International Society for Cellular Therapy
ISCT

TELEGRAFT

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A QUARTERLY NEWSLETTER

ISCT 2010 Annual Meeting Speakers Featured on 60 Minutes

Anthony Atala of the Wake Forest University Institute for Regenerative Medicine and Stephen Badylak of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh were recently featured in a 60 Minutes TV story on Regenerative Medicine entitled "Growing Body Parts". Both Dr. Atala and Dr. Badylak will be speaking in the Strategies for Commercialization track at the ISCT Annual Meeting in Philadelphia May 23-26, 2010. The text of the 60 Minutes story can be found at http://www.cbsnews.com/stories/2009/12/11/60minutes/main5968057.shtml?tag=contentMain;contentBody. In addition, regenerative medicine will be featured in a plenary session at the Annual Meeting chaired by Chris Mason of the University College London, and with Robert Nerem and Paolo Macchiarini as speakers. These high caliber speakers are just a part of a varied and exciting program for the Annual Meeting. Please see the preliminary program starting on page 15 of this issue and our meeting web page at www.CellTherapy2010.com. We hope to see you in Philadelphia!

Bruce Levine and David Porter
ISCT 2010 Co-Chairs

EUROCELLS: European LeukemiaNet
A Model of Transnational Collaboration

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Summary

The ELN is an established network of excellence, composed of internationally recognised clinicians and scientists, medical study groups and interdisciplinary research centers reaching across four continents (Europe, North America, Asia and Australia). The ELN has a landmark history of enabling the best therapeutic options

EUROCELLS

The European Union (EU) Framework Programme (FP) is the EU's main instrument for research funding in Europe. Each FP is proposed by the European Commission and adopted by Council and the European Parliament following a co-decision procedure. FPs cover a period of five years with the last year of one FP and the first year of the following FP overlapping. FPs have been implemented since 1984 and focus on establishing cooperative groups or consortia, both within the EU and globally. The Sixth FP (FP6, 2003-2007) funded numerous projects involving cellular therapeutic approaches or stem cell research, some of which are in their final year of funding. FP7 (2007-2013) is now underway, and already 100 projects involving stem cells have been funded.

This Eurocells column is dedicated to broadening the exposure for these consortia by providing them with a platform to present their focus, goals, history, organization, work packages, collaborators and achievements.

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EUROCELLS: European LeukemiaNet continued from page 1

to leukemia patients, combining forces to make all types of leukemia curable diseases. Rapid exchange of novel research data and treatment outcome has set milestones in the survival and quality of life of leukemia patients worldwide.

The ELN has its roots in the collaboration of European Investigators on chronic myeloid leukemia (EI-CML), since 1992, and of the German competence network on "Acute and chronic leukemias", since 1997. In 2004 the ELN was funded as a network of excellence (NoE) within the EU 6th framework program. The ELN has set the goals to strengthen and develop scientific and technological excellence in research, diagnosis and therapy of leukemia, comprising CML, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), myelodysplastic syndroms (MDS), and chronic myeloproliferative disease (CMPD).

The ELN has joined forces to avoid the duplication and fragmentation of clinical trials, to improve definitions and standards in diagnosis and therapy and to achieve a more complete registration of leukemia patients. The need to assemble a critical mass of patients is imperious in rare cancers and makes collaboration both necessary and attractive. The ELN assesses and compares treatment options across Europe including combinations of drugs, dose escalation, state of the art transplantation technology and new agents. The collection of data in patient registries and of patient samples in a uniform and standardized manner will provide the information needed to develop and validate prognostic models for the different leukemic disease entities. For each patient this means to be registered and followed in a standardized high quality clinical setting, in order to receive the best possible therapy through optimised diagnosis and treatment approaches. High throughput technology such as microarrays has already revealed novel disease patterns and combined with the outcome of clinical trials, these patterns are now beginning to be related to prognostic factors and survival of the patients. This will allow new disease classifications, and treatment can then be customised towards novel targets. As a result, joined development of evidence-based guidelines within the European LeukemiaNet accelerates the translation of peer reviewed results into applications and improves patients' survival.

Several 10000 patients are diagnosed with leukemia each year within Europe. The challenge is to stall the disease before it progresses to a fatal stage. Molecular tests are developed to determine minute amounts of cancer cells, chromosome defects or gene mutations or to define subgroups of patients with specific prognostic patterns or resistances against drugs. This will answer questions on outcome with more certainty and opens ways to individual drug design and personalised medicine.

Figure 1: The ELN structure: 16 workpackages representing three platforms within the ELN serve various areas of research:

1. NMC (Network Management Center, WP 1)
2. ELIC (European Leukemia Information Center, WP 2)
3. CICS (Central Information and Communication Services, WP 3)
4. Biometry of registry, epidemiology, metaanalysis and prognosis (WP17)

PLATFORM 1
Central Services (4 WPs)

5. CML (WP 4)
6. AML (WP 5)
7. ALL (WP 6)
8. CLL (WP 7)
9. MDS (WP 8)
10. CMPD (WP 9)

PLATFORM 2
Leukemia Trial Groups (6 WPs)

11. Diagnostics (WP 10)
12. Cytogenetics (WP 11)
13. Minimal residual disease (WP 12)
14. Gene profiling (WP 13)
15. Stem cell transplantation (WP 14)
16. Supportive care/anti-infection prophylaxis and treatment (WP 15)

PLATFORM 3
Interdisciplinary Partner Groups for Diagnosis & Follow up and Treatment Research (6 WPs)

The network started with 18 workpackages. WP 16 and WP 18 are integrated into the clinical trial platform (P2).

EUROCELLS: European LeukemiaNet

The ELN structure

The ELN is a two layer networking organization, with a network level and a workpackage (WP) level, harbouring clinical trial groups for each leukemia and their interdisciplinary partners (Figure 1). The leadership of the workpackages is spread all over Europe.

Six WPs, 4-9, deal with the different leukemia entities: AML, ALL, CLL, CML, MDS, CMPD. The six WPs, 10-15 comprise diagnostic and therapeutic research groups, including diagnostics, cytogenetics, minimal residual disease, gene profiling, stem cell transplantation and supportive care/anti-infection prophylaxis and treatment, respectively. Four WPs offer central services to the network, a unique infrastructure, integrating management support (NMC), information through the ELN website (ELIC), computer support (CICS) and Biometry of registry, epidemiology, metaanalysis and prognosis. All together, they are the basis for high quality research and patient care, essential for European excellence in the field of leukemia.

To date the ELN network brings together over 100 national Leukemia study groups and their interdisciplinary partner groups with about a 1000 physicians and scientists, located in 161 institutions in 32 countries caring for some ten thousand leukemia patients. This collaborative activity across Europe has far reaching impacts in the transfer of scientific data into patient care. The joint development of a coordinated clinical and scientific strategy should result in comprehensive prognostic models to optimize the treatment of acute and chronic leukemia on a European scale. The existing expertise creates synergies in leukemia research and patient care by standardizing diagnostic and therapeutic procedures with quality assurance, establishing baseline standard data sets for controlled clinical and intergroup trials, and providing critical patient numbers for studies on rare disease subentities.

Durable integration needs strong governance

The Network management, information and communication centers (NMC, ELIC and CICS) offer infrastructure, guidance and services.

The NMC facilitates contractual or financial issues and organizational support:

- project management of multinational collaborative leukemia projects
- communication within the network's study or -interdisciplinary groups, but also with industry, key stakeholders, patient organizations and public relations
- training of health care personnel and spread of excellence to institutions and countries not yet participating in the network
- spread of information on network activities and achievements in research and partnering
- external visibility of the network to everyone with an interest in leukemia
  - » information on participating centers
  - » integration of new members into the network
  - » provision of a networking and meeting platform to enhance knowledge transfer from bench to bedside with close to a 100 annual ELN activities at international leukemia events: organization of the international annual ELN symposium (Figure 2) or presence at major hematology and oncology congresses with WP meetings, brainstorming events and workshops, but also educational events, training courses and exchange visits for young scientists
  - » PR activities, like press conferences, and provision of PR materials (exhibition booth, flyers, newsletters and posters)

Figure 2: The participants of the annual ELN Symposium in Mannheim 2009, 2-4 of February

EUROCELLS: European LeukemiaNet

The ELIC offers an-up-to date ELN-web interface (www.leukemianet.org) for regularly updated information on the projects and state-of-the-art scientific knowhow, including:

- an EU leukemia trial registry for physicians (WHO linked)
- up-to-date clinical trial and research protocols and procedures
- templates for quality assurance and standard operating procedures in clinical trial management
  - » up-dates and guidance on new trial legislation and registration, offering consultancy and training courses
- links to related project websites, like the European treatment and outcome study (EUTOS) for CML, with information material for download, and the European MDS registry (EUMDS) (www.eutos.org; www.eumds.org)
- information on the disease for patients, press and media
- an easily accessible ELN member database to facilitate spread of information within the network

The ELN website carries the HON Logo from the "Quality on the net foundation" for trustworthy health information (www.hon.ch).

The CICS facilitates computational structures for the network, like data management, algorithmic instruments, statistical networks and profiling structures:

- central registry services help to channel international registry data collection through electronic case report forms (eCRFs).
- a central randomization facility accompanies clinical trials
- the data capture facility MACRO (GCP-compliant) is available to research groups within the consortium.
- a Microarray–Analysis–Pipeline has been designed to automate standard working steps enabling the development of a gene signature for predicting patient survival.

The ELN exists through its members

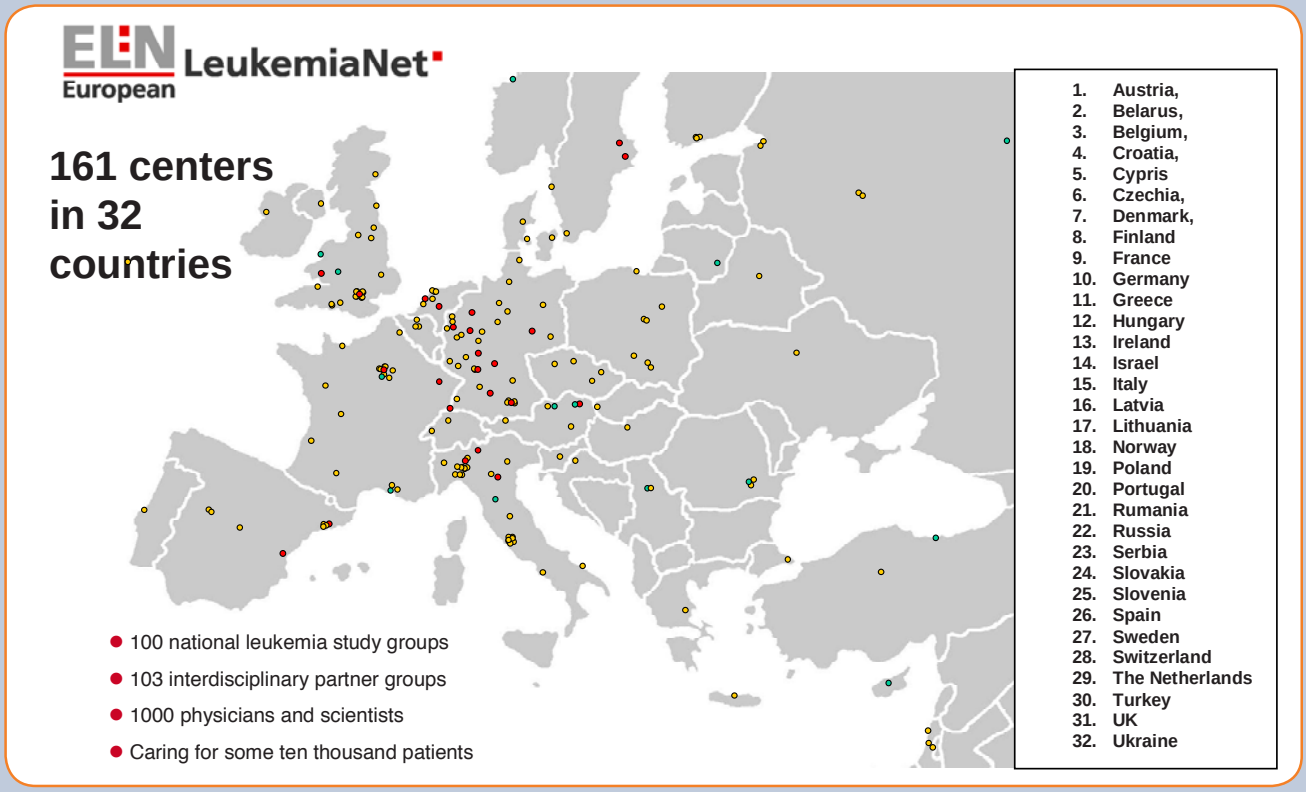
In 2009, the General Assembly agreed on the participation of fifteen new participants integrating five additional countries, namely Portugal, Latvia, Slovakia, Slovenia, and Ukraine (Figure 3: The 32 ELN member states in 2009).

In 2010, the participation of 8 new participants integrating one additional country, namely Estonia, is planned increasing the number of participants to 169 and the number of countries to 33.

This large partnership is a managerial challenge for the network, but each country has its own areas of activities adding value to the research community.

Spread of excellence into all countries is a key goal of the ELN, supporting local infrastructures to optimize treatment options for patients. Integration activities such as pursued by the ELN support the scientific communities in reaching self-sustaining integration.

The ELN offers combined European excellence with intellectual diversity and competitive projects in one organization. Scientific issues are addressed



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from complementary points of views, not always with a consensus, but with high-level competence in discussions and recommendations.

Impact of ELN activities in Europe and beyond

Patient needs have to be looked at as a global responsibility to avoid negligence or exclusion of population groups. Clinical trials are ongoing in every country, and harmonisation across Europe through common guidelines and laboratory standards are major goals for the medical and scientific community. A major responsibility lays in solving ethical issues for example collection, storage and retrieval of human biological samples, which should be approached in a multinational concerted effort, especially within established network structures, like the ELN. The ELN is known for its achievements in research and therapy of leukemia. Examples are:

- trials on a European level (CLL, ALL, CML, SCT)
- European Trial Registry (ELTR) connected to the WHO website
- European leukemia patient registry with data from 3000 patients with CML or MDS (WP17, WP4, WP8) (www.eutos.org; www.eumds.org).
- implementation of ELN guidelines and treatment recommendations (Table 1)
- standardization of laboratories for molecular and pharmacological monitoring to achieve equal standards in diagnostics, pharmacokinetics and treatment optimization worldwide
- spread of excellence by more than 100 educational activities each year at the major hematology congresses, educational meetings, and several hundred manuscripts published each year
- the ELN Newsletter as a medium to summarize major news on hot topics in the world of leukemia research, treatment and cooperation
- achievements of public–private partnerships between ELN and industry in the fields of CML (EUTOS for CML) and MDS (EUMDS):
  - » established in-study, out-study and population-based patient registries to achieve participation and regular monitoring of all patients in Europe
  - » established European standardization laboratories for molecular diagnosis and pharmacokinetics in many European countries
  - » accomplished spread of excellence by educational meetings and publications

Consensus recommendations and guidelines

The ELN has promoted and published in its five years of EU funding more than 25 management recommendations and guidelines (Table 1) providing the basis for high quality patient care in Europe and beyond. Their distribution and update is a continuous process involving international partners like the European Group for Blood and Marrow Transplantation (EBMT), the European Organization on Research and Treatment of Cancer (EORTC) or the International Association for Comparative Research on Leukemia and

Area	Publication
CML management recommendations	Baccarani M. et al., JCO 2009 Hehlmann R. et al., Lancet 2007 Baccarani M. et al., Blood 2006
CML molecular monitoring	Müller M.C. et al., Leukemia 2009 Hughes T.P. et al., Blood 2006
CLL guidelines	Hallek M. et al., Blood 2008
AML management recommendations	Döhner H. et al., Blood 2009
APL management recommendations	Sanz M.A. et al., Blood 2009
Response criteria for essential thrombocythemia and polycythemia vera	Barosi G. et al., Blood 2009
Consensus on definitions of clinical resistance/intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis	Barosi G. et al. Br J Haematol. 2009
Evidence- and consensus-based European therapy guidelines on MDS	ELN Homepage (4th edition 2008)
Standardized WT1 PCR assay in AML	Cillioni D. et al., JCO 2009
FIP1L1-PDGFRA–positive chronic eosinophilic leukemia diagnosis recommendations	Jovanovic J.V. et al., Blood 2007
Proposals for Standardized Protocols for Cytogenetic Analyses of Acute Leukemias, CLL, CML, CMPD and MDS	Haferlach C. et al., Genes, Chromosomes and Cancer 2007
BCR-ABL diagnosis recommendations	Branford S.et al., Leukemia 2007
Standardization of flow cytometry in MDS	Van de Loosdrecht A.A. Haematologica 2009
Gene expression profiling recommendations	Kohlmann A. et al., Br J H, 2008
Microarray analyses guidelines	Staal F.J.T. et al., Leukemia 2006
Transplant-associated microangiopathy recommendations	Ruutu T. et al., Haematologica 2007
Stem cell transplantation recommendations	Styczynski J. et al., BMT 2008 Dreger P. et al., Leukemia 2007 De Witte, T. et al., Haematologica 2006
Antifungal treatment recommendations	Herbrecht R. et al., EJC 2007 Bucaneve G. et al., EJC 2007 Marchetti O. et al., EJC 2007 Maertens J.A. EJC 2007 Ljungman et al., BMT 2005

Table 1: ELN recommendations on the management of leukemia and associated conditions

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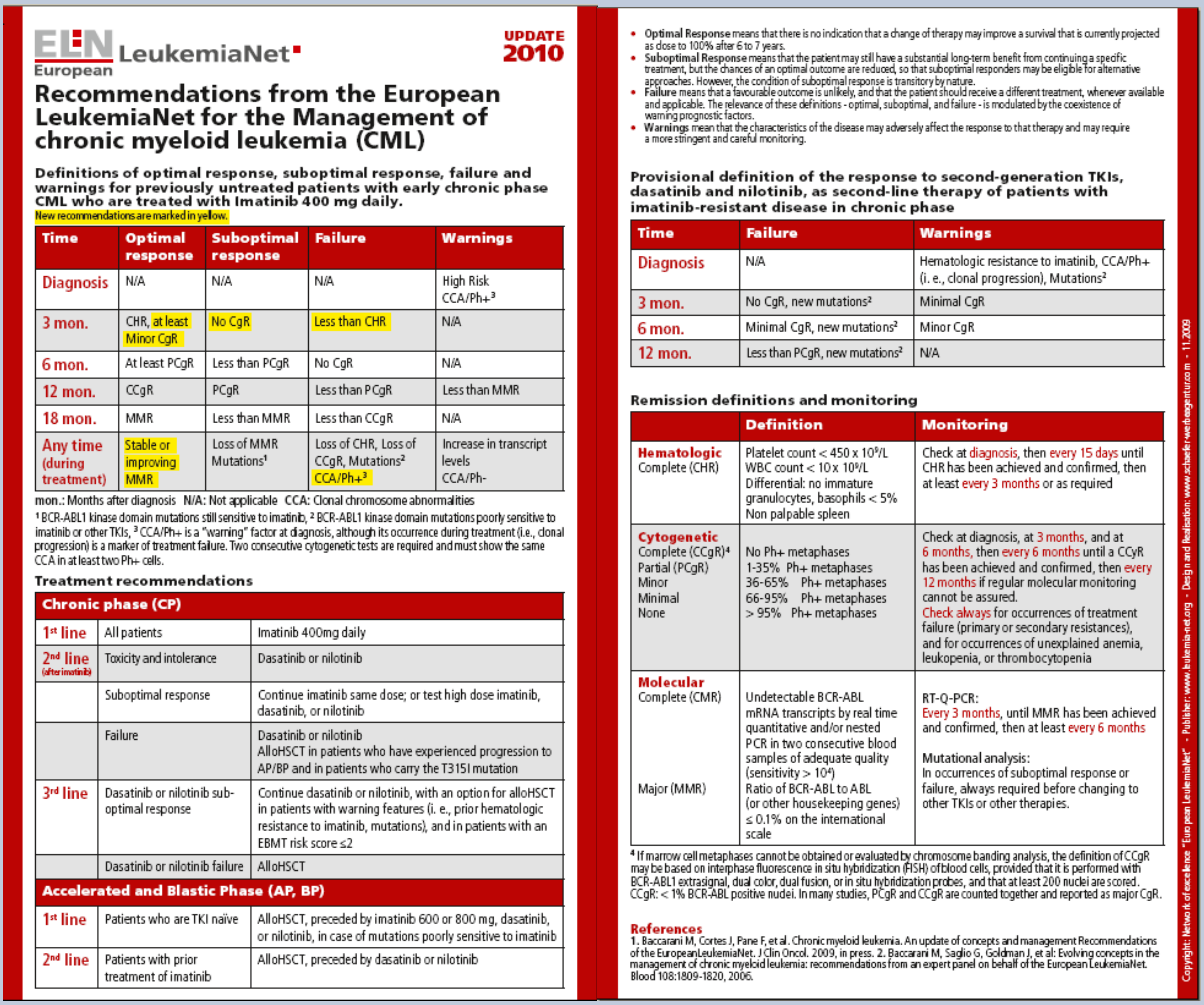
Figure 4: The updated pocket card with the ELN treatment recommendations on the management of CML for physicians (two-sided), as presented at the ASH conference 2009 in New Orleans



ELN European LeukemiaNet

UPDATE 2010

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

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

New recommendations are marked in yellow.

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

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

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

Treatment recommendations

Chronic phase (CP)		
1st line	All patients	Imatinib 400mg daily
2nd line (after imatinib)	Toxicity and intolerance	Dasatinib or nilotinib
	Suboptimal response	Continue imatinib same dose; or test high dose imatinib, dasatinib, or nilotinib
	Failure	Dasatinib or nilotinib AlloHSCT in patients who have experienced progression to AP/BP and in patients who carry the T315I mutation
3rd line	Dasatinib or nilotinib sub-optimal response	Continue dasatinib or nilotinib, with an option for alloHSCT in patients with warning features (i. e., prior hematologic resistance to imatinib, mutations), and in patients with an EBMT risk score ≤2
	Dasatinib or nilotinib failure	AlloHSCT
Accelerated and Blastic Phase (AP, BP)		
1st line	Patients who are TKI naïve	AlloHSCT, preceded by imatinib 600 or 800 mg, dasatinib, or nilotinib, in case of mutations poorly sensitive to imatinib
2nd line	Patients with prior treatment of imatinib	AlloHSCT, preceded by dasatinib or nilotinib

- **Optimal Response** means that there is no indication that a change of therapy may improve a survival that is currently projected as close to 100% after 6 to 7 years.
- **Suboptimal Response** means that the patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced, so that suboptimal responders may be eligible for alternative approaches. However, the condition of suboptimal response is transitory by nature.
- **Failure** means that a favourable outcome is unlikely, and that the patient should receive a different treatment, whenever available and applicable. The relevance of these definitions - optimal, suboptimal, and failure - is modulated by the coexistence of warning prognostic factors.
- **Warnings** mean that the characteristics of the disease may adversely affect the response to that therapy and may require a more stringent and careful monitoring.

Provisional definition of the response to second-generation TKIs, dasatinib and nilotinib, as second-line therapy of patients with imatinib-resistant disease in chronic phase

Time	Failure	Warnings
Diagnosis	N/A	Hematologic resistance to imatinib, CCA/Ph+ (i. e., clonal progression), Mutations[2]
3 mon.	No CgR, new mutations[2]	Minimal CgR
6 mon.	Minimal CgR, new mutations[2]	Minor CgR
12 mon.	Less than PCgR, new mutations[2]	N/A

Remission definitions and monitoring

	Definition	Monitoring
Hematologic Complete (CHR)	Platelet count < 450 x 10⁹/L WBC count < 10 x 10⁹/L Differential: no immature granulocytes, basophils < 5% Non palpable spleen	Check at diagnosis, then every 15 days until CHR has been achieved and confirmed, then at least every 3 months or as required
Cytogenetic Complete (CCgR)[4] Partial (PCgR) Minor Minimal None	No Ph+ metaphases 1-35% Ph+ metaphases 36-65% Ph+ metaphases 66-95% Ph+ metaphases > 95% Ph+ metaphases	Check at diagnosis, at 3 months, and at 6 months, then every 6 months until a CCyR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured. Check always for occurrences of treatment failure (primary or secondary resistances), and for occurrences of unexplained anemia, leukopenia, or thrombocytopenia
Molecular Complete (CMR)	Undetectable BCR-ABL mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10^4)	RT-Q-PCR: Every 3 months, until MMR has been achieved and confirmed, then at least every 6 months Mutational analysis: In occurrences of suboptimal response or failure, always required before changing to other TKIs or other therapies.
Major (MMR)	Ratio of BCR-ABL to ABL (or other housekeeping genes) ≤ 0.1% on the international scale	

[4] If marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCgR may be based on interphase fluorescence in situ hybridization (FISH) of blood cells, provided that it is performed with BCR-ABL1 extrasignal, dual color, dual fusion, or in situ hybridization probes, and that at least 200 nuclei are scored. CCgR: < 1% BCR-ABL positive nuclei. In many studies, PCgR and CCgR are counted together and reported as major CgR.

References

1. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia. An update of concepts and management Recommendations of the EuropeanLeukemiaNet. J Clin Oncol. 2009, in press. 2. Baccarani M, Saglio G, Goldman J, et al: Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 108:1809-1820, 2006.

Related Diseases (IACRLD). Partnerships with industry play an important role in spreading knowledge and excellence. The public-private partnership projects "EUTOS" and "EUMDS" with Novartis have made resources available to speed up processes within the CML and MDS working groups.

The implementation of international ELN guidelines and recommendations on the treatment of leukemia will help provide patients optimal health care across the globe.

Evidence- and consensus-based European management guidelines are available on the ELN homepage. This includes the CML management recommendations for physicians in a "pocket card" format (Figure 4), which will be distributed at all public events where the ELN is represented.

Clinical trials

The ELN defines and applies common standards and protocols and utilizes uniform common data sets established by WPs 10-13, diagnostics, and WP17, biometry. These are essential tools for comparable study outcomes and evaluations. The ELN benchmarks diagnostic and treatment procedures at international levels and evaluates novel concepts and technologies. Several new clinical trials have been started. The ELN trial registry database shows up-to-date information on more than 60 active clinical studies (www.leukemia-net.org/content/leukemias/trial_registry/database/).

The EC directive 2001/20/EC on clinical trials is a major challenge for all trial groups. An information platform on international investigator-initiated studies (IITs) is implemented in the ELN website with examples of such trials within the ELN (WP6, WP8). The ELN takes discussions as part of an internal IIT working group with ECRIN (European Clinical Research Infrastructure Network), EORTC, EBMT and the KPOH (Competence Network on Pediatric Oncology and Hematology).

In 2009, WP 7, ERIC/CLL, received a prestigious approval as a Scientific Working Group (SWG) within the European Hematology Association (EHA) for 3 years. This achievement acknowledges and fosters the scientific credibility, competence and excellence of ERIC as a European non-profit organization.

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Furthermore, it connects the European LeukemiaNet and EHA as interacting European promoters of competence in hematology and leukemia.

Major progress was achieved in setting up an international randomized study in elderly AML patients according to the new EU directive. This is the first randomized study in the elderly using stem cell transplantation (WP 14 and the EBMT). A new definition of inclusion criteria in older patients (frailty index) is under discussion and in preparation.

There is intensive work of representatives of all major European AML trial groups (the AML Intergroup) to coordinate European trials and harmonize various criteria according to European guidelines. Treatment protocols, future strategies and comparability parameters between European AML studies are in discussion. These activities will enhance performance and comparability of trials across Europe leading to better synergies and improved outcomes in research and patient care.

European Leukemia Registries

The collection of baseline, treatment and outcome data across Europe in a registry (database) is an essential tool in disease control, healthcare planning and research. Registries can provide data on:

- epidemiology of leukemia with incidence and disease patterns across Europe including gender, age and ethnic differences
- quality controlled outcomes and development of prognostic scores
- standardized diagnostics and therapy
- familial predisposition, overlap syndromes or precursor conditions, risk factor associations and differences in gene environment interaction, utilizing data from cytogenetic analyses and genomic profiling
- quality of life assessments
- definition of leukemia subentities on the basis of cytogenetic or gene profiling information
- proportions of patients in individual countries treated according to specific protocols or with specific therapies

The registries established by the network will have far-reaching implications for research and public health planning in the future. European registries for CML and ALL started in 2005. The CML registry was expanded in 2007 (EUTOS for CML), a MDS registry started in 2008 (EUMDS), both funded by Novartis. The EUTOS for CML registry comprises study patients from already existing trials (in-study registry) or databases (out-study registry) and a prospective population based registry. Significant progress has been made with the in- and out-study registries. Data from Czechia, France, Germany, Italy, Poland, Romania, Russia, Slovakia, Spain, Switzerland, and the Nordic countries have been collected. Data collection for the prospective registry will start in 2009. In CMPD (WP9), the registry on pregnancies under various treatments is continued. The registry on anagrelide (Exels-study) is also still ongoing. Registries and surveys are in development for transplantation in CLL, and leukemic evolution in CMPD.

Figure 5 A: Standardization efforts across Europe in Molecular Monitoring in CML

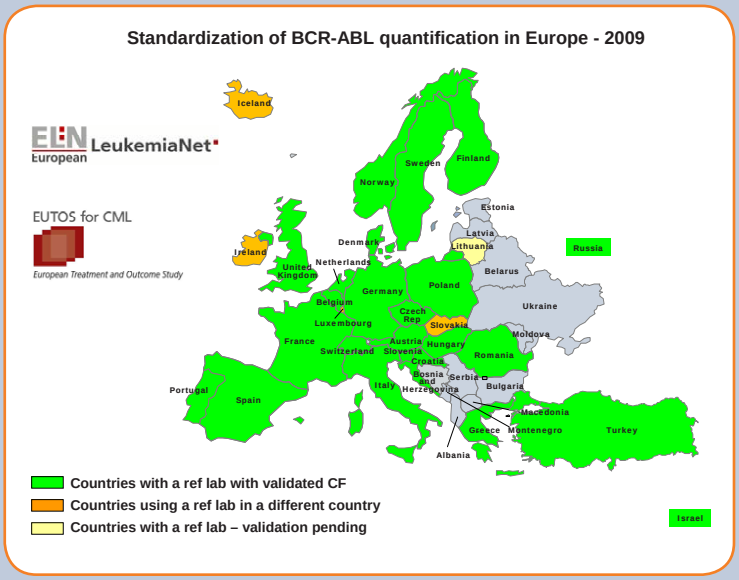
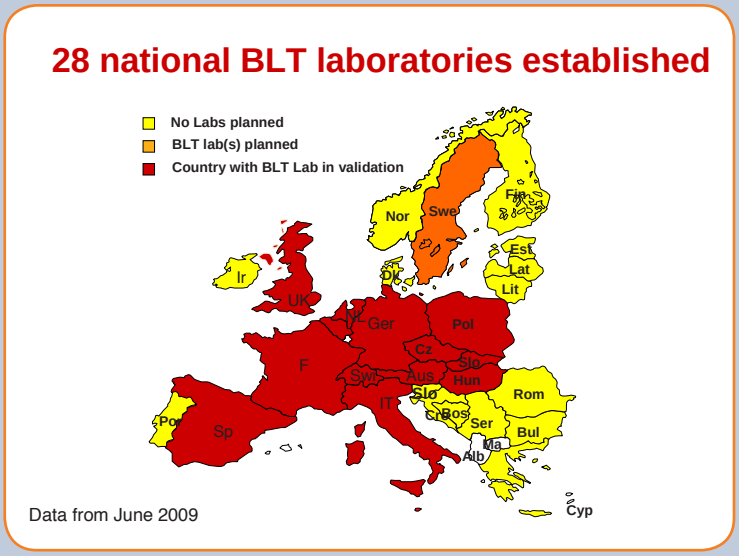


Figure 5 B: Standardization efforts across Europe in Pharmacological Monitoring in CML



Novel Treatment options: Risk adapted, personalized medicine through improved individual diagnosis and high throughput analysis

The ELN offers a basis for collecting data across 32 countries. Comparison of long term clinical trial outcomes throughout Europe and the availability of various treatment options enable a detailed analysis of life quality and life expectancy. The large diversity of patients across Europe offers an excellent pool for genetic or mutational analysis and comparison.

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Standardized and quality controlled diagnostics and therapies constitute the basis for improvements of clinical outcomes. This concerns virtually all diagnostic procedures such as morphology of blood and marrow cells (WP 10), cytogenetics (WP 11), detection of minimal residual disease (WP 12) or gene expression profiling (WP 13) and treatment approaches including stem cell transplantation and anti-infection prophylaxis and treatment (WP 14, 15). The ELN has created an infrastructure of standardized laboratories across Europe offering know-how and services, free of charge for ELN members with weak scientific infrastructure. Major activities have focused on the development and validation of conversion factors between laboratories and on the development of accredited reference reagents to establish reliable assays. The detection and mutational analysis of the disease relevant gene BCR-ABL, within the EUTOS for CML project, was expanded to 26 national reference laboratories in 24 European countries (Figure 5 A). Blood level testing of imatinib was established in 28 national reference laboratories in 14 countries by the EUTOS collaboration (Figure 5 B).

The power of collaborative networks has further been demonstrated by WP 13, which has brought together eleven laboratories across three continents on gene expression profiling in leukemia (MIcorarray Innovations in LEukaemia-MILE-study): seven laboratories from the ELN, three from the US and one in Singapore. This large scale study reveals new patient subgroups with their own specific prognosis and survival. The use of gene expression profiling as "diagnostics in leukaemia" for investigating basic research topics and application in a clinical setting is strongly supported by biostaticians and further funded by external research grants from ROCHE Diagnostics. The MILE project integrates data from morphology, cytogenetics, molecular genetics and immunophenotyping from more than 4000 patient samples including all types of acute and chronic leukemia and MDS. Study outcomes resulted in publications and presentations at international hematology conferences. Microarray raw data from the MILE study was submitted to the GEO database at the National Center for Biotechnology Information in the US (NCBI).

Microarray technology provides an improvement for the actual classification of leukemias through identification and definition of new subgroups, whose gene expression profile can be correlated with a calculated survival rate or quality of life. The MILE study led to the development of a prognostic algorithm that can identify MDS patients with high, intermediate, and low risk of progression to AML (Figure 6). Molecular signatures may go beyond morphology, immunophenotype, and cytogenetics by replacing subjective assessment by an objective assessment based on microarrays. The genes involved might also allow the development of targeted therapies for MDS

Figure 6: The hierarchical clustering of MDS samples and their classification in high, intermediate and low risk of disease progression (with kind permission from T. Haferlach and K. I. Mills, presented at the EHA congress 2008 in Copenhagen)

patients with poor prognosis.

The DACH study (short form for ELN centers in Germany (D), Austria (A), and Switzerland (CH)), a follow up of the MILE-study, demonstrated that microarray analysis can be performed with high inter-laboratory reproducibility, comparable quality and high technical precision across laboratories. Progress in the detection of minimal residual disease, by molecular or cytometric methods, has also been largely discussed within the ELN WP10 and WP11. New or improved diagnostics enable risk stratification and improved prognosis of resistances towards specific medication or of increased tumour risk. This leads to the design of specific medication, targeting individual disease related molecules in a selective therapy with a better response towards the disease.

Cooperations, synergies and public-private partnerships

Multinational cooperations of the ELN include other European networks and institutions such as the EBMT, EORTC, ESH and ECRIN. Common issues regarding trial registries and trial infrastructure in Europe, trial evaluation criteria, data management, laboratory and diagnostic standardizations as well as educational symposia and laboratory training courses to reach to as many physicians as possible are high on the agenda.

Cooperations with industry are opportunities for both sides. The ELN offers a unique medical network of excellence in leukemia across Europe and beyond, a "one stop shop" for industry. Private partners can offer support in creating appropriate infrastructure for registries, quality controls, educational exchange, innovative research and disease management.

The EUTOS and EUMDS projects register CML and MDS patients in Europe. The patients will be followed over several years to collect baseline, treatment and outcome data for representative samples of patients with a common effort of standardisation. Spread of excellence within the EUTOS project is highlighted by the annual educational CML symposia across Europe (Venice 2006, Budapest 2007, Cannes 2008, Barcelona 2009, London 2010), through the EUTOS-Website and PR materials (booth, newsletter, flyer, pocket cards).

Sustainability concepts have been intensively evaluated with the decision to establish an ELN Foundation.

The development and sharing of joint infrastructures, integration of research activities and institutions has created durable structures with good prospects for sustainability well beyond the period of EU-funding. WP7 for example, with the ERIC initiative (European Research Initiative on CLL) is becoming an incorporated legal entity (ERIC e.V.) in Germany.

In June 2009, 13 ELN lead participants signed the ELN Foundation act and in August 2009, the ELN Foundation was officially legalized by the governmental authorities in Germany. The ELN Foundation is a non-profit charitable organization, supporting the goals of the ELN and advancing leukemia research in Europe and beyond to save lives and to cure by improving medical care and treatment.

The ELN Foundation will offer companies access to its European academic clinical research network, providing knowledge and expertise in the development, placement and conduct of early phase clinical trials and providing infrastructure for larger, multi-centre clinical trials. The collaboration basis will be mutual trust and independence (associated ELN institutions, Figure 7).

Figure 7: The logos below represent the institutions with which the ELN is associated

Conclusion

- The ELN has established a network of clinicians and researchers with the aim of 'durable integration'.
- Many years of successful and fruitful, competitive and synergistic interactions in clinical trials and research have created 'incubators' for excellence and for exploratory activities towards new scientific issues in the field of leukemia.
- Participants from specifically evaluated institutions with a recognized record in leukemia research and treatment, in long-term cooperation and in education contribute with new ideas to the emergence of new scientific fields beyond traditional modes.
- This network provides a critical mass for creative and productive exchange of views, progress at the research front and promotion of interdisciplinary cooperations by supporting high-level research and training. Interaction across scientific boundaries creates new and unprecedented opportunities for innovative research.
- While assembling the best available expertise in Europe, representing leukemia in Europe 'with one voice', the ELN collaborates internationally with research and study groups, e.g. in the US, in Japan and in Australia on new research fields and treatment strategies.
- By communicating with science policy stakeholders and reaching out to the public through web based information tools and PR materials, the ELN supports European and international visibility and competitiveness.
- A network like the ELN with its transnational 'integration' in research, diagnosis, treatment and education provides transparency in research, a critical mass for excellence and a competitive advantage for participants and their partners, including industry, setting the stage for future strategies and progress.