehydrogenase 2 (IDH2) R140Q heterozygous mutation deriving from a G to A nucleotide substitution on chromosome 15, position 88432938 (hg18, NCBI build 36.1) by massively parallel sequencing (Solexa Illumina Genome Analyzer II platform) of the transcriptome of a Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) at the time of progression to lymphoid blast cell crisis [5]. This variant was not seen in the sample collected at the time of diagnosis nor in the sample collected at the time of remission. Somatic mutations of IDH1 and 2 have been recently described in patients with de novo AML, in patients with chronic and blast phase Philadelphia chromosome-positive myeloproliferative neoplasms and in patients with early and accelerated phase myelodysplastic syndromes.
In order to define the full repertoire of leukemia-related mutations, changes in expression profiles and alternative splicing events, we also sequenced the leukemia transcriptome of a BCR-ABL1+ acute lymphoblastic leukemia (ALL) patient at diagnosis and at the time of relapse using a whole transcriptome deep sequencing [6]. This approach allowed us the discovery of novel missense mutations, as well as exhaustive alternative splicing and gene expression profiles, demonstrating that next-generation sequencing is a suitable approach for identifying a wide spectrum of genetic alterations in leukemia patients.

This work was supported by LEUKEMI-ANET, Gimena Onlus, Regione ER, AIL and AIRC grants.

References

Dates/Meetings

1. – 2.2.2011
8th Annual Symposium of the European LeukemiaNet
12th Annual Symposium of the German Competence Network
“Acute and chronic Leukemias”
Link: http://www.leukemia-net.org

6. – 17.5.2011
Young hematologist’s day-EUTOS for CML
Naples

18. – 21.5.2011
The 11th International Symposium on Myelodysplastic Syndromes
Link: http://hosted-p0.vresp.com/211457/8abae928b6/ARCHIVE#

9. – 12.6.2011
EHA 2011: 16th Congress of the EHA
Link: http://ehaweb.org/congress/future_congresses

1. – 2.7.2011
CML Study Group Meeting/20th International CML-Workshop
Link: www.kompetenznetz-leukaemie.de

8. – 11.9.2011
The International Congress on Controversies in Stem Cell Transplantation and Cellular Therapies (COSTEM)

30.9 – 4.10.2011
DGHO, ÖGHO, SGMO und SGH+SSH - Jahrestagung
Link: http://www.haematologie- onkologie-2011.ch/

2. – 6.12.2011
http://www.hematology.org/meetings/Annual-Meeting/

EHA 2012: 17th Congress of the EHA
Link: http://ehaweb.org/congress/future_congresses

LATEST NEWS

EUTOS contract prolongation was signed on 20.12.2010
EUTOS for CML Registries

Leukemia is a rare disease and successful strategies emerge through international collaborations. The European Treatment and Outcome Study (EUTOS) for CML is a public-private partnership between the European LeukemiaNet (ELN) and Novartis Oncology Europe. The aim is to collect pan-European baseline, treatment, and outcome data in Chronic Myeloid Leukemia (CML) [1]. Patient registries are a key objective of the EUTOS collaboration. The EUTOS registry project is based on the inclusion of different patient populations to evaluate real-world patient treatment. The aim is to collect data on (1) In-Study, (2) Out-Study, and (3) population-based (prospectively registered) patients.

Structure, Steering Committee and Working Parties

Three registries, named respectively, were established since 2007. They are directed by a Steering Committee whose members are: M. Baccarani (Università di Bologna, Italy), J. Guilhot (Université de Poitiers, France), J. Hasford (Ludwig-Maximilians-Universität, Germany), B. Simonsson (Uppsala Universitetet, Sweden), and Carmen Piccolo (Novartis). The Steering Committee is responsible for research plans, implementation, raising awareness, and reviewing progress and deliverables. The Central Data Center (CDC) in Munich and the Scientific Registry Headquarters in Bologna manage the day-to-day tasks (Figure 1). Study plans are prepared by working parties (WP) and need approval by the Steering Committee. The WPs are responsible to achieve the objectives.

Achievements 2007-2010

I. In- and Out-Study registries

Mandatory variables for the In- and Out-Study registry

All participating countries must ensure that the mandatory baseline data for all patients are included within the EUTOS for CML Registry. These are essential demographic variables, hematological, cytogenetic, and molecular data confirming the diagnosis, the phase of the disease, and the prognostic score. For the follow-up, it is important to include all treatment, responses to treatment (hematological, cytogenetic and molecular), and safety and survival data.

In-Study Registry

The In-Study registry includes patients enrolled in trials from national study groups, who are taking imatinib frontline and are diagnosed between 2002 and 2006. To date seven study groups from 11 European countries (Figure 2, Table 1), registered data from 2,389 patients including follow-up data from 2007-10 (status from the 02.12.2010; Table 2).

<table>
<thead>
<tr>
<th>Study Groups</th>
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<tr>
<td>1 PETHEMA</td>
<td>Spain</td>
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<td>2 GIMEMA CML WP</td>
<td>Italy</td>
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<tr>
<td>3 The German CML Study Group</td>
<td>Germany/ Switzerland</td>
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<td>4 NCRN CML Working Group New-</td>
<td>United Kingdom</td>
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<td>5 Nordic CML- Study Group</td>
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<td>6 Fi-LMC</td>
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<td>7 HOVON</td>
<td>The Netherlands</td>
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Figure 2/Table 1: The 11 European countries participating in the EUTOS In-Study registry. The Table lists the countries and their affiliated study groups.

11 European countries registered data from 2389 patients

<table>
<thead>
<tr>
<th>Initially registered</th>
<th>2007 follow up</th>
<th>2008 follow up</th>
<th>2009 follow up</th>
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<tr>
<td>2,389</td>
<td>1,897</td>
<td>1,519</td>
<td>966</td>
<td>584</td>
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A new prognostic score
One milestone in the EUTOS for CML registry collaboration is the prognostic evaluation of CML based on Tyrosine Kinase Inhibitors (TKIs)-treated patients. No systematic approach to prognosis has been developed as yet, and two prognostic classifications that were developed from patients treated with conventional chemotherapy (Sokal score) [2] or IFNa (Euro score) [3] have continued to be used not only in imatinib-treated patients, but also to stratify the patients in the most recent studies of therapy with 2nd generation TKIs [4,5]. From the In-Study registry data, a new prognostic risk score has been developed, to predict the probability of achieving a complete cytogenetic response (CCgR) within 18 months, which is the most solid and confirmed surrogate marker of survival [6]. This score allows a better prognostic prediction than Sokal or Euro scores, with only two variables (percentage of basophils in blood, and spleen size). Both parameters can be easily and inexpensively measured in routine health care, worldwide [7].

2. Out–study registry
The Out-Study registry collects data on patients already registered in the databases of the respective country. Patients were diagnosed between 2002 and 2006. They take imatinib treatment front line. They serve as a control group to the In-Study patients. To date eight study groups from seven European countries (Table 3) registered data from 1582 patients, including follow-up data from 2007-10 (status from the 02.12.2010; Table 4).

3. Population-based registry
The population-based registry is the youngest registry, launched in July 2009. The goal is to register 2500 patients in a timeframe of about 12 months. Patients (age ≥ 18) with documented Philadelphia (Ph) or BCR-ABL-positive (Ph+ or BCR-ABL+) CML who are newly diagnosed and resident within a specified country, or one or more specified regions or districts of a country, covering a maximum of 10 million people are documented. Incidence rates of Ph+/BCR-ABL+ CML vary from 0.6 to 2.0 cases per 100,000 inhabitants, increase with age and are higher in men than in women [2].

<table>
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<td>1 Bucharest</td>
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<td>2 Danzig</td>
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<td>3 CZ-Infinity</td>
<td>Czech Republic</td>
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<td>4 CZ-Camelia</td>
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<td>5 RELMC</td>
<td>Spain</td>
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<td>6 RU-Moscow</td>
<td>Russia</td>
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<td>7 RU-St. Peters-burg</td>
<td>Russia</td>
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<tr>
<td>8 UK-Hammersmith</td>
<td>United Kingdom</td>
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Table 3: The 7 European countries participating in the EUTOS Out-Study registry. The Table lists the countries and their affiliated study groups.

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<tr>
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<td>5 RELMC</td>
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<tr>
<td>8 UK-Hammersmith</td>
<td>United Kingdom</td>
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Table 4: Number of patients registered and followed in the Out-Study registry from 2007-2010

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<tr>
<th>Initially registered</th>
<th>2007 follow up</th>
<th>2008 follow up</th>
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<tbody>
<tr>
<td>1,582</td>
<td>1,252</td>
<td>1,158</td>
<td>665</td>
<td>362</td>
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Figure 3: 24 European countries (indicated in red) joined the population-based registry so far. The Table lists the countries and their affiliated study groups.
Ethics
Ethical and regulatory procedures differ between the participating countries and were dealt with accordingly. Informed consent is provided according to local guidelines and requirements.

Registry activation
Activation of each country for the registry is managed by the Steering Committee of the registry.

Project duration
Each participating country is required to register for a minimum of 12 months, beginning from the date of its activation.

Data collection
The patients are followed for treatment and outcome including cytogenetic and molecular response as well as specific BCR-ABL-KD mutations. Data is collected via an electronic case report form (eCRF), which is available on the EU-TOS for CML homepage (http://www.eutos.org/content/registry/data_entry/).

Variables
Unlike with the In- and Out-Study EU-TOS for CML Registries, it is not possible to specify which variables are mandatory because this registry is population-based. Data that can be captured are grouped in two parts:

1. Baseline variables (part I) include:
   - Demographics (date of birth, gender, height, weight, comorbidities, etc.)
   - Clinical data before any treatment, including hematological, cytogenetic, and molecular measurements, risk scores, phase of the disease and informed consent information

2. Follow-up variables (part II) include:
   - Treatment received during the first year, including frontline use of imatinib and details of dose, discontinuation or allo-SCT
   - Cytogenetic and molecular response, mutational analysis, serious adverse events, grade 3/4 adverse events, and survival

Follow-up data are due every 12 months.

Evaluated regions
25 study groups from 24 European countries have joined the registry so far (Figure 3) after presenting official approval by their authorities.

Pop-registry data to date:
25 study groups from 24 countries registered 658 newly diagnosed CML patients (Figure 4), through an electronic case-report form (eCRF). The first patient was registered January 28th, 2010, and the last patient included in this report was registered November 24th, 2010. 573 patients are evaluable, 53% of these patients are male. The median age at diagnosis was 55 years (range 18-88 years).

Conclusions
The collection of baseline, treatment and outcome data in a registry (database) across Europe is an essential tool in disease control, healthcare planning, and research. Currently there are no population-based registries, apart from Sweden. The EU-TOS project delivers a unique network of registries promoting health care in leukemia all across Europe. The registries established by the European LeukemiaNet-EUTOS collaboration covering representative areas or regions of Europe will be an important epidemiological, scientific and clinical achievement.

Literature
7. Hasford et al., manuscript in preparation: Predicting complete cytogenetic response and progression-free survival in patients with Philadelphia-positive chronic myeloid leukemia on imatinib treatment. The EU-TOS (European Treatment and Outcome Study) Score.

Figure 4: Registered patients per country/study group; the total number of patients is 658.
Acute Myeloid Leukemia (AML): Prospective comparison of different treatments with a common standard treatment - A Study by the German AML Intergroup


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Eight years from the start of a cooperation among five multicenter study groups in Germany, and three years after entering the last patient we here present updated therapeutic results. A total of 3171 patients 16-60 years of age with AML including primary and secondary AML and high-risk MDS, and excluding APL with t(15;17), were treated in the five study groups cooperating by a general upfront randomization allocating 10% of their patients to a common standard treatment and 90% to the study group own regimens before any treatment had been started. The standard treatment consisted of remission induction by two courses of standard dose araC over seven days with daunorubicin 60mg/m²/d on three days. Patients in complete remission received three monthly courses of high-dose araC 3g/m²q 12 h on day 1,3 and 5. In the participating study groups a total of 2866 patients eligible by the inclusion criteria of the AML Intergroup study were treated according to the study group own regimens with 828 patients in study group A, 373 in B, 235 in C, 806 in D, 622 in E, and 305 patients were treated according to the common standard. In an attempt to conduct treatment optimization trials the study group own strategies relied on a risk-oriented stratification among treatment options (group A), a randomized stratification (group D), or combinations of randomization and risk-adaption (B, C, E). Cytarabine was used up to cumulative 40mg/m² in groups B and D, 45g/m² in C, and 55g/m² in A, E, and standard arm. Marked differences were also seen in the use of allogeneic stem cell transplantation with 27% allografts in 1st CR in study group A, 33% in B, 19% in C, 23% in D, 25% in group E, and 21% in the common standard arm. Unlike the differences in the study groups strategies in the amounts of cytarabine and in the numbers of allografts in 1st remission, the risk profiles regarding age, secondary AML, cytogenetic groups, mutations in NPM1/FLT3-ITD, levels of WBC and LDH were concordant between the common standard arm and the study group own populations, except for single differences in secondary leukemia (group B), cytogenetics (C), and WBC (D). The study group itself was not an independent prognostic factor for any outcome. Similar patient populations could thus be evaluated to compare the treatment strategy of each study group with that of the common standard arm. The outcome of the standard treatment was 66.7% (95% CI 61.0-72.0) complete remissions, an overall survival of 44.3% (95% CI 37.9-50.9), and a relapse free survival of 44.9% (95% CI 36.9-52.5) at 5 years. Adjusted for prognostic baseline variables no significant difference in the remission rate and overall survival between the standard arm and any of the study groups were observed. Comparable patterns were also found for relapse free survival where the long-term results of the standard treatment were not further improved in any of the five study groups. We conclude that in unselected patients with AML a prospective comparison shows very similar outcomes of any current treatment strategy when compared with that of the common standard treatment. Present reliable and unbiased analyses became possible by a strictly prospective approach and intent-to-treat evaluation. These representative results can form a solid basis for novel therapeutic approaches.

WP 5 - AML

References

Paper presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) 2010 in Orlando/USA
The AML Study "A Randomized Phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and hematopoietic cell transplantation (HCT) from related and unrelated donors as consolidation therapy for older Patients with AML in first Complete Remission HCT 2007-003514-34" has started recruiting or chemotherapy. Patients with excess of blasts are included. Induction therapy is administered according to current participating cooperative group protocols and patients must have a Karnofsky score ≥ 70%. The primary endpoint is being leukemia free survival and secondary endpoints are OS, cumulative incidence of relapse, treatment related mortality, incidence of myelosuppression and acute and chronic GvHD. The outcome analysis will be performed as an intention to treat analysis with the logrank test. 231 patients will be needed at randomization. Study coordination, safety, biometry and data management is performed by the ZKS Leipzig. The study is supported by the Deutsche Krebshilfe. The interest in this study, which is the first randomized study in hematopoietic cell transplantation and the first in this age group, is considerable and the recruitment proceeding according to the time lines.

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Recently, the tet oncogene family member 2 (TET2) gene was identified as a candidate tumor suppressor gene in a variety of myeloid disorders. Subsequent sequencing analysis revealed heterogeneous TET2 mutations in 12 to 26% of patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN) [1,2]. Until this recent identification of inactivating TET2 mutations a leukemogenic role of TET (Ten-Eleven Translocation) family gene members (TET1, TET2, TET3) was only known for the involvement of TET1 as a translocation partner in MLL-rearranged AML. TET2 has two highly conserved regions one of which is 2-oxoglutarate (2OG)-dependent. A recent study by Ko and colleagues showed that TET2, like TET1, also converts 5mC into 5hmC, a process thought to play an important role in DNA demethylation and thus epigenetic regulation [3,4]. Furthermore, it was shown that TET2-mutated AML samples display uniformly low levels of 5hmC in comparison to normal controls, thereby supporting a functional relevance of TET2 mutations in leukemogenesis. In line, shRNA-mediated TET2 knockdown affected myeloid differentiation with an expansion of monocyte/macrophage lineages following cytokine stimulation [4]. Interestingly, low 5hmC levels were also observed in a fraction of TET2 wildtype cases clinically resembling TET2 mutated patients [4]. A recent publication by Figueroa and colleagues showed that activating mutations of the isocitrate dehydrogenase (IDH1/2) genes might affect TET2 function in AML via the conversion of 2OG to 2-hydroxyglutarate (2HG) that inhibits the hydroxylation of 5mC by TET2 and subsequent DNA demethylation [5]. In line, TET2 and IDH1/2 mutations harbored similar epigenetic profiles. This might explain why first studies in small cohorts of AML revealed inconclusive results regarding the prognostic impact of TET2 mutations.
TET2 Mutations in Acute Myeloid Leukemia (AML): Results on 783 patients treated within the AML HD98A Study of the AML Study Group (AMLSG)

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In our study we aimed to explore frequency and clinical impact of TET2 mutations in a large cohort of AML patients (16 to 60 years) who were treated within the AML HD98A study (n=870). TET2 mutation screening was performed in 783 of 870 (90%) AML patients using a DNA-based PCR assay amplifying all coding exons (3-11) of the gene followed by sequencing analysis. Patients were also studied for NPM1, FLT3-ITD (internal tandem duplication), FLT3-TKD (tyrosine kinase domain), CEBPA, and RUNX1 mutations as well as for IDH1/II mutations. The median follow-up for survival was 6.5 years. In addition, we performed global gene expression profiling (GEP) to search for a TET2 mutation-associated gene signature in 333 patients of our cohort including 31 TET2-mutated cases.

We found 66 TET2 mutations in 60 (60/783; 7.6%) patients with 6 (10%) cases exhibiting more than one mutation. All but one (461X) mutations were heterozygous. TET2 mutations were spread all over the gene, mostly affecting exon 3 (n=28) and exon 11 (n=11). TET2 sequence alterations included 16 frameshift (24%), 15 nonsense (23%), and 35 missense (53%) mutations. Correlation of TET2 mutations with distinct clinical features (gender, age, de novo vs. secondary vs. therapy-related AML, white blood cell and platelet counts, bone marrow and peripheral blood blasts) and defined genetic alterations (normal karyotype, t(8;21), inv(16), trisomy 8, t(15;17), t(6;9), complex karyotype, NPM1, CEBPA, RUNX1 mutation, FLT3-ITD, FLT3-TKD) did not reveal any significant association; the only correlation was found for IDH1/2 mutations that were mutually exclusive in TET2-mutated patients (P=0.0004). This finding is in accordance with the recent findings by Figueroa and colleagues, suggesting a biologically redundancy as both TET2 and activating IDH1/2 mutations affect the 2OG-dependent TET2 enzyme function and thereby induce subsequent DNA hypermethylation.

We next evaluated the impact of the TET2 mutation status on clinical outcome in the whole study population: TET2 mutations did not impact response to induction therapy (P=.77), event-free survival (EFS) P=.67, relapse-free survival (RFS) P=.49, cumulative incidence of relapse ([CIR] P=.045) and overall survival ([OS] P=.43); the same was true when performing the analysis for the subgroup of cytogenetically normal (CN)-AML ([EFS] P=.94; [RFS] P=.22; [CIR] P=.34; [OS] P=.36). Finally, we evaluated the prognostic value of TET2 mutations in the favorable NPM1mut/FLT3-ITDnegative genotype, but again TET2 mutations did not impact survival (CIR P=.88; OS P=.33). In accordance with the observations by Ko and colleagues, GEP identified a relatively weak TET2 mutation-associated signature that was not mutually exclusive to TET2-mutated cases, but also shared by a large number of TET2-wildtype cases [4]. Of note, a significant proportion of these cases (~30%) were IDH1/2-mutated, which is in line with the findings by Figueroa and colleagues suggesting a common deregulation of TET2 in these cases [5]. Pathway comparison analysis for Biocarta pathways revealed several pathways significantly enriched, including e.g. the “monocyte and its surface molecules” pathway. Again, this finding is consistent with the recently observed impaired myeloid differentiation following TET2 inactivation that results in a monocyte/macrophage phenotype [8].

In summary, in this cohort of 783 younger adult AML patients TET2 mutations were identified with a frequency of 7.6%. TET2 mutations were distributed over all cytogenetic and, with the exception of IDH, over all other molecular genetic markers; TET2 mutations did not impact clinical outcome in the whole population as well as in the subgroups of CN-AML or the NPM1mut/FLT3-ITDnegative genotype. However, based on the recent findings that IDH1/2 mutations also affect TET2 function, the clinical impact of TET2 alterations has to be reevaluated.

References

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Bispecific T-cell engaging (BiTE) antibody Blinatumomab: Immunotherapy of B-precursor ALL

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Blinatumomab (MT103) is a single-chain bispecific antibody construct designed to use a patient’s own cytotoxic T cells to attack CD19 positive B lineage leukemia cells. Blinatumomab belongs to a new class of agents called bispecific T cell engager (BiTE) antibodies (Löffler et al., 2000). BiTE antibodies function as adaptors that not only physically link T cells and tumor cells but, at the same time, can potently trigger the signaling cascade of the T cell receptor complex by binding to the invariant CD3 component of the receptor. This can redirect virtually any antigen-experienced cytotoxic T cell against tumor cells at low picomolar concentrations of a BiTE antibody. BiTE antibodies appear to functionally replace in terms of size and functionality the HLA class I/peptide/T cell receptor complex (Figure 1). Data from animal models support a high activity of BiTE antibodies at very low doses against established subcutaneous tumors and disseminated tumor cells including lymphoma and leukemia models (Dreier et al., 2003, Schlereth et al., 2006). CD19 is the earliest B lineage-restricted antigen expressed on the surface of B lymphocytes. With the exception of plasma cells, CD19 is expressed on all development stages of B cells, including all B-lineage derived leukemias, where it is used as classification marker.

Blinatumomab has been tested as a continuous intravenous infusion in two clinical trials in Germany, one trial in relapsed non-Hodgkin’s lymphoma (NHL) and one trial in MRD positive B precursor acute lymphoblastic leukemia (ALL). In the relapsed B-NHL phase I trial (Bargou et al., 2008 Science; Viardot et al., 2010 ASH), seven dose levels have been tested in 62 patients as of October 2010: 0.5 µg/m²/d up to 90 µg/m²/d. Most adverse events (AEs), often flu-like symptoms, transient lymphopenias and leukopenias, were early-onset, transient, reversible, easily managed, and did not require treatment discontinuations. The clinically most relevant AEs were fully reversible CNS events seen primarily at the onset of treatment. By intervention with dexamethasone these events can be managed in most patients without interruption of treatment with blinatumomab.

An analysis of efficacy data suggests that blinatumomab produces a high response rate and duration of response in a broad spectrum of NHL subtypes (follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, diffuse large B cell lymphoma). Among evaluable patients who received the dose level of 60 µg/m²/d, 82% (18 out of 22) achieved an objective response, all within the first cycle. In general, the drug has shown a favorable benefit/risk profile in patients with NHL.

Based on very promising data at a lower dose of 15 µg/m²/d, which eradicated lymphoma bone marrow infiltration in most tested NHL patients, a second continuous infusion trial was started in patients with B precursor ALL (Topp et al., 2010, ASH). Twenty-one patients with a median age of 48 years (range 20-77) were enrolled. Patients received four 4-week cycles, which in general were well tolerated. Pyrexia, chills, headache, and fatigue were the most common adverse events and mainly occurred during the first days of treatment. Most of these events were considered grade 1-2. Treatment had to be stopped in two patients due to CNS events (seizure on day 2 of cycle 1, syncope on day 7 of cycle 3). Of 20 evaluable patients, 80% (16 out of 20) achieved a molecular complete response (complete MRD response). Responses were rapid, all occurring within the first cycle of treatment. Responders include three out of five patients with Ph+ ALL (one T315I mutation) and one out of two patients with t(4;11). An analysis of long-term efficacy data demonstrated that blinatumomab produced prolonged hematologic remissions in this patient population. With a follow-up period of up to 27.5 months, the median RFS for evaluable patients has not yet been reached. In addition, the data indicate that blinatumomab allows for safe subsequent allogeneic transplantation with no 100-day-transplantation mortality observed in all nine transplanted patients.

Based on these pilot phase II data, in September 2010, a confirmatory international multicenter clinical trial MT103-203 (BLAST trial) was initiated in collaboration with EWALL. This BLAST trial (NCT01207388) is conducted in patients with MRD-positive ALL after at least 3 intensive chemotherapies with an MRD level of ≥ 10-3. It is mandatory that a pre-initial-treatment bone marrow aspirate with blast infiltration is available for the central MRD lab to identify appropriate patient specific primers to evaluate the MRD burden for trial participants. Eligible patients will receive up to four cycle of blinatumomab as a 4-week continuous intravenous infusion with 2-week treatment-free intervals. More than 60 centers in 11 countries across Europe will participate in this study. Detailed information can be obtained from the protocol synopsis in the ELN leukemia trial registry (www.leukemia-net.org).

Observations from clinical trials conducted to date suggest that blinatumomab can effectively engage cytotoxic T cells for tumor cells lysis in patients heavily pre-treated with immunosuppressive chemotherapeutic regimen. Based on these very encouraging data, an additional Phase 2 trial in relapsed or refractory B-precursor ALL was started in September 2010 and is enrolling patients at sites in Germany. A phase II trial for pediatric patients in second bone marrow relapse also will be initiated in the near future.

Figure 1: Blinatumomab is a Bispecific T-Cell Engaging (BiTE) Antibody.
Philadelphia–Negative Classical Myeloproliferative Neoplasms: Critical concepts and Management Recommendations from European LeukemiaNet


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Topp M.S., Zugmaier G., Goebuget N., et al. CD19/CD3 Bispecific Antibody Blinatumomab (MT103) is Highly Effective in Treatment of Patients with Minimal Residual Disease (MRD) from Chemotherapy-resistant B-Pre-cursor Acute Lymphoblastic Leukemia. ASH Abstract # 174, 2010.

Viardot A., Goebeler M., Scheeie, J. et al. Treatment of Patients With Non-Hodgkin Lymphoma With CD19/CD3 Bispecific Antibody Blinatumomab (MT103): Double-Step Dose Increase to Continuous Infusion of 60 µg/m²/day is Tolerable and Highly Effective. ASH Abstract # 2880, 2010.

Purpose
To review critical concepts and produce recommendations on the management of Philadelphia-negative classical myeloproliferative neoplasms, including monitoring, response definition, first- and second-line therapy, and therapy for special issues.

Methods
Key questions were selected according the criterion of clinical relevance. Statements were produced using a Delphi process and two consensus conferences involving a panel of 21 experts appointed by the European LeukemiaNet (ELN) were convened.

Critical Concepts
Patients with polycythemia vera (PV) and essential thrombocythemia (eT) should be defined at high-risk if age is over 60 or having previous thrombosis. Risk stratification in primary myelofibrosis (PMF) should start with International Prognostic Scoring System (IPSS) for newly diagnosed patients and dynamic-IPSS (d-IPSS) for patients being seen during their disease course, with the addition of cytogenetics evaluation and transfusion status.

Management Recommendations
Patients with PV should be managed with phlebotomy, low-dose aspirin, and cytoreduction in high-risk cases, with either hydroxyurea or interferon at any age. ET patients should be managed with cytoreduction in high-risk cases, using hydroxyurea at any age. Monitoring response in PV and ET should utilise the ELN clinico-hematological criteria. Corticosteroids, androgens, erythropoiesis stimulating agents, and immunomodulators are recommended to treat anemia of PMF; while Hydroxyurea is the first-line treatment of PMF-associated splenomegaly. Indications for splenectomy include symptomatic portal hypertension, drug-refractory painful splenomegaly, and frequent red blood cell transfusions. The risk of allogeneic stem cell transplantation (allo-SCT)-related complications is justified in transplant-eligible patients whose median survivorship is expected to be less than 5 years.
A European consensus report on blood cell identification


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Morphological evaluation of peripheral blood (PB) and bone marrow (BM) cells through microscopic examination of properly stained smears remains crucial in haematological diagnosis mostly for differences in bone marrow processing procedures, staining, degree of skill in interpretation and terminology used, contributing to a lack of standardization of this diagnostic tool. The new WHO classification highlights the importance of morphological aspects, quantitative as well as qualitative, for the diagnosis and follow up particularly of myeloid neoplasms, and above all neoplasms of myeloid neoplasms, and above all the diagnosis and follow up particularly of myeloid neoplasms, and above all myelodysplastic syndromes: therefore microscope still remains a very important tool in the integrated diagnostic process of haematological diseases. The Information and Communication Technology provides the opportunity to exchange images and information without geographic limitation, saving time and resources and many studies highlight the robustness of ICT for diagnostic assessment of blood cell morphology.

The ELN Morphology Faculty (EMF), composed of 28 expert morphologists from 17 European countries, was organized within the activities of the Diagnostic WP10 with the goal to increase quality of diagnostics based on cytomorphology, as the first technique worldwide, and to support this by a web based consensus report, including a uniform nomenclature.

This study was carried out, by using anonymous files, in three consecutive steps, aimed to take advantage of individual competences, to train each other, and to reach a full consensus by the end of the study. Statistical analyses were performed on the obtained results.

First phase
To test the methodology, 50 images with 139 consecutively numbered cells were uploaded onto a restricted web page together a database containing name proposals (cell lineage and maturation stage). The initial lineage/morphological categories were six: erythroid (Ery), granulocytic (Gra), lymphoid (Lym), megakaryocytic (Mgk), monocytic (Mon), blast (Bl) and “other” (Oth). EMF members were asked to indicate whether they agreed with proposed terminology or give an alternative definition. After collecting data, a preliminary version of a consensual ELN Blood Cells Glossary (EBCG) of morphological terms was created. Five meaningful cell images together with the proposed cell definition(s) (according to the EBCG nomenclature when available) were provided by each of the 21 members of the EMF and submitted to all for the cell definition. A cell definition was considered approved if agreement from at least 17 members was obtained (consensus > 80%). The Delphi technique was applied to obtain better consensus for cells without a full agreement during the first round. As a pre-requisite, one alternative term had to have been proposed by at least 3 members to be included into the options of the Delphi questionnaire. Cells with a full agreement (≥17/21) but with a different classification provided by at least 3/2 members were submitted to the Delphi questionnaire too, in order to enlarge the discussion. A list of cells together with the proposed options for terminology was sent to the participants: for each option, the rate of initial agreement was indicated as the number of EMF members in agreement. Each option should be scored between 3 and 1, full agreement, partial agreement and full disagreement, respectively. After collecting data, a new Delphi questionnaire was performed for those cells presenting with a low final score (<7) resulting from at least 2 full agreements.

Second phase
The EMF was extended to 28 morphologists to achieve a broader representation: each member submitted two new images without providing cell names. Participants were asked to name these cells using terminology from the EBCG, whenever possible. Data were collected, grouped and analysed with the same requirement of at least 80% agreement for definite term used for a given cell.

Third phase
During a two-day consensus meeting, EMF members collectively reviewed i) the set of 79 cells with a scoring difference <7 between two options after the first Delphi round and ii) the set of 98 not fully agreed cells submitted in the second phase.

Consensus Meeting: Nancy October 25-26, 2008
One-hundred-sixty-four images containing 438 labelled blood cells were initially collected from the e MF members with the submitter’s proposal(s) of term(s) for each labelled cell. A full consensus (≥ 17/21) was achieved for 250 cells (59.4%): major discrepancies concerned blasts and monocytic series and discrepancies in the nomenclature used to identify the differentiation stages of the erythroid series: the e MF decided to add the alternative denomination in brackets, i.e., “erythroblast basophilic (early erythroblast)”, and the EBCG was prepared. The first Delphi questionnaire was applied to a total of 216 cells. The eMF created a new category, “Cell to delete”, for a set of 8 cells, since failure to reach a firm decision was mostly due to the poor quality of the images. Full agreement (lineage, cell differentiation level, normal vs dysplastic feature) was reached on all of the 216 submitted cells and the EBCG was implemented. Seventy-nine cells, showing a scoring difference <7 between two options, were listed to be discussed during the consensus meeting together with several additional issues, such as the limitation of microscopic evaluation alone to define a lymphocyte as atypical or reactive, the term which had to be used to identify a “morphologically abnormal” plasma cell (atypical vs. dysplastic), the question if the term “dysplastic” should be used only for the three myeloid lineages or not. The majority of morphological discrepancies concerned: i) 34 cells (2 Mgk, 8 Ery, 24 Gra) if they should be considered normal or dysplastic, ii) 7 cells (3 Gra, 3 Mon, 1 Ery) concerning the differentiation stage, iii) 10 cells, whether they should be identified as blast versus monoblast (5), promonocyte (4) and promyelocyte (1). In the second phase of the study, 64 new images with 162 labelled cells were collected and submitted to EMF members without any cell name proposal. According to the cell name provided by the submitters, the initial distribution of these 162 cells showed an increase in monocytes and an equivalent decrease in granulocytes compared to the proportions of the first set of 438 cells. Full agreement, including use of the same denomination, was reached immediately for 60 cells (36.14%). This was considered an important achievement, especially in the view of the heterogeneity of the glossaries used in practice in hematology laboratories all over Europe. The remaining 102 cells were collectively discussed, agreed upon and named during the two-day meeting. Three additional cells were deleted, due to the poor quality of the images. During the interactive discussion on the images, the EMF decided to label 4 more cells because of their relevance in the context (1 blast NOC, 1 promyelocyte, 1 promonocyte and 1 megakaryoblast, respectively) and to add the category “Cytologically unclassifiable” for 5 images displaying metastatic cells, previously included in the category “other”. The ECBG was updated. Major discrepancies on this set of cells concerned the appropriate use of terms such as dysplasia, atypical or Mott cell. At the end of the meeting, 228 images with 604 labelled blood cells were uploaded onto the ELN website together with an Excel file (EBCG) where each cell is identified by its code, the type of stain used, the lineage and the consensus name agreed by the EMF. This image library is currently freely available on the ELN web site (www.leukemia-net.org) and is linked to the EHA web site (http://ehaweb.org) too.

Finally, a set of 239 cells was submitted via internet to a recognized expert morphologist (JMB) external to the EMF: after the first round, it was obtained a full agreement on 96 cells (46%) with the EMF identification. After a meeting focused on re-examining disagreements, only 7 cells were confirmed as disagreed and a final agreement was reached on 205 valuable cells (96.6%). The quite full concordance achieved after the second interactive reviewing process support the realistic need in the field of cytomorphology to share consensus, including nomenclature, to increase quality of diagnostics according to WHO 2008 goals and guidelines.
Minimal residual disease (MRD) is rapidly emerging as a valuable tool for determining disease state in patients with hematological malignancies. Standardized implementation of this concept holds promise to i) stratify patients according to initial response to cytodestruction, ii) identify patients who obtain a “deep” molecular complete remission (CRm), and iii) rapidly diagnosis of treatment failure/relapse to direct preemptive therapy and develop more individualized treatment strategies.

Several techniques are currently being evaluated for suitability in the daily clinical setting. While flow cytometry is both fast and quite sensitive (usually to the $10^{-6}$ level), real-time quantitative PCR (RQ-PCR) is both more sensitive (usually to the $10^{-5}$ level) and more pre-clinically validated, particularly for monitoring response to targeted therapies in patients with BCR-ABL+ leukemias and acute promyelocytic leukemia.

Irrespective of the advantages and drawbacks of the various techniques, it is a major challenge to present MRD data to the clinical hematologist and to the patient, who could be confronted with evidence suggesting an impending relapse, despite being in good health.

To obviate these logistical difficulties an MRD reporting package has been developed over the course of the last few years as a collaborative venture between WP12 and a Danish Software house (Langtved Data). From the outset it was decided that the program should encompass every step in the process from the initial input of raw data from various RQ-PCR platforms in common usage to the final generation of a report, which could be flexibly tailored to the needs of the individual end-user (Fig. 1).

After several beta versions and user meetings in Aarhus and London, a near-final version has been subjected to two rounds of quality control (QC) testing.

In the first QC round, the aim was to provide an overall validation of the package. To this end, CDNA from a CML patient, an AML patient as well as from the K562 cell line was distributed from Aarhus to 8 laboratories (who had markedly differing levels of prior experience with the software). Since longitudinal samples were provided from the two patients, this enabled the construction of graphs from the RQ-PCR reactions performed at each center. Based on the read-only graphs provided from the labs we were able to pinpoint a few minor software glitches which have now been corrected. More importantly, it could be concluded that the software performed robustly. Thus, the collated graphs demonstrated a high degree of concordance in the MRD curves between the laboratories. In the second QC round we wished to demonstrate the usefulness of the software for harmonizing MRD data reporting between laboratories, exemplified by the use of center-specific international scale conversion factors in CML. To this end, CML samples were shipped from Aarhus to five laboratories, which purified RNA and performed RQ-PCR according to their standard routines. The participants were asked to report MRD levels both according to their standard practice (normalized to K562, BCR-ABL copies per 10,000 ABL copies or bCR-ABL copies per 100 GUS copies) and also according to the CML international scale after employing their recently obtained international scale conversion factors.

We feel that this software package constitutes a valuable step for harmonizing RQ-PCR data across hardware platforms. It will be available free of charge to all interested members of ELN, but its use is accompanied by a service charge levied by Langtved Data that will cover support for ongoing use of the program.

### Table: MRD reporting software

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### Diagram 1: MRD analysis module

- qPCR
- Sample info
- Database
- Database browser
- MRD analysis module
- MRD evaluation & conclusive text
- Calculation & report type

### Diagram 2: MRD results

**Primary MRD results**

- Lab C (K562 equivalents)
- Lab F (BCR-ABL copes per 10,000 ABL copies)
- Lab H (K562 equivalents)
- Lab G (BCR-ABL copies per 100 GUS copies)

**CF-adjusted MRD results**

- Lab C (K562 equivalents)
- Lab F (BCR-ABL copies per 10,000 ABL copies)
- Lab H (BCR-ABL copies per 100 GUS copies)

**MRD by $2^{-\Delta\DeltaCt}$**

- Lab C (K562 equivalents)
- Lab F (BCR-ABL copies per 10,000 ABL copies)
- Lab H (BCR-ABL copies per 100 GUS copies)
The EU-directive 2001/20/EC on Clinical Trials (CTD) scheduled on 4th April 2001 “is arguably the most criticised piece of legislation in the Union acquis on medicines” [1]. Since CTD the “number of applications to run clinical trials in Europe fell by 10% between 2007 – 2009” and “the number of participants in proposed trials fell too, from 535.481 to 358.429. Of the 4.491 trials running in 2009, only 21 per cent involved sites in more than one European country” [2]. It is generally agreed that the situation became particularly difficult for investigator-initiated trials (IITs).

Three years ago the CTD was nominated for an impact assessment conducted by Directorate General (DG) Health (Sanco) and Enterprise/Industries at the European Commission. The process of regulatory amendment is operated by three steps:

1. Impact assessment and drawing up a legislative proposal
2. Submission of proposal to the Council of Ministers and the Parliament and

The EU-directive on good clinical practice: Impact for independent research?

Stakeholder workshops
Beside, various conferences of stakeholder has been taken place and ELIC was part of the organisation team of a series of workshops and participating in the final workshop “Final Multidisciplinary Workshop: Designing the Future Conditions for Clinical Research” with the aim, to influence on reports towards DG Sanco (Health)/DG Enterprise.

Meetings at Health Directorate and DG Enterprise
In 2009 and 2010 dedicated meetings with expert-stakeholders has been conducted by DG Enterprise and Industry (e.g. patient organisations). In 2010 Dr. Gökbuget (ELIC) and Dr.Dreyling visited Stephan Führing at DG Enterprise, with the aim to specify the problematic situation for multinational IITs in the frame of the ELN.

Summary
The European Commission summary paper displays the overall comments of all contributors, representing academic researchers, pharmaceuticals/CRO, national competent authorities, ethic committees, patient organisations and others. Although the summary of the public consultations lists some positive results of the CTD [3] it also confirms:

- There are doubts about the CTD improvements in terms of safety and rights of participants.
- Although concepts were in principle good, they did not work in practice or did not achieve their aim (e.g. SUSAR reporting).

Unfortunately, during the whole assessment the role of academic research was only slightly touched, which is caused by the initial setting of the impact assessment – focusing on EU market aspects (e.g. harmonisation, administrative burden) [4].

Currently, the impact assessment is still in progress and the Commission plans a firm proposal for revision of the CTD for 2011. Possible issues that would be addressed are reduction of administrative delays prior to the commencement of clinical trials, avoiding divergent decisions throughout the EU and streamlining of reporting procedures. Apparently there is no focus on the specific problems of rare diseases and independent researchers. Also, one has to consider, that the final decision relies only on the parliament and the representatives. Additionally, the whole process is time-consuming and it could take years to turn an amendment active - even after the written proposal - and some more to adopt the directive in the member states.

In between, the ELIC could focus once more on various practical fields for facilitation of clinical trials to promote independent clinical research. The ELN should in addition participate in public consultation of further guidelines (which have effect without legal amendment) and/or follow-up on new guidelines or procedures relevant for clinical researchers. Therefore a workshop addressing selected topics will be organized by ELIC at the 7th ELN symposium in February 2011. All ELN members are invited to participate and are highly welcome to contact the ELN-website http://www.leukemia-net.org > international trials and the ELIC Team.

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4. Roadmap of Impact Assessment, V2, 23/03/2010
Since 1st of July 2010 the European LeukemiaNet (ELN) is funded through a Research Networking Programme (RNP), initiated by the European Science Foundation (ESF), which is called ESF-ELN RNP. The ESF RNPs bring together nationally funded research activities, to address a major scientific issue or a science-driven topic of research infrastructure, at the European level with the aim of advancing the frontiers of science. The ESF-ELN RNP is funded for 5 years (07/2010-06/2015) with an annual budget of 84220 € for networking activities.

Key objectives of this collaboration are

- Support of health related sciences and research as well as improving medical care in acute and chronic leukemia
- Expansion of common information and communication structures of the ELN, reaching out to countries that do not yet participate in the ELN
- Performance of clinical trials on an European level and improvement of the related trial infrastructure
- Establishment of European leukemia registries for each leukemia entity
- International exchange and training of young scientists
- Development of internationally accepted guidelines and meta-analyses
- Spread of excellence

Activities in 2010

The first Steering Committee meeting was held on July, 1, 2010, in Mannheim (DE). Dr. Maria M. Nogueira initiated the project on behalf of ESF. After initiation of the project Dr. Kirsten Steinhausen will now be the responsible science officer for the ESF-ELN RNP on behalf of ESF. Dr. Steinhausen formerly represented the BMBF in Germany related to clinical trial activities. At the launch meeting questions regarding project organisation, Steering Committee, financials and deliverables of the Programme were settled.

Activities in 2011

The ELN Annual Symposium will be supported by the RNP, taking place on February, 1-2, 2011 in Mannheim (DE) with a joint ESF-ELN Steering Committee meeting and joint working group meetings. Reports on the outcome and discussions of this symposium predominantly by member countries of the ESF-ELN RNP will be submitted to ESF.

Financially contributing countries and the steering committee members (nominated by the respective national research organization) can be found on http://www.leukemia-net.org/content/home/esf

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Detailed information can be found on the following websites:
for ESF: www.esf.org
for ESF-ELN RNP: www.esf.org/esf-eln
for the ELN: www.leukemia-net.org

Achievements and benefits of the ESF-ELN RNP

Envisaged achievement of the ESF-ELN RNP will be the continuation of the international ELN activities, which improve and enhance cooperation among network members and will in addition update and inform the public. Expected benefits of the programme will be a comprehensive prognostic model to optimize treatment of acute and chronic leukemia on a European scale and enhanced performance and comparability of trials across Europe leading to better synergies and improved outcomes in leukemia research and patient care. The project will foster current and envisaged internationally visible ELN-activities, promote implementation of ELN management recommendations and improve understanding and treatment of the different leukemia entities in Europe. The major sponsored ELN event will be the annual symposium with workshops, scientific symposium, educational activities, progress reports, novel proposals and collaborations and extensive networking opportunities.
Ongoing studies in the ELTR
(European Leukemia Trial Registry)

The European Leukemia Trial Registry (ELTR) includes active clinical trials administered by study groups of the ELN. Currently over 100 european leukemia studies are listed. Detailed study information and short-protocols are available for free download from the website (www.leukemia-net.org). The ELTR is the first international leukemia register with expert service and is constantly expanding. If you need more information, contact the European Leukemia Information Center ELIC (Elic@em.uni-frankfurt.de).

ALL: Acute lymphoblastic leukemia

All subtypes:
De novo/non-treated
- GIMEMA 0904: Treatment of high-risk ALL and MRD-monitoring
- GIMEMA LAL1104: “Geriatric Assessment Adapted” Therapy for Ph- ALL Elderly Patients
- GIMEMA LAL1308: Combination Chemotherapy in Treating Young Adult Patients With ALL
- GRAALL 02/2005: HyperC vs. standard induction and late intensification in Ph neg. ALL
- PALG 5-2007 MRD: Optimization of the therapy of adult acute lymphoblastic leukemia according to risk factors and monitoring of minimal residual disease
- PETHEMA LAL-AR-03: Therapy of high-risk ALL
- NILG 10/07: Study on CNS Prophylaxis With Liposome-Encapsulated Cytarabine in Association With a Lineage-Targeted and MRD-Oriented Postremission Strategy in Adult ALL
- GMALL 07/2003: Therapy optimization by MRD-evaluation
- HOVON 100 ALL Clofarabine added to prephase and consolidation therapy in acute lymphoblastic leukemia in adults
- B Precursor ALL:
  De novo/non-treated
  - GRAALL 02/2005-R: Mabthera + induction, consolidation and late intensification in Ph neg., CD20+ ALL
- Molecular relapse
  - MT103-203: Confirmatory Phase II Study of Blinatumomab (MT103) in Patients With Minimal Residual Disease
  - GMALL B-ALL/NHL 2002: Study to Optimize Therapy of B-ALL and High-grade Non-Hodgkin’s Lymphoma in Adults

B Precursor ALL:

De novo/non-treated
- GIMEMA 0201: Imatinib in Ph+ and/or BCR/ABL ALL
- GGRAAPH 02/2005: Imatinib-based vs. standard imatinib containing Hyper CVAD induction in de novo Ph+ ALL
- LAL1408: Front-line Treatment with Two Tyrosine Kinase Inhibitors (TKI) Imatinib and Nilotinib

Mature B-ALL / NHL

De novo/non-treated
- GMALL B-ALL/NHL 2002: Study to Optimize Therapy of B-ALL and High-grade Non-Hodgkin’s Lymphoma in Adults

AML: Acute myeloid leukemia

AML all subtypes without FAB M3:

De novo/non-treated
- ALL SCT Ph negative: Role of autologous bone marrow transplantation plus maintenance therapy
- ALFA -0701: Study of Gemtuzumab Ozogamycin (GO) With Daunorubicine and Cytarabine
- AMLSG 11-08: Study For the Evaluation of Dasatinib Following Induction and Consolidation Therapy as well as in Maintenance Therapy
- AMLSG 12-09: Trial evaluating induction therapy with idarubicin and etoposide plus 5-azacitidine and maintenance therapy with 5-azacitidine
- AMLSG 09-09: Study of chemotherapy in combination with ATRA with or without gemtuzumab ozogamycin in patients with acute myeloid leukemia and NPM1 gene mutation
- CP 4055: A Study of Elacetylarabine (CP-4055) Plus Idarubicin as Second Course Remission-Induction Therapy in Patients With AML
- HEMOS 0106: Study to Assess the Safety, Tolerability, and Efficacy of Tipifarnib Plus Bortezomib in the Treatment; Unfit for Conventional Chemotherapy (>18 Years) or in Patients With Acute Myeloid Leukemia in First Relapse (> 60 Years
- HOVON 102 AML: Randomized study with a run-in feasibility phase to assess the added value of Clofarabine in combination with standard remission-induction chemotherapy in patients aged 18–65 years with previously untreated AML or MDS
- LAM07: PETHEMA LAM07: Study to Analyze the Efficacy of a Risk Adapted Treatment Strategy, Including Gemtuzumab Ozogamycin (GO) During Consolidation
- Trial of Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase (MEK) Inhibitor: Trial With Safety-Run-In of MEK Inhibitor AS703026 In Subjects With Poor Prognosis AML and Other Hematological Malignancies
- Untreated CD33 Positive AML: Induction, Consolidation and Intensification Therapy for Patients Younger Than 66 Years
  - <60 years
    - ALFA -0702: The CLARA Study from the Acute Leukemia French Association
    - Combination Chemotherapy With or Without Gemtuzumab Ozogamycin or Tipifarnib in Treating Patients With AML or High-Risk
    - MDS Clofarabine: Clofarabine in combination with a standard remission induction regimen (AraC and idarubicin) in patients 18–60 years old with previously untreated intermediate and bad risk acute AML or high risk MDS
    - LAM2006IR: Trial Testing Efficacy of Gemtuzumab Ozogamycin (MYLOTARG) Associated to Intensive Chemotherapy for Patients Aged Between 18–60 Years
    - Timed-Sequential Induction in CBF-AML: Trial of Systematic Versus Response-Adapted Timed-Sequential Induction in Patients With Core Binding Factor (CBF) AML
Ongoing studies in the ELTR (European Leukemia Trial Registry)

>=60 years

- ALFA-0703: Study to Evaluate the Role of All-trans Retinoic Acid (ATRA) in Combination with Induction Chemotherapy, or Azacitidine and Idarubicin as salvage therapy and Idarubicin with Cytarabine or Azacitidine as Maintenance Therapy in Older Patients
- AC-ILSG 10-07 FLT3m-Sunitinib: SU11248 Combined With Standard Chemotherapy in Patients With FLT3 Mutated AML
- AMLSA-01: Study of Azacitidine (Vidaza®) Versus Conventional Care Regimens for the Treatment of Older Subjects
- GIMEMA AML208: Everolimus and Mitoxantrone Hydrochloride, Cytarabine, Etoposide, and Idarubicin in Treating Older Patients
- LAM-SA 2007: Study of Adding Lomustine to Idarubicin and Cytarabine for Induction and Post-Remission Chemotherapy in Older Patients With AML, and Feasibility of Allogeneic Transplantation for Patients From 60 to 65 Years Old
- PANOBIDARA: Study of Panobinostat in Combination With Idarubicin and Cytarabine in Patients Aged 65 Years or Older

>=60 years

- HOVON 103 AML Tosedostat: Randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral tosedostat to standard induction therapy in AML and RAEB ≥ 66 years and very poor risk AML ≥ 18 years

all stages / not specified

- AC220-002: Monotherapy Efficacy (ACE) Study in Patients AML With FLT3-ITD Activating Mutations
- Adoptive Immunotherapy of High Risk AML Patients Using Haploidentical KIR Ligand-mismatched Natural Killer Cells
- AML A2D1152: Safety, Tolerability, PK and Efficacy of A2D1152
- AML CP4055: Study of CP-4055 in Patients With Refractory/Relapsed Hematologic Malignancies
- HOVON 103 AML Tosedostat: Randomized phase II multicenter study with a safety run-in to assess the tolerability and efficacy of the addition of oral tosedostat to standard induction therapy in AML and RAEB ≥ 66 years and very poor risk AML ≥ 18 years

Diagnostic study

- MDS CytogeneticAnalysis: Cytogenetic Analysis Using Blood and Tissue Samples From Young Patients With MDS, Juvenile Myelomonocytic Leukemia, or Down Syndrome and AML

Supportive

- MDS/AML Eltrombopag: Eltrombopag bei MDS und AML

AML with FAB M3 (APL):

De novo/non-treated

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

CLL: Chronic lymphoblastic leukemia (external website www.ericll.org)

All subtypes:

- European survey on current treatment modalities in CLL patients
- Treatment of T-Prolymphocytic Leukemia with Fludarabine, Mitoxantrone, Cyclophosphamide and Alemtuzumab (phase II trial)
- Evaluation of early treatment versus watch&wait of early stage high risk CLL with FCR (phase III trial of the the French and German CLL study group)
- Erasmus TCRgd LGL study
Not specified / all stages

- CLL 7: CLL7 Study for previously untreated patients in early stage
- CLL 21: CLL 21 protocol of the German-CLL Study Group (DCLLSG)
- CLL 2L: CLL 2L protocol of the German CLL-Study Group (GCLLSG)
- CLL 2M: CLL2M – BR for previously untreated or relapsed CLL
- CLL 10: CLL10 Study – FCR vs. BR in first line therapy of CLL
- GIMEMA LLC0606: Lenalidomide, Fludarabine, and Cyclophosphamide in Treating Patients With Advanced CLL that Did Not Respond to Previous Therapy
- HOVON 88 CLL: Allogeneic Stem Cell Transplantation after Reduced Intensity Conditioning for High-risk Relapsed or Refractory CllA prospective multi-centre phase II study
- HOVON 68 CLL: A randomized phase III study in previously untreated patients with biological high-risk CLL: Fludarabine + cyclophosphamide (FC) versus FC + low-dose alemtuzumab.

CML: Chronic myeloid leukemia

Chronic Phase:

**Newly diagnosed:**
- B1371001: Study To Evaluate The Safety, Pharmacokinetics, And Pharmacodynamics Of PF-04449913, An Oral Hedgehog Inhibitor, Administered As Single Agent In Select Hematologic Malignancies Or In Combination With Dasatinib In Chronic Myeloid Leukemia
- CML IV (Active): Imatinib vs. Imatinib+Interferon or Imatinib 800mg and SCT in CML
- ENEST1st: Study with Nilotinib in adult patients with newly diagnosed Philadelphia-Chromosome- and/or BCR-ABLpositive CML
- GIMEMA CML0408: Nilotinib and Imatinib Mesylate in Treating Patients With Early Chronic Phase CML
- NordCML006: Study of imatinib or dasatinib treatment response in CML stem cells
- SPIRIT 2: Comparison of imatinib (STI571, Glivec/Gleevec) 400mg daily versus dasatinib (Sprycel) 100mg daily

**Intolerant/resistant to one TKI**
- AMN2128: To Evaluate the Effects of Multiple Doses of Nilotinib on the Pharmacokinetics and Metabolism of Midazolam in CML Patients With Additional Extension Phase to Evaluate the Safety of Nilotinib
- B1371001: Study To Evaluate The Safety, Pharmacokinetics, And Pharmacodynamics Of PF-04449913, An Oral Hedgehog Inhibitor, Administered As Single Agent In Select Hematologic Malignancies Or In Combination With Dasatinib In Chronic Myeloid Leukemia

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

MDS: Myelodysplastic Syndrome

**Different risk groups:**
- AML RICMAC/MDSsAML: Dose reduced vs. standard conditioning + SCT in MDS or sAML
- 5-Azacytidine II: Study of maintenance with Azacitidine in MDS patients achieving complete or partial remission (CR or PR) after intensive chemotherapy
- MDS Decitabine: Study of Decitabine in patients with CML
- MDS Lenalidomide II (pending): A phase II trial to assess the efficacy Lenalidomide with or without Erythropoietin and granulocyte-colony stimulating factor in patients with low and intermediate-1 risk MDS
- Lenalidomide I: Lenalidomide vs Placebo in RBC-dependent low- or intermediate-1 risk MDS with Sq-
Intermediate II and high risk:

- S-Azacitidine: Subcutaneous Azacitidine + best supportive care vs. conventional regimens + best supportive care
- Erlotinib: Erlotinib in high risk MDS
- Lenalidomide III: This is a study of oral lenalidomide administered in adult subjects
- HOVON 81 AML: Study to assess the tolerability and efficacy of the addition of Bevacizumab to standard induction therapy in AML and high risk MDS above 60 years
- MDS Combi-Chemo: Combination chemotherapy with or without Gemtuzumab or Tipifarnib in high-risk MDS
- MDS Clofarabine: Clofarabine in combination with a standard remission induction regimen (AraC and idarubicin) in patients 18-60 years old with previously untreated intermediate and bad risk acute AML or high risk MDS
- MDS QOL II: Quality of Life and Symptoms
- MDS-005 Lenalidomide: Study of the Efficacy and Safety of Lenalidomide (Revlimid) versus Placebo in Subjects with

Transfusion-Dependent Anemia due to IPSS Low or Intermediate 1 Risk MDS without Deletion 5Q
- Velcade Zanrestra: Bortezomib and Tipifarnib in MDS
- Vorinostat: Study of Vorinostat in Combination With Low Dose Ara-C

Monosomy 5 or 6q5:
- Lenalidomide III: This is a study of oral lenalidomide administered in adult subjects
- Lenalidomide I: Lenalidomide vs Placebo in RBC-dependent low- or intermediate-1 risk MDS with 5q-

Supportive studies MDS:
- MDS/AML Eltrombopag: Eltrombopag bei MDS und AML
- Darbepoetin-Filgrastim: Darbepoetin alpha and G-CSF vs. best supportive care
- MDS Exjade: Exjade(Re'El) in transfusion dependent anemia overloade (2008)
- Darbepoetin Epoetin II: Darbepoetin in low- or intermediate-1 risk MDS with anemia
- Romiplostim I: Evaluating the Safety of Long Term Dosing of Romiplostim (formerly AMG 531)

Diagnostic /biomarker studies MDS:
- Biomarkers: Biomarkers in Patients at Risk of Developing Myelodysplastic Syndrome or Other Disorders and in Healthy Participants
- MDS Biomarkers: Molecular and functional characterization of bone marrow function in patients with MDS and secondary disorders of hematopoiesis
- CytogeneticAnalysis: Cytogenetic Analysis Using Blood and Tissue Samples From Young Patients With Myelodysplastic Syndromes, Juvenile Myelomonocytic Leukemia, or Down Syndrome and Acute Myeloid Leukemia

other:
- NMDSG03A: Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- MDS Quality of life I: Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function

CMPD: Chronic myeloproliferative disorder

Polycythaemia vera
- PV Venesection: Symptoms of iron deficiency in patients with polycythaemia vera treated with venesection

SCT: Stem cell transplantation

Stem cell transplantation Not specified / all stages:
- 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
- StemCellTransplant II: Pilot Study of Reduced Intensity Haematopoietic Stem Cell Transplantation in Patients With Poor Risk MDS and AML Utilising Conditioning With Fludarabine, Busulphan and Thymoglobulin (FB-ATG)
- Velcade: Phase II Study of PS341 (VELCADE) in MDS
- MDS AlloSCT-Clofarabine: Allogeneic Stem Cell Transplant With Clofarabine, Busulfan and Anthymoglobulin (ATG) for Adult Patients With High-Risk AML/MDS or ALL

Ongoing studies in the ELTR (European Leukemia Trial Registry)

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