Dear colleagues,

More than 18 months have passed since the successful start of our European LeukemiaNet (ELN), a network of excellence within the 6th Framework Programme, in January 2004. Through organizational and research work performed by all participants and associated scientists, this network has developed into a well functioning tool for research and patient care integrating 78 leading leukemia trial groups, their 83 interdisciplinary partner groups (diagnostics, treatment, research, registry, guidelines), industry and SMEs across Europe. The integration and interdisciplinary cooperation brings together 117 participants and approximately 900 researchers from 22 countries. Within the first 12 months nearly 60 workpackage-meetings were held, several studies were initiated on an European level and 80 publications including guidelines for diagnostics and therapy were published or submitted. Regular meetings of all network members have supported communication and cooperation of the different workpackages. The European LeukemiaNet was presented at international meetings such as EHA, ASH and DGHO/ÖGHO/SGH. New participants and associated members have been integrated due to widespread acceptance of the ELN. We are proud to say that the network has the expertise and critical mass for European added value and international leadership to achieve research and treatment goals that cannot be achieved by single groups or countries. It will structure European research durably and spread scientific excellence in the field of leukemias. We thank all participants, associated scientists and associated members for their cooperation in the ELN. This will only be the start of even more successful progress, more exciting scientific results and inspiring networking during the next 18 months.

Prof. Dr. Rüdiger Hehlmann
Network Coordinator
Periodic report to the Commission
(Activity report, Management report)

After each 12 months, the network has to deliver a management and activity report to the EC to document the proceeding and to state the expenditures. Deadline for this first report was February 15, 2005 (45 days after ending of the first reporting period), but due to the partially tenacious return of the forms concerning the management report (which had to be filled out by all 117 participants) the first annual report could only be delivered by the end of May. According to the contract, the commission has a time period of 45 days to proceed the reports. The deferment on our part will lead to a delay in the allocation of the EC contribution for the next funding period. For the next report, which is due February 15, we should try to avoid this by observing the deadline. Even in the following reporting periods each of the 117 participants has to fill out the financial form C, irrespectively whether they receive funding or not.

The good news is that the Commission has composed a special clause regarding the periodic audit certificates. According to this clause contractors requesting a Community financial contribution for one or more reporting periods of less than €150,000 need not submit an audit certificate, until the cumulative financial contribution is equal to or exceeds €150,000. In all cases an audit certificate shall be submitted at the latest 45 days after the final reporting period. This final audit certificate shall cover all periods for which an audit certificate has not been previously submitted.

This special clause would save a lot of time and money for most of the participants of the ELN. We asked to amend the contract immediately after the announcement in May 2005 and should receive an answer from the Commission very soon.

Online Registration

An online registration to the ELN as associated member or associate is possible via the website www.leukemia-net.org (link “The project”, “How to join”) by now. In Table 1 the different types of membership are described. As an associated member you have access to all relevant information regarding the ELN. Please keep in mind, that the number of active network members has to be restricted and is bound to active scientific work in one of the workpackages. To become an active member you have to contact the according workpackage leader. With the recommendation of a WP-leader your institution has to fill out the CPF forms to become a contract partner of the EC. In the end of the procedure, the Network Governing Board has to confirm the new participant.
Amendment to the Consortium Agreement

The Consortium Agreement (CA), which has been signed by all 117 participants, required a list of changes, as demonstrated in the last Network Governing Board during the ELN meeting in February 2005 in Heidelberg. With the solution of some juridical problems an amendment to the CA was composed and recently sent to all participants. For a time period of 4 weeks we will collect appeals and objections. A revised version of the amendment will be mailed again by the beginning of September and the according legal representative of each participating institution is then asked to sign the amendment. One important point in the amendment will prevent the necessity to confirm the agreement every year again by the signatures of all participants.

Fourth Call for Proposal of an integrated project-LSH-2005-2.2.0-1

In the context of limited funding of the European LeukemiaNet it has been proposed that we file an application for an integrated project to broaden the financial basis of our activities. This integrated project could address the topic LSH-2005-2.2.0-1: “Broadening the knowledge base on the molecular mechanisms underlying chemotherapy resistance, therapeutic escape, efficacy and toxicity”. This is of relevance for the clinical trials of the network and meets the interest and expertise of many of us. At least 15% of the budget has to be reserved for SME participation. The deadline for submission of the proposal is November 9, 2005, which means that we have about 3 months time to prepare the proposal. The lead participants of all workpackages have already been asked for their interest in

Dates/Meetings

47th Annual Meeting of the American Society of Hematology (ASH)
December 10 - 13, 2005
Atlanta, Georgia

Annual Meeting of the Competence Network “Acute and chronic leukemias” and the European LeukemiaNet in Heidelberg (DKFZ)
January 31 - February 2, 2006
Heidelberg, Germany

Acute Leukemias XI Prognostic Factors and Treatment Strategies
February 18 - 22, 2006
Munich, Germany

Table 1. Types of membership in the ELN

<table>
<thead>
<tr>
<th>Type of membership</th>
<th>Description</th>
<th>Access to:</th>
<th>Registration:</th>
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<tbody>
<tr>
<td>Network member (=associated scientists)</td>
<td>Physicians, researcher or scientists, actively working within one of the 18 Projects, and whose institution has signed the contract with the European Community</td>
<td>• Internet &amp; Internal WP communication&lt;br&gt;• Newsletter&lt;br&gt;• Discussion Forums&lt;br&gt;• Access to member database (addresses)&lt;br&gt;• Invitation for meetings&lt;br&gt;• Travel cost funding by the network</td>
<td>Only scientists who belong to institutions which are a contract partner of the ELN can become an official member of the ELN (associated scientists). If so, scientists will be registered upon the recommendation of the relevant Workpackage leader. If not, the corresponding institution has to ask for accession to the contract. According to the rules of the European Commission, each institution - willing to become a contractor - has to provide form B (request for accession) and the contract preparation form (CPF). The Network governing board has to agree the accession of a new institution.</td>
</tr>
<tr>
<td>Associated member with confirmed registration</td>
<td>Physicians, researchers, scientists</td>
<td>• Internet&lt;br&gt;• Newsletter&lt;br&gt;• Discussion forums&lt;br&gt;• Access to member database (addresses)&lt;br&gt;• Invitation for meetings</td>
<td>Registration has to be confirmed by a person and/or institution, who is already registered in the network (signature and/or stamp is required)</td>
</tr>
<tr>
<td>Associates without confirmed registration</td>
<td>All other groups e.g. nurses, patients, press &amp; media, laymen etc.</td>
<td>• Internet&lt;br&gt;• Newsletter</td>
<td>Only online registration</td>
</tr>
</tbody>
</table>


As one of the central network projects, ELIC is responsible for the internal information exchange between network projects and their members. ELIC generates information for different user groups such as patients & relatives and is responsible for the structured presentation of all information contents on the website www.leukemia-net.org

To achieve this aim, a close cooperation with the two other central projects “Network Management Center (NMC)” and “Central Information & Communication Structures (CICS)” is necessary. ELIC cooperates with NMC concerning public relations, presentation at congresses and preparation of meetings and with CICS regarding the technical part of the website http://www.leukemia-net.org/

The Website www.leukemia-net.org

The website is of utmost importance for all projects of the network as confirmed by several questionnaires http://www.leukemia-net.org/...

Based on feedback from the projects, ELIC has developed a general website structure which provides a separate area for each project. The aim for this year is to complete at least the following topics:

• general information about project-related activities
• scientific results
• dates and meetings, including meeting reports
• study protocols (see below)
• consensus documents and other scientific results
• interim/progress reports

This work should be done by the projects, as well as the preparation of additional contents, which indicate individual needs and aims. Each network participant has the opportunity to add documents and other contents for this purpose.

In a next step, all network members are invited to prepare general information about leukemias for other website-users (physicians, patients, public and media).

The European Leukemia Study registry

A further central part of the website is the upcoming registry for ongoing clinical leukemia trials in Europe. This online registry will contain short-versions of all main study-protocols (e.g. de novo studies).

To present the protocols in a structured and consistent form, a template was developed, which is available on the website http://www.leukemia-net.org/...
or which can be obtained directly from ELIC.

First short-protocols were already published by project 8 (MDS) and 6 (ALL). The study database is of utmost importance to provide an overview on clinical leukemia research in Europe.

Practical procedure

For the moment, ELIC offers an additional service: Website contents (Word, PDF and all other formats) should be send to ELIC who will prepare the documents for online presentation. In the near future, each project will have the possibility to supply, add and modify contents independently online via a Content-Management-System (CMS). This will be realized by the "web-editor", who should be named by each project. The web-editor will get access to the CMS and is the primary contact person for ELIC. Of course ELIC supports also all other network participants regarding questions and problems of web-publishing.

The E-mail Newsletter

An e-mail newsletter - sent out every 3 months to the network members - will inform about new topics of the website, e.g. new studies or actual dates and meetings. All projects are invited to use the newsletter for distribution of information which is relevant for the whole network.

The Online Information Letter

In cooperation with the Network Management Center (NMC) an Information Letter (IL) will be published bimonthly. Main focus are scientific results and research activities of the network projects. Due to limited financial resources, the IL will not be published as printed version, but is available as online journal (PDF).

ELIC supports all projects in their tasks regarding visibility, spread of excellence and vertical and horizontal networking. The project leader Nicola Gökbuget and the webmaster Anja Hellenbrecht cordially invite the projects to contribute ideas and projects for web-publishing.
Many of the participating investigators of WP4 have experienced a nearly 10 year fruitful collaboration in the European Intergroup for CML (EICML). Within the WP4 this collaboration is expanding with new participants creating a solid platform within Europe. WP4 (CML) currently includes 26 participants, representing 17 countries.

The WP management structure was generated with 5 lead participants: M. Baccaïrani, Italy, F. Guilhot, France, R Hehlmann, Germany, A. Hochhaus, Germany and B. Simonsson, Sweden. Regular WP meetings were organized, to which all interested CML investigators have been invited. The latest one took place in Stockholm June 1, and the next one will be held in New Orleans (during ASH) Sunday December 4 very early in the morning.

Progress report of the deliverables (first 12 months)

1. Common uniform datasets for newly activated clinical trials are defined. This work is coordinated by J. Hasford in Munich. All participants of WP 4 agreed to add these common datasets to their clinical study protocols in all larger clinical trials. The forms will be published soon and can be ordered already from J. Hasford.

2. A European registry for CML trial patients is under preparation. J. Hasford chairs a data management and statistician network for core dataset and SOP for data handling. A comprehensive protocol with research plan, methodological description and specific subproject protocols has been approved by Munich Ethics Committee. The activated specific substudy protocols are: “Imatinib failure” (Guilhot et al.), “Additional cytogenetic abnormalities” (Fischer, O’Dwyer and Baccarani), “Complete cytogenetic responders to imatinib” (Martinelli and Barbany) and “Discontinuation of imatinib in CCR” (Hochhaus et al.).

3. An Italian registry for prognosis of imatinib treated patients has been activated.

4. A manuscript dealing with gender aspects in the treatment of CML has been completed and published Berger et al).

5. Two large multicenter-studies (German and French) dealing with imatinib in different dosages given as single drug or in combination with IFN or ara-C are recruiting patients at a rapid pace. No interim analysis has been performed so far.

6. One paper dealing with a phase II study of imatinib and peg-intron has been published (Baccarani et al).

7. An Italian-Nordic-Turkish study comparing 800 with 400 mg imatinib in high risk patients was initiated and is recruiting patients rapidly.

8. In coordination with WP12, standardisation concerning the definition and determination of minimal residual disease in CML on an European level is in progress. Thirtyfive European laboratories are engaged. Main tasks are to establish control rounds for BCR/ABL mRNA quantification and standardization in calculation of expression levels of minimal residual disease.

9. A number of Phase I-II studies with at least 5 new drugs alone or in combination with imatinib have been initiated.

10. A very important work comprising definitions and standardisation of relevant diagnostic and therapeutic procedures in CML is under progress. Deadline for submitting a manuscript for publication is december 2005.
Experiences from a Network of AML Trials using General Up-Front Randomization and a Common Standard Treatment Arm


Universities of Münster, Ulm, Hannover, Heidelberg, Frankfurt, Leipzig, Munich, Germany

Improved comparability of therapeutic strategies among different multicenter AML trials could help identifying superior treatments. In 2002 five AML trial groups in Germany decided to share a common standard treatment arm and to randomize 10% of the patients in each trial to the common arm before any treatment starts. Derived from CALGB (NEJM 1994;331:896) and restricted to patients under 60 years of age the standard induction treatment is to contain two courses of 7+3 with araC 100mg/m² per day continuous i.v. infusion on day 1-7 and DNR 60mg/m² per day by two-hour i.v. infusion on days 3,4, and 5. Patients in CR are to receive 3 courses of araC 3g/m² q12 hours by 3-hour i.v. infusion on days 1,3, and 5. The alternative regimens in the five trials basically consist of high-dose araC combinations and autologous stem cell transplantation (SCT) either risk adapted or randomized, and priority allogeneic SCT either according to family donor availability or according to a special risk.

Between February 2002 and June 2005 a total of 1846 patients have been randomized with 185 patients allocated to the common standard arm. The overall CR rate is 73%, the rate of persistent leukemias is 19% and the rate of early and hypoplastic death is 8%. The probability of overall survival at 2 years is 0.48 (95% CI 0.43 – 0.53) and of relapse-free survival is 0.43 (0.36 – 0.51). There were no imbalances in the representation of prognostic factors between the standard arm and any of the trial populations. Defined stopping criteria considering response, mortality, survival and relapse-free survival did not demand discontinuation of any specific trial or of the common standard arm. When the different trial results will be unblinded, later-updates will allow validations in comparison with the standard arm, and on the same basis cross-trial comparisons by which the network can contribute to the therapeutic progress in patients with AML.

References
Cytogenetic diagnostics in leukemia is mandatory. The results of cytogenetic analyses are necessary for the classification of leukemia according to the WHO-classification. In addition, they provide very important information on patients' prognosis. Furthermore, with respect to a growing number of specific, targeted treatment approaches the genetic findings are guiding the therapy, because certain drugs are only efficient in certain subtypes of leukemia carrying a specific genetic abnormality.

The description of the results of chromosome banding and fluorescence in situ hybridization (FISH) analyses has already been standardized and has to be reported according to the International Systems of Nomenclature (ISCN). All published aberrant karyotypes in leukemia can be found in the Mitelman database (http://cgap.nci.nih.gov/Chromosomes/Mitelman). Furthermore, partial karyotypes and the most important data on the most frequent chromosome abnormalities in leukemia can be found in the internet (Atlas of chromosomes). With respect to protocols how to perform cytogenetic diagnostics in leukemia some efforts on standardization have been undertaken by centers responsible for quality control in local regions. However, consensus guidelines are missing so far. The workpackage “Cytogenetics” of the European LeukemiaNet collected protocols from all participating countries, evaluated and condensed these to a consensus in order to provide a comprehensive protocol for cytogeneticists and clinicians working in the field of leukemia.

As different leukemia subtypes benefit from different culture conditions and as different genetic abnormalities occur in leukemia subtypes which require different probes for FISH under certain circumstances, separate consensus protocols have been established for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL). In addition protocols for myelodysplastic syndrome and myeloproliferative disorders have been established. More detailed information and updates can be found at the website of the European LeukemiaNet www.leukemia-net.org
WP 9 - CMPD
Progress report Chronic Myeloproliferative Disorders

G. Finazzi, Dept. of Hematology, Ospedali Riuniti de Bergamo, Italy

The general aim of the work in the first year was to establish the basic conditions for conducting collaborative clinical and biological studies in the field of CMPD in Europe. Specific objectives included: a) creation of WP management and communication structures and organization of regular meetings; b) establishment of common criteria for diagnosing and staging CMPD and for creating registries of variant forms and rare complications; c) standardization of diagnostic and prognostic tests; d) definition of priorities for future studies and review of the current status of knowledge about priority issues (e.g. new drugs).

Substantial progress towards objectives has been achieved as follows: a) WP management and communication structure have been set up and participants meet regularly; b) written reports on test standardization and registries of rare forms have been produced; c) priorities for future collaborative initiatives have been discussed and current status-of-art regarding new drugs for CMPD reviewed. The following documents have been prepared and can be retrieved in the LeukemiaNet webpage or required at the WP Coordinator Dr. Guido Finazzi, e-mail address: gfinazzi@ospedaliriiuniti.bergamo.it

Standardization protocols
1. PRV-1 mRNA quantification (Dr. H. Pahl)
2. Circulating CD34+ cell quantification by flow cytometry (Dr. Le Bousse-Kerdiles)
3. Bone marrow biopsy reporting in Ph+ CMPD (Dr. Schmitt-Graeff)
4. Erythropoietin measurements (Dr. G. Birgegard)
5. Clonal analysis using X-chromosome inactivation patterns (XCIP) (Dr. C. Harrison)

Status Reports
1. Imatinib mesylate in Polycythemia Vera (Drs. H. Hasselbalch and E. Lengfelder)
2. Thalidomide in Idiopathic Myelofibrosis (Drs. H. Hasselbalch and E. Lengfelder)

Registry
1. Registry of ongoing clinical trials in CMPD
The substantial achievement of the general objective established for the first year allowed WP participants to plan phase II studies of standard and new therapies as well as implementation of registries of uncommon CMPD variants and complications to be carried out in the forthcoming period.

WP 10 - Diagnostic platform
European Immunophenotyping Panels

M.C. Béné, Laboratoire d’Immunologie du CHU, Faculté de Médecine, Université Henri Poincare Nancy I, France

Workpackage 10 of the European LeukemiaNet was set up to work on Diagnostic procedures. Its major initial aims were to facilitate access to existing morphology databases, organize cytology workshops, and establish consensual recommendations about immunophenotyping. A first cytology workshop was organized in November 2004, and another is scheduled for 2005.

In January, a series of meetings of the EGIL group and of participants of WP10 was organized around the general assembly in Heidelberg. This allowed to make backbone proposals for diagnostic panels of monoclonal antibodies in the respective fields of acute leukemia and lymphoproliferative disorders. Expert discussions then were organized around these proposals to implement and complete the panels. The working frame chosen allowed to propose three types of items for both clinical conditions:
- a list of the diseases that should be properly diagnosed through immunophenotyping
- a mandatory panel of diagnostic and prognostic markers
- a complementary panel of markers useful in specific conditions to strengthen the diagnosis and/or provide for patterns of expression useful for patients’ follow-up and minimal residual disease/relapse monitoring.

After these meetings, the proposals were edited in a publishable form, and circulated several times among the participants. The aim of this Delphi-like consensus was to document each proposal based on referenced data published in peer-reviewed international journals. The ELN panels thus appear as evidence-based medicine recommendations, supported by recent literature.

The final document, after approval by WP10 members, was posted on the internet sites of EGIL and ELN in mid-April 2005.

The next planned steps will use the same type of consensual implementation and approval, and are twofold:
- provide pre-analytical guidelines, as the quality of samples is mandatory for proper immunophenotypic analyses
- propose validated multiparametric panels, i.e. marker sets to be tested simultaneously using up to 4 different fluorochromes.

As a session of WP10 took place in June in Stockholm, it is expected that these two further steps will be completed in Autumn 2005.

I would like to take the opportunity of this information letter to gratefully thank all WP10 participants who really implemented positively both discussions and the final product now officially available through Internet.
In the post-genome era, molecular aberrations in leukemia are discovered with ever increasing speed. Many of these newly discovered oncogenes represent novel molecular drug targets that could be therapeutically exploited. Besides that, our understanding of immune tolerance and rejection allows immune-therapeutic approaches of unanticipated sophistication. However, these promising and exciting discoveries have to be met by designing new strategies to translate them into preclinical and clinical development. The purpose of WP16, the European Leukemia Treatment Research Association (ELTRA) is to provide a framework for scientists who are interested in this translational effort. ELTRA helps its participants to enhance scientific discussions, train each other in critical methodology and to find partners for the conduction of collaborative research. As the individual disease-specific working parties standardize their diagnostic criteria, conduct epidemiological studies and harmonize their clinical protocols, ELTRA addresses groups engaged in identifying novel targets and contemporary therapeutic approaches in early stages of development, in preclinical trials in animal models or that have just matured to human clinical trials. To this end, ELTRA has established work groups that currently are in the process of gathering information on new therapeutic targets for the treatment of specific diseases, respective compounds in preclinical and early clinical development and on specific laboratory and clinical methodology for their evaluation. The results of these work groups will be available shortly on the ELN website and will be regularly updated. Also, we organize site visits of participating scientists to enhance the spread of up to date technology and several members of ELTRA got involved in joint publications of review articles on targeted therapy of hematological malignancies. In Stockholm, we invited to a very interesting international symposium where distinguished scientists from Europe and the States reported about exciting novel concepts in molecularly targeted therapy. It is the aim of ELTRA to provide a forum for discussion and the advancement of translational science for the treatment of leukemia. You are very welcome to join us in this effort.

Contact Address:
H. Serve, MD
Professor of Medicine
Department of Medicine, Hematology/Oncology
University of Münster, Germany
Albert-Schweitzer-Strasse 33
48149 Münster.

ELTRA: European Leukemia Treatment Research Association

H. Serve, W.E. Berdel, Dept of Medicine, Hematology/Oncology and Interdisciplinary Center for Clinical Research, University Münster, Germany
R. A. Padua, Leukaemia Sciences Laboratories, Department of Haematological Medicine, King’s College London, UK