INFORMATION LETTER Nº6 FEBRUARY 2010

Dear Colleagues,

In 2010 we enter the 7th year of European funding for the European LeukemiaNet (ELN). The EU extended the contract with the ELN until February 2011, stating that the ELN is “a very successful network that warrants support and extension”. This is indeed a success and motivation for all of us, members and partners.

Years of joint efforts in the management of leukemias have shaped the ELN to what it currently is. 170 institutions from 33 countries participate and contribute, each within their particular field of knowledge and expertise. The ELN offers intellectual diversity. Scientific issues are addressed from complementary points of view with high-level competence in discussions and recommendations. Sustainability is a key issue to keep this source of interaction and cooperativity alive.

In 2009 the ELN Foundation was constituted and has started its activities. The Foundation presents its structure and activities in a first ELN Foundation Newsletter, which is available in seven languages at the annual ELN Symposium in Mannheim February 1-3, 2010. We thank all ELN members, partners and friends for their engagement and enthusiasm.

In 2009, the ELN Symposium took place in Mannheim, Rosengarten for the first time. It attracted 439 ELN participants from 30 countries. Challenges and new directions in leukemia and related disease entities were highlighted and complemented by a presentation on rare cancers. Regulatory issues of the new European drug law continue to pose a major hurdle to investigators for initiating international collaborative trials. Therefore a special teaching event on the situation of international investigator-initiated trials in Europe was offered. A training course in good clinical practice presented up-to-date information on the actual consequences of changing regulations. During 2009 ELN workshops and scientific meetings stimulated many fruitful projects among participants.

Progress within the different leukemias is highlighted in the ELN homepage. The ELN trial registry database shows information on more than 70 active clinical trials. Intensive efforts are ongoing to coordinate trials and to harmonize criteria according to European guidelines. Management recommendations were published in 2009 on AML and APiT and updated on CML, and also on consensus response criteria to treatment in polycythemia vera and myelofibrosis. Pocket cards on the CML treatment recommendations were distributed at ASH 2009 in New Orleans and can be ordered via our website.

The public-private-partnership between ELN and Novartis (EUTOS for CML) continued successfully. Standardization of BCR-ABL diagnostics and blood level testing of imatinib made progress, 26 national reference laboratories have been established in 24 countries for molecular monitoring and 28 reference laboratories in 14 countries for drug level determination. The population-based registry was activated in several countries after facing challenges and hurdles with the regulatory environments. The EUTOS website now contains the presentations of the last CML educational in Barcelona, September 2009, the molecular monitoring standardization workshop on RQ-PCR in Berlin, and the Naples educational on CML management for young hematologists. The next CML educational symposium will take place in Vienna, 22-24 October, 2010. This ELN-Newsletter again presents current activities within the ELN and reflects the ongoing discussions in leukemia research and management. I am sure this will catch your attention.

The articles deal with the update of the ELN management recommendations for CML, the EUTOS collaboration, the role of immunotherapy in AML, a pilot project of outcome determinants in AML, factors predicting the outcome after hematopoietic SCT, gene polymorphisms in CLL, the ELIC initiatives around the EU-directive on GCP, activities of the ELN Foundation, news on ALL, upcoming meeting dates and ongoing studies of the ELN in the ELTR. A summary table of published ELN guidelines and recommendations is also included in this issue of the ELN Newsletter.

The ELN provides transparency in leukemia research, a critical mass for excellence and a competitive advantage for participants and their partners, including industry. The ELN aims at durable integration of all interested in leukemia, setting the stage for future strategies and progress. I wish you a successful 2010.

Sincerely yours,

Prof. Dr. Rüdiger Hehlmann
Network Coordinator
1. Prior recommendations were mostly based on data reported orally at international meetings. In three years, more data on imatinib therapy have matured and have been reported in peer-reviewed papers. More solid evidence was acquired.

2. Three years ago, at the time of prior recommendations, the treatment of CML included imatinib standard dose (400 mg daily), allogeneic hematopoietic stem cell transplantation (alloHSCT), and still interferon and hydroxyurea. Since then, two potent second generation tyrosine kinase inhibitors (TKIs) have become available and were registered for 2nd line therapy.

3. The introduction of 2nd generation TKIs in 2nd line treatment required the urgent definition of the response to these agents. Response to treatment Failure is identified at 3 months in case of non complete hematologic response (CHR), at 6 months in case of no cytogenetic response (CgR) (Ph+ > 95%), at 12 months in case of less than partial CgR (Ph+ > 35%), at 18 months in case of less than complete CgR (primary failures or primary resistance), and at any time during treatment in case of CHR loss, or CcgR loss, or clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), or the detection of BCR-ABL kinase domain mutations poorly sensitive to imatinib.

4. Three years ago, CML was still considered a fatal disease with an excellent response to imatinib. In the past three years the medical and patients communities have changed their attitude, and consider more and more CML as a maybe chronic condition that may be cured.

Major new statements for the updated recommendations are summarized in the following:

Response to treatment Failure is identified at 3 months in case of non complete hematologic response (CHR), at 6 months in case of no cytogenetic response (CgR) (Ph+ > 95%), at 12 months in case of less than partial CgR (Ph+ > 35%), at 18 months in case of less than complete CgR (primary failures or primary resistance), and at any time during treatment in case of CHR loss, or CcgR loss, or clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), or the detection of BCR-ABL kinase domain mutations poorly sensitive to imatinib.
**Optimal response** is identified at 3 months by CHR and at least minor CgR (Ph+ ≤ 65%), at 6 months by an at least partial CgR (Ph+ ≤ 35%), at 12 months by a CCgR, and at 18 months by a major molecular response (MMolR) (bCR-MMolR at 18 months.

**Suboptimal response** covers a grey or intermediate area, where some patients may become optimal responders, while some others can fail on imatinib. It is identified by no CgR (Ph+ > 95%) at 3 months, less than PCgR at 6 months, a PCgR at 12 months, and a less than MMolR at 18 months.

**Treatment consequences**
Failure requires a change of treatment, 2nd generation TKIs first, and alloHSCT in case of secondary failure. Optimal response requires that the patient continues the treatment indefinitely, although he/she may become eligible for investigational studies aiming for treatment discontinuation. The best treatment of suboptimal responders is uncertain, whether they may continue imatinib same dose, or increase imatinib dose, or be switched to experimental treatment with 2nd generation TKIs.

**Risk factors**
Warnings (that means that some patients may not become optimal responders and should be monitored very carefully) are high Sokal risk and CCA/Ph+ at baseline, less than MMolR at 12 months, or any increase of BCR-ABL transcript level during treatment.

**Response to 2nd generation TKIs**
A provisional definition of failure on 2nd generation 2nd line TKIs (dasatinib and nilotinib) is provided, based mainly on the finding that the response to these agents is very rapid; no CgR (Ph+ > 95%) at 3 months, minimal CgR (Ph+ 66% - 95%) at 6 months, less than PCgR (Ph+ > 35%) at 12 months, or the appearance of new mutations during treatment.

**Role of allogeneic SCT**
AlloHSCT is recommended in all patients in accelerated and blastic phase, preceeded by a TKI, in all patients with a T315I mutation, and in all eligible patients who fail on dasatinib or nilotinib 2nd line.

**A successful collaboration**

Baccarani (IT), Cervantes (ES), Cross (UK), Engstroem (IT), Guidi (IT), F. Guilhot (FR), J. Guilhot (FR), Hasford (DE), Hehlmann (DE), Hochhaus (DE), Mahon (FR), Montrucchio (IT), Pane (IT), Rancati (IT), Saglio (IT), Saussele (DE), Schuld (IT) and Simonsson (SE)

EUTOS for CML – a successful collaboration to improve the outcome for patients with CML

The European Outcome and Treatment Study for CML (EUTOS), is a unique collaboration between the pharmaceutical industry and the European LeukemiaNet (ELN). The objectives of this partnership are to:

- Ensure optimal uptake of the ELN treatment recommendations across Europe by providing clinicians access to latest disease management tools and techniques
- Increase understanding of the incidence and management of CML
- Expand access to a state-of-the-art clinical support program
- Improve outcomes for CML patients across Europe

The EUTOS for CML is focussed on the following key areas:

- CML-Registry: to collect baseline, treatment, and outcome data across Europe for patients with CML in order to gain valuable epidemiological data
- Molecular Monitoring: to distribute standardized RQ-PCR analyses for BCR-ABL quantification and assessment of resistance in CML.
- Pharmacological Monitoring: to make available to all European physicians treating patients with CML a standardized facility established to monitor drug treatment parameters to ensure a correct therapeutic response in each patient.
- Spread of excellence: to raise awareness and education around the EUTOS for CML project.

**About the CML Registry**
One of the key objectives of the EUTOS for CML registry is to provide a clear epidemiological picture of CML and patient treatment and outcomes across Europe. To date 27 centres (ELN institutions) from 25 countries across Europe are part of the EUTOS for CML registry. They are collecting baseline, treatment and outcomes data for patients with CML and submitting this to the central data centre (CDC) in Munich for analysis. To achieve its objectives, the EUTOS for CML Registry is divided into three patient groups:

- In-study: patients diagnosed between 2002 and 2006 from national study groups enrolled in prospective studies, who are taking imatinib frontline
- Out-study: patients diagnosed between 2002 and 2006 already registered in existing databases, who are taking imatinib front-line
- Population-based: newly diagnosed patients from 2009 onwards not previously in registries or clinical studies, irrespective of front-line treatment

The in- and out-study registries are ongoing. The population-based registry has now successfully launched with the first countries activated in June 2009. Activation of the participating countries for the Registry is managed by the Steering Committee of the Registry (M. Baccarani, J. Guilhot, J. Hasford, B. Simonsson).

**About molecular monitoring**
The rationale for the development of this subproject was to:

- Improve the early recognition of relapse
- Provide prognostic information

Thus this project aims to bring about the standardization of RQ-PCR throughout Europe ensuring an alignment with the International Scale (IS). A good network of standardized labs currently exists across Europe: 57 labs are participating in this project with 26 national reference labs (including Mannheim) validated across Europe so far. Preliminary conversion factors (CF) are calculated using standard samples sent from the central laboratory in Mannheim to national labs and then validation of these CFs occurs by sending patient samples from the national labs to the central lab. Once validated the national reference labs are equipped to propagate validated CFs and allow local labs in their respective countries to express their BCR-ABL levels on the IS.

The plan moving forward is to expand the project to include around 200 labs across Europe, to perform regular certified control rounds in validated labs and to initiate exchange programs to educate laboratory personnel on RQ-PCR and mutational analysis, allowing rapid implementation of the standards in all participating European countries.
Recommendations for the propagation of the IS by national or regional laboratory networks were recently published in Leukemia (Mueller MC et al. Harmonization of molecular monitoring of CML therapy in Europe. Leukemia 2009).

About pharmacological monitoring
This subproject was set up to:
• Expand availability of imatinib BLT to a European level Free of charge at a central facility (Bordeaux University Hospital)
• Establish monitoring facilities in respective countries, using a standardized monitoring protocol with quality control performed by Bordeaux team
• Construct a dosing database to verify / define the therapeutic threshold (around 1000 ng/ml)

All logistical steps of the EUTOS Pharmacological Monitoring subproject have been implemented and are active in a majority of European countries. There is sample submission to Bordeaux from 22 countries. There have been three validation rounds including 28 national reference labs from 14 countries.

About the spread of excellence
The rationale for the development of this subproject was to
• Bring together the other EUTOS for CML projects into a clearly defined offering for physicians
• Ensure all physicians receive high-quality medical education and resources that support them in caring for patients with CML

With these aims in mind the spread of excellence subproject has driven the production of many EUTOS educational materials and resources including the highly successful educational day for European fellows that was held in Naples, May 2009.

An educational day for European fellows on behalf of EUTOS for CML, Policlinico Universitario, Naples 18 – 19 May 2009

This educational day was the first of its kind from the EUTOS for CML project, a meeting dedicated to European hematology fellows who do not usually have an opportunity to attend large international congresses. The aim of the meeting was to provide hematology fellows currently working within ELN institutions with the most up-to-date information in the field of CML treatment and give them an opportunity to connect with leading hematologists.
Is there a role for immunotherapy in maintaining complete remission in acute myeloid leukemia?

G. Ossenkoppele, Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands

For patients with AML who achieve complete remission after intensive induction treatment that do not achieve intensive post-induction therapy cure is very unlikely. Certainly in younger patients clear benefit for intensive consolidation therapy has been shown although many questions about the optimal type and duration of treatment are unresolved. Post remission therapy in younger AML varies among the various cooperative AML trial groups ranging from multiple cycles of chemotherapy, autologous and allogeneic stem cell transplantation. The benefit of post-consolidation therapy in elderly AML is currently less clear, i.e. a beneficial role of reduced intensity stem cell transplantation has been suggested for this age category and is currently being investigated in a prospective way in an ELN/EBMT trial. In general it is accepted that in all AMLs post remission therapy is warranted.

In contrast maintenance treatment for AML defined as low intensity therapy delivered over a prolonged period of time after achieving complete remission with standard induction and post remission therapy is currently not regarded as effective and in general not administered outside clinical trials. This contrasts sharply with other leukemias like acute lymphoblastic leukemia and acute promyelocytic leukemia in which maintenance treatment delivered over a prolonged period has improved the outcome.

The rationale of maintenance treatment is to eradicate minimal residual disease still present after completion of post remission therapy and regarded responsible for relapse. One of the strategies for maintenance therapy in AML is applying immunotherapy to further reduce the number of residual leukemic cells. The immune system certainly plays a role especially in situations where the leukemic burden is small. Cytotoxic effectors such as T-cells and natural killer (NK) cells are thought to participate in preventing relapse. The graft versus leukemia effect in the allogeneic transplant setting relies on the presence of active T-cells as indirectly demonstrated by increasing relapse rate in case of T-cell depletion.

Also alloreactive NK cells are important in the elimination of residual leukemia cells in the recipient as is shown in haplotype-mismatched transplants. The major immunotherapeutic approaches used in AML can be divided into either vaccine therapy or IL-2 administration.

Tumor vaccination is based on the induction of a long-lasting immunologic memory characterized by mechanisms endowed with high cytotoxic potential and specificity. Identification of leukemia-associated antigens (LAA) has been instrumental to develop a variety of strategies for anti-leukemia vaccination to induce specific recognition of LAA that will eradicate residual leukemic cells and protect recipients from relapses. Strategies that have been shown in preclinical models to be effective comprises vaccination by means of soluble proteins or peptides, recombinant viruses or bacteria as tumor associated antigens (TAA) gene vectors, DNA injection, tumor cells genetically modified to express co-stimulatory molecules and/or cytokines. The use of dendritic cells, either pulsed with TAA or transduced with tumor-specific genes, provides a useful alternative for inducing antitumor cytotoxicity. Some of these approaches have been investigated in phase I/II clinical trials in hematological malignancies. Further exploration of these strategies is clearly indicated.

IL-2 is an endogenous T-cell and NK cell activating agent that has been administered to patients with AML in order to eradicate residual leukemic cells in a number of non-randomized trials and in 3 randomized clinical trials. In none of these trials a reduction in the relapse frequency has been observed. IL-2 is known to expand and activate T- and NK-cells. However, in vitro data have shown that myeloid-derived suppressor cells efficiently inhibit functions of IL-2 and inactivate the anti-leukemic lymphocytes by triggering apoptosis in these cells.

References:
A novel approach of IL-2 directed treatment is based on the in vitro observation that histamine dihydrochloride (HDC, CepleneR) can reduce the inhibitory effects of myeloid-derived suppressor cells and thus protect T-cells and NK-cells and synergizes with IL-2 to induce killing of leukemic cells. Feasibility studies in melanoma and AML have shown that cytotoxic lymphocytes are more efficiently activated by the combination of HDC/IL-2 than by IL-2 alone and also that the administration of HDC/IL-2 approved to be safe. The results from a phase III randomised controlled trial in 320 patients with AML ranging from 18-84 years of which 39% were older than 60 y, 260 were in CR1 and 59 in subsequent CR were published by Mats Brune in Blood 2006. HDC/IL-2 (low dose!) was administered subcutaneously in repeated 3-week courses. In cycle 1-3 off-treatment periods were 3 weeks, in cycle 4-10 4 weeks. A total of 10 courses of HDC (CepleneR)/IL-2 were given during 18 months, thus coinciding with the period of highest relapse risk.

Patients received HDC 0.5mg and IL-2 16.400 U/kg subcutaneously twice a day and treated safely themselves at home without supervision throughout the trial. The control arm received no treatment and was only observed.

The primary trial endpoint was improvement of leukemia-free survival (LFS), the trial met its primary endpoint and demonstrated that the combination of HDC (CepleneR)/IL-2 improved the LFS by reducing the incidence of relapse at 3 years by approximately 50% (p=0.008, log rank test). For patients in CR1 3-year LFS estimates 40% (HDC/IL-2) compared with 26% (control arm) (see figure).

The prevention of relapse was particularly pronounced in patients < 60 years (p<0.005), but a strong treatment effect was observed also in patients < 70 years (p=0.0047).

The trial was not powered for differences in survival however a trend towards improved overall survival (OS) was observed with a 64-week prolongation of median OS for patients receiving CepleneR/IL-2. The side-effect profile for the HDC (CepleneR) /IL-2 combination was typically mild to moderate and there were no therapy-related deaths. Severe IL-2 related toxicities were not observed because the dose of IL-2 was considerably lower than in other trials. The EORTC QLC 30 analysis showed no significant impairment of global health status or quality of life in the CepleneR/IL-2 treated patients.

**Conclusion**

Maintenance therapy after induction and consolidation treatment is generally not recommended in AML. However immunotherapy can change the paradigm. The combination of HDC (CepleneR) /IL-2 is the first and only approved remission maintenance immunotherapy for AML and has the potential to significantly improve post-consolidation management of AML patients. As authorized by the EMEA, HDC (CepleneR) is administered in conjunction with low-dose IL-2 and is indicated as maintenance therapy for adult patients with AML in first remission. Vaccination strategies are still experimental and have to be performed within clinical trials.
In an attempt to assess the role of major treatment variables and risk factors in the management of AML, a multicenter trial with 56 centers participating started in 1999. A total of 2693 patients with primary and secondary AML and an age of 16-85 years with 55% being 60 years or older entered the trial. By randomization, the treatment variables TAD (standard dose) – HAM (high-dose) vs. HAM-HAM induction, G-CSF priming vs no G-CSF, and maintenance vs autologous SCT were compared (see figure 1). For age adaptation patients over 60 years received if possible only one induction course, high-dose araC at 1g instead of 3g/m² x6, and were excluded from autologous SCT. All randomizations were done upfront in one step, and were balanced against each other and balanced for major risk factors as well (see figure 1). In the entire patients younger than 60 years the complete remission rate (CR) was 70.2% vs 53.3% in those of 60 years or older. As projected to 7 years the overall survival (OS) was 38% vs 9%, and the relapse rate (RR) was 50% vs 74%. Patient’s outcome was substantially determined by individual risk factors and only modestly by treatment variables. In a multivariate analysis (see figure 2) genetic changes and older age within the age groups (16-60 and 60-85 years) resulted as the strongest risk factor.

The prospective analysis of the influence by multiple treatment variables and biological features in unselected pts became possible by the strategy of upfront randomization preferred in the trials of the AMLCG (1-4). The AMLCG1999 trial may serve as a model of cooperation and a basis for the introduction of novel therapeutic approaches.

References:
1. Büchner T, Hiddemann W, Berdel WE, et al.; 6-Thioguanine, cytarabine, and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced monthly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML); a randomized trial of the German AML Cooperative Group. J Clin Oncol 2003; 21:4496-504.
3. Büchner T, Berdel WE, Schoch C, et al.; Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem cell transplantation or by prolonged maintenance for acute myeloid leukemia; J Clin Oncol 2006; 24:2480-9.
Main factors predicting outcome after hematopoietic stem cell transplantation.

A. Gratwohl, J. Apperley and D. Niederwieser

1Department of Hematology, University Hospital, University of Basel, Switzerland
2Department of Hematology, Hammersmith Hospital, London, United Kingdom
3Division of Hematology and Oncology, University Hospital, Leipzig, Germany

One of the key deliverables of the WP 14 stem cell transplantation was to develop a tool to assess the potential risk of planned allogeneic hematopoietic stem cell transplantation (HSCT) reasonably well prior to transplantation. The reason is easy to understand. Allogeneic HSCT has become an established tool for the treatment of severe congenital and acquired disorders of the hematopoietic system. It represents the most powerful antileukemic therapy as shown by many prospective donors versus no donor analyses. Still, it remains associated with substantial morbidity and mortality; the benefit of reduced relapse might be offset by the high transplant related mortality. For these reasons many groups advocate a strategy, to postpone HSCT e.g. for patients with a donor but low risk AML, to proceed always with HSCT for high risk AML patients (1).

This old concept of donor versus no donor, good risk versus non good risk leukemia which was introduced decades ago has become outdated. Major advancements have been achieved in risk assessment of leukemias. Similarly, outcome of HSCT is not an erratic event; clear predictions can be made today. More than 10 years ago, EBMT developed a simple risk score for patients with CML, based on five pre-transplant characteristics: age of the patient, disease stage, time interval from diagnosis to transplant, donor type and donor recipient sex combination (see table 1). Survival decreased with increasing risk score as a consequence of increased transplant related mortality (TRM). This risk score was validated in several independent cohorts of CML patients worldwide (2, 3).

This same score was then tested in a cohort of 56,505 patients with an acquired hematological disorder and reported to the EBMT megagroup between 1980 and 2005 from 384 institutions in 47 countries. The patient population had a median age of 33 years (0 - 77 years) with 58% male patients; indications were leukemia (83%), lymphoproliferative disorders (10%), and aplastic anemia (8%). Transplants were obtained from HLA-identical siblings (74%) or unrelated donors (26%) with bone marrow (63%), peripheral blood (35%), or cord blood (2%) as stem cell source. Conditioning intensity was myeloablative in 86% of reduced intensity in 14%.

Age was categorized as <20 years (0 points), 20 to 40 years (1 point), and >40 years (2 points). Disease stage was classified for each main disease category, based on previous analyses, as follows. Early disease stage (0 points) included: acute leukemia transplanted in first complete remission, MDS transplanted either untreated or in first complete remission, chronic myeloid leukemia in first chronic phase, and non-Hodgkin lymphoma and multiple myeloma transplanted untreated or in first complete remission. Intermediate disease stage (1 point) included: acute leukemia in second complete remission; CML in all other stages than chronic phase or blast crisis; MDS in second complete remission or in partial remission; and non-Hodgkin lymphoma and multiple myeloma in second complete remission, in partial remission, or stable disease. Late stage disease (2 points) included: acute leukemia in all other disease stages, CML in blast crisis, MDS in all other disease stages, and multiple myeloma and lymphoma in all other disease stages than those defined as early or intermediate. Stage was not applicable for patients with aplastic anemia.

Time from diagnosis to transplant was categorized into <12 months (0 points) and >12 months (1 point). Donor type separated HLA-identical sibling transplants (0 points) from unrelated donor transplants (1 point). Donor recipient sex combination separated all others (0 points) from the male recipient with a female donor (1 point).

Table 1: EBMT risk score table for patients with CML

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of the patient, y</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>20 - 40</td>
<td>1</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2</td>
</tr>
<tr>
<td><strong>Disease stage</strong></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
</tr>
<tr>
<td>Late</td>
<td>2</td>
</tr>
<tr>
<td><strong>Time interval from diagnosis to transplant, mo</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>0</td>
</tr>
<tr>
<td>&gt;12</td>
<td>1</td>
</tr>
<tr>
<td><strong>Donor type</strong></td>
<td></td>
</tr>
<tr>
<td>HLA-identical sibling donor</td>
<td>0</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>1</td>
</tr>
<tr>
<td><strong>Donor-recipient sex combination</strong></td>
<td></td>
</tr>
<tr>
<td>All Other</td>
<td>0</td>
</tr>
<tr>
<td>Donor female, male recipient</td>
<td>1</td>
</tr>
</tbody>
</table>

* See text for the definitions according to main disease category; does not apply for patients with severe aplastic anemia (score 0).
** Does not apply for patients transplanted in first complete remission (score 0).
Results showed the same pattern as previously observed for CML. Survival decreased in a systematic and monotonic way with increasing risk score while TRM increased from 11% in the lowest to 45% in the highest risk group (see figure 1). All risk factors had a significant impact in all disease categories even though the relative weight of the individual risk factors varied (see figure 2). Still, older male patients, transplanted in more advanced disease stage, after a longer time interval from diagnosis with a female donor other than a HLA identical sibling had always a worse outcome than a young patient transplanted early in the disease course with a sex matched HLA identical sibling donor. This pattern was not changed, whether the conditioning was of standard or reduced intensity, whether graft source was bone marrow or peripheral blood and was not changed by T-cell depletion. It was not altered by performance score or CMV serostatus; both, low performance score or positive CMV serostatus just increased the risk in an additive way. Hence, prediction of HSCT risk follows a standard pattern (4). These results have clear consequences. They form a rational basis for risk-adapted treatment strategies. The choice between HSCT and a non transplant strategy should be based on the risk of the disease, the chances of the non-transplant strategy succeeding, and the risk of the transplant (5). HSCT might be considered for a patient with low risk AML, if there is a low-risk transplant possible (score 0–1 and no other comorbidities); vice versa, it might be deferred until progression for a patient with intermediate-risk disease but a high risk (score >3 and poor Karnofsky score). All risk elements, EBMT score and additional elements, comorbidity score, CMV serostatus, cytokine polymorphisms should be used to tip the balance in favour or against HSCT, or to select another more suitable donor. Above all, this implies that HSCT has to be integrated into the treatment algorithm at diagnosis, that a donor search, family or unrelated donor should be initiated at diagnosis as well.
Chronic lymphocytic leukemia (CLL) has a highly heterogeneous clinical course. The common staging systems (1, 2) do not allow prediction of the clinical course for patients in early stages. Therefore, additional factors have been established to identify patients with a more favorable or a more unfavorable prognosis. Powerful prognostic factors are acquired chromosomal aberrations (3). However, further prognostic factors would be very beneficial for an improved prognosis for an individual patient. Possible additional prognostic markers may be inherited factors that predispose to CLL.

To investigate the influence of genetic polymorphisms on the susceptibility to CLL we analyzed 461 CLL patients and an equal number of sex and age matched healthy controls using PCR followed by digestion with restriction enzymes. The odds ratios (OR) and P-values were estimated by logistic regression analysis. We included seven polymorphisms in five genes encoding DNA repair enzymes and 17 polymorphisms in 13 genes encoding metabolizing enzymes and identified those variants that occur more frequently in CLL patients than in healthy controls. As acquired chromosomal aberrations have a significant influence on the clinical course of CLL, we additionally analyzed the frequency of these variants in cytogenetic subgroups. FISH results were obtained for all 461 CLL patients enrolled in this study (see figure). We concentrated on the 133 patients with a more favorable prognosis (del(13q) as the sole abnormality) and the 69 patients with a more unfavorable prognosis (del(11q) and/or del(17p)). CLL patients with del(6)(q23), trisomy 12, and 14q32 rearrangements, that have an intermediate prognosis, were not evaluated separately.

The most significant differences in genotype frequencies were observed between cytogenetically high-risk CLL patients and controls for the SNPs rs13181 in ERCC2 (A/C and C/C vs. A/A: OR = 2.44, P = 0.01) and rs25487 in XRCC1 (A/A vs. G/G: OR = 2.66, P = 0.024) (4). Both SNPs are located in DNA repair genes. Regarding genotypes in metabolizing enzymes, differences between cytogenetically high-risk CLL patients and controls were detected for rs1056836 in CYP1B1 (G/G vs. C/C: OR = 2.62).

In conclusion and based on the results of our study, it is likely that polymorphisms in DNA repair genes and in metabolizing genes influence CLL risk. There is a tendency that special variants are especially associated with poor risk cytogenetic aberrations. The study contributes to the understanding of the involvement of genetic polymorphisms in DNA repair genes and in metabolizing genes in the development of CLL.

This study was supported by the Austrian Science Fund (FWF P18043).

References:
The EU-directive 2001/20/EC aimed to implement good clinical practice in the conduct of clinical trials on medicinal products for human use in the EU member states. But it turns out that the changes have been of huge and negative effect for investigator-initiated (“investigator-driven”; “investigator-sponsored”) trials (IITs): administrative burden and costs were extremely rising and independence and trial performance particularly in an optimum-use scenario are dramatically damaged.

To react on the poor situation and to foster multinational leukemia trials several actions have been taken by ELIC and members of the ELN, ranging from two organized workshops on “International IITs”, implementation of a new website-element (www.leukemia-net.org > International Trials) and sending out newsletters with relevant information. Furthermore ELIC is participating in the Road Map Initiative for Clinical Research in Europe which organizes workshops for stakeholders in the area of clinical trials.

Summaries on workshop 1 and 2 (“single CTA”, “Co-Sponsoring”) are available at the website and further summaries will follow (next workshops concerning “Pharmacovigilance”, “Risk-based approach” and “Research Ethics-Committees and Ethical Review in Europe”). The aim is to build a strong lobby group and to elaborate detailed suggestion for changes in the legislation.

The Directorate-General Enterprise and Industry (DG Enterprise) at the European Commission (EC) initiated an impact assessment for the “Clinical Trials Directive”. This assessment would consider various options for improving the functioning of the Clinical Trials Directive with a view to making legislative proposals, if appropriate. The process includes public consultation of the paper until 8th of January 2010 (www.leukemia-net.org > International Trials > Basic information). The ELIC recently asked ELN members via e-mail newsletter to comment on the paper. A comprehensive commentary to the public consultation paper was prepared by ELIC on behalf of the ELN, the European Mantle Cell Lymphoma Networks, the working group on drug law of the German Society for Hematology/Oncology and the Competence Networks for Leukemias and Lymphomas. A short summary is presented here and the entire version is made available on the website.

Failures and weaknesses of the directive 2001/20/EC

- **Overregulation for academic, independent research:** Directive 2001/20/EC may have had some positive effects for pharmaceutical clinical trials, but disregarded independent clinical trials in an unacceptable way. The problems in independent research especially arise from the fact that academic clinical trials are handled in the same way as industry sponsored trials. Therefore comments are focused on academic, optimum-use trials in any aspect.

- **Main target “improved safety protection”:** No examples can be given for improved protection. In contrast the patient safety is reduced since less patients with life-threatening diseases such as leukemias and lymphomas are treated within clinical trials and therefore without defined treatment protocols and without collection and evaluation of safety and outcome data.

- **Target “harmonisation for EU members”:** The interpretation of regulations is different in different European countries. There are examples for trials which could not even be activated in single countries due to prolonged procedures and different interpretations (e.g. interventional vs. non-interventional).

Furthermore optimum-use trials are now even more disharmonised, especially in some member states. These trials had considered safety aspects also before the directive (e.g. acknowledgement of the competent authority, approval by ethic-committee, working principles as given by a directive for medical professions in the Declaration of Helsinki, continuing education and introduction in the clinical trial concept, offer and regular use of expert consultations during conduction of the trial) but now activation is endangered due to higher bureaucratic and administrative requirements with presumably no positive effect for patient safety.
The ELN Foundation is a non-profit charitable organization that was created to support the European LeukemiaNet (ELN). The ELN needs to be financially independent by 2011, when the currently extended contract with the EU ends. The structural framework of the ELN given by the EU will continue and requires a continuous reassessment of the progress by the ELN and the Foundation Steering Boards. The ELN Foundation supports the European LeukemiaNet in its goals to

- improve the care of leukemia patients in Europe and globally,
- ensure that patients have faster access to innovative medicines with a greater certainty about their use than currently possible,
- improve the quality of life and life expectancy of leukemia patients,
- spread excellence through rapid educational activities on all levels.

Activities in the newly founded ELN Foundation are at full speed.

**Concept of integration**

The Network will offer a balanced spectrum of integrative activities, including infrastructure support with the expertise and skill for managing organizational development and change.

**Members & Partners & Patients**

The ELN Foundation will integrate all ELN members in clinical trials and research, collaborators and newcomers, friends and partners, patients and relatives, health care professionals, politicians, industry, press and media and everyone with an interest in leukemia.

**Information**

ELN Foundation Newsletter

An ELN Foundation Newsletter will distribute news on fundraising activities and partnering across the network, to friends and partners registered with the ELN foundation. The first Newsletter is available in parallel to this ELN-Newsletter at the ELN Symposium 1-3 February, 2010 in Mannheim or through the ELN Foundation office in Mannheim. It contains more detailed information on strategy, goals, partnering or how you can contribute.

It will be available in seven languages, namely English, French, German, Italian, Russian, Spanish and Swedish.

**Website**

An ELN Foundation Website will be available soon making registration possible for all having an interest in leukemia. The ELN Foundation and the ELN website will be linked together and a new interactive site called “My Leukemia Space” should provide all possibilities for safe and password protected information exchange, document storage, chat or video conferences.

**Our Mission**

The ELN Foundation will use the power of ELN as a grown and responsible network of excellence to build up new partnerships and ideas and join all forces to fight leukemia.

**The Foundation Board**

After presenting the idea of the ELN Foundation at the ELN breakfast symposium in Atlanta in 2007 and at the ELN Symposia in Heidelberg 2008 and Mannheim 2009, 13 lead participants decided to become part of the ELN Foundation Board, demonstrating the acceptance of the ELN amongst its members and the personal commitment. In June 2009 at the time of the EHA congress in Berlin (European Hematology Association) all Founders signed the ELN Foundation act and committed themselves officially to further sustain the ELN in its new legal entity.

**Founders are**

Prof. Rüdiger Hehlmann, Germany (Chairman)
Prof. Baccarani, Italy
Prof. Barbui, Italy
Prof. Büchner, Germany
Prof. de Witte, The Netherlands
Prof. Grimwade, United Kingdom
Prof. Guilhot, France
Prof. Hochhaus, Germany
Prof. Hoelzer, Germany
Prof. Niedierwieser, Germany
Prof. Ossenkoppele, The Netherlands
Prof. Saussele, Germany
Prof. Simonsson, Sweden

**Scientific Advisors**

All ELN WP Leaders and International Partners

**ELN Members**

All current certified members, registered via the EU are integrated

**Board of Trustees**

Dr. N. Huber, University of Heidelberg

**ELN Foundation-Pharma Advisory Board**

The ELN Foundation is prepared to establish a joint ELN Foundation-Pharma Advisory Board.

**Official recognised non-profit Foundation with legal status**

In August 2009 the ELN Foundation was legalized by the German governmental authorities (http://www.rp-kalsruhe.de/servlet/Pb/menu/1111579/index.html).

**Bank Account Details**

Name of the bank: Sparkasse Rhein Neckar Nord
Address of the bank: D1, 1-3, 68159 Mannheim, Germany
Holder of the account: ELN Foundation Account number: 38 90 98 43
BLZ: 670 505 05
IBAN number: DE 68 6705 0505 0038 9098 43
BIC/Swift number: MANSDE 66XXX

**Contact**

ELN Foundation Office
Dr. Petra Schrotz-King
Pettenkoferstrasse 22
68169 Mannheim
Germany
Fax +49-621-383-6966
Email: nmc@leukemia-net.org

ELN Foundation Fundraising Office
Dr. Colin Bradley
Lochside Cottage, West Glen Road
Houston, Renfrewshire, PA6 7GU
United Kingdom
Tel: +44-777-150-8405
E-mail: dbradley@leukemia-net.org
Acute lymphoblastic leukemia

N. Gökbuget¹ and D. Hoelzer²
¹Department of Medicine II, Hematology / Oncology, Goethe University Hospital, Frankfurt, Germany,
²ONKOLOGIKUM Frankfurt am Museumsufer, Frankfurt, Germany

The European Working Group for Adult ALL has been funded short before the European LeukemiaNet and developed prosperously since then. The group has organized in the meantime two clinical trial update sessions during EHA meetings which were very well visited.

Therefore and in order to strengthen sustainability Dieter Hoelzer and Nicola Gökbuget have applied on behalf of the group for acceptance as a Scientific Working Group of the European Haematology Association.

After approval by the EHA the first meeting of the EHA-SWG-EWALL will take place during the forthcoming EHA meeting in Barcelona!

The EWALL thanks the EHA president Robin Foà and the president elect Ulrich Jäger – both members of the EWALL.

New colleague in the Information Center in Frankfurt, Germany

Since June 2009 Dr. Silvia Schäfer is part of the European Leukemia Information Center (ELIC) in Frankfurt, Germany. She is in charge of the websites, namely European LeukemiaNet (www.leukemia-net.org), the German Competence Network “Acute and chronic Leukemias” (www.kompetenznetz-leukaemie.de) and the European Treatment and Outcome Study (www.eutos.org).

Before her function as webmaster she worked as analytical food chemist in pharmacy in Granada (Spain), did a PhD in biotechnology of natural flavouring compounds, graduated in Business Administration and gained experience in management consultancy.

WP 6 - ALL

7th Annual Symposium of the "European LeukemiaNet"
11th Annual Symposium of the German Competence Network "Acute and chronic Leukemias"
Mannheim, Germany
Mo 2010/02/01 - We 2010/02/03
Link: http://www.leukemia-net.org

4th Central European Course (CEC 2010) Methodology of Clinical Trials in Oncology
Vienna, Austria
Th 2010/03/11 - Fr 2010/03/12
Link: http://www.cesar.or.at

15th Congress of the EHA
Barcelona, Spain
Th 2010/06/10 - Su 2010/06/13
Link: http://ehaweb.org/congress/future_congresses

ELN Frontiers Meeting
Vienna, Austria
Fr 2010/10/22 - Su 2010/10/24
### Ongoing studies of the European LeukemiaNet (European Leukemia Trial Registry)

The European Leukemia Trial Registry (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). 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 (Ellic@em.uni-frankfurt.de).

#### ALL: Acute lymphatic leukemia

**ALL subtypes:**
- **De novo/non-treated**
  - GIMEMA 0904: Treatment of high-risk ALL and MRD-monitoring
  - GRAALL 02/2005: Hyper CV vs. standard induction and late intensification in Ph neg. ALL
  - NILG 09/00: Postremission programme according to MRD
  - PALG 5-2007 MRD (Active): Optimization of the therapy of adult acute lymphoblastic leukemia according to risk factors and monitoring of minimal residual disease
  - PETHERMA LAL-AR-03: Therapy of high-risk ALL
  - GMALL 07/2003: Therapy optimization by MRD-evaluation
  - GYALL 01/2000: Integrate intensive induction and consolidation therapy for ALL patients > 55 years
  - Role of autologous hematopoietic SCT plus maintenance therapy in Ph negative ALL in adults
  - NILG-ALL 10/07: Intrathecal DepoCyte and Lineage-targeted Minimal Residual Disease-oriented Therapy of Acute Lymphoblastic Leukemia
  - Intrathecal DepoCyte and Lineage-targeted MRD-oriented Therapy of ALL

#### B-Precursor ALL:

- **De novo/non-treated**
  - GRAALL 02/2005-R: Mabthera + induction, consolidation and late intensification in Ph neg., CD20+ ALL relapsed/refractory

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

- **De novo/non-treated**
  - GIMEMA 0201: Imatinib in Ph+ and/or BCR/ABL ALL
  - NILG 09/00/Ph+: Intermittent Imatinib programme in Ph+ ALL and CML blast crisis
  - GRAALLPHAG06/ EWALL-PH-01 (Active): Effectiveness and compatibility of a combination therapy of Dasatinib (trade name: Sprycel)
  - GMALL Post-SCT: Randomised study with Imatinib post-SCT in Ph+ ALL

#### Mature B-ALL / NHL:

- **De novo/non-treated**
  - 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)

#### T-lymphoblastic lymphoma:

- **GMALL T-lbl 1/2004**: Treatment for T-lymphoblastic lymphoma based on GMAll study 07/2003

#### AML: Acute myeloid leukemia

**AML all subtypes without FAB M3:**

- **De novo/non-treated**
  - ALFA -0701 (Active): A Randomized Study of Gemtuzumab Ozogamicin (GO) With Daunorubicine and Cytarabine in Intreated Acute Myeloid Leukemia (AML)
  - ALFA -0702 (Active): The CLARA Study from the Acute Leukemia French Association
  - ALFA -0703 (Active): ALFA-0703 Study A Randomized Multicenter Phase III 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 with Acute Myeloblastic Leukemia (AML)
  - SG 11-08 (Active): Phase Ib/Ila Study For the Evaluation of Dasatinib Following Induction and Consolidation Therapy as well as in Maintenance Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia (AML)
  - Azo1152: Safety, Tolerability, PK and Efficacy of Azo1152 in Patients With Relapsed Acute Myeloid Leukemia
  - Aracl-IL2: Combination Chemotherapy, Interleukin-2 and Peripheral Stem Cell Transplant in Treating Patients With Acute Myeloid Leukemia
  - CP4055: A Phase I/II Study of CP-4055 in Patients With Refractory/Relapsed Hematologic Malignancies
  - Systematic Vs. Response: Timed-Sequential Induction in CBF-AML
  - A Remission Induction Therapy and Risk-oriented Postremission Strategy for Adult AML

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

- **De novo/non-treated**
  - APL Arsenic Tioxide/ATRA: Acute Promyelocytic Leukemia 2006 (APL)

#### CLL: Chronic lymphatic 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
**CML: Chronic myeloid leukemia**

**All subtypes:**
- **De novo/non-treated**
  - Imatinib+Zoledronic Acid: Imatinib Mesylate and Zoledronic Acid in Patients With Chronic Myeloid Leukaemia in Cyto genetic Response Without Molecular Response
  - SPIRIT 2 – ST1571 Prospective International Randomised Trial 2

**Chronic Phase:**
- **All stages/not specified**
  - A phase II study to assess efficacy and safety of pioglitazone as add-on therapy to imatinib mesylate in CP-CML patients in major molecular response
  - Dasatinib Vs. High Dose Imatinib: Study of Dasatinib in Patients With Chronic Myeloid Leukemia (CML) and a Suboptimal Response to Imatinib
  - SKI606: Study evaluating SKI-606 in Philadelphia Chromosome Positive Leukemias
  - STI571 Spirit: High-dose of Imatinib (STI571) vs. low-dose Imatinib in combination with cytostatics vs. reference-dose of Imatinib (SPIRIT-study)
  - Dasatinib Vs. Imatinib 400 mg (Active): A Phase III Study of Dasatinib vs. Imatinib in Patients With Newly Diagnosed Chronic Phase CML
  - CMl IV (Active): Imatinib vs. Imatinib+Interferon or Imatinib 800mg and SCT in CML
  - A prospective randomized phase II study evaluating the optimization of the residual plasmatic level of dasatinib in patients newly diagnosed with CP-CML

**Lymphatic blast crisis:**
- **De novo/non-treated**
  - NIlG 09/00/Ph+: Intermittent Imatinib programme in Ph+ ALL and CML blast crisis

**CMPD: Chronic myeloproliferative disease**

**Polycythemia vera**
- **all stages / not specified**
  - PV Venesection: Symptoms of iron deficiency in patients with polycytemia vera treated with venesection

**Essential Thrombocythaemia**

**Myelofibrosis**
- **de novo/non-treated**
  - INCb018424 (Active): Myelofibrosis Study With Oral Janus Kinase (JAK) Inhibitor Treatment Therapy: The COMFORT-II Trial

**MDS: Myelodysplastic Syndrome**

**All subtypes:**
- **De novo / non treated**
  - 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]
  - Velcada Zanestrna (Active): Bortezomib and Tipifarnib in MDS

**All stages / not specified**
- AMLCG-2000 (Active): Biology and therapystrategy of AML an its subgroups
- 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
- S-Azacitidine II: A phase II study of maintenance with Azacitidine in MDS patients achieving complete or partial remission (CR or PR) after intensive chemotherapy
- AMGS31: 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)
- 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.
- Darbepoetin alpha: A phase II study of Darbepoetin alpha in MDS with low or intermediate 1 risk according to IPSS, with significant anemia (transfusion dependant or not)
- 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)
- NMDSG03A: Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- Velcado: A phase II study of PS341 (Velcado) in patients with myelodysplastic syndromes. GIMEMA MDS0104
- Bortezomib/Cytarabine: Adult subjects with Myelodysplastic Syndromes (MDS) will receive Bortezomib and Low Dose Cytarabine
- RICMAC/MDSsAML: Dose reduced vs. standard conditioning + SCT in MDS or sAML
- S-Azacitidine (Active): Subcutaneous Azacitidine + best supportive care vs. conventional regimens + best supportive care
- EORTC06011 (Elderly) (Active): Low-dose decitabine vs. best supportive care in elderly patients
- Exjade (Active): Exjade(ICL670) in transfusion dependent iron overload
- Lenalidomide (Active): Lenalidomide vs Placebo in RBC-dependent low- or intermediate-1 risk MDS with 5q-
- 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
Recommendations and Guidelines

The development of standards and guidelines is one of the central aims of ELN. In the meantime a number of important recommendations have been developed and published by ELN associated working groups (see table). Links to abstracts were added on the ELN website at the sub-pages for the respective disease related working groups.

Table: Recommendations and guidelines published via the ELN

<table>
<thead>
<tr>
<th>Topic</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML management recommendations</td>
<td>Baccarani et al., J Clin Oncol 2009;27:6041-51</td>
</tr>
<tr>
<td></td>
<td>Hehlmann et al., Lancet 2007;370:342-50</td>
</tr>
<tr>
<td></td>
<td>Baccarani et al., Blood 2006;108:1809-20</td>
</tr>
<tr>
<td>CML molecular monitoring</td>
<td>Müller et al., Leukemia 2009;1957-63</td>
</tr>
<tr>
<td></td>
<td>Hughes et al., Blood 2006;108:28-37</td>
</tr>
<tr>
<td>CLL guidelines</td>
<td>Hallek et al., Blood 2008;111:5446-56</td>
</tr>
<tr>
<td></td>
<td>Rawstron et al., Leukemia 2007;21:956-64</td>
</tr>
<tr>
<td>AML management recommendations</td>
<td>Döhner et al., Blood 2009, e-pub ahead of print</td>
</tr>
<tr>
<td>APL management recommendations</td>
<td>Sanz et al., Blood 2009;113:1875-9</td>
</tr>
<tr>
<td>Response criteria for ET and PV</td>
<td>Barosi et al., Blood 2009;113:4829-33</td>
</tr>
<tr>
<td>Definition of resistance and intolerance to hydroxyurea in P. vera and myelofibrosis</td>
<td>Barosi et al., Br J Haematol 2009, e-pub ahead of print</td>
</tr>
<tr>
<td>Evidence- and consensus-based European guidelines on MDS</td>
<td>ELN Homepage (fourth edition 2008)</td>
</tr>
<tr>
<td></td>
<td><a href="http://www.leukemia-net.org">www.leukemia-net.org</a></td>
</tr>
<tr>
<td>Reference document for four- and five-color flow cytometry</td>
<td>Arnoulet et al., Cytometry B Clin Cytom 2010, 78:4-10</td>
</tr>
<tr>
<td>Consensual morphology collection</td>
<td>ELEN homepage: <a href="http://www.leukemianet.eu">www.leukemianet.eu</a></td>
</tr>
<tr>
<td>Flow cytometry in MDS</td>
<td>van de Loosdrecht et al.; Haematologica 2009: 34:1124-34</td>
</tr>
<tr>
<td>WT1 PCR standardization</td>
<td>Cilloni et al., J Clin Oncol 2009; 27:5195-2012</td>
</tr>
<tr>
<td>FIP1L1-PDGFRα – recommendations for diagnosis &amp; molecular monitoring</td>
<td>Jovanovic et al., Blood 2007;109:4635-40</td>
</tr>
<tr>
<td></td>
<td>Score et al. Leukemia 2009; 23:332-335</td>
</tr>
<tr>
<td>Proposals for standardization of cytogenetic analyses</td>
<td>Haferlach et al., Genes Chromosomes Cancer 2007;46:494-9</td>
</tr>
<tr>
<td>BCR-ABL diagnosis recommendations</td>
<td>Branford et al., Leukemia 2006:1925-30</td>
</tr>
<tr>
<td>Gene expression profiling recommendations</td>
<td>Kohlmann et al., Br J Haematol 2008;142:802-7</td>
</tr>
<tr>
<td>Microarray analyses guidelines</td>
<td>Staal et al., Leukemia 2006;20:1385-9</td>
</tr>
<tr>
<td>Transplant-associated microangiopathy recommendations</td>
<td>Ruutu et al., Haematologica 2007; 92:95-100</td>
</tr>
<tr>
<td>Stem cell transplantation recommendations</td>
<td>Drexler et al., Leukemia 2007;21:12-7</td>
</tr>
<tr>
<td></td>
<td>De Witte et al., Haematologica 2006;91:750-6</td>
</tr>
<tr>
<td>Recommendations for management of infections</td>
<td>Herbret et al., EJC Supplements 2007 (Vol. 5, 49-59)</td>
</tr>
<tr>
<td></td>
<td>Bucaneev et al., EJC Supplements 2007 (Vol. 5, 5-12)</td>
</tr>
<tr>
<td></td>
<td>Marchetti et al., EJC Supplements 2007 (Vol. 5, 32-42)</td>
</tr>
<tr>
<td></td>
<td>Maertens et al., EJC Supplements 2007 (Vol. 5, 43-48)</td>
</tr>
<tr>
<td></td>
<td>Ljungman et al., Bone Marrow Transplant 2005; 35, 737-746</td>
</tr>
<tr>
<td></td>
<td>Styczynski et al., Bone Marrow Transplant 2009; 43:757-70</td>
</tr>
<tr>
<td></td>
<td>Ljungman et al. Bone Marrow Transplant 2008; 42:227-40</td>
</tr>
</tbody>
</table>

Authors contributed to this issue:

Prof. J. Apperley
Prof. M. Baccarani
Prof. W. Berdel
Dr. C. Bradley
Prof. T. Büchner
Prof. F. Cervantes
Prof. N. Cross
Dr. E. Engstroem
Prof. H. Estertuber
Prof. C. Fonatsch
DI C. Ganster
Dr. N. Gökbuget
Prof. A. Gratwohl
Dr. G. Guidi
Prof. F. Guilhot
Prof. J. Guilhot
Prof. J. Hasford
Prof. R. Hehlmann
Prof. W. Hiddemann
Prof. A. Hochhaus
Prof. D. Hoelzer
K. Ihrig
Prof. U. Jäger
Prof. F. Mahon
L. Montrucchio
PD. Dr. J. Neesen
Prof. D. Niedervierer
Prof. G. Ossenkoppele
Prof. F. Pane
Dr. F. Rancati
Prof. G. Saglio
Dr. S. Sauêsle
Dr. P. Schrott-King
Dr. P. Schuld
Prof. B. Simonsson
Prof. B. Wörmann

Design and Realisation:
Schäfer Werbeagentur GmbH
Phone: ++49 (0) 6201 6049656
www.schaefer-werbeagentur.com

available online at
www.leukemia-net.org

Network Management Center:
Dr. S. Saulele
Dr. P. Schrott-King (Deputy)
III. Medizinische Universitätsklinik
Pettenkoferstrasse 22
D-68169 Mannheim (Germany)
Phone: ++49 (0) 621 383 6962
Fax: ++49 (0) 621 383 6969
eMail: 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 7463
Fax: ++49 (0) 69 6301 7463
eMail: elic@leukemia-net.org

Homepage:
www.leukemia-net.org
ISSN 1862-8885