SIXTH FRAMEWORK PROGRAMME
LSH-2002-2.2.0-3
Life Sciences, genomics and biotechnology for health
(LifeSciHealth)

Proposal/Contract no.: 503216
Project acronym: European LeukemiaNet
Project full title: Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe
Network of Excellence

Seventh Annual Activity Report

Period covered: from 01/01/2010 to 28/02/2011
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Duration: 86 months

Project coordinator: Prof. Rüdiger Hehlmann
Project coordinator organization name: Universität Heidelberg
Publishable Executive Summary

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Publishable Executive Summary

The European Leukemia Net (ELN) stands for more than 8 years cooperative research in a network of excellence (NoE), including over 1000 leukemia specialists from 182 institutions in 34 countries across Europe. ELN has become a landmark in the medical history of leukemia. Honoring the success of ELN, the contract between the EU and the ELN was extended over the regular period of six years until February 2011. This was the last month of EU funding within the 6th framework programme, but not the last month of ELN. Looking back the ELN has published over 35 guidelines and management recommendations on leukemia diagnosis and therapy. These are the basis for high quality patient care in leukemia across Europe. More leukemia patients survive longer times. In chronic myeloid leukemia the survival time increased almost 10 fold, from 3 years in 1982 to over 25 years in 2011. Will curing the disease be possible in the near future?

ELN funding will continue through the European Science Foundation (ESF), which can secure the ELN Symposia and some of the networking activities until 2015. Together with ESF, the ELN engages in a European initiative to revise the legislation in the field of clinical trials and has taken position in the "Revision of the ‘Clinical Trials Directive’ 2001/20/EC, Concept Paper’. Motivation and vision has driven the ELN to found the ELN Foundation in 2009, which will sustain and support goals and activities of ELN through donations for ELN research activities. The ELN Foundation website was launched in 2010 (www.elnfoundation.org). In 2011, ELN may assume a new identity, developing from an EU NoE-project to an organisation with legal status. The ELN Steering Committee has taken decisions during the ELN symposium in February 2011 in Mannheim. New collaborations and research goals will be started between partners, new participants will continue to join. ELN has steadily expanded and has made fragmentation of leukemia research in Europe an issue of the past. 2011 and future years will bring many new ideas and good partnerships within the cooperative research of ELNs evolving identity.

In support of this, EUTOS for CML (European treatment and outcome study for chronic myeloid leukemia), a public-private partnership between the ELN and Novartis was recently updated and extended until 2012. This collaboration has already achieved major milestones in CML research by enabling access to the largest CML population ever studied, aiming for a cure of this devastating disease.

The ELN will continue to set high standards for the investigation of all leukemias in Europe and qualify medical doctors and scientists with educational activities on treatment recommendations, new insights in the emergence of the disease and innovative research. Other Public-Private-Partnerships have been established (e.g. EUMDS).

Major achievements during the EU funding period are summarized in the publication “The European LeukemiaNet: achievements and perspectives” (Hehlmann, R; Grimwade, D; Simonsson, B, et al. Haematologica 2011,96:156-162).
Examples are listed below:

- Cooperation instead of fragmentation within the European leukemia research arena
- International cooperation with the US, Japan and Australia.
- Accomplishment of a unique leukemia specific infrastructure given by the three network centers, responsible for management (NMC), information (ELIC) and statistics/biometry (CICS) (WP1-3,17).
- Clinical trials on a European scale through collaboration of the leading national leukemia trial groups of the different leukemia entities (WP4-9) and the interdisciplinary partner groups in diagnostics and therapy research (WP10-15)
- Standardized protocols for clinical trials and diagnostic procedures to achieve comparable data, resulting in better and equal treatment options across national borders
- Networks of reference laboratories in leukemia diagnostics and pharmacokinetics across Europe (WP12, EUTOS for CML)
- Management recommendations for all leukemias
- Patient registries for information on current treatment and best treatment options (EUTOS for CML, EU-MDS)
- Improvement of patient care due to personalized treatment options
- Spread of excellence (ELN Website and publications) and high level training and education to all physicians and researchers within leukemia research.

The ELN is committed to sustain the collaborations within and outside the network and to further develop high quality standards in leukemia research, diagnosis and treatment.

Highlights in 2010 and 2011 include:

- The ELN symposia in Mannheim which attracted 460 ELN participants from 33 countries in 2010 and 425 participants from 34 countries in 2011
- In 2010 acceptance of fourteen new participants to ELN integrating one additional country, namely Estonia
- In 2011 acceptance of eight new participants integrating one additional country, namely Bulgaria
- The ELN increased in its last year of EU funding to 182 participants and 34 countries.
- Trials on a European level
- Consensus proposals (immunophenotyping of acute leukemia and lymphoproliferative disorders), reports (on blood cell identification from 17 countries within the European LeukemiaNet network) and management recommendations, (Philadelphia-negative classical myeloproliferative neoplasms)
• Funding of the ELN Networking Programmes through the European Science Foundation (ESF). ESF will fund the ESF-ELN RNP with more that 80,000 € per year. This will support the Annual ELN Symposium, ELN workshops and exchange visits, as well as public relations, like website, publications, and printed information material.

• Public-private-partnerships between ELN and Novartis successfully continue until 2012, including “A Path to Cure” project.

• In conjunction with the EUTOS elongation, the CML Registry offers access to the largest CML population ever studied (www.eutos.org).

• In European registries in MDS, 1000 included patients have been reached. The follow-up period has been extended by 3 years (www.eumds.org).

• Spread of excellence by close to 80 educational activities at the annual congresses of ASH, EHA and the German/Austrian/Swiss Societies of Hematology and Oncology, the annual CML-educational meetings, more than 15 specialty workshops, publication or completion of more than 550 manuscripts in 2010/2011, the 7th Information Letter, the information booth, the ELN website and more than 800 lectures by ELN-participants.

• The launch of the ELN Foundation website: www.elnfoundation.org to fundraise donations with the aim to cure leukemia.

• An ELN Foundation information newsletter in 7 languages.

• Project websites like ESF-ELN Research Networking Programme.


ELN as a network recruits larger patient cohorts in shorter time periods from across Europe than any national network and has made a durable impact by promoting leukemia research and improving treatment options.

Uniform definitions, common clinical trials and research projects, prolonged partnerships, new proposals, publications and the steadily increasing number of ELN participants characterise the ELN in 2011. These activities, the international acceptance and the application of ELN criteria point to sustainability and further development of the ELN.

The ELN will continue beyond NoE funding on the forefront of leukemia science, sharing members with the European working groups of EHA (European hematology association), COST-, ESF Research Networking - and EU 7th framework programmes but also public- private partnerships and many more research activities, challenging current knowledge and aiming for a cure of all leukemias.
Section 1: Project objectives and major achievements during the reporting period

1.: Financial sustainability, integration and cooperation, central information and communication, central data management and spread of excellence (WP1-3, 17)

The four network service centers offer a unique leukemia specific infrastructure in regards to network management (NMC), European leukemia information center (ELIC), central information and communicating service (CICS), and registry (WP17).

Sustainability was and is the key project for the NMC (WP1). Final reporting of the ELN-EU FP6 project and reorganisation of the ELN beyond EU support constitutes the NMCs actual programme. Inquiring novel funding sources is a continuously ongoing process. Support from the ELN Foundation, from the European Science Foundation (ESF) and through a new EUTOS contract in 2010 could be secured, and applications to the EU 7th framework programme and the German BMBF International bureau were submitted. Contract renewals, stimulation of partners to write new proposals, activation of additional collaborations and organizational support to all ELN activities at national and international levels are major tasks. Leukemia events in 2010 and 2011, including training of young hematologists, communication with industry, patient organizations and public relations as well as the distribution of information on network activities and achievements are managed by the NMC (PR material: flyer, booth, Information Letter). Brainstorming for innovative ideas and new milestones and deliverables are a continuous process.

In 2010, the annual ELN symposium in Mannheim attracted 460 ELN participants from 33 countries and in 2011 425 participants from 34 countries.

In 2010 a workshop on “Regulatory requirements for the clinical development of cell therapeutics and biologicals” directed by Prof. U. Mansmann, Munich, preceded the symposium and attracted a major audience.

A session on “Life quality and late effects: activities and future collaboration in the European LeukemiaNet” emphasised an important part of clinical studies and started up the first day of the symposium. The sustainability topic was introduced through the ELN Foundation.

Current collaborations, challenges and new directions in leukemia and related disease entities were highlighted in the WP meetings. The scientific symposium highlighted different methodologies, like whole genome sequencing, molecular biology of MDS, molecular pathogenesis of atypical MPN, the relevance of molecular monitoring for prognosis and treatment of CML and, from a very different point of view, health economic issues in leukemia.
In 2010, the General Assembly accepted fourteen new participants to ELN, integrating one additional country, namely Estonia. In 2010 the ELN comprised 176 institutions from 33 countries working together in now 105 leading national leukemia trial groups and 105 interdisciplinary partner groups.

In 2011, the 8th Annual Symposium of the European LeukemiaNet was held again in Mannheim on February 1-2. This was the last ELN Symposium under EU funding as a Network of Excellence within the 6th European Union Framework Programme (2004-2011). NMC organized the scientific program and provided the operational and organizational infrastructure of the symposium and workshops. This includes the scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs. Again it was a major goal and challenge at this annual conference to get the members of all ELN workpackages face-to-face together. In total, 425 participants from 34 countries attended the Symposium in 2011. The ELN is still increasing in 2011. At the end of EU funding the General Assembly agreed, in 2011, on eight new participants integrating one additional country, namely Bulgaria, increasing the number of participants to 182 and the number of countries to 34 (Fig. I.1).
About a 1000 internationally recognized clinicians and scientists combine forces within 108 national leukemia study groups and 105 interdisciplinary partner groups in diagnostics, cytogenetics, MRD-research, gene expression profiling and registry, guidelines and industry (Fig. I.2 and I.3).

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Figure 1.2: 108 National ELN Leukemia Study Groups
Two sessions preceded the Annual Symposium of the European LeukemiaNet in 2011 directly: New developments around the Clinical Trial Directive (CTD)” organized jointly by WP1 and WP2 and the 2nd ESF-ELN Steering Committee Meeting, which was by invitation only.

Dr. Steinhausen, Strasbourg, from the European Science Foundation (ESF) participated in both meetings, introducing the role of ESF (“Forward Look” on Investigator-Driven Clinical Trials) and of the European Medical Research Councils (“Position Paper”, CTD, available summer 2011) in the modification process of the CTD and thereafter representing the ESF in the ESF-ELN RNP SC meeting.

The CTD session gave insight into the latest development on Investigator Initiated Trials (IITs) in Europe. Speakers from different stakeholders’ perspective, ESF (Dr. Steinhausen), ELN (Ihrig) and the Patient advocacy group (Geissler, Leukämie-Online e.V. / LeukaNET / CML Advocates Network) discussed their efforts in the past and gave direction for future changes. Practical approaches, like a “Voluntary harmonization process for regulatory approval” were introduced by the German Paul-Ehrlich Institute (Krafft). The “Risk-adapted approach to clinical trial regulation and monitoring” was presented by the European Clinical Infrastructure Network (ECRIN, Jaques Demotes). It was stressed that the revision of the ‘clinical trials directive’ 2001/20/ec concept paper”
submitted for public consultation will be published by the European commission and that a concerted effort from all groups present is needed to respond.

Challenges and new directions in leukemia and related disease entities were highlighted during the workpackage meeting in three consecutive sessions. Each WP reported on the different projects and discussed future objectives of the group for the coming year.

The Scientific Symposium finalised the symposium with speakers from Europe and the US, presenting outstanding issues within leukemia research such as a revisit of HTLV-I in ATL, a rising CLL incidence after Chernobyl, a new stem cell marker in CLL, progress with MDS and standardized molecular monitoring across Europe. On day two each WP presented the highlights, results and the prospective outlines for the future in a plenary session. The programme was available for download via the ELN homepage (see Figure I.4). The event was further announced at the ESF homepage, at “my medical education” and at the University of Heidelberg homepage (see section 2, Figure 1.7 and 1.8).

**WP2 (ELIC)** prepared a sponsoring concept to gain funding for the ELN. This will enable the ELN to accept funding for service in return. The ELN will in future have the possibility for sponsoring contracts as an additional tool to get financial support. Characteristics of sponsorship is that the sponsors (main target group: pharmaceutical companies) will receive a specific service in return for their financial support - mainly through the benefits of the network and public relation, like the ELN website. Aim of the sponsoring concept is to generate a budget for the ELN which is distributed according to transparent criteria. It serves as a concept for the financial sustainability of the ELN by attracting sponsors who give regular funds to the ELN with transparent service in return. Target groups will be pharmaceutical companies (one-stop-shop).

Sustainability/ELN Foundation: In contrast, the ELN foundation will collect donations. Its non-profit status does not allow contracts or service to companies in return. Target groups of the ELN foundation are non pharmaceutical companies, private persons and major Foundations. A fundraiser is in charge to contact these target groups.

ELIC is continuously updating the ELN homepage in regards to meetings and conferences, clinical trials, project updates, dissemination of news and the set up of new project sites. In 2010 two new subpages were added informing on the activities of the ELN Foundation and the ESF-ELN-RNP site linking directly to the related homepages [www.elnfoundation.org](http://www.elnfoundation.org) and [www.esf.org/esf-eln](http://www.esf.org/esf-eln). The ELN Foundation Website was launched in 2010 as a completely new website. A project to add information about patient advocates has been started to further enhance the benefit of the ELN webpage for patients.
The leukemia trial registry (ELTR) has currently registered up to 100 European leukemia trials and was recently restructured. ELIC also links to and updates the homepage of the public-private partnership “European treatment and outcome study (EUTOS) for CML”.

Figure I.4: ELN Homepage with 2 new project sites and the links to the European Leukemia Trial registry and the EUTOS project

The seventh Information Letter was prepared for the symposium in 2011 (WP2, ELIC, in cooperation with WP1, NMC), highlighting the current progress on projects, collaborations, meetings, website content and lists upcoming meetings. It fosters cooperation amongst network members and informs the public on hot topics in leukemia.
In the name of the ELN ELIC together with the NMC and the European Science Foundation coordinate ELN activities around a response to the ‘clinical trials directive’ 2001/20/ec concept paper” which was submitted for public consultation beginning of 2011.

**WP3 (CICS)** offered computational services to the network:

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

In 2010 the range of functions of the software ‘RANDOULETTE’ was extended. Randoullette allows online randomisation of individual patients in clinical trials according to Good Clinical Practice The randomisation facility is available at no additional costs for trials conducted within the European LeukemiaNet. The GCP-compliant electronic data capture facility MACRO is also available to research groups within the consortium.

In addition WP3 has developed a web-based online electronic case report form (eCRF) for the European Treatment Outcome Study (EUTOS) for CML Registry organised by WP17. Case reports
include baseline information and yearly follow-ups. The registry currently covers 52 regions in 23 different countries. More are expected to join in 2010.

A Microarray – Analysis – Pipeline developed in cooperation with the University Regensburg and designed to automate standard working steps was used on 151 CLL samples to develop a prognostic score for patient survival time and time to treatment.

In 2010 WP3 participated in the planning of pseudonymization issues in a large register trial researching outcome of acute myeloid leukemia (AMLSG-BiO Study), which will start in 2011. Furthermore, WP3 (IBE, LMU Munich) participates in the FLAMSA 101, 102, 103 studies in high risk AML patients with IT and biometrical services (RANDOULETTE and statistical analysis).

WP17 (Biometry of registry, epidemiology and prognosis) continued to expand the CML and MDS registries together with WP3, WP4 and WP8. Together, both registries account for data from more than 4700 eligible CML and more than 1000 MDS patients. In CML, 24 countries participated in the population-based-registry, collecting baseline and follow up data on new patients diagnosed with CML. A report was provided by WP17. The challenge will be to assure proper monitoring and follow-ups, to reach the goal of developing and validating a comprehensive prognostic model that allows optimization of individual treatment choices.

Recently, an AML-registry, has started in Germany with data input within the AML-Intergroup, aiming towards an European AML-registry.

2. Performance of clinical trials (WP4-9, 14-15)

ELN overcomes national fragmentation of clinical trials, avoids duplication of efforts and accelerates outcome by recruiting larger patient cohorts in shorter periods from across Europe. Uniform definitions, protocols and outcome measures allow comparison of research results and lead to common guidelines and treatment recommendations. This impacts patients, health care economics and society and results in faster implementation of best treatment options for all patients across Europe. 36 recommendations were published in the funding period, three of these in 2010 and 2011 (see Table I.1 below). In leukemia ELN sets the standards, protocols and common data sets. The trial registry on the ELN website informs on all active, but also inactive clinical trials, which are not recruiting but evaluating results and follow-up data.

WP4 (CML) has six multicenter clinical trials ongoing. Trials with new signal transduction inhibitors, new immunotherapy (vaccination, interferon) and with attempts to stop imatinib therapy are running successfully across Europe. The European registry and the subregistries have grown rapidly and enrolled more than 4000 patients. Standardization rounds and harmonization for molecular monitoring of residual CML with 58 ELN laboratories (including 28 national reference laboratories) are ongoing. A consensus manuscript on molecular monitoring and a follow up paper were published.
WP4 is closely networking with WPs 1-3, 10-14, 17, CML Study Groups outside EU and pharmaceutical industry. EUTOS (European Treatment and Outcome Study) for CML was prolonged for another 2 years until December 2012. Spread of excellence activities were focussing on hematology conferences and educational.

In the last funding period the AML Groups (WP5) achieved further progress and experience in the field of molecular markers and new drugs targets (Hematologic Malignancies conference in Brussels, 2010). Promising therapeutic results were confirmed mainly in promyelocytic leukemia. First updates suggested a successful cooperation of trials in the AML Intergroup in younger patients, while data and experiences in older age AML increased Europe wide. An increasing availability of data on allogeneic SCT suggested the use in high-risk disease even in older patients (see Annex Section 3, WP5 publication list 2010).

The AML Intergroup as an ELN pilot study has now recruited more than 3000 patients. The latest update allows reliable projections to 5 years. Uniform European recommendations on all clinical aspects of AML were published. Multiple approaches and experiences were reported on the field of allogeneic SCT. The AML Intergroup coordinates European trials and harmonizes treatment protocols, future strategies and comparability parameters according to European guidelines. The comparability of trials across Europe will lead to synergies and improved outcomes in research and patient care.

The successful national European study groups for ALL (EWALL, WP6) aim to combine their efforts in order to create a world-wide leading research group for adult ALL. Integrating activities are of major importance and include the development of standardized laboratory procedures for diagnostic confirmation, an overview on prognostic factors and on ongoing European studies in ALL within a study registry. Phase I-III intergroup studies and the combination and standardization of methods, definitions and clinical application of MRD are jointly executed research activities.

The first meeting of the EHA-SWG-EWALL took place at EHA in Barcelona 2010 with about a 100 participants. EWALL was extended by a Slowakian study group for adult ALL. Several publications on studies and standardisation in diagnoses and follow up were published in 2010 and beginning 2011.

In 2010, WP7 (CLL), ERIC has fostered scientific credibility, competence and excellence of ERIC as a European non-profit organization. Furthermore, it connects the European LeukemiaNet and EHA as interacting European promoters of competence in hematology and leukemia. In 2010 three ERIC meetings and one ERIC/EHA SWG workshop were held (between 40 and 120 participants). The outcomes of the clinical trials were presented at ASH 2010 in Orlando.

The MDS working group (WP8) has started attempts in 2010 to integrate into the Working group of the European Hematology association, EHA MDS Working group. An EHA MDS working group met in December 2010 to discuss the future EHA meetings and the collaboration on projects on clinical and laboratory research. The second major goal of WP8 is to set up an international MDS clinical trial
platform to standardize methodology of diagnosis (flow cytometry), therapy (Vidaza, Lenalidomide) and follow up in MDS an to allow better comparison of results. Discussions with Dr. Hartmut Kraft (PEI), co-chair of the Clinical Trial facilitation Group (CTFG) are ongoing (http://www.hma.eu/77.html). Therapeutic guidelines on treatment of MDS can be found on the website: http://mds.haematologica.org (Fig. I.6).

**Figure I.6:** Therapeutic guidelines on treatment of MDS on the website: [http://mds.haematologica.org](http://mds.haematologica.org)

As the second WP that has started a European MDS-registry (EUMDS) with the private partner Novartis, WP8 has reached the milestone of including 1000 patients to this registry. 15 countries participate currently. The follow-up period has been extended to 3 years. It is the aim to enhance the value of the registry by integrating and matching biobanking. WP8 plans to apply in the EU 7th framework programme “Rare diseases”.

The **CMPD working group (WP9)** reported within the ELN in 2010 and 2011 on ongoing clinical trials in myeloproliferative neoplasms (MPN) in Europe. New proposals for the next period 2011 were discussed, like a consensus on the outcome measures for clinical trials in MPNs or a booklet for MPN patients, harmonized throughout Europe. In addition, an update on the MPNMPN-EuroNet activities was given (Molecular Diagnosis of MyeloProliferative Neoplasms (MPN) and MPN-related congenital diseases (MPNr) (COST Action BM 0902)).

The **diagnostics platform (WP10)** focussed attention to the development of optimized protocols for flow cytometric detection of MRD. Together with WP12, a joint program was established to investigate the optimal approach for MRD- directed therapy in leukemia patients with AML, which lack a leukemia-specific marker (publications see Annex Section 3).

The **cytogenetics working group (WP11)** aimed to intensify harmonization of cytogenetic techniques between laboratories based on consensus protocols and practical training in other laboratories and to improve analysis of large and complex cytogenetic data sets, using the Cytogenetic Data Analysis System (CyDAS.org). New cases with rare chromosome aberrations were collected in collaboration
with the Atlas of Genetics and Cytogenetics in Oncology and Hematology. Cryptic and complex chromosome aberrations were revealed by SNP microarray analysis. The continuous interlaboratory development and provision of methods lead to a number of publications on chromosomal abnormalities in different leukemias, especially AML and MDS in 2010 and 11.

The minimal residual disease (MRD) working group (WP12) established assays from which patients with myeloid leukemias/myeloproliferative disorders (MPDs) can benefit from. Key approach is the monitoring of minimal residual disease (MRD) using real-time quantitative PCR (RQ-PCR). Key objectives over the last year have been to continue to improve standardization of established assays (i.e. BCR-ABL, JAK2 V617F in collaboration with WP4 and WP9, respectively), the evaluation of novel RQ-PCR assays (i.e. Wilms’ Tumor gene (WT1) and nucleophosmin (NPM1) mutation) and the validation and implementation of a computer software reporting package to improve standards of reporting of RQ-PCR data to clinicians, which also serves to facilitate comparison of results between laboratories. MRD assessment enables to guide therapies leading to improved management and clinical outcome.

The gene profiling platform (WP13) was first interested in using gene expression profiling for investigating basic research topics and the application of microarrays in a clinical setting. Since 2010 next generation sequencing is of high interest and takes over the focus. The evaluation of both screening methodologies is strongly supported by biostatisticians. Microarray data as well as NGS data very recently were collected within the ELN network and involved respective subgroups in WP13 as well as other WPs in close collaborations. The DACH and the MILE studies are published and data is publicly available in the GEO database. In parallel, all biostatistical platforms have been upgraded in 2010 and expanded to NHS data sets: GAP is freely available for all ELN members, and not restricted to the MILE subgroups. In the ELN GAP database, data can easily be stored, exchanged and analyzed within the participating WPs. Many results were published in 2010, many more are in preparation (see Annex Section 3).

Several important deliverables were obtained in the stem cell transplantation group (WP14) during 2010. The stem cell transplant survey was performed in Europe and World wide, but also the harmonization process between Europe and the US was continued, providing valid information on changes in indications, frequencies among the different countries but also among diseases. WP14 makes use of synergies with the European Group for Blood and Marrow Transplantation (EBMT). The main activities include regular surveys on the transplantation activity in Europe, recommendations for the use of stem cell transplantation assessment of key factors responsible for outcome and, as a current focus, the adaptation of transplantation conditions to the needs of elderly patients, mainly with AML and ALL. In CML, an improvement of transplantation outcome has been achieved with low transplantation mortality (<10%) and 3-year survival-rates of approximately 90% in chronic phase and more than 50% in advanced phase patients. These favorable developments are mediated by improvements in patient and donor selection, transplantation procedures and supportive care.
The working group on supportive care and antiinfection prophylaxis (WP15) initiated collaboration with IDSA regarding guidelines for vaccination of patients with hematological malignancies in general and after stem cell transplantation. These have been presented at the IDSA meeting in Vancouver, Canada in October 2010 and the manuscript is in the final stages of preparation. The 13th training course of the Infectious disease working party (IDWP) was held in 23-25 September, 2010, Paris, France. A 4th European Conference regarding Infections in Leukemia is planned for September 2011, updating previous guidelines and covering new topics.

3. European Leukemia Registries

The ELN established patient registries for CML and ALL in 2005. The CML registry was expanded in 2007 (EUTOS for CML), a MDS registry started in 2008 (EUMDS), both funded by Novartis, currently until 2012. An AML registry was initiated in 2010, intending to act as a data repository for the different AML trial groups.

One of the key objectives is to provide a clear epidemiological picture of the disease and a real world information on patient treatment and outcomes across Europe. EUTOS for CML is collecting baseline, treatment and outcomes data for patients with CML. The final report from the central data centre (CDC) in Munich summarises the current state:

The three sections (in-study, out-study, and population-based) of the EUTOS CML-Registry have been successfully established. With 2389 eligible CML-patients in the in-study and 1582 patients in the out-study section even more patients than initially expected could be recruited.

24 countries participated in the prospective population-based study. It did take time to agree on the research plan, so the majority of the data was collected in 2010. Considering the challenges of a European registry and the differences in ethics and regulatory affairs for each individual country, the reporting of 731 eligible patients is as a success. Altogether data of 4703 eligible CML-patients have been registered in the reporting period.

Typically registers take years before data can be analysed and manuscripts can be submitted, due to different laws and regulations in each country. In contrast, the EUTOS registry has already provided several detailed reports and presentations, summary articles in the ELN Newsletter and PR documentation. In addition, a manuscript has been finalized about a new prognostic model which allows to predict complete cytogenetic response (CCgR) at 18 months using two variables only (see Hasford et al., Annex Section 3 WP17).

The major challenge in the coming period is to safeguard that all patients are monitored according to the research plan and that the registry receives the follow-up patient data.

The European MDS registry (WP8) has now data on more than 1000 patients from 15 countries and plans to register 2000 patients in the next 3 to 5 years. First results were presented at ASH 2010, Orlando.
A German AML registry started in 2010 with the plan to develop this registry into a common European AML registry, which will provide information on differences in treatment, treatment outcomes, on needs for improvement, and on life expectancy of AML patients across Europe.

4. Diagnosis / Follow-up (WP10-13)

Early diagnostic, proper classification of disease and the follow up on minimal residual disease are essential for optimal treatment of each patient. The cooperation between the diagnostics WPs: morphology (WP10), cytogenetics (WP11), detection of minimal residual disease (WP12) and gene profiling (WP13) lead to a European consensus report on blood cell differentiation (Zini et al. 2010, see Annex section 3, WP10) and to a consensus proposal in immunophenotyping of acute leukemia lymphoproliferative disorders (Béné et al., 2011).

WP11 (cytogenetics) and WP13 (gene profiling) developed the “Leukemia Gene Atlas”, a new web-based tool for the ELN (leukemia-gene-atlas.org), a new web-based tool for the ELN (leukemia-gene-atlas.org). The IRON study of WP13 was analysing the interlab robustness of next generation sequencing (NGS) data. The future plan is to use NGS in the standardisation process of diagnosis, prognosis and follow up, finding markers in those patients who survive. A gene list of hematological malignancies will be of common interest and needs a concerted effort of all leukemia groups.

WP12 has linked up with the international standardization efforts for RQ-PCR analysis and reporting of BCR-ABL results in chronic myeloid leukemia (CML) (WP4). The BCR-ABL related work within WP12 has focused on the development of accredited reference reagents as a means to facilitate the implementation of the International Scale (IS) for MRD determination in CML. The documentation describing these experiments was submitted by NIBSC to the World Health Organisation (WHO) in July 2009 and following assessment of the evidence, the materials were approved as primary reference reagents in November 2009. The supply of these reagents will be limited to companies and reference laboratories that are able to generate the secondary reference materials that will actually be used by testing laboratories. This work was presented at EHA 2010 (White et al., Haematologica 2010;95; Suppl2:84-85) and recently published (White et al., Blood 2010;116:e111-7).

The EUTOS project (WP4) has focused very productively on the establishment of conversion factors (CFs) for at least one laboratory per country or region. An evaluation concerning the stability of CFs over time has been presented at ASH 2010 (Müller et al., Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 893). A control round to assess the ability of laboratories to detect resistance-associated mutations was performed and results presented at ASH 2010 (Ernst et al., Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 894).

Reference or consensus documents in cytometric methods have also been achieved within the ELN (see Table below: Recommendations and guidelines).
5. Consensus recommendations and guidelines

The ELN published during the EU funding period 41 European standards, consensual recommendations and guidelines in high impact journals (see Table 1). ELN criteria are widely used. This was and still is one of the central aims of ELN. A special article on “The European LeukemiaNet: achievements and perspectives” was published this year (2011) in Haematologica. It includes a table summarising 35 of these 41 publications, explains the start of ELN, reflects on past and future highlights and the aera of ELN.

Also in the last funding period, consensus proposals (immunophenotyping of acute leukemia and lymphoproliferative disorders), reports (on blood cell identification from 17 countries within the European LeukemiaNet network), management recommendations, (Philadelphia-negative classical myeloproliferative neoplasms) and guidelines (antifungal management) were published by ELN.

The table below includes all 41 ELN standards, consensual recommendations and guidelines, published so far.
Table I.1: The ELN standards, consensual recommendations and guidelines, published until 3/2011.

<table>
<thead>
<tr>
<th>Recommendations and Guidelines</th>
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| **CML management recommendations** | Baccarani et al., Blood 2006; 108: 1809 – 1820  
Hehlmann et al., Lancet 2007; 370: 342 – 350  
Baccarani et al., J Clin Oncol 2009; 27: 6041 – 6051 |
| **CML molecular monitoring** | Müller et al., Leukemia 2009: 1957 – 1963  
Hughes et al., Blood 2006; 108: 28 – 37  
Branford et al., Leukemia 2006: 1925 – 1930 |
| **CML-prognosis – EUTOS-score** | Hasford et al., Blood 2011, in press |
| **AML management recommendations** | Döhner et al., Blood 2009, 10; 115: 453 – 474 |
| **APL management recommendations** | Sanz et al., Blood 2009; 113: 1875 – 1891 |
| **APL molecular monitoring** | Grimwade et al.; J Clin Oncol 2009; 27: 3650 – 3658 |
| **CLL guidelines** |  |
| **CLL molecular and flow-cytometric monitoring** | Ghia et al.; Leukemia 2007; 21: 1 – 3  
Rawstron et al., Leukemia 2007; 21: 956 – 964 |
| **Evidence- and consensus-based European guidelines on MDS** | ELN Homepage: http://www.leukemianet.org/content/leukemias/mds/recommendations |
| **CMPD management recommendations (PV, ET, PMF)** | Barbui et al., J Clin Oncol 2011; 29: 761 – 770. |
| **Response criteria for ET and PV** | Barosi et al., Blood 2009; 113: 4829 – 3314 |
| **Definition of resistance and intolerance to hydroxyurea in PV and myelofibrosis** | Barosi et al., Br J Haematol 2010; 148: 961 – 963 |
| **Flow-cytometry in MDS** | van de Loosdrecht et al.; Haematologica 2009: 94: 1124 – 1134 |
| **A European consensus report on blood cell identification** | Zini et al., Br J Haematol 2010; 151: 359 – 364 |
| **Immunophenotyping** | Haferlach et al., Genes Chromosomes Cancer 2007; 46: 494 – 499  
Béné et al., Leukemia 2011; 25: 567 – 574. |
Score et al. Leukemia 2009; 23: 332 – 339 |
| **MRD – standardized approaches to reporting of minimal residual disease** | Ostergaard et al., Leukemia 2011; Apr. 15, Epub ahead of print |
| **WT1 PCR standardization** | Cilloni et al., J Clin Oncol 2009; 27: 5195 – 5201 |
| **Gene expression profiling recommendations** | Kohlmann et al., Br J Haematol 2008; 142: 802 – 807 |
| **Microarray analyses guidelines** | Staal et al., Leukemia 2006; 20: 1385 – 1392 |
| **Transplantation associated microangiopathy recommendations** | Ruutu et al., Haematologica 2007; 92: 95 – 100 |
| **Stem cell transplantation recommendations in CLL in MDS** | Dreger et al., Leukemia 2007; 21: 12 – 17  
De Witte et al., Haematologica 2006; 91: 750 – 756 |
| **Recommendations for management of infections** |  |
| **Quinolone prophylaxis for bacterial infections in neutropenia** | Bucanove et al., EJC Supplements 2007 (Vol. 5, 5 – 12)  
Styczynski et al., Bone Marrow Transplant 2009; 43: 757 – 770  
Ljungman et al., Bone Marrow Transplant 2005; 35, 737 – 746  
Marchetti et al., EJC Supplements 2007 (Vol. 5, 32 – 42)  
Maertens et al., EJC Supplements 2007 (Vol. 5, 43 – 48)  
Herbrecht et al., EJC Supplements 2007 (Vol. 5, 49 – 59)  
Ljungman et al. Bone Marrow Transplant 2008; 42: 227 – 240 |
| **Primary prophylaxis for bacterial infections in febrile neutropenic patients** |  |
| **Candida and Aspergillus** |  |
| **Vaccination in stem cell transplant recipients** |  |
| **CML management recommendations** | Baccarani et al., Blood 2006; 108: 1809 – 1820  
Hehlmann et al., Lancet 2007; 370: 342 – 350  
Baccarani et al., J Clin Oncol 2009; 27: 6041 – 6051 |
6. Synergies, cooperations and sustainability

Leukemia is a rare disease and European clinical trials are a prerequisite to gain a broad patient collective, to discuss and compare results and offer optimal treatment to the patient. European harmonisation efforts are of major importance for progress in all leukemias. In 2011 at the end of EU funding ELN integrates 182 centres in 34 countries. ELN clinicians and researchers aim for the cure of leukemia.

ELN is a network grown by mutual trust, synergies and competition. It stands for innovation in the field of leukemia and offers internationally recognized researchers. ELN integrates a large portfolio of new disease markers, novel targets, drugs, drug-combination and dose-optimisation studies, vaccination approaches and next generation high-throughput technologies developed in a harmonised setting of European collaborations. Joint infrastructures, the research activities and the enormous diversity of ELN member institutions enable durability well beyond the period of EU-funding.

Important activities include consensus decisions in clinical study endpoints, the set up of patient registries for all leukemias, common standardisation procedures and classification systems in diagnosis and follow up (molecular monitoring, cytogenetics, minimal residual disease assessment) but also harmonisation in data evaluation and reporting. Cooperative research is the only way to cure leukemia. The ELN is likely to have a durable impact on leukemia research in Europe. Infrastructure and the productive collaboration provided by the ELN have accomplished a valuable contribution to progress in the field of leukemia.

ELN will continue beyond NoE funding on the forefront of leukemia science, sharing members with the European working groups of EHA (European hematology association), COST-, ESF Research Networking - and EU 7th framework programmes but also within public-private partnerships and non-profit organisations (ELN Foundation), challenging current knowledge and aiming for a cure of all leukemias.
Section 2: Workpackage progress of the period

1 NMC (WP01)

Objectives and starting point of work at the beginning of the reporting period

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

In 2010 and 2011 the key issue for the NMC was to attract funding to sustain the ELN Network. In addition, the final reporting of the ELN project with information to all members on finances and audits was executed. While a new identity of the ELN is in progress, support from the ELN Foundation and through the European Science Foundation (ESF) could be settled. In addition, EUTOS for CML, the public-private partnership between ELN and Novartis was prolonged until 2012. Furthermore applications to the EU 7th framework programme and the German BMBF International bureau were submitted. Contract renewals, stimulation of partners to write new proposals, activation of additional collaborations and organizational support to all ELN activities at national and international level were major tasks. Success is again observed in the international acceptance of ELN and in the growth of ELN in 2011 to 182 institutions from 34 countries.

1.3f Operating management of networking, i.e. legal and contractual, dissemination and knowledge (including 1.14, 1.20)

In 2010 and 11 the NMC offered again a high degree of managerial services, fundraising activities and the presentation of sustainability concepts:

- Meetings organized by NMC:
  - The 7th and 8th Annual ELN Symposia in 2010 and 2011 with 460 participants from 33 countries and 425 participants from 34 countries, respectively.
  - The WP-meetings at EHA in Barcelona 2010 (more than 200 participants), and the ELN-breakfast meeting and WP meetings at ASH in Orlando in December 2010 (over 150 participants).
  - Educational day for young hematologists in conjunction with EUTOS for CML, Naples, May 2010
  - 19th International CML-Workshop with EUTOS meeting in Heidelberg, July 2010
  - ESH-ELN joined CML meeting in Bordeaux, 2010
  - ELN-CML Educational Symposium (ELN Frontiers) in conjunction with EUTOS for CML including a press conference, Vienna, October 2010
Figure 1.1: Poster on the EUTOS registry presented at the DGHO in 2010.

Figure 1.2: EUTOS brochure: Achievements 2007-2010.

- Presentations:
  - Poster on the ELN Registry at the German Hematology Oncology Congress (DGHO) in Berlin 2010 (Figure 1.1).
  - Summary Information Letter on Achievements: EUTOS 2007-2010 (Figure 1.2).
  - 7th ELN newsletter at the Annual ELN Symposium 2011
  - Presentation of the ELN Foundation and the EUTOS for CML project at ASH 2010.
  - Presentation of the ELN exhibition booth at international hematology meetings in 2010 and 2011 (EHA, ASH, DGHO)
Publications

- Dissemination of reprints of research articles, guidelines and recommendations, ELN flyers, newsletters, treatment recommendations in pocket card format, ELN booth exhibition at conferences,

Figure 1.3: ELN publication on achievements and perspectives in Hematologica in 2011
Foundation Newsletter in 7 languages, the EUTOS-Newsletter, the ELN and ELN Foundation websites, including project sites like ESF-ELN RNP, and more than 500 lectures by ELN-participants.

- **Sustainability**
  - Funding of the ELN Networking Programmes through the European Science Foundation (ESF), 2010-2015. ESF will fund the ESF-ELN RNP with more than 80,000 € per year. This will support the Annual ELN Symposium, ELN workshops and exchange visits, as well as public relations, like the website, publications, and printed information material.
  - Prolongation of EUTOS for CML public-private-partnership between ELN and Novartis until 2012.
  - The launch of the ELN Foundation website: [www.elnfoundation.org](http://www.elnfoundation.org) to fundraise donations with the aim to cure leukemia.
  - Acceptance of fourteen new participants to ELN integrating one additional country, namely Estonia, in 2010
  - In 2011 acceptance of eight new participants integrating one additional country, namely Bulgaria
  - Growth of ELN in 2011 to 182 participants and 34 countries
  - Plans for an infrastructure platform for international studies (for example for MDS and CML), proposals in the 7th framework programme submitted

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1.4f Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network, for example setting up the ELN Foundation

The NMC gave also for the last period advice for the preparation of the financial reports i.e. which costs are eligible and how Forms C are prepared. Due to the constantly increasing number of participants, this is time consuming but also rewarding due to the growing impact of ELN. A new financial plan of budget allocation for the 7th funding period was prepared.

During 2009 and 2010 all institutions were informed on their remaining budget and their expenses. Institutions which did not spend their money were asked to pay it back. More than 120,000€ were returned to the NMC. The General Assembly and the Steering Committee decided to use this money for future ELN symposia.

In addition the NMC centrally managed the reimbursement of all travel costs arising from the Annual Symposia 2010 and 2011 and all WP meetings and workshops.

The ELN proposal to the European Science Foundation was accepted in 2010. The ESF-ELN RNP started in July 2010 with a kick-off meeting in Mannheim. ESF will fund the ESF-ELN RNP for 5 years (2010-2015). This will support the Annual ELN Symposium, ELN workshops and exchange visits, as well as public relations, like the website, publications, and printed information material.
First time in 2011 the ESF partially funded the ELN Annual symposium, reflected in the last page of the Programme brochure 2011.

The EUTOS for CML public private partnership was continued in a new contract until 2012. Now, subcontracts between the University of Heidelberg and the ELN on one hand and ELN member countries on the other hand are being signed.

The ELN Foundation launched its website in 2010 and continued to fundraise donations to support ELN research.

New proposals to the European Commission were sent or are in preparation to the 7th framework programme.

A proposal was sent in 2011 to the International Bureau of the BMBF (Federal Ministry of Education and Research) in Germany to support the scientific networking between Russia and Germany.
1.5f Organization of internal and external reporting ensuring that milestones are effectively reached
During 2010 and 2011 progress reports, meeting minutes, presentations and summary notes of meetings and symposia are collected and available at the management center for external reporting.

1.6f Organization of regular meetings held by the Steering Committee
Two SC meetings were organized in 2010: in February 2010 in Mannheim and in June 2010 in Barcelona. In 2011 an SC Meeting took place at the Annual symposium in Mannheim. Discussed and agreed issues were communicated to all participants for information and coordination of the annual meetings, deliverables, reporting and contractual affairs also in 2011 (see Annex Section 3, WP1-5 and 1-6). In future, the ELN SC-Meetings will be held together with the ESF-ELN RNP SC-Meetings. The next ELN SC-Meeting is planned for June 2011 in London during EHA congress.

1.7f Organization of the Annual Network’s Symposium 2010
In 2010, the annual ELN symposium was held in Mannheim on February 1-3. It attracted 460 ELN participants from 33 countries. A workshop on "Regulatory requirements for the clinical development of cell therapeutics and biologicals" directed by Prof. U. Mansmann preceded the symposium and attracted a major audience. A session on “Life quality and late effects: activities and future collaboration in the European LeukemiaNet” emphasised an important part of clinical studies and started up the first day of the symposium. The sustainability topic was introduced through the ELN Foundation. Current collaborations, challenges and new directions in leukemia and related disease entities were highlighted in the WP meetings. The scientific symposium highlighted different methodologies, like whole genome sequencing, molecular biology of MDS, molecular pathogenesis of atypical MPN, the relevance of molecular monitoring for prognosis and treatment of CML and from a very different point of view, health economic issues in leukemia.
In 2010, the General Assembly accepted fourteen new participants to ELN integrating one additional country, namely Estonia. In 2010 the ELN included 176 institutions from 33 countries working together in now 105 leading national leukemia trial groups and 105 interdisciplinary partner groups.

1.7g Organization of the Annual Network’s Symposium 2011
In 2011, the 8th Annual Symposium of the European LeukemiaNet was held again in Mannheim on February 1-2. This was the last ELN Symposium under EU funding as a Network of Excellence within 6th European Union Framework Programme (2004-2011). NMC organized the scientific program and provided the operational and organizational infrastructure of symposium and workshops. This included the scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs. Again it was a major goal and challenge at this annual conference to get the members of
all ELN workpackages face-to-face together. In total, 425 participants from 34 countries attended the Symposium in 2011. The ELN is still increasing in 2011, at the end of EU funding the General Assembly agreed in 2011 on eight new participants integrating one additional country, namely Bulgaria, increasing the number of participants to 182 and the number of countries to 34.

Two sessions preceded the 8th Annual Symposium directly: New developments around the Clinical Trial Directive (CTD)” organized jointly by WP1 and WP2 and the 2nd ESF-ELN Steering Committee Meeting, which was by invitation only.

Dr. Steinhausen from the European Science Foundation (ESF) participated in both meetings, introducing the role of ESF (“Forward Look” on Investigator-Driven Clinical Trials) and of the European Medical Research Councils (“Position Paper” CTD, available summer 2011) in the modification process of the CTD and thereafter representing the ESF in the ESF-ELN RNP SC meeting.

The CTD session gave insight into the latest development on Investigator Initiated Trials (IITs) in Europe. Speakers from different stakeholders’ perspective, ESF (Dr. Steinhausen), ELN (Ihrig) and the Patient advocacy group (Geissler, Leukämie-Online e.V. / LeukaNET / CML Advocates Network) discussed their efforts in the past and gave directions for future changes. Practical approaches, like a
“Voluntary harmonization process for regulatory approval” were introduced by the German Paul-Ehrlich Institute (Krafft) and the “Risk-adapted approach to clinical trial regulation and monitoring” was presented by the European Clinical Infrastructure Network (ECRIN, Jaques Demotes). It was stressed several times, that the revision of the ‘clinical trials directive’ 2001/20/ec concept paper” submitted for public consultation, will be published by the European commission and that a concerted effort from all groups present is needed to respond.

Challenges and new directions in leukemia and related disease entities were highlighted during the workpackage meeting in three consecutive sessions. Each WP reported on the different projects and discussed future objectives of the group for the coming year.

On day two each WP presented the highlights, results and the prospective outlines for the future of their session from the day before in a plenary session. A scientific symposium with invited speakers from Europe and US presenting outstanding issues within leukemia research finalised the ELN Symposium. The NMC organized the scientific program and provided the operational and organizational structure of symposium and workshops. This includes scientific program, meeting facilities, catering, accommodations and reimbursement of travel costs.

The programme invitations for 2010 and 2011 were available for download via the ELN homepage (see Figure 1.6).

![Invitations and Programs](Figure 1.6: The invitations and programs of the joint annual symposium of the European LeukemiaNet and the German Competence Network “Acute and chronic Leukemias”, February 2010 and 2011)
The event in 2010 was further announced at the TMF (Telematik Platform für medizinische Forschungsnetze) homepage.

The programme 2011 was further announced at the ESF homepage, at “my medical education” and at the University of Heidelberg homepage (See Figure 1.10).

*Figure 1.7: ESF-ELN homepage, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network “Acute and chronic Leukemias”.*

*Figure 1.8: ELN homepage, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network “Acute and chronic Leukemias”.*
Figure 1.9: Mymedicaleducation homepage, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network “Acute and chronic Leukemias”.

Figure 1.10: Homepage of the University of Heidelberg, announcing the 8th Annual Symposium of the European LeukemiaNet in conjunction with the 12th Annual Symposium of the German Competence Network “Acute and chronic Leukemias”.

1.9e Continuation of delivering all integrated trials to the integrated web site, progress report in conjunction with ELIC

The trial list and charts were updated in 2010 through ELIC and the NMC and the help of all leukemia clinical trial WPs. Continuous updating of the trials is promoted by the NMC.
1.10f Annual reports to the EC

i) The activity report, the comprehensive summary and information on the scientific activities of the project. Reports of all 16 workpackages were collected, edited and combined.

ii) The management report (including Form C, Summary Form C and the “Report on the Distribution of the Community’s contribution”) providing the administrative and financial information. Collecting forms C of 175 funded participants and financial audits of 72 participants funded with 63,333 € was again a tremendous and time-consuming effort. Again, extensive advice had to be provided. Requests especially on Forms C by the EC were answered ASAP; iii) the new implementation plan in 2010 with the new list of deliverables was prepared in agreement with the workpackage leaders with approval of the General Assembly; iv) the financial planning for the seventh period was prepared on the basis of the new implementation plan) updated CPF (contract preparation form) file, updated Annex I and updated list of researchers were prepared.

1.10g Annual reports to the EC

Organizational work for the report 2010 started in November 2010 with completion of templates for activity and management reports. Due to the cost-neutral prolongation of the financing period to March 2011 further EC deliverables and financial issues are closed by March 2011. For the period after funding through the EC planning of deliverables and financial issues is in progress.

1.11g Continuation of public relations activities to enhance public visibility of the European LeukemiaNet

The ELN-booth was presented at several meetings during 2010 and 2011, DHGO, EHA, ASH, and ELN Frontiers. Flyers, pocket cards, ELN publications, ELN newsletters, ELN Foundation and EUTOS for CML material were distributed at the same occasions.

Publications on the ELN:

- Poster on the ELN Registry at the German Hematology Oncology Congress (DGHO) in Berlin 2010.
- Summary Information Letter on Achievements: EUTOS 2007-2010 at the Annual ELN Symposium 2011 (Fig. X).
- 7th ELN Information Letter
Figure 1.11: The invitation to the EUTOS educational meeting on CML in Vienna 2010.

1.12f Issue of the biannual network’s Information Letter in conjunction with ELIC
The seventh ELN Information Letter was prepared in 2010 to be available at the ELN Symposium in 2011 (see Annex Section 3, WP1+2).

1.14f, 1.21g Continuation of organization of workshops, seminars, conferences etc.
The ELN was presented at multiple national and international congresses. Time slots for WP meetings were arranged at the Annual ELN Symposium in February, the EHA congress in June 2010 and at the ELN breakfast meeting at the ASH conference in Orlando, December 2010.

1.17g Continuous support of quality control measures, e.g. consensus protocols, quality control rounds, and reference laboratories (see also 1.21.e)
Quality control measures are a major topic at all ELN meetings. They are also a key topic of the EUTOS for CML project regarding all 4 subprojects, registry, molecular and pharmacological monitoring and spread of excellence. The number of reference laboratories across Europe is increasing steadily.
The ELN is supporting the spread of information to physicians across Europe. A table of over 38 recommendations and guidelines on leukemia management is available in this report. A summary table is also shown on the exhibition booth. Recommendations can be ordered by clinicians as pocket card via the ELN homepage. Slide kits for physicians on all four EUTOS subprojects are available on the EUTOS homepage.
1.20g Integrating new partners, industry and key stakeholders including patient organizations, support activities that constitute synergism, e.g. cooperations, partnership, funds

In 2010, fourteen new institutions were included into the consortium after approval by the Assembly on 2. February 2010 (see Annex Section 3, WP1). All documents were adapted accordingly.

1. Russian Research Institute of Hematology and Transfusiology, Russian Federation, represented by Prof. Kudrat Abdulkadyrov, WP4
2. Haematology and Oncology Clinic, Tartu University Hospital, Estonia, represented by Prof. Hele Everaus, WP4
3. SA Pohja-Eesti Regionaalhaigla (foundation North Estonia Medical Centre), Tallinn, Estonia, represented by Dr. Edward Laane, WP4
4. State Institution "Institute of Blood Pathology and Transfusion Medicine of UAMS", Lviv, Ukraine, represented by Prof. Zvenyslava Maslyak, WP4
5. Hellenic Society of Haematology, Athens, Greece, represented by Prof. Panayiotis Panayiotidis, WP4
6. Universitätsklinikum Jena, Germany, represented by Prof. Andreas Hochhaus, WP4
7. Centre Hospitaller Universitaire de Nantes, France, represented by Dr. Sylvie Hermouet, WP9
8. Stockholm South Hospital, Sweden, represented by Dr. Jan Samuelsson, WP9
9. TYKSLAB at Tyks-Sapa utility unit of Hospital District of Southwestern Finland, Turku, Finland, represented by Dr. Veli Kairisto, WP12
10. Universitätsklinikum Aachen, Germany, represented by Prof. Tim Brümmendorf, WP4
11. Université de Liège, Belgium, represented by Prof. Vincent Bours, WP11
12. Rostov State Medical University, Russian Federation, represented by Prof. Sergey Kutsev, WP4
13. Hospices Civils Ce Lyon, France, represented by Dr. Franck Nicolini, WP4
14. University of Copenhagen, Roskilde, Denmark, represented by Prof. Hans Hasselbalch, WP9

Contacts to potential new participants were arranged.

In 2011 acceptance of eight new participants integrating one additional country, namely Bulgaria

15. G. Papanicolaou Hospital of Thessaloniki, Thessaloniki, Greece, represented by Dr. C. Kelaidi, WP11
16. Cliniques Universitaires Saint-Luc Brussels, Belgium Dr. L. Knoops, WP9
17. Fundación Investigación Biomédica Hospital Universitario 12 de Octubre, Madrid, Spain, represented by Dr. J. Martinez-Lopez, WP4, 9, 12
18. Azienda Ospedaliero-Universitaria "Policlinico - Vittorio Emanuele", Catania, Italy, represented by Prof. F. Di Raimondo, WP4
19. National Specialized Hospital for Active Treatment of Haematological Diseases EAD, Sofia, Bulgaria, represented by Prof. G. Mihaylov, WP4, 5
20. Clinical Centre of Vojvodina, Novi Sad, Serbia, represented by Prof. S. Popovic, WP4
21. Siena University, Siena, Italy, represented by Prof. M. Bocchia, WP4
22. National Cancer Institute, Kyiv, Ukraine, represented by Dr. K. Filonenko, WP7

The ELN increased in its last year of EU funding to 182 participants and 34 countries.

1.22g Organization of panel meetings and preparation of ELN management recommendations:

In the last period of EU funding further consensus proposals (immunophenotyping of acute leukemia and lymphoproliferative disorders), reports (on blood cell identification from 17 countries within the European LeukemiaNet network) and management recommendations, (Philadelphia-negative classical myeloproliferative neoplasms, antifungal management) were published.

Panel meetings were organized by NMC especially for the MPN panel.

Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

No deviations.
<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
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<td>Organization of internal and external reporting ensuring that milestones are effectively reached</td>
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<tr>
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<td>Reiter, Müller M</td>
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<td>1.20g</td>
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<td>1.22c</td>
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<td>86</td>
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<td>2</td>
<td>Hehlmann Saußele</td>
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*) if available
### Table 1.2 List of milestones WP1, 2010

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<tr>
<td>1.4f</td>
<td>Operating financial infrastructure and support of initiatives to build up sustainability and durability of the network, for example setting up the ELN Foundation</td>
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<td>86</td>
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<td>1.7f</td>
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<td>75</td>
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<td>1.10g</td>
<td>Annual reports to EC 2011</td>
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<td>88</td>
<td>Saußele Hehlmann</td>
</tr>
<tr>
<td>1.12f</td>
<td>Issue of the biannual network’s Information Letter in conjunction with ELIC</td>
<td>84</td>
<td>85</td>
<td>Saußele Schrotz-King</td>
</tr>
<tr>
<td>1.22c</td>
<td>Organization of panel meetings and preparation of ELN management recommendations: • CMPD</td>
<td>73-86</td>
<td>86</td>
<td>Hehlmann Saußele</td>
</tr>
</tbody>
</table>

### Section 3: Consortium management

14 new institutions including 1 new country (Estonia) were presented at the General Assembly on 2 February 2010 in Mannheim and 8 new institutions at the Assemböly in 2011 for accession to the contract:

1. Russian Research Institute of Hematology and Transfusiology, St. Petersburg, Russian Federation, Prof. K. Abdulkadyrov (WP4)
2. Haematology and Oncology Clinic, Tartu University Hospital, Tartu, Estonia, Prof. H. Everaus (WP4)
3. SA Pohja-Eesti Regionaalhaigla (foundation North Estonia Medical Centre), Tallinn, Estonia, Dr. E. Laane (WP4)
4. State Institution “Institute of Blood Pathology and Transfusion Medicine of UAMS”, Lviv, Ukraine, Prof. Z. Maslyak (WP4)
5. Hellenic Society of Haematology, Athens, Greece, Prof. P. Panayiotidis (WP4)
6. Universitätsklinikum Jena, Germany, Prof. A. Hochhaus (WP4)
7. Centre Hospitalier Universitaire de Nantes, Nantes, France, Dr. S. Hermouet (WP9)
8. Stockholm South Hospital, Stockholm, Sweden, Pr. Dr. J. Samuelsson
9. TYKSLAB at Tyks-Sapa utility unit of Hospital District of Southwestern Finland, Turku, Finland, Dr. V. Kairisto
10. Universitätsklinikum Aachen, Aachen, Germany, Prof. Dr. T. Brümmendorf
11. Université de Liège, Liège, France, Prof. V. Bours
12. Rostov State Medical University, Rostov-on-Don, Russia Federation, Prof. S. Kutsev
13. Hospices Civils Ce Lyon, Lyon, France, Dr. F. Nicolini
14. University of Copenhagen, Danmark, Prof. H. Hasselbalch
Section 4: Other Issues

Ethical issues - none

Competitive calls - none

Section 5: WP-Performance

<table>
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<th>Performance indicators</th>
<th>Status</th>
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<tbody>
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<td>Number of participating trial groups, centers, researchers</td>
<td>182 institutions</td>
</tr>
<tr>
<td>Annual symposia</td>
<td>done</td>
</tr>
<tr>
<td>6-monthly workshops of trial groups and interdisciplinary partners</td>
<td>done</td>
</tr>
<tr>
<td>Collection and distribution of information on ongoing projects</td>
<td>done</td>
</tr>
</tbody>
</table>
2 ELIC (WP02)

Objectives and starting point of work at beginning of reporting period

- Preparation of a sponsoring concept for the ELN
- Maintenance of current website with a content-management-system (CMS)
- Maintenance and improvement of the European Leukemia Trial Registry (ELTR)
- Classification of the clinical trials in the ELTR has been restructured
- Launch of the website www.elnfoundation.org
- Browser-based opportunity of editing special parts of the website by web-editors
- Web-contents for all different user groups and all parts of the website
- Preparation of the 7th Information Letter and e-mail Newsletters, to present the network towards the network members, as well as to spread information to public, press and media

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

2.24e Maintenance and extension of website-contents

Existing content was continuously revised. ELIC verified and updated relevant content of the website. All recommendations within the ELN network have been presented at the website with a direct link to pubmed.gov. Contact information of all WP members as well as promotion slides with information of the ELN structure and member status of the ELN have been updated regularly. A subpage of ESF has been integrated to the ELN website with further information about the collaboration. A project to update and add useful information about patient advocates has been started to enhance the benefit of the ELN webpage for patients and to attract more visitors.

An enquiry to provide slidesets of specific actual topics in present research for further education and advanced training purposes to be presented on the website for the ELN members remained as an unsuccessful call and could not be realised so far.

Pageviews, visits and average time on site of the website users have been continuously analysed and evaluated statistically. User rates and usage characteristics of the website have been analysed continuously throughout 2010. There was a 20% increase of visits compared to 2009. Around 48,000 visits from 148 countries were registered in 2010.

A major work task was to launch the website www.elnfoundation.org within the corporate design of the ELN website. This site has been completely structured and optimised to attract potential donators for the ELN to generate further budget to continue with the ELN. Furthermore it has been laid out with the possibility to present videos directly from that website to cover upcoming demands of the internet user community (cf. web2.0).
2.35c Maintenance of ELTR (entry of new studies provided by the WPs)
The completion of the European Leukemia Trial Registry (ELTR) was intensified and this was a major work topic. All study leaders were contacted and requested to insert their leukemia trials into the ELTR. ELIC kept on screening the NCI register www.clinicaltrials.gov for listed leukemia trials to transfer them to the ELTR. All leukemia-diseases and all countries, represented in the ELN, were included into that survey. Responsible study leaders were contacted to update the studies, before integrating them into the ELTR. To facilitate this process of updating the trials a reminder function has been implemented and can be used to automatise the sending of reminder emails to the study leaders. This process will automatically sort out studies which have not been revised for a certain time and request the study leaders to check the trials if updating is necessary.
The classification of the ongoing studies has been adapted to practical requirements and restructured with the assistance of the WP leaders. This process is still ongoing.
At present up to 100 European Leukemia trials were provided in the ELTR:
- Acute lymphoblastic leukemia (ALL)
- Acute myeloblastic leukemia (AML)
- Chronic lymphoblastic leukemia (CLL)
- Chronic myeloblastic leukemia (CML)
- Chronic myelodysplastic Disease (CMPD)
- Myelodydysplastic Syndrome (MDS)
- Stem Cell Transplantation (SCT)

2.47b Continuous website-linking with European institutions
Manual cross-linking with all major hematology associations and patient groups was continued. The idea of taking the ELN website forward with a project for GOOGLE optimization and backlinking was not realized due to lack of funding.
58% of the users came from search engines. This result indicates that an improved ranking in major search engines due to persistent cross-linking to relevant sites has been achieved.

2.48b Realization of website sponsoring and acquisition of support
A sponsor-concept including fundraising was developed by ELIC. It has been discussed with the network management center at several occasions intensively with regard to integration in the future ELN fundraising strategy. Two main options for sponsorship are being considered: sponsoring the ELN in general or sponsoring parts of the ELN with a specific service in return. The realization of the sponsor-concept will continue after the acceptance of the steering committee.
2.49b Participation in an international expert group for novellation of the European Drug Law and coauthorship for recommendations

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 caused huge and negative effects 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 ELIC is participating in the Road Map Initiative for Clinical Research in Europe, which organizes workshops for stakeholders in the area of clinical trials.

Workshop schedule:
- 18 January 2010: Meeting in Barcelona (Spain): Risk based approach organised by ECRIN
- 19 January 2010: Meeting in Barcelona (Spain): Research Ethic Committees and Ethical Review in Europe organised by ECRIN
- 8 February 2010: Meeting in Brussels (The Netherlands): Towards a better Future for Pharmacovigilance in Clinical Trials organised by EORTC
- 17 March 2010: Meeting in Brussels (The Netherlands): Designing the Future Conditions for Clinical Research in Europe by EFGCP

Details to the workshops are disseminated on the website.

3rd Workshop of the ELN in 2011:
- 1 February 2011: Workshop in Mannheim about European Clinical Trials Directive: Suggestions for modification and practical approaches

This workshop has been organised and chaired by ELIC.

2.52 Contribution to the impact assessment of the EU directive on clinical trials

The ELIC group has prepared in collaboration with other European societies a comprehensive contribution to the impact assessment of the CT directive. The document which places a focus on the specific tremendous problems of academic clinical trials is made available on the website (http://www.leukemia-net.org/content/international_trials/basic_information/).

A step towards building up a strong group was the visit at the Directorate General in Brussels and a fruitful discussion with S. Fuehring. The aim is to elaborate detailed suggestions for changes in the legislation and to estimate the practical approaches to be considered in the upcoming proposal to the EU.

2.53 7th Information Letter

In 2010 the 7th Information Letter has been prepared to be presented at the network meeting in February 2011. The newsletters are available online.
2.54 Quality of life WS
At the network meeting in 2010 in Mannheim an internal workshop for Quality of life and late effects has been organised and chaired by ELIC.

Internal Workshop of the ELN in 2010:

- February 2010: Workshop in Mannheim about Quality of Life and Late Effects in Hematolgocial Malignancies

2.55 Coordination and monitoring of website contents entered by other WPs
Website contents have been entered by other WPs via the CMS System and/or via delivering the data by email to the webmaster.

Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

WP2 is a workpackage with mainly service purposes for other WPs – in contrast to the other scientific workpackages. In 2010 the work had nevertheless to be provided without any funding. The payment of staff had to be made from other projects at the University of Frankfurt, which cannot be continued. Nevertheless we tried to maintain and extend the function of the website as the essential communication and information platform and even started new projects. With regard to the future maintenance of the existing websites www.leukemia-net.org and www.elnfoundation.org and to carry out the sponsoring concept it is necessary to get financial support for previous expenses to pay staff and technical equipment.
Table 2.1 List of deliverables WP2, 2010

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<th>Deliv. No.</th>
<th>Deliverable Name</th>
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*) if available

Table 2.2 List of milestones WP2, 2010

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Section 4: Other Issues

Ethical issues - none

Competitive calls - none
3 CICS (WP03)

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

3.3 LP reports to NMC regarding structure, activities and integration of national groups

Reports were sent as requested.

3.31 Operation of central web-based recruitment and randomisation facility

This deliverable covers operation of the facility from project month 73 (1.1.2010) to month 86 (28.2.2011). See also deliverable D3.7, D3.12, D3.16 and D3.18.

The central web-based facility ‘RANDOULETTE’ for conducting randomisation in clinical trials has been developed, operated and provided for use in clinical trials of the network. Randoulette allows for online randomisation of individual patients at any time using a standard web browser. The software Randoulette has been implemented as a java web application and is hosted on a server at the IBE, LMU Munich. Randoulette provides a randomisation result for patients in stratified, blinded clinical trials with block randomisation with or without stratification or alternatively full randomisation. The block lengths can be defined as randomly variable. The number of appliable treatment arms and study centers is unlimited and treatment arms can be parametrized by weighting. Stratification by centers or other factors is also possible limitless. Lists of blinded labels of drug packages can be created and provided for blinded drug manufacturing. The sections of a list are assignable to one or more trial sites for random assignment. Breaking of single blinded codes is supported and available online. In all processes Randoulette offers full conformity to concerns of Good Clinical Practice (GCP).

In 2010 the range of functions of the software ‘RANDOULETTE’ was extended. Reporting facilities were implemented and are now available for authorized trial coordinators. Quality assurance measures are customizable for each trial. The user interfaces were redesigned. Randomisation notifications can be sent by email to all authorized persons.

The randomisation facility is available at no additional costs for trials conducted within the European LeukemiaNet. Interested trial group leaders should contact WP3 participant A. Fischer by randoulette@ibe.med.uni-muenchen.de or the Network Management Center.
3.32 Operation of central electronic data capture facility
This deliverable extends the results of deliverables D3.8, D3.13, D3.17, D.3.19 and D3.27 and covers operation of the facility from project month 73 (1.1.2010) to month 84 (28.02.2011).

The GCP-compliant electronic data capture facility MACRO has been installed. Both services are available to research groups within the consortium, but there will be extra license-costs for additional users. For further information see deliverable D3.8 and D.3.14.

In addition WP3 has developed a web-based online electronic case report form (eCRF) for the European Treatment Outcome Study (EUTOS) for CML Registry organised by WP17. Case reports include baseline information and yearly follow-ups. The registry currently covers 52 regions in 23 different countries. More are expected to join in 2010. The system is based on proven open source software components such as the Linux platform, the Apache webserver, and the PostgreSQL database as well as several tools stemming from in-house development that have been successfully used in a number of web-based projects and continuously enhanced. Due to pre-existing structures, the allocation of responsibilities differs in various member countries and regions. This is accommodated by a simple and yet versatile role-based authorisation scheme.

3.33 Operation of the PID-Generator
This deliverable extends the results of deliverables D3.21, D3.25 and D3.28 and covers operation of the facility from project month 73 (1.1.2010) to month 84 (28.02.2011).

The second version of the PID-Generator developed by the TMF has been installed on a server at the IBE Munich. The various configuration possibilities the software offers have been deployed and tested by WP3 participants. The software which implements an algorithm providing unique pseudonyms for subjects of research collectives such as trials and disease registers is available for all ELN member projects. WP3 offers interested research projects guidance in concerns of data protection and pseudonymization.

In 2010 WP3 installed the infrastructure to handle pseudonymization issues in a large register trial researching outcome of acute myeloid leukemia (AMLSG-BiO Study). An implementation scenario integrating the PID service in the existing data collection platform has been developed. In this context the PID-Generator service has been custom-configured and was tested against available real-life datasets. The planning of the AMLSG-BiO study is finished and the inclusion of patients started in 2010.
3.34 Enhancement and Operation of the analysis pipeline for DNA-Microarrays

This deliverable extends the results of deliverables D3.23 and D3.29 and covers operation of the facility from project month 73 (1.1.2010) to month 84 (28.02.2011).

The Microarray – Analysis – Pipeline has been designed to automate standard working steps in microarray data analysis such as preprocessing, assessment of differentially expressed genes or annotation. In 2009 it was used on 151 CLL samples to create preprocessed and normalized data which were then used to develop a prognostic score for patient survival time and time to treatment.

The pipeline was developed in cooperation with the “Computational Diagnostics Group” at the University Regensburg (http://www-compdiag.uni-regensburg.de). Two projects were started and finished. Work on a CLL prognostic gene signature by Herold, Jurinovic et al. is completed and a manuscript is submitted. Herold & Jurinovic also studied transcription activities of genes located in the minimally deleted regions of 13q14 and 11q22-23 in chronic lymphocytic leukemia and explored evidence for a common pathogenetic pathway. This paper is in print.

3.35 Development of a concept for extending the German AML register to a European level

A pilot for the German AML register was presented during the annual meeting of the ELN in Mannheim (February 2011). A national and European framework to use this registry was discussed. This registry acts as a meta-registry which does not contain the patient information but information on the availability of patient data. The meta register also offers the infrastructure to use this meta-information to produce specific data sets related to research questions of the consortium.
Table 3.2 List of deliverables WP3, 2010

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months*)</th>
<th>Used indicative person months*)</th>
<th>Lead contractor</th>
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<tbody>
<tr>
<td>WP3</td>
<td>CICS</td>
<td></td>
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</tr>
<tr>
<td>3.3</td>
<td>LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style)</td>
<td>79.85</td>
<td>86</td>
<td>1</td>
<td>2</td>
<td>Mansmann</td>
</tr>
<tr>
<td>3.31</td>
<td>Operation of central web-based recruitment and randomization facility</td>
<td>73-86</td>
<td>86</td>
<td>2</td>
<td>2</td>
<td>Mansmann</td>
</tr>
<tr>
<td>3.32</td>
<td>Operation of central electronic data capture facility</td>
<td>73-86</td>
<td>86</td>
<td>3</td>
<td>2</td>
<td>Mansmann</td>
</tr>
<tr>
<td>3.33</td>
<td>Operation of the PID-Generator</td>
<td>73-86</td>
<td>86</td>
<td>2</td>
<td>2</td>
<td>Mansmann</td>
</tr>
<tr>
<td>3.34</td>
<td>Enhancement and Operation of the analysis pipeline for DNA-Microarrays</td>
<td>73-86</td>
<td>86</td>
<td>7</td>
<td>2</td>
<td>Mansmann</td>
</tr>
<tr>
<td>3.35</td>
<td>Development of a concept for extending the German AML register to a European level</td>
<td>73-86</td>
<td>86</td>
<td>9</td>
<td>2</td>
<td>Mansmann</td>
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</table>

*) if available

Table 3.3 List of milestones WP3, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
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<td>WP3</td>
<td>CICS</td>
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</tr>
<tr>
<td>3.34</td>
<td>Enhancement and Operation of the analysis pipeline for DNA-Microarrays</td>
<td>73-86</td>
<td>presented in February 2011</td>
<td>Mansmann</td>
</tr>
<tr>
<td>3.35</td>
<td>Development of a concept for extending the German AML register to a European level</td>
<td>73-86</td>
<td>presented in February 2011</td>
<td>Mansmann</td>
</tr>
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Section 5: Workpackage performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Number of patients randomized in clinical studies 2011</td>
<td>1132</td>
</tr>
<tr>
<td>Number and quality of papers published or presented based on then achieved research results of the network</td>
<td>See WP1 and Section3</td>
</tr>
<tr>
<td>Number of visits at the homepage</td>
<td>Prospectively done by WP2</td>
</tr>
</tbody>
</table>
4 CML (WP04)

Cooperation between European study groups on CML has a long standing tradition since establishment of the group of “European investigators on CML” (EICML) in 1992. Thus, EICML represents one of the founding collaborative groups for the European LeukemiaNet. Another important background structure is the “German Competence Network Leukemias”, which was founded in 1999. WP4 has now (2010) 62 participants representing 34 countries. Major goals of the WP with regard to the optimization of treatment strategies in CML are:

- Establishment of comprehensive registries for patients across Europe
- Elaboration and updating of common definitions and guidelines for diagnostic and therapeutic procedures
- Creation of a European trial platform
- Standardization and harmonization of molecular methodologies for diagnosis and follow up
- Laboratory and experimental studies of different aspects of CML
- Spread of excellence

This seventh period was characterized by an active communication process with three WP meetings and several meetings of specific groups working on particular deliverables (e.g. registries, sub-registries, standardization and harmonization of molecular monitoring, different clinical trials, implementation of guidelines, spread of excellence activities).

WP4 is closely networking with WPs 1-3, 10-14, 17, CML Study Groups outside EU and pharmaceutical industry. The collaboration atmosphere is indeed creative. The five WP lead participants have a tight communication by mail and phone and at meetings.

Highlights of the cooperative work include:

- EUTOS (European Treatment and Outcome Study) for CML
- Standardization rounds with 58 ELN laboratories (including 28 national reference labs) for molecular monitoring of residual CML in cooperation with WP12
- Consensus manuscript on molecular monitoring and a follow up paper published
- Trials with new signal transduction inhibitors, new immunotherapy (vaccination, interferon) and with attempts to stop imatinib therapy are running successfully across Europe
- Six ongoing collaborative trials on an European level (EICML)
- The European registry and the subregistries have grown rapidly and now enrolled more than 5000 patients.
- A European population based registry was launched in 2009 - 10
- Several multicenter upfront clinical trials have been reported in high input journals
Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

4.5 Regular WP meetings

Three WP meetings were organized in February (Mannheim), June (EHA, Barcelona) and December (ASH, Orlando) (see Annex section II).

4.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

Reports (as minutes from WP meetings) on the status of the deliverables have been sent to NMC.

Deliverables

Registries

4.14e Report of study patients to registries (n > 400 per year)

1. In-Study registry (i.e. on patients enrolled in clinical trials):

Registry for prognosis of imatinib treated patients: All new cases of CML from the Italian GIM-EMA, the German CML IV, the Nordic (Denmark, Finland, Norway, Sweden) the Spanish (from Barcelona), the French, the Netherlands and the UK study groups have been made available. Total number of registered cases over a 5-year period (2002-2006) amounts to 2389 patients. Reports were given at ISH and ASH 2010. For more details see also Annual Activity Report of WP17.

2. Out-Study registry (i.e. on patients not enrolled in clinical trials):

Patients (n=1582) registered in Spain (Madrid), Czech Republic (Infinity), Czech Republic (Camelia), Russia (Moscow and St. Petersburg), Romania, UK (Hammersmith) and Poland are included. In- and out-study registry contains altogether 3971 patients.

3. Population-based registry:

National/international based registries are running in Czech Republic, Finland, the Netherlands, Poland, Sweden and Spain and a new common European population based registry was launched in 2009. This registry is now active in 24 European countries. More than 800 patients from 25 Study groups are included.

4. The subregistry of patients with additional cytogenetic abnormalities in Ph-positive and Ph-negative hematopoiesis after imatinib therapy has enrolled 40 patients.

Direct results out of registries: See also Annual Activity Report from WP17.

5. Imatinib-discontinuation registry:

This registry was reorganized within the Imatinib failure patients (IFP)-Registry. Additional projects are defined under 4.46 and 4.49. The IFP-registry is organized under the European CML Registry (WP4). It is supported by a grant from the 6th European Framework program and by Novartis Pharma. French authorities approved it in accordance with the European Community and the Helsinki protocol. Currently, 1029 cases have been registered from 15 European countries. The registry is now closed for
registration. Data completion is ongoing. Results were presented at EHA 2010. A final draft of a manuscript is planned for Q2 2011.

Studies

4.19f Study imatinib + IFN or AraC, progress reports

Prospective studies investigating standard dose imatinib and the combination of imatinib and IFN or imatinib and ara-C are running in Germany (recombinant IFN, ara-C) and France (Peg-IFN, ara-C), the Nordic countries (Denmark, Finland, Norway and Sweden; Peg-IFN), and UK (Peg-IFN). In total, more than 2500 patients have been enrolled. Analyses from German, French and Nordic groups have been presented at several international meetings (see Annex/Section 3 WP4) and demonstrate the feasibility of the combinations.

The phase III prospective randomized trial investigating the impact of higher dose imatinib and of the combination of imatinib and Peg-IFN or imatinib and ara-C is still running in France (SPIRIT study). As of December 31 2010, 789 patients were included and accrual was stopped. The data were presented for the first time at ASH 2008. The final results of the first part of the trial has been recently published (Preudhomme C, et al N Engl J Med, 2010, 363: 2511-21). The Major Molecular Response (MMR) rate at 24 months is significantly improved with combination of imatinib plus Peg-IFN. The patients will be followed until December 2013. Patients are still treated according to their treatment assignment. The dose of Peg-IFN has been reduced to 45µg for the first 2 months and then patients are asked to increase the dose up to 90µg/week if tolerability is good.

In the Nordic study (n=112), also reported at ASH 2009 and EHA 2010, imatinib was compared with imatinib + Peg-IFN. The 12 month rate of MMR was also here significantly improved in the combination arm. A manuscript has been submitted for publication.

The German group found no effect on 24 months molecular or cytogenetic reponses by adding regular IFN to imatinib (n=562) (GEIST-study, reported at ASH 2009). To analyse a non-significant survival advantage for the combination with IFN after a median survival of 5 years, a survival update is currently performed. Concerning the combination with ara-C, an evaluation of the combined German and French patient groups is planned.

4.21d Study high dose Imatinib in high risk chronic phase CML, update and follow up

120 high risk patients who were assigned to receive 400 or 800 mg Imatinib front-line have been regularly followed and updated, for a final report, that will be completed and published in 2011.
4.22d Study high dose imatinib vs imatinib in standard dose (CML-Study IV), progress report, publication

The German CML Study Group compared imatinib 800 mg with standard dose imatinib +/- IFN. 1014 newly diagnosed CP-CML patients were randomly assigned to imatinib 800 mg (n=338), imatinib 400 mg (n=325) or imatinib 400 + IFN (n=351). Dose adaptation to avoid higher-grade toxicity was recommended. First primary endpoint was MMR at 12 months. A higher rate of MMR at 12 months occurred with tolerability-adapted imatinib 800 mg than with imatinib 400 mg (59% [95%CI: 53-65%] vs 44% [95%CI: 37-50%]; p= 0.0003) or imatinib 400 mg + IFN (59% vs 46% [95%CI: 40-52%], p= 0.002). Median average dose in the 800mg arm was 628 mg with a maximum of 737 mg during months 4 – 6 and a maintenance-dose of 600 mg. All three treatment approaches were well tolerated with similar grade 3 and 4 adverse events (AEs). Independent of treatment approach, MMR at 12 months showed better progression-free (99% vs. 94%;p=0.0023) and overall survival (99% vs 93%; p= 0.0011) at 3 years if compared to >1% International Scale (IS) or no MMR, but showed no difference to 0.1% - < 1% IS which closely correlates with CCgR. It is concluded that treatment of early-phase CML with imatinib can be optimized. Early high-dose followed by rapid adaptation to good tolerability increases rate of MMR at 12 months. Achievement of MMR by month 12 is directly associated with improved survival. (See also Tabler 4.1).

4.30e Preclinical and phase 1 – 2 clinical studies of tyrosine kinase and Src inhibitors

A prospective, multicentre study of nilotinib and imatinib, given in a 3-month rotation, frontline in CP CML has enrolled 120 patients who have now a follow up close to 12 months.

4.36d Phase II study of peptide vaccine to potentiate and stabilize imatinib effect in CP

Sixty patients who were in CCgR on imatinib have been enrolled in a phase II study of a B3A2 peptidic vaccine, and have been treated and observed for 12-24 months. A full report is scheduled for 2011.

4.38d Nilotinib upfront in CP, progress report

A cohort of 73 patients who have been treated frontline with Nilotinib 800 mg has been followed-up for a minimum of 30 months, to assess CMR rate and the frequency of mutations. A full report will be presented in 2011.
Table 4.1: Cumulative Incidences of MMR, CMR\(^4\) and CCgR.

<table>
<thead>
<tr>
<th>Time after start of treatment (months)</th>
<th>Cumulative incidences (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IM400 n=306</td>
<td>∆</td>
</tr>
<tr>
<td></td>
<td>MMR (%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8.6 (5.2-11.3)</td>
<td>9.5</td>
</tr>
<tr>
<td>12</td>
<td>30.8 (26.6-36.1)</td>
<td>24.0</td>
</tr>
<tr>
<td>18</td>
<td>50.3 (44.0-55.5)</td>
<td>18.1</td>
</tr>
<tr>
<td>24</td>
<td>63 (56.7-68.0)</td>
<td>13.0</td>
</tr>
<tr>
<td>36</td>
<td>79.3 (73.9-83.7)</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>CMR(^4) (%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 (1.2-4.9)</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>7.5 (4.8-10.8)</td>
<td>12.3</td>
</tr>
<tr>
<td>18</td>
<td>21.2 (16.6-26.1)</td>
<td>12.2</td>
</tr>
<tr>
<td>24</td>
<td>30.7 (24.9-35.8)</td>
<td>12.3</td>
</tr>
<tr>
<td>36</td>
<td>45.5 (38.7-51.0)</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>CCgR(%)*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>21.3 (16.4-25.8)</td>
<td>10.2</td>
</tr>
<tr>
<td>12</td>
<td>49.4 (42.6-54.4)</td>
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<tr>
<td>18</td>
<td>66.0 (59.4-70.9)</td>
<td>8.9</td>
</tr>
<tr>
<td>24</td>
<td>74.3 (67.6-78.9)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

\(\Delta\): Difference between IM 800 and IM 400, or IM 800 and IM 400+IFN, respectively.

*number of patients with cytogenetic evaluations: IM 400, n= 303; IM 800, n= 311; IM + IFN, n= 326
4.40b Long term effects of imatinib therapy, progress

Imatinib slows development of CML. However, available information on morbidity and mortality is largely based on sponsored trials whereas independent long-term field studies are lacking. The independent, multicenter Imatinib Long Term side Effects study assessed overall survival, loss of CCgR, attainment of CMR, SAEs, and toxicities not qualifying as SAE (NSAE) but judged by treating physicians as substantially affecting quality of life. Consecutive CML patients who started imatinib before 2005 and who were in CCgR after two years (plus or minus 3 months) were eligible. Overall survival, incidence of the first adverse events, and loss of CCgR were estimated according to the Kaplan-Meier method and compared with the standard log-rank test. Cumulative incidence of death was broken down into incidence related or unrelated to CML, accounting for competing risks, according to the Kalbfleisch-Prentice method. Standardized incidence ratios were calculated based on population rates specific for gender and age classes. Confidence intervals were calculated by the exact method based on the chi-square distribution. All statistical tests were two-sided.

Overall, 832 patients were enrolled with a median treatment duration of 5.8 years. Twenty deaths were observed (6 [30%] associated with CML), with a 4.8% mortality incidence rate (standardized incidence ratio = 0.7, 95% confidence interval = 0.40 to 1.01, P = 0.08). There were 139 recorded SAEs, of which 19.4% were related to imatinib. Among the 830 NSAEs (which developed in 53% of patients), the most frequent were muscle cramps, asthenia, edema, skin fragility, diarrhea, tendon or ligament lesions (68% were imatinib-related). Nineteen patients (2.3%) discontinued imatinib because of drug-related toxicities. Forty-five patients lost CCgR, corresponding to a rate of 1.4 per 100 person years. Durable (> 1 year) CMR was attained by 179 patients.

CML-related deaths are uncommon in CML patients who are in CCgR two years after starting imatinib and survival is not statistically significantly different from that of the general population.

The results presented here have been accepted as full article in the Journal of National Cancer Institute.

4.41 Allo-SCT after second generation TKI

Work in progress.

4.44b Imatinib +/- hydroxyurea

After a phase I study in newly diagnosed (n=18) or IFN refractory (n=2) CML patients, 80 newly diagnosed patients were randomized 2:1 for the combination treatment imatinib 400mg + hydroxyurea 500mg (n=53) with a progressive escalation of the hydroxyurea dose to attain mild leukopenia (3-4 Gpt/l) or imatinib 400mg alone (n=27). The primary endpoint of the study is the achievement of MMR after 18 months.

Until now the combination of imatinib 400 mg with hydroxyurea doses up to 3000 mg results in a low toxicity profile compared to other combination treatment strategies. Looking at the most recent interim
analysis favourable responses have been observed in the combination arm. Statistical analysis together with CML IV data have been planned for 2011.

4.46b European study on imatinib withdrawal

After a long discussion during the last year we have now decided to go for a common European study, hopefully starting this year which is entitled EURO-SKI (EURO-StoptyrosineKinaseInhibitors). A large number of countries and study groups have accepted the study design and to join the study.

4.49b Imatinib D/C in patients with CMR (STIM)

In a pilot study of imatinib treated patients achieving CMR for at least two years and thereafter stopped treatment, a molecular relapse rate of 50% was observed. All patients had prior to imatinib been treated with IFN. Then, we performed a prospective new multicentre study “Stop Imatinib” (STIM), including also newly-diagnosed patients, initiated in July 2007 to evaluate the persistence of CMR after discontinuation of the drug, and to determine the factors that could be associated with CMR persistence. The research team enrolled 100 patients with CP or AP CML with a sustained CMR, defined as a 5 log reduction in BCR-ABL and ABL levels as well as undetectable transcripts on RT-PCR, for at least two years. Fifty-one patients were previously treated with IFN. After stopping imatinib, molecular relapse was seen in 54 patients after a median follow-up of 17 months. Forty-six patients remained in CMR at a median follow-up of 14 months, with the overall probability of maintaining a CMR at 12 months of 43%. In the subset of 69 patients with follow-up over one year (median 24 months), molecular relapse occurred in 42, usually within 6 months. Molecular relapse free survival in this group was 41% at one year and 38% at 2 years. Patients treated with IFN prior to imatinib showed no differences in relapse rates compared to those treated with imatinib only. Molecular relapse at or before 18 months occurred in 70% of men and 46% of women. Among patients with high, intermediate and low Sokal risk scores molecular relapses were detected in 88%, 65%, and 49%, respectively. Further, patients with a duration of imatinib therapy of at least 50 months had a 53% likelihood of molecular relapse, whereas 78% of patients with shorter duration of treatment relapsed. When these three factors, gender, Sokal group and duration of treatment, were entered into a Cox regression model they all significantly and independently predicted likelihood of molecular relapse. All patients who relapsed were retreated with imatinib and all patients responded well. No loss of hematologic response was seen or progression to advanced phase. Of the 42 who relapsed, 26 achieved a CMR with imatinib retreatment at the time of the analysis. The identification of patients who would benefit most from discontinuation of imatinib remains a key issue.( Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial (Mahon, Lancet Oncol. 2010; 11:1029-35.)
4.50 IFN plus dasatinib front line and in MMR patients
No update.

4.51 Optimization of the treatment with dasatinib for newly diagnosed chronic phase CML
The French group started in 2009 a new trial entitled: "A prospective randomized phase II study evaluating the optimization of the residual plasmatic level of dasatinib (Sprycel®) in patients newly diagnosed with CP CML”.

Dasatinib is a new, multitargeted, tyrosine kinase inhibitor with a 300 fold more potent activity on the BCR-ABL tyrosine kinase in vitro compared to imatinib mesylate. Dasatinib has been extensively studied in the setting of imatinib failure with a rate of 40% of CCR in case of failure to imatinib. The dose of 100mg QD of dasatinib is now labelled for patients with CP CML. Based on preliminary results of dasatinib in de novo CML, the estimated rates of MMR at 6 and 12 months are 19% and 33% respectively. The estimated rates of CCR at 3, 6 and 12 months are 72%, 94% and 100% respectively. A CCR rate of 81% is expected from the assumption made for the sample size calculation of the BMS 056 dasatinib front line study.

AEs observed with dasatinib include fluid retention, pleural effusions and cytopenia (especially thrombocytopenia). These AEs require dose reduction or dasatinib interruption.

A subanalysis of the BMS 034 study indicated that the main factor associated with these adverse events is the level of the residual dosage of dasatinib (Cmin). Cmin correlates with the risk of adverse events such as fluid retention, pleural effusion and thrombocytopenia. In this study, the cut off value for Cmin was below 5nM. This analysis demonstrated also that the cumulative duration of dasatinib interruption is an independent factor inversely correlated to the quality of the response (Nicaise et al. EHA 2008).

We propose to prospectively assess the Cmin values of patients with de novo chronic phase CML treated with dasatinib as a first line therapy. Patients with a dasatinib plasmatic Cmin over 5nM will be randomized between a prospective adaptation strategy of the dasatinib daily dose based on the monitoring of the Cmin value (arm A1) versus observation only (arm A2). The other patients with a dasatinib plasmatic Cmin value below 5nM will be follow up according the ELN recommendation (arm A3). Dasatinib plasmatic Cmin will then be rechecked at two weeks interval (arms A1 and A2) until reaching the optimal dosage of dasatinib (arm A1) and every month in arm A3. The objective of the study is to reduce the rate of adverse events in arm A1 compared to arm A2. Patients in arm A3 will provide an estimate of the best expected difference between arm A1 and arm A2.

Initial results of this trial were presented during EHA 2010 and ASH 2010 (see Rousselot et al., Annex section 3 WP4).
4.57 Induction/Maintenance strategies in newly diagnosed CML patients using nilotinib and IFN – German CML study V. Start 2010

A prospective study on nilotinib vs. nilotinib + IFN induction therapy and nilotinib vs. Peg-IFN maintenance therapy after confirmed MMR and treatment discontinuation after >12 mo. stable CMR is in preparation in Germany and Switzerland. The protocol has been discussed in the steering board, the budget is in place. The study will start after stop of recruitment of ENEST1st. n=644 patients will be recruited.

Laboratory issues

4.29e Dynamics of response and resistance in CML patients treated with tyrosine kinase inhibitors beyond imatinib (AMN 107, BMS 354825). Progress reports.

Nilotinib and dasatinib are novel BCR-ABL inhibitors and are tested in clinical phase II/III trials. Levels of residual disease, BCR-ABL mutation analysis, and proportion of phosphorylated CRKL are determined in laboratories in Mannheim, Torino and Bologna.

Dasatinib efficacy was analyzed in patients recruited to phase II/III trials with CP CML with or without BCR-ABL mutations after prior imatinib. Among 1043 patients, 39% had a preexisting BCR-ABL mutation, including 48% of 805 patients with imatinib resistance or suboptimal response. Sixty-three different BCR-ABL mutations affecting 49 amino acids were detected at baseline, with G250, M351, M244, and F359 most frequently affected. After 2 years of follow-up, dasatinib treatment of imatinib-resistant patients with or without a mutation resulted in notable response rates (CCgR: 43% vs 47%) and durable progression-free survival (70% vs 80%). High response rates were achieved with different mutations except T315I, including highly imatinib-resistant mutations in the P-loop region. Impaired responses were observed with some mutations with a dasatinib median inhibitory concentration (IC(50)) greater than 3nM; among patients with mutations with lower or unknown IC(50), efficacy was comparable with those with no mutation. Overall, dasatinib has durable efficacy in patients with or without BCR-ABL mutations (see Annex Section 3, WP4).

In a subanalysis of a phase II nilotinib registration trial study in patients with imatinib-resistant or imatinib-intolerant CML-CP, the occurrence and impact of baseline and newly detectable BCR-ABL mutations were assessed. Baseline mutation data were assessed in 281 (88%) of 321 patients. Among imatinib-resistant patients, the frequency of mutations at baseline was 55%. After 12 months of therapy, MCyR was achieved in 60%, CCyR in 40% and MMR in 29% of patients without baseline mutations versus 49% (P = .145), 32% (P = .285), and 22% (P = .366), respectively, of patients with mutations. Responses in patients who harbored mutations with high in vitro sensitivity to nilotinib (50% inhibitory concentration [IC(50)] <or= 150 nM) or mutations with unknown nilotinib sensitivity were equivalent to those responses for patients without mutations (not significant). Patients with mutations that were less sensitive to nilotinib in vitro (IC(50) > 150 nM; Y253H, E255V/K, F359V/C)
had less favorable responses, as 13%, 43%, and 9% of patients with each of these mutations, respectively, achieved PCyR. For most patients with imatinib resistance and with mutations, nilotinib offers a substantial probability of response. However, mutational status at baseline may influence response. Less sensitive mutations that occurred at three residues defined in this study, as well as the T315I mutation, may be associated with less favorable responses to nilotinib (see Annex Section 3, WP4).

Molecular responses to first line nilotinib and dasatinib therapies were reported at ASH 2010 (Rosti, Hochhaus, Hughes, Shah, see Annex Section 3, WP4).

**4.34d European control round for BCR-ABL mRNA quantification (overlap with WP12), Progress report**

The rationale for the development of this subproject was to
(i) improve the early recognition of relapse
(ii) 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: 58 labs are participating in this project with 28 national reference labs (including Mannheim) validated across Europe so far (see Figure 4.3). Preliminary conversion factors (CFs) 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. Recommendations for the propagation of the IS by national or regional laboratory networks were recently published in Leukemia (see Annex Section 3, WP4).

The validation of CFs to the International Scale within the network was reported at ASH 2010 (Müller et al.). The Mannheim lab has received patient samples (each 25-35 samples) from 25 laboratories in 2010, worked them up and calculated or validated CFs by mathematical comparison with the results obtained in the sending laboratories. So far, 32 laboratories have sent two rounds of patient samples and received a certificate until the end of 2010.

Exchange programs were initiated to educate the personnel from laboratories starting with the Q-PCR and mutations analyses in order to allow rapid implementation of the standards in all participating European countries. Importantly, the whole process will be adapted to the international standardization process allowing implementation of the international standard to all European countries, but avoiding the risk of heterogeneous standards in different parts of the world. Workshops were performed in Mannheim for 7 colleagues from 4 participating laboratories (03/10 Jena, 09/10 Kiev, 10/10 Krakow, 11/10 Hamburg) to improve performance and standardization.
Figure 4.1: A summary of the standardization progress of BCR-ABL quantification in Europe between 2006 and 2011.

4.58 Definition and European Standardization of CMR

Standardization of CMR assessment is a crucial topic for future trials since most trials will include CMR as primary or secondary endpoint.

Thirteen labs have been selected to serve as reference laboratories for Q-PCR within the ENEST1st study and to establish and validate definitions of CMR on various sensitivity levels (CMR4, CMR4.5, CMR5). A survey was conducted to establish common pre-analytical and analytical procedures and to estimate the sensitivity level achieved in each lab. Improvement of the performance will be achieved by workshops and ongoing control rounds.

CMR data have been reported from the German CML Study IV and the French SPIRIT study in two publications.

4.35b Mutated bcr-abl clones – level, control rounds

Harmonized Testing for BCR-ABL Kinase Domain Mutations In CML: Results of a Survey and First Control Round within 28 National Reference Laboratories In Europe.

Standardized techniques and protocols for the detection of BCR-ABL mutations will be necessary in the future to obtain comparable mutation results within clinical studies. The first objective of this study conducted within the EUTOS (European Treatment and Outcome Study) for CML program was to record the mutation analysis techniques and protocols that are used for routine diagnostics by 28 national reference laboratories in 23 European countries, 9 of whom perform regular mutation analyses as a central laboratory for national or international clinical trials. A web-based survey was
conducted with a total of 39 technical and PCR-specific questions. The second objective was to evaluate the techniques by analysis of blinded samples containing various BCR-ABL kinase domain mutations. Control samples were prepared and distributed in a blinded fashion to testing laboratories. Seventeen Ba/F3\textsuperscript{BCR-ABL} cell lines harboring various BCR-ABL kinase domain mutations were mixed with non-mutated Ba/F3\textsuperscript{BCR-ABL} to produce dilutions ranging from 1\% to 100\% of mutant alleles. Mutated and non-mutated Ba/F3\textsuperscript{BCR-ABL} cell lines were diluted into HL60 cells to simulate a BCR-ABL level of 10\% on the International Scale. Twenty blinded cDNA samples were sent out on dry ice to each participating laboratory (total of 560 samples). The results have shown that Sanger sequencing is the most frequently applied technique for routine analysis of BCR-ABL kinase domain mutations in CML in Europe. In general it reliably identifies mutations when the proportion of mutant alleles comprise 20\% or more. Nevertheless, false negative and false positive results were reported in a substantial proportion of samples with \( \geq 20\% \) mutation level (35/253, 14\%). For mutations that are present at 10\% or less mutant alleles, routine methods mainly failed to identify mutations. The study provides a basis for further comparisons and standardization efforts comparable with the introduction of the international scale for quantification of BCR-ABL transcripts. The study was presented as an oral presentation at the 52\textsuperscript{nd} ASH annual meeting 2010 in Orlando, Florida (see Annex Section 3 WP4). A manuscript will be submitted in 2011.

4.45 Allo-HSCT in low risk patients. Second report
The evaluation of allo-SCT in low risk Gratwohl score CML patients has been published (Saussele et al, see Annex Section 3 WP4).

Patients with CML and a low EBMT risk score have an excellent survival with a transplant related mortality of 10\% only and a survival which was not different from a similar cohort of patients without a donor but treated within the prospective controlled German-Swiss CML IV study. Similar excellent survival was documented in a cohort of more than a 100 patients of the EBMT.

Other

4.43b Dasatinib and immunomodulation, progress report
Background:
Targeted inhibition of the oncogenic BCR-ABL tyrosine kinase by TKIs has profoundly changed the therapy of CML. Imatinib mesylate was the first drug approved for clinical use and currently is the standard first-line therapy for all CML patients. Imatinib is well tolerated and has few significant side-effects, as it predominantly only targets cells with the mutated kinase. However, the inhibition profile of many 2nd generation TKIs is much broader. This may be therapeutically advantageous, but as long-term effects on normal cells are largely unknown, significant side-effects may emerge. We have recently observed a massive clonal expansion of cytotoxic LGL (large granular lymphocyte)-cells in blood of several CML and acute lymphoblastic leukemia patients during dasatinib (2nd
generation TKI) therapy. The aim of this project has been to characterize the clinical features of the phenomenon and to study background mechanisms.

Current status of the project (January 2011).

We have collected a case series of patients with LGL expansion during dasatinib therapy (n>25) from different centers in Europe and US. Several clinical and basic research investigators (from Finland, Norway, Sweden, Germany, France, Spain and US) have participated in the project. We have found that the expansion of immune effector cells is linked to autoimmune reactivity, such as severe diarrhea and lung toxicity, as accumulation of clonal T-cells was also observed in these organs. Furthermore, several patients with advanced, poor-prognosis leukemia achieved long-lasting complete responses to dasatinib, thus strongly suggesting an antitumor effect of the expanded cytotoxic cells. We postulate that by inhibiting kinases in immune effector cells, dasatinib induces a reversible state of autoimmune reactivity resulting in host organ damage and in enhanced anti-leukemic control, both driven by cytotoxic T/NK LGL cells. These results have now been published in Leukemia journal (see Annex Section 3, WP4).

In our follow-up projects, we discovered that the expanding lymphocyte clones exist already before start of dasatinib therapy and remarkably, they can be detected at low levels already at the diagnostic phase of CML. Therefore our current working hypothesis is that clonal lymphocytes present at CML diagnosis are anergic/exhausted anti-leukemic lymphocytes and part of the immune escape mechanisms inherent to leukemogenesis. Dasatinib therapy may break this immune tolerance and revert anti-leukemic potential of pre-existing cytotoxic lymphocytes. Results were published recently in Blood journal (Kreutzman et al) (see Annex Section 3, WP4).

As in our previous studies we noticed that lymphocytosis is oscillating in most patients, we collected follow-up samples from dasatinib treated patients before and after (0, 1, 2 and 4 hours) drug oral administration to assess the relation of drug intake, plasma level and lymphocyte counts. To our surprise, in all patients and in one healthy control dasatinib induced a rapid and marked mobilization of blood leukocytes with peak values after 1-2 hours of oral drug intake. Most substantial mobilization was observed for lymphocytes and it correlated closely with dasatinib plasma concentration. In other TKI treated patients (imatinib, nilotinib, bosutinib), no similar changes were observed. These results were presented at ASH with the poster presentation (Mustjoki et al) and manuscript is under preparation.

**Further aims and future activities:**
Currently we are studying in vitro the effects of TKIs on immune effector cells and we aim to isolate target kinase(s) (for example kinases related to downstream signalling of adhesion molecules), which, when inhibited by dasatinib, cause mobilization of cytotoxic T/NK cells. We also aim to identify the antigen targets of the activated cytotoxic cells on both normal and malignant cells and to assess the role of these cytotoxic cells in autoimmune/anti-leukemia manifestations in patients treated with TKI
therapy. Further, we try to find the genetic factors, which determine whether the patients develop lymphocytosis during dasatinib therapy and have therefore better therapy response. We hypothesize that KIR/HLA mismatch could be one of the mechanisms and we are currently collecting samples from different centers in order to have big enough patient material.

Collaboration with international investigators continues actively as we try to study patient samples in vitro to be able to draw direct conclusions to patient care.

Importance of the study

The aim of this project is to uncover the cellular and molecular mechanisms of TKI-induced anti-leukemia immune response in order to develop a novel, specific immunotargeting drug.

If successful, this project will introduce a significant addendum to the armament of treating leukemia: use of a molecularly targeted drug to induce a potent, durable anti-leukemia immune response.

(See Annex Section 3 WP4, Kreutzmann et al., Mustjoki et al.)

4.48b Quality of life during imatinib treatment

Monitoring the quality of life should be an essential part of treatment of patients with CML. Validated testing methods enable us to monitor the physical, mental and social state together with spiritual aspects of patients. There exists a wide range of validated questionnaires which assess how patients feel about their quality of life in different stages of treatment and which compare the achieved quality of life when introducing new medicaments and medical methods. The aim of all testings is to know the needs of patients and to improve the quality of their lives during and after the treatment. The achieved results of the quality of life measurements need to be statistically processed and evaluated in short studies and both semi-longitudinal and longitudinal research. Instruments: Generic questionnaires: SF 36 (Short Form 36 Health Subject Questionnaire), EuroQolEQ-5D (European Duality of Life Questionnaire Version EQ-5D). Specific questionnaires: EORTC QLQ-C30, QHOQOL 100, FACT).

Work done: Extensive questionnaire testing of 50 imatinib treated patients at least 1 year on treatment.

Plans for the year 2011: Manuscript will be submitted for publication.

4.55b Immunosuppressive mechanisms in CML

We have screened CML patients at the time of diagnosis for their immunological status. Similarly to that of many other cancer types, the level of Tregs in CML patients was increased compared to healthy controls. We have previously published that sCD25 is used by Tregs to suppress T-cell proliferation (Lindqvist C et al, Immunology 2010). In CML patients, sCD25 was markedly increased in plasma but TKI therapy decreased the release of this modulator significantly. Similarly, CML patients have an increase of the T-cell suppressor IL10 in plasma.

Furthermore, the CML tumor was shown to express the regulator PDL1 on the cell surface and we are currently evaluating the capability of those to directly suppress T-cells since the PDL1 receptor PD1 is
expressed on activated T-cells. Preliminary results on four patients demonstrate that CML cells are able to inhibit the proliferation of autologous T-cells but blocking PDL1 on CML cells by antibodies will increase T-cell proliferation in patients and to some extent in healthy controls.

We have created a peptide mix of bcr-abl that can activate both CD4\(^+\) and CD8\(^+\) T-cells independently of HLA background. Using this peptide mix we can activate and thereby detect T-cells from CML patients that react against bcr-abl (tumor-reactive T-cells). Using this peptide-stimulation we will determine if TKI therapy will affect the number of tumor-reactive T-cells. Similar protocols for detection of CMV positive cells are available at our laboratory.

In patients with B-cell malignancies we have shown that the FoxP3\(^+\) Treg cells express increased levels of CD107a which is a marker for degranulation/effector function. However, this increase was more prominent in the CD127\(^+\) Treg cells then in the CD127\(^-\) Tregs. These cells were then used in a cytotoxic assay against the patients circulating B-cells consisting mostly of tumor cells. The results revealed that the patients Treg cells were capable of killing tumor cells in vitro. Hence, the Tregs in patients with leukemia may not only control anti-tumor T-cells and NK-cells but may as well be controlling the tumor cell since it is derived from the immune system. These results have recently been submitted to Immunology. Tregs may have a similar function in CML patients which we will further investigate in the proposed project.

4.59 Relevant definitions for future trials.
A manuscript is in preparation, including consideration about Imatinib and also 2nd generation of TKIs. To be published 2011.

4.60 Clinical Recommendations for mutation analysis in CML
No updating

4.61 A phase II trial comparing the depletion of malignant stem cells with dasatinib vs imatinib in newly diagnosed CP CML

Background
Imatinib efficiently induces rapid hematologic and cytogenetic remission in most CML patients. However, a small population of resistant primitive leukemia stem cells remains even after years on therapy. Also in vitro experiments have shown that CML stem cells are resistant to TKIs. The clinical implication of stem cell resistance is a rapid leukemia relapse in patients who discontinue imatinib. This residual population also serves as a reservoir for development of drug resistant clones, as it has been shown that most often drug resistance arises as a result of kinase domain mutations in the stem or progenitor cell compartment that affect imatinib binding.

Although the precise phenotype of CML stem cell is not fully characterized, it is likely that the most primitive leukemic stem cells reside in the CD38-negative fraction of CD34-positive hematopoietic
stem cells. The effects of TKI therapy on different fractions of stem cells in vivo are largely unknown. Recent in vitro data on human primary cells have indicated that dasatinib targets an earlier stem cell population than imatinib. Preclinical data need to be confirmed in patients by utilizing state-of-the-art stem cell enumeration and kinetics assays. The aim of this project is to set up a program to routinely enumerate the BM stem cell pool (both malignant and non-malignant) with flow cytometry and fluorescence in situ hybridization (FISH). The correlation between the malignant stem cell burden and the clinical response in CML patients participating in the proposed trial will be monitored. In addition, we hypothesize that initial leukemia burden at the early progenitor and stem cell level may predict therapeutic response. Close monitoring of the kinetics of drug response at the progenitor and stem cell level might serve as an important surrogate marker for long term response and may predict likelihood of early relapse.

Current status of the project (January 2011):

The clinical study (NordCML006) started in Nordic countries (Denmark, Finland, Norway and Sweden) in 2009 and the first patient was recruited in March 2009. The study was closed for inclusion in September 2010 when all 46 planned patients were recruited. Patients were randomized to receive dasatinib at a starting dose of 100 mg QD or imatinib at a starting dose of 400 mg QD. The primary endpoint of the study was the comparison of proportion of Ph+ cells in stem cell compartments (CD34+CD38- and CD34+CD38+) at 6 months between the study arms. This was analyzed by counting Ph+ cells from flow cytometry separated stem cell fractions by FISH method. The secondary aims of the study were: correlate the size of the Ph+ stem cell compartment at diagnosis with (a) therapeutic response at 12 months, (b) kinetics of response at 1, 3, and 12 months (c) hematological toxicity.

First interim results of the diagnostic phase situation were analysed in July 2010 and presented orally at ASH 2010 (Mustjoki et al., ). The results showed that the proportion of Ph+ stem cells at the time of diagnosis varied from 1 to 100% between individual CML patients. It was correlated with hemoglobin concentration, leukocyte count, blast percentage and spleen size at diagnosis and with hematological toxicity during early course of treatment, mirroring paucity of healthy hematopoietic stem cell reservoir. The size of the leukemic stem cell pool at diagnosis may be a powerful prognostic marker and a major biological determinant for the high Sokal risk group.

Further aims and future activities:

The effect of TKI therapy on the malignant stem cell pool size and correlation to therapy responses will be evaluated when all patients have reached the primary study endpoint of 6 months. We plan to present the data from these results at EHA 2011 and/or ASH 2011 meetings.

Importance of the study

The first-line treatment of CML is currently changing with the invention of 2nd generation TKIs. However, probably not all newly diagnosed patients would require more broad spectrum drugs and imatinib could be still drug of choice for them. If the proportion of malignant stem cell pool at the
diagnosis is the major determinant of therapy response, it could serve as a prognostic marker when considering which patients need more robust treatment at the beginning. Furthermore, the proportion of malignant stem cells could be an important biological determinant of the disease and could define a group of patients, who are able to discontinue the treatment after receiving complete molecular response. This needs to be evaluated in future clinical trials. (Reference abstract: see Annex Section 3 WP4, Mustjoki et al.)

4.62 Recommendations regarding CML biobank
Delivery will not occur

4.63 A vaccination trial with WT1 mRNA-electroporated dendritic cells in TKI treated CML patients
No updating

Table 4.2 List of deliverables WP4, 2011

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*) if available

**Note:** The table entries are from a report that seems to discuss various deliverables related to the treatment and research of chronic myeloid leukemia (CML), with focus on specific drugs like imatinib and dasatinib, treatment strategies, and related research activities. The dates and metrics (like Estimated and Used indicative person months) suggest a planned timeline or progress report structure.
### Table 4.3 List of milestones WP4, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
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<tr>
<td>WP4</td>
<td>CML</td>
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<td></td>
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<tr>
<td>4.14e</td>
<td>Report of study patients to registries (n &gt; 400 per year)</td>
<td>73-86</td>
<td></td>
<td>Baccarani, Guilhot, Hasford, Hehlmann, O’Brien, Simonsson, Thaler, Cervantes, Steegmann, Ossenkoppele</td>
</tr>
<tr>
<td>4.58</td>
<td>Definition and European Standardization of CMR</td>
<td>73-86</td>
<td></td>
<td>Cross, Müller, Hochhaus, Saglio</td>
</tr>
<tr>
<td>4.35b</td>
<td>Mutated bcr-abl clones – level, control rounds</td>
<td>73-86</td>
<td></td>
<td>Müller, Gruber, Lange, Ernst</td>
</tr>
<tr>
<td>4.43b</td>
<td>Dasatinib and immunomodulation, progress report</td>
<td>73-86</td>
<td></td>
<td>Porkka</td>
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<tr>
<td>4.59</td>
<td>Relevant definitions for future trials, Manuscript 2010</td>
<td>73-86</td>
<td></td>
<td>J Guilhot</td>
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</tbody>
</table>

### Section 3: Consortium management

WP4 in conjunction with the group of European Investigators on CML (EICML) has been a successful group of scientists, which is well recognized internationally. This group represents a solid basis for setting standards and for the rapid investigation of new drugs.

WP4 is managed by five lead participants with the help of the NMC in Mannheim. Three successful WP meetings (and one EICML meeting) demonstrate the active work in this group.

Communication between participants and with the NMC is running well.

### Section 4: Other Issues

Ethical issues – none, Competitive calls - none

### Section 5: WP-Performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinical trials started and/or completed</td>
<td>6</td>
</tr>
<tr>
<td>Number of patients included into registries</td>
<td>approx. 3500</td>
</tr>
<tr>
<td>Improved predictive, prognostic or quality of life assessments</td>
<td>Guidelines of diagnostic and therapeutic procedures updated for submission, inter-laboratory control rounds continue</td>
</tr>
<tr>
<td>Degree of harmonization of trials</td>
<td>4 collaborative trials on an European level</td>
</tr>
<tr>
<td>Number of SOPs and consensus papers</td>
<td>2</td>
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<tr>
<td>Number of publications</td>
<td>85</td>
</tr>
<tr>
<td>Number of meetings</td>
<td>6</td>
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<tr>
<td>Number of meta-analyses</td>
<td>0</td>
</tr>
<tr>
<td>Number of accredited trials</td>
<td>see website</td>
</tr>
</tbody>
</table>
5 **AML (WP05)**

*Objectives and starting point of work at beginning of the reporting period*

At the beginning of 2010 the situation was characterized by further progress and experience in the field of molecular markers. Besides their role as risk factors, the genetic and metabolic peculiarities of AML cells increasingly appeared as targets for new drugs. Promising therapeutic results were confirmed mainly in promyelocytic leukemia. First updates suggested a successful cooperation of trials in the AML Intergroup in younger patients, while data and experiences in older age AML increased Europe wide. An increasing availability of data on allogeneic SCT suggested the use in high-risk disease even in older patients. Publications see Annex Section 3, WP5.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

During 2010 further progress has been achieved in the European AML network (WP5). At the annual Reisensburg Symposium new data on gene mutations have been presented and T.Haferlach gave a comprehensive overview of the field (see minutes). New drugs and targets were updated at the Hematologic Malignancies conference in Brussels and by a survey. Epigenetic changes in AML related to age became the subject of a DFG funded research project (see application summary) and also a therapeutic target. The AML Intergroup as an ELN pilot study has now recruited more than 3000 patients. The latest update allows reliable projections to 5 years, (7). As another ELN pilot study a scoring system of older age AML was elaborated in a large multicenter trial and validated in an independent trial (8,9). Uniform European recommendations on all clinical aspects of AML were published for both general AML (13) and APL (4). APL relapse, data and treatment, were contributed in an own publication (5,6). Multiple approaches and experiences were reported on the field of allogeneic SCT (11,14). The role of growth factor priming in AML could be elucidated in a large multicenter trial as an ELN pilot project (see Annex section 3, WP5-2).

*Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

No substantial deviations of the workprogram.

**5.5 Regular WP meetings**

WP5 Meeting at ELN Symposium Mannheim, 03.02.2010
AML Intergroup Meeting, Frankfurt, 03.05.2010
WP5 Meeting at EHA Barcelona, 10.06.2010
AML Intergroup Meeting, at ASH Orlando, 05.12.2010
WP5 Meeting at ELN Symposium Mannheim, 02.02.2011
5.6 LP Reports to NMC regarding structure, trial activities and integration of national leukemia trial groups, continued
AML Intergroup Symposium Reisensburg, 12.02.2010 (see minutes)
AML Intergroup Symposium Reisensburg, 11.02.2011 (see minutes)
WP5 meetings (see 5.5).

5.12g Current trials on novel therapies in Europe (new drugs new targets), continued
Report at International Symposium Hematological Malignancies, Brussels 01.10.2009

5.13f Pilot study treatment in subgroups defined by genetic markers, up-front randomized, intention-to-treat, continued
Büchner et al, JCO 2009 (see Annex section 3, WP5).

5.15f Pilot study AML Intergroup and a European AML network, continued
New update from the AML Intergroup: Participation of 5 trial groups, recruitment of 3602 patients age 16 to 60 years, median observation time between 2.0 and 4.8 years, 358 patients (10% from all groups) in the common standard arm, overall survival probability at 5 years standard arm 0.41, all 5 participating trials within the 95% CI. Büchner et al. ASH 2010 (see Annex section 3, WP5).

5.16f Establishing a European network on management of Acute Promyelocytic Leukemia
Sanz et al., Blood 2009 (see Annex section 3, WP5).

5.17f Establishing a European network on management of AML in older patients
As a pilot project a scoring system of elderly AML has been established in the AML Intergroup (Krug et al. 2010 Lancet (see Annex section 3, WP5).

5.18f Develop frailty index for leukemia in older patients, continuation
A novel risk score that predicts the likelihood of a complete remission after intensive induction therapy in older patients has been published in 2009. A publication on the frailty index in older patients is in preparation (see Annex section 3, WP5).
A publication by Lübbert M. et al. concerning the frailty index in older patients with AML has been prepared.

5.21e Harmonizing the criteria of biologic subgroups, risk categories and treatment strategies for patients with AML in Europe, continued
Recommendations for the diagnosis and management of AML in adults have been published in 2009 Döhner H et al. Blood 2010 (see Annex section 3, WP5).
5.25b Epigenetic pattern of AML with respect to patients age and risk profile
The project “Die Bedeutung altersabhängiger genomweiter DNA-Methylierungsmuster bei der Akuten Myeloischen Leukämie/ Kennwort: Biologie der AML im Alter”, submitted by C. Müller-Tidow and T. Büchner, has been accepted for funding by the DFG/German Research Community.

5.26b Growth factor priming in AML: Long-term results
Long-term results in patients with acute myeloid leukemia (AML) and data of the AMLCG 1999 trial were published in Blood 2009 and in ASH Highlights (see Annex section 3, WP5).
There was a contribution of WP5 to the current ELN Information Letter concerning the prospective assessment of outcome determinants in AML (see Annex section 3, WP2).

5.27b European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation
WP5 maintained several fruitful cooperation with European trialists, resulting in 3 publications in 2010 (see Annex section 3, WP5).

5.28 European recommendation on diagnostic, classification and treatment of AML
Döhner et al. Blood 2010 (13) (See Annex section 3, WP5)
<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months*)</th>
<th>Used indicative person months*)</th>
<th>Lead contractor</th>
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<td>Büchner</td>
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<tr>
<td>5.5</td>
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<td>78,84,86</td>
<td>86 and beyond</td>
<td>0</td>
<td>4</td>
<td>Ossenkoppele</td>
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<tr>
<td></td>
<td>LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style), continued</td>
<td>79,86</td>
<td>86</td>
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<td>Current trials on novel therapies in Europe (new drugs new targets), continued</td>
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<td>86 and beyond</td>
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<td>2</td>
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<td>5.12g</td>
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<td>86 and beyond</td>
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<td>2</td>
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<td>5.16f</td>
<td>Establishing a European network on management of AML in older patients, continued</td>
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<td>86 and beyond</td>
<td>0</td>
<td>6</td>
<td>Büchner Ossenkoppele Sanz Berdel Müller-Tidow Krug Serve Holowiecki Lübbert Büchner Berdel Kienast, Heinecke Serve Büchner Döhner Ehninger Ganser Niederwieser Pfirmann Gratwohl</td>
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<tr>
<td>5.17f</td>
<td>Develop frailty index for leukemia in older patients, continued</td>
<td>86</td>
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<td>4</td>
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<td>5.18f</td>
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<td>5.21e</td>
<td>Establishing a European network on management of acute promyelocytic leukemia, continued</td>
<td>86</td>
<td>86 and beyond</td>
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<td>6</td>
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<tr>
<td>5.25b</td>
<td>Epigenetic pattern of AML with respect to patients age and risk profile, continued</td>
<td>86</td>
<td>86 and beyond</td>
<td>0</td>
<td>6</td>
<td>Büchner Ossenkoppele Sanz Berdel Müller-Tidow Krug Serve Holowiecki Lübbert Büchner Berdel Kienast, Heinecke Serve Büchner Döhner Ehninger Ganser Niederwieser Pfirmann Gratwohl</td>
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<tr>
<td>5.26b</td>
<td>Growth factor priming in AML: Long-term results, continued</td>
<td>78</td>
<td>78</td>
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<td>2</td>
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<tr>
<td>5.27b</td>
<td>European cooperation of trialists on the evaluation of allogeneic and autologous stem cell transplantation, continued</td>
<td>86</td>
<td>86 and beyond</td>
<td>0</td>
<td>6</td>
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<td>5.28</td>
<td>European recommendation on diagnostic, classification and treatment of AML</td>
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<td>86 and beyond</td>
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Table 5.2: List of milestones WP5, 2010

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<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
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<td>Pilot study, AML Intergroup and a European AML network, continued</td>
<td>86 and beyond</td>
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<td>5.16f</td>
<td>Establishing a European network on management of acute promyelocytic leukemia, continued</td>
<td>86 and beyond</td>
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<td>Sanz Lengfelder</td>
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<td>5.17f</td>
<td>Scoring of elderly AML</td>
<td>86 and beyond</td>
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<td>5.27b</td>
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<td>86 and beyond</td>
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<td>4</td>
<td>Döhner Büchner Löwenberg</td>
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</table>

Section 4: Other Issues

Ethical issues - none

Competitive calls – none

Section 5: WP-Performance

No major changes since 03/07

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
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<tr>
<td>Number of patients recruited into clinical trials</td>
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<tr>
<td>Number of patients included into registries</td>
<td>approx. 1500</td>
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<tr>
<td>Improved predictive, prognostic or quality of life assessments</td>
<td>New AML European guidelines published (Blood 2009)</td>
</tr>
<tr>
<td>Degree of harmonization of trials</td>
<td>see publication (Blood 2009)</td>
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<tr>
<td>Number of SOPs and consensus papers</td>
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<td>Number of publications</td>
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<td>Number of meetings</td>
<td>10</td>
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<tr>
<td>Number of meta-analyses</td>
<td>2</td>
</tr>
<tr>
<td>Number of accredited trials</td>
<td>20</td>
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</tbody>
</table>
6  **ALL (WP06)**

The successful national European study groups for ALL aim to combine their efforts in order to create a world-wide leading research group for adult ALL. Thus the essential aims of WP6 remained the same since the beginning of the funding. Major aim is to strengthen collaboration between the national European ALL study groups, to initiate new national study groups, to provide a platform for trustfull discussion of data and future plans and to encourage and initiate collaborative projects.

**Integrating activities**

- Maintenance of central management structures
- Development of standardized laboratory procedures for diagnostic confirmation
- Overview on prognostic factors used in the different trials
- Overview on ongoing European studies in ALL with a study registry
- Discussion of results and future plans of the national ALL study groups

**Jointly executed research activities**

- Combination and standardization of methods, definitions and clinical application of MRD
- Phase I-III intergroup studies

**Spread of excellence**

- Internet-based information on adult ALL
- Evidence-based guidelines for diagnosis and treatment of ALL
- Presentation of the network at national and international meetings
- Extension of network

**Integrating activities**

**Management and structure of the working group:**

The collaboration within EWALL was further extended. According to a defined meeting plan three meetings were organised by EWALL alone or in collaboration with other groups. The communication between the participants is based on regular e-mail exchange.

**New members in 2010**

In 2010 the newly founded Slowakian working group for adult ALL joined the EWALL.

**Meetings in 2010**

Two meetings were organised in the context of other international meetings (Heidelberg, Network Symposium; informal come-together at ASH, Orlando). Beyond this the EWALL organised two separate 1 day internal meetings. One of these traditionally takes place in Frankfurt and the other by rotation in different member countries. The collaboration with the ESG-MRD group and joint meetings for standardisation of bcr-abl diagnostics continued.
EWALL meeting February 2010, Mannheim:
The meeting covered two major topics. (1) **Ph-positive ALL.** Contributions were made regarding BCR-ABL diagnostics and mutation analysis. An update on the EWALL elderly trial with Dasatinib was presented and the planned GIMEMA combination trial was discussed. (2) **New drugs in Ph-negative ALL.** Planned or ongoing studies with Clofarabine, MT103, Erythrocyte-encapsulated asparaginase and antifungal prophylaxis were presented.

EWALL meeting June 2010, Milano
Before EWALL and EHA relationships were discussed with the aim to develop the ALL-EHA-Scientific Working group. Two major topics were discussed. (1) **Relapsed and Refractory ALL.** (a) Clofarabine/ Cyclophosphamide protocol for relapsed/refractory ALL, (b) GIMEMA experience with clofarabine for highly resistant ALL, (c) FLAM and FLAM-Cam for relapsed/refractory ALL (PALG studies), (d) Relapse treatment in the GMALL studies, (e) PETHEMA studies in refractory/relapsed ALL and (e) Considerations on biology of relapse in Ph+ ALL were presented. The second major topic was (2) **Treatment of T-ALL.** Results from ongoing (a) GMALL-studies, (b) NILG studies, (c) PETHEMA studies were discussed and as a guest A.Biondi presented (d) data from pediatric patients. Additional topics were (3) Ofatumumab in association with chemotherapy in Burkitt Lymphoma and B-ALL and (4) Haploidentical SCT for highly resistant ALL

EWALL meeting November 2010, Frankfurt
Two major topics and a number of specific topics were discussed. (1) **New drugs for ALL.** Presentations were given on (a) Clofarabine in de novo ALL, (b) Protocols with Notch 1 inhibitors and (c) Erythrocyte encapsulated asparaginase. (2) **Ph+ ALL – Results of stem cell transplantation.** Data from the (a) GRAALL, (b) Pethema, (c) GIMEMA, (d) NILG, (e) GMALL and (f) MRC were presented. Furthermore a joint project on (3) Prophylactic use of G-CSF during induction and consolidation in ALL (a joint analysis of five randomized trials) was discussed. (4) The collaborative study of Gilead Sciences and EWALL was presented and discussed. (5) Updates on ongoing and planned studies with 2nd generation inhibitors in Ph+ ALL (Dasatinib, Nilotinib) were presented and 3rd generation inhibitors for relapsed Ph+ ALL were discussed. (6) Final decisions on the EWALL standard recommendation were made and (7) future meetings, particularly the EWALL meeting in London discussed.

EWALL meeting, ASH New Orleans, December 2010: The group presented in the plenary session major achievements and future plans to the other network members. Thereafter an informal come-together took place.
Web presentation
Further website contents were entered by WP2.

Study registry
The registry with ongoing European studies on adult ALL was maintained and extended.

**Jointly executed research activities**

Collaborative trials
The initiation of international joint European trials still is in practice extremely difficult and time-consuming – actually nearly impossible without large funds.

**The following studies are ongoing or in preparation:**

- **GMALL B-ALL/NHL 2002**
  The study conducted by the German ALL Study Group (GMALL) is ongoing in the Northern Italian Leukemia Group (NILG), the Polish Leukemia Group and the Spanish PETHEMA group. Since 2007 the Swedish group uses the protocol.

- **EWALL Depocyte Trials**
  The NILG study with Depocyte in prophylaxis was started. In the GMALL elderly study the planned patient number was achieved and follow-up is awaited.

- **EWALL Chemotherapy Backbone for Elderly ALL**
  The trial with Dasatinib for elderly Ph+ ALL was extended in order to achieve a sufficient number of Dasatinib treated patients. A trial with Nilotinib was prepared and will start in 2011.

- **Clofarabine in relapsed ALL**
  A new study with a clofarabine combination in relapsed ALL was initiated by R.Bassan.

- **Blinatumomab**
  A joint European trial with Blinatumomab in MRD positive ALL was started as a company sponsored trial

- **Antifungal prophylaxis**
  An international trial with Ambisome prophylaxis during induction therapy of ALL was started as a company sponsored trial.

**Spread of excellence**

With the website of the project a basis for internet-based information exchange and creation of a virtual center of excellence on adult ALL was maintained.

Members of the WP were also active speakers of educational sessions on national and international meetings and made contributions to textbooks.

Ottmann O.G.: Treatment of Ph+ adult ALL (EHA Education Session 2010)
Ribera J.M.: MRD oriented treatment in PH-adult ALL (EHA Education Session 2010)

Marks D.: Treating the "Older" Adult With Acute Lymphoblastic Leukemia (ASH Education Session 2010)

Foundation of a EHA-EWALL Working Group
A first workshop of the newly founded EHA-EWALL working group was organized during the EHA meeting in Barcelona and well attended (100 participants).

- Interim results of the new MRD and risk oriented study 10/07 (R.Bassan)
- Results of the GRAALL Studies 2003 and 2005 in Ph-negative ALL (H.Dombret)
- MRD-based treatment in GMALL study 07/2003 (N.Gökbuget)
- The GIMEMA strategy for Ph+ ALL (R.Foa)
- UKALL12 final analysis of Imatinib in Ph+ ALL (A.Fielding)
- Results of specific immunochemotherapy in HIV-related Burkitts leukemia and lymphoma (J.Ribera)

Extension of the network
Another important goal was the extension of network by inclusion of additional network participants from other European countries. The aim is to integrate countries which have national study groups dedicated to ALL but not individual hospitals. The EWALL supported the foundation of a Slowakian study group for adult ALL headed by Eva Demeckova.

Publications
The members of the workpackage have developed a large number of national and international publications and were international opinion-leaders in many respects although these publications were not directly initiated by the network.

Deviation from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

In 2010 the work of the European Working Group for Adult ALL (EWALL) was continued although – despite travel expenses for one working group meeting - no funding was available.
Table 6.1 List of deliverables WP6, 2010

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months*</th>
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<tr>
<td>6.5</td>
<td>Regular WP meetings and symposiums (during international meetings)</td>
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<td>Support of newly funded European study groups and education</td>
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<td>Extension of registry of ongoing European ALL studies</td>
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<td>86</td>
<td>0 6</td>
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<tr>
<td>6.27e</td>
<td>Activation of further European studies</td>
<td>73-86</td>
<td>86</td>
<td>0 6</td>
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<td>6.28e</td>
<td>Publication of Consensus Paper</td>
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<td>86</td>
<td>0 6</td>
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<td>0 4</td>
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Table 6.2 List of milestones WP6, 2010

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<td>73-86</td>
<td>86</td>
<td>Gökbuget, Hoelzer</td>
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Section 3: Consortium management
New participants of the WP: The Slovakian ALL study group with the following representatives joined the EWALL: E.Demeckova.

Section 4: Other Issues
Ethical issues: none, Competitive calls: none

Section 5: WP-Performance

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<td>Degree of harmonization of trials</td>
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<tr>
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CLL (WP07)

Objectives and starting point of work at beginning of report period:
The European Research Initiative on Chronic Lymphocytic Leukemia (ERIC/WP7) comprises a well established association of more than 300 European/international clinicians and/or scientists, dedicated to creating a translational platform for clinical and basic research activities in the field of chronic lymphocytic leukemia (CLL). Over the past 9 years, ERIC has established an excellently working information- and communication structure and a notable core of world-wide recognized CLL specialists. With the election of a new board of directors, including Professor Emili Montserrat (Barcelona/Spain) as the executive chairman of ERIC in December 2008, ERIC has entered a new era of further development, restructuring and activities. During 2010, the main ERIC Secretariat office was consolidated in Barcelona. However, parts of the ELN related administration and representation of ERIC are still carried out in Germany thanks to the support of the former ERIC chairman Professor Michael Hallek and the Cologne office (University of Cologne, Department of Internal Medicine I).

2010 was the second year that ERIC has successfully performed as a Scientific Working Group (SWG) within the European Hematology Association (EHA). As per the deliverables of WP7/ERIC, the following activities have been carried out during the past 12 months:

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

7.5 Regular WP meetings

3 business meetings, one scientific symposium and one scientific workshop were held by ERIC/WP7 in 2010:

1. 22nd ERIC Meeting at the 7th Annual Symposium of the ELN, Tuesday, February 02, 2010
   Attendance: Approximately 50 participants from EU and non EU countries
   The major results of this ERIC/WP7 meeting, were:
   - An Executive Committee presentation by Professor Montserrat.
   - A presentation on ‘Potential collaboration to evaluate prognostic role and potential role as therapeutic target of Cdc7 in CLL’ by Prof. M. O’Dwyer
   - A decision to add Dr Sarka Pospisilova to the ERIC Board, accepted by meeting participants.
   - A plan for an ‘ERIC retreat’ of key members prior to the next ERIC General Meeting
   The meeting was kept informal for open discussion.

2. 23rd ERIC Meeting at the European Hematology Association (EHA) Congress, Barcelona, Thursday 10th June 2010.
   Attendance: Approximately 55 participants from EU and non EU countries
   As mentioned in recent reports, for the past years the annual EHA congress has become a
fixed meeting venue for a series of very successful Scientific Workshops/Symposiums, carried out by ERIC/WP7. In 2010, the tradition was continued by ERIC, now additionally representing a Scientific Working Group of EHA, with a series of invited top speakers from Europe and the U.S. (see two events detailed below). The topic of “CLL/T-PLL transplants” was selected by the Scientific Committees of ERIC for a special symposium dedicated to the memory of a recently departed and dearly loved colleague. The p53 scientific workshop was also well anticipated and visited by members and other EHA congress attendees.


5. 24th General Meeting of ERIC Members, Orlando, 5th December 2010 Attendance: Approximately 50 participants from EU and non EU countries. As every year, the ERIC/WP7 community was gathering in context of the “ASH Breakfast Meeting” carried out by the ELN at the annual congress of the American Society of Hematology (ASH, Orlando, USA). A major section of the agenda was given over to working group/project updates and in particular the ‘resetting’ of working group activities within a new detailed ‘project’ modality with improved reporting lines. Final agenda and minutes available at the ERIC website: www.ericll.org.

6. The next ERIC assembly took place in Mannheim/Germany during the 8th Annual Symposium of the European LeukemiaNet (Feb 1, 2011).

7.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

See schedules for the ERIC/WP07 meetings in Mannheim, Barcelona and Orlando 2010.

7.8f Treatment of early stage, high risk CLL with FCR continued

The results of this important clinical randomized trials led by Professor Michael Hallek as principal investigator, the German CLL Study Group and many other European CLL Working Groups, most of them linked to ERIC, have been presented at different international meetings and successfully published in Lancet.
7.9f Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups

The development of new potential curative treatment modalities for CLL and related diseases is one long-term goal of WP7/ERIC. Therefore, one ERIC objective is to support phase I/II/III trials with new agents alone or in combination with established therapies (purine analogues, alkylating agents) in CLL and/or related entities. According to previous reports, the following protocol exchanges have been active within ERIC:

- Protocol on chemoimmunotherapy with FCR versus watch and wait in early CLL; German/French study group (GCLLSG/FCGCLL)
- Protocol on recommendations for stem cell transplantation in T prolymphocytic leukemia (T-PLL) and development of a national registry documentation for transplant cases in T-PLL (responsible: P. Dreger, Heidelberg/Germany, see D7.16c)

CLL cases with p53-abnormalities are continuously collected on a molecular and clinical basis (including sequence characteristics but also clinical routine data) by the p53 working group (responsible: Stephan Stilgenbauer, Ulm, Germany), as previously described. Deliverable D7.9 belongs to the long-term efforts of WP7/ERIC and fulfilment will last up to and exceed month 91.

Moreover, ERIC has collected information on other clinical trials for CLL across Europe that are available at ERIC webpage (www.ericll.org). ERIC will update this information on a yearly basis.

7.10d Common data safety monitoring boards in clinical trial on CLL in Europe

The first exemplary Data Safety Monitoring Board (DSMB) within ERIC was constituted for the ERIC supported clinical trial protocol on early stage CLL patients, which is part of deliverable 7.8. Eva Kimby (Stockholm/Sweden) and Peter Hillmen (Leeds/UK) have been selected as independent reviewers of data acquired within this transnational study for any interim, final or follow up analysis in future. The DSMB has been instituted by the German and French CLL study groups to review the clinical plausibility and safety of data collected during the study, as previously described. With finished patient recruitment for deliverable 7.8e, data for a first interim analysis are expected to be available in fall 2011.

7.11f Web-based information- and communication services on CLL refined and up-dated

One of the major goals of deliverable 7.11 is to maintain and spread updated information on the mission, goals and activities of ERIC/WP7 to clinicians/scientists, who are interested and/or active in the field of CLL. During the past 12 months the content of the ERIC core webpage (http://www.ericll.org) has been maintained and updated on a regular basis. Upcoming meetings, meeting agendas and minutes have been announced on the web page regularly. In addition to the core web page, the concordance of project specific web pages for “the harmonization of MRD analysis in CLL” (deliverable 7.24, www.mrd-clf.org) and the “ERIC consensus and review board on IGHV-
analysis in CLL” (deliverable 7.23, www.ericll.org/projects/IGVHMutationalAnalysis.php) require additional web skills and high maintenance efforts: Continuous improvements and further development of the webpage setup, programming, structure and contents are ongoing. This task will be continued as deliverable 7.11. of WP7 beyond month 91.

7.16f Harmonisation of clinical study protocols and trial accessories between national CLL study groups
The harmonization of clinical study protocols and trial accessories between national CLL study groups has been exemplary initiated within deliverable D7.8 (treatment of early stage, high risk CLL with FCR versus watch and wait). In this pilot trial, the harmonization of the complete data management process including data documentation, handling of queries, adverse events, SOPs etc. between the cooperating study groups in Germany, France and other participating countries has been difficult, and by far more time and man power consuming than originally assumed. It also exceeded the input and operating expenses provided by each country for the “regular” trial conduction. As one successful step within the past 12 months, two data bases with an agreed framework consensus of patient data items have been established between German and French study groups in collaboration with the company WISP (Wissenschaftlicher Service Pharma GmbH, Langenfeld, Germany). While quality control and assurance activities by data base programmers on both sides are ongoing, both countries continue to collect completed CRFs and continue to perform continuous medical review, query processing and monitoring of participating study sites. The goal of deliverable 7.16 is to create exemplary harmonized trial accessories required to ensure high data quality in transnationally performed clinical trials. Setup of a completely harmonized and audit-withstanding clinical trial between several countries continues to stay a big challenge for established study groups. According to our experience it is not accomplishable for public study groups without industrial support and funding. Further progress of this deliverable will take at least further months up to month 91 and requires more person-months.

7.19d Continued follow-up of patients with advanced CLL treated with FCR/FC – progress report
Albeit this trial has been terminated and published, continuous follow up of patients is planned as per the rules established in the protocol. The deliverable confirmed that treatment with FCR chemoimmunotherapy is more effective than FC chemotherapy in previously untreated CLL patients. Furthermore, for the first time a survival benefit was demonstrated in a randomized setting for first-line treatment in CLL. The partial failure to demonstrate a benefit for FCR treatment in Binet stage C patients was discussed as potentially related to the higher tumor load in such patients. However, the results corroborate the recommendation to use FCR as standard treatment in physically fit patients with CLL and in need of therapy.
7.20e European platform for phase I/II trials

Some approaches have been made with Pharma, particularly with GSK and we are now in the process of negotiating.

In the past funding periods the difficult aspects of performing clinical trials in rare disease entities have been discussed intensively in our activity reports at the examples of the following ERIC-supported trial protocols (deliverable 7.26):

- Protocol of primary or advanced T-PLL (Phase II trial of combined immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab (FMC-alemtuzumab) in patients with previously treated or untreated T-prolymphocytic leukemia T-PLL2, responsible: Georg Hopfinger, Vienna/Austria)
- Protocol of primary or advanced B-PLL (Phase II trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab in previously treated or untreated B-prolymphocytic leukemia, B-PLL, responsible: Michael Herold, Erfurt, Germany)

Despite tremendous efforts by local and European wide study groups, the spread of trial information via ERIC and negotiations with companies and application for public funding, as previously described, it was not possible to overcome financial and regulatory requirements to launch these trials in the sponsoring countries so far. This has been disappointing for responsible investigators, the ERIC community and patients. Current rescue strategies are considering re-application to public funding opportunities and design of a register trial. Further ideas and strategies are currently discussed among ERIC investigators and will be topic of future ERIC meetings. Thus deliverable will be a continuous task of ERIC/WP beyond month 78.

7.21e European survey on treatment modalities in CLL patients

Under guidance of Vincent Levy (Paris), ERIC is performing a prospective multicenter international internet-based survey on clinical CLL practice. Aim of the project is the evaluation of treatment modalities and behaviour of clinicians in selecting diagnostic and treatment regimens for CLL patients in different situations of clinical disease presentation. As an assessment tool, 7 CLL specific case vignettes are used, which have been shown to be valid tools to assess the quality of clinical practice. The study is conducted among hematologists within Europe, Israel, South America and Australia, actively engaged in treating CLL patients, participating or not in clinical trials and from all types of medical structures (from private practice to large tertiary centres). Within the past 12 months the following steps have been accomplished:

After an initial phase of vignette quality assessment and control the study is currently running in second phase and evaluated as a large-scale European and International survey. Contacts to European and other countries interested in participation have been partially established via ERIC.

Responsible contact person for the project is Vincent Lévy (Centre d’Investigations Cliniques, Hôpital Saint Louis, Paris, France). This interesting and innovative deliverable is not yet fulfilled and will last
until month 78 for being fully accomplished.

7.23d Harmonization, consensus, online support for interpretation and collection of “problematic cases” in IGHV gene mutational analysis

The “IGHV”-working group is dedicated to standardize, harmonize and teach the correct way of mutation-analysis of rearranged immunoglobulin heavy chain variable (IGHV) region genes in patients with CLL. In several trials the IgHV mutation status has been proven to be one of the most potent prognostic factors for treatment and long-term outcome in CLL patients. This WG has now been divided in two relevant projects on the analysis of IgHV genes:

1) Towards standardization of immunoglobulin gene analysis in CLL.

General aims are to investigate how laboratories currently are performing and interpreting immunoglobulin gene analysis in CLL, a comprehensive online questionnaire will be created which will cover important technical and bioinformatic aspects as well as their interpretation of results. As a second step, we will develop a program for quality control of immunoglobulin gene analysis for ERIC laboratories and our plan is to annually send around a number of “unknown” CLL samples for analysis and interpretation.

2) Immunoglobulin gene analysis in CLL: Prognostic and biological implications of cases difficult to categorize

With the aims of creating a comprehensive catalogue of all possible types of problems that may be encountered during immunoglobulin gene analysis, the collection of clinical information and biological material from all cases with problematic IGHV-IGHD-IGHJ sequences is planned in order to reach a significant number of each category, thus enabling to investigate potential prognostic and biological implications.

The IGHV group has established a very successful online system, offering online consultation/support for centers having difficulties in interpreting IgHV sequences and collecting IgHV sequences from participating centers throughout Europe (see previous activity reports). In 2010 the IGHV group had the following activities:

1. Continuous web-based/online support for trouble-shooting in IgHV sequence analyses:
   Over the year 15 queries from several countries throughout Europe and the US were received. Most frequently, “troubled” sequences included insertions and/or deletions or single unproductive rearrangements, which hindered complete alignment with IgHV germline sequences.

2. The IGHV group is definitely collaborating with IMGT (International Immunogenetics Information System) in order to refine the programmed analytical tools for the automated IgHV sequence analysis and alignment with germline sequences offered by www.imgt.org (IMGT/V-Quest). With the implementation of new bioinformatic/programmed tools, the detection and denomination of insertions, duplications and deletions with the IMGT/V-Quest
system has been improved tremendously. Clinicians/scientists using IMGT/V-Quest can now retrieve more comprehensive and detailed information about inserted/deleted or duplicated nucleotides, when analyzing an affected IGHV sequence case. Everybody can connect to http://imgt.cines.fr/, to scroll down to "Databases" and you will find to "IMGT/CLL-DB (bylaws) LIGM, Montpellier, France IG sequences from CLL, an initiative of the IMGT/CLL-DB group"

3. An educational workshop on IGHV sequence analysis in CLL in Stressa (Italy) is planned for the next 6th-7th April 2011, sponsored by the ELN/ERIC and industrial support.

4. Following the very successful first book release (title: “Immunoglobulin gene analysis in chronic lymphocytic leukemia”), which was also supported by the ELN/ERIC, a second book about “biological diagnostic markers in CLL” has already been published and distributed among ERIC members. It includes modern diagnostic tools, like the immunoglobulin analysis, MBL diagnostics, flow cytometry, microRNA analysis etc. and focus on the future clinical application and potential of such diagnostic parameters.

7.24d Harmonization and quality control of MRD diagnostics
The MRD (minimal residual disease) working group under guidance of Andy Rawstron (Leeds, UK) focuses on continuous improvements and standardization of MRD analysis techniques in CLL, as described in earlier activity reports. Besides the ongoing online support provided by the management and maintenance of an ERIC-connected MRD web page (www.mrd-cll.org), the working group continues to work on the following goals:

- To develop a quality control system for MRD analysis which simplifies a sort of “screening” assay for routine MRD assessment in CLL
- To develop a standardized 6-colour flow cytometric assay running under the quality control aspects developed above.

Compared to 2008, ongoing activities of the working group in 2009 have not changed and concentrate on the following aspects.

- To determine optimal antibody combinations by investigating electronically manipulated data in 4/5/6-color formats
- To conduct dilution studies between European wide participating centers: representative data files were sent to Milano, Kiel & Barcelona and are under investigation
- To establish/re-develop a “rapid screening approach” of MRD by flow cytometry using the minimally required antibody combination for the highest number of correct MRD estimations (500 cases are tested so far, further tests are ongoing, this approach may be highly effective during treatment but response assessment usually requires a full MRD panel)
- To establish, evaluate and improve an MRD quality control data analysis scheme: First e-trial-results have been collected from 16 centres (of 31 registered, each centre has to process a
given CLL case with a certain amount of residual CLL cells and denominate the number/percentage of detected CLL cells).

- Collection and review of difficult MRD cases, discussion and continuous online support.

The accomplishment of these tasks has to be continued under the auspices of ERIC beyond month 91. First results will be presented and discussed in the ERIC community in 2011.

### 7.26d Collection & investigation of functional aspects of p53 mutation

The “p53 working group” within ERIC comprises a very active subgroup of scientists/clinicians from 9 European countries interested in p53 (a tumor suppressor inactivated in several tumor subtypes, also in a subgroup of CLL patients with very poor prognosis) related translational and basic research.

Within the past year the following activities have been accomplished:

- A large series of 268 different p53 mutations in 254 patients has been collected and characterized. Mutations have been identified as mostly missense mutations (74%), followed by deletions/insertions (20%), nonsense mutations (4%) and affecting splice sites (2%). The most frequent amino acid positions of mutations have been determined (i.e. AA 175, 179, 248, 273). Detailed results were published by the p53 working group in several journals or at ASH (see Annex Section 3, WP7).

- Further focus of the p53 working group is to retrieve clinical correlations between p53 mutations and treatment outcome and longterm prognosis in clinical trials. Therefore, the group is promoting “p53 trials”, where refractory CLL patients with or without affected p53 gene loci can be included. One example is the CLL20 trial by the German CLL study group (phase II study of subcutaneous alemtuzumab combined with oral dexamethasone, followed by alemtuzumab maintenance or allogeneic stem-cell transplantation, in CLL associated with 17p deletion or refractory to fludarabine) or the meanwhile closed CLL206 NCRI trial (phase II study investigating the role of alemtuzumab (iv or sc) plus methylprednisolone in CLL patients with p53 deletion)

- A “p53 workshop” for ERIC members and interested non-members to encourage scientific exchange and discussion on p53-related topics in CLL was performed in context of the ERIC meeting at the EHA congress in Barcelona, June 2010. The workshop was very well anticipated and visited by ca. 50 participants. Due to its success, the working group is planning to set up p53-workshops on an annual basis, if respective funding is available.

The deliverable has been successfully established and produced publishable results. However, due to the biological and clinical high relevance of p53-aberrations for CLL treatment outcome and prognosis, the deliverable will be an ongoing and long-lasting “task-force” of ERIC. Several initiatives have emerged from this group:

1. Establish clinical use of p53 pathway analysis in CLL.
Scientific deliverables: Guideline p53 mutation detection, Assess clinical impact of MDM2SN309 SNP by individual patient data metaanalysis (publication early 2011) (with Rosenquist, Rossi, Majid, Linderholm, Greil, Pospisilova & Trbusek), Metaanalysis of clinical impact of different p53 mutations in CLL (prospective trial data) (publication)


Scientific deliverables: Development of novel techniques (publication), Test clinical relevance of p53-assays in prospective trials (publication), Harmonization (guidelines)

7.27d Phase I/II trial platform for the treatment of rare subentities T-PLL and B-PLL

With the phase I/II trial platform launched in deliverable 7.20 focusing on the so far NOT successfully activated studies on

- the reatment of primary or advanced T-PLL (Phase II trial of combined immunochemotherapy with fludarabine, mitoxantrone, cyclophosphamide and alemtuzumab (FMC-alemtuzumab) in patients with previously treated or untreated T-prolymphocytic leukemia T-PLL2, responsible: Georg Hopfinger, Vienna/Austria),
- the treatment or advanced B-PLL (Phase II trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab in previously treated or untreated B-prolymphocytic leukemia, B-PLL, responsible: Michael Herold, Erfurt, Germany,

Deliverable 7.20 covers contents of 7.27, please see there for details. The creation of a common diagnostic platform on prolymphocytic diseases in Germany with a new central reference laboratory in Cologne (responsible: Dr. Marco Herling, University of Cologne) has been one step forward within the past year. First diagnostic samples have been received and processed by the Cologne laboratory. Other European diagnostic laboratories interested in PLL-diagnostics have shown their interest and willingness to collaborate for future European wide trials on PLL-related diseases. Deliverable D7.27 is ongoing beyond month 91.

7.28b Recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)

ERIC and the CLL subcommittee of the EBMT (European group for blood and bone marrow transplant, responsible subcommittee chairman: Johannes Schetelig) consolidated on the occasion of the last meeting held in Manheim an ad hoc joint group. Both groups have been collaborating to define “recommendations for (allogeneic) stem cell transplantation (SCT) in T prolymphocytic leukemia (T-PLL)”. The final edition of the recommendations has been published on the ERIC webpage
(www.ericll.org), as previously described (deliverable partially fulfilled). Since it has been impossible under the current regulatory framework to perform an international prospective trial on stem cell transplantation in T-PLL (see deliverable 7.27), this group has established a register trial, were transplanted T-PLL patients can be registered and be evaluated retrospectively. In addition to retrospective patient registration and analysis, 23 European centers have agreed to register T-PLL patients prospectively, prior performance of their transplantation, to allow early data collection and evaluation. The trial is supported by ERIC and first data status and results of 13 autologous transplanted patients, 52 allogeneic transplanted patients and 27 prospectively registered patients were discussed at the latest ERIC meeting in New Orleans. Deliverable 7.28 will stay a long-lasting activity of ERIC/WP7 with fulfilment beyond month 91. Main goal of the activity is to intensify networking between WP7 and WP14 as well as the exchange and spread of expertise and trial efforts on stem cell transplantation in CLL.

7.29b Improvement of long-term follow-up of CLL patients in European trials

One of the recently launched ERIC projects is the implementation of a new trial system to collect long-term follow-up data in randomized phase III trials within Europe. Previously published phase III trials in CLL show median observation times ranging from 22 to 41 months, most of the trials exhibit only around 2 years of observation time. One reason for the unacceptable availability of long-term follow up data in clinical trials is the limited affordability for non-commercial study groups to accomplish long-term follow up data collection, management and evaluation. The ERIC trial system is planned to be conducted as a web-based repository, further details have been described in the last activity report. The project is aiming to collect long-term data including the following items: the date of the annual follow-up, status of the patient (alive/dead), disease status (CR, PR, SD or PD), incidence of secondary diseases, further therapies and responses and death related informations. Responsible leaders of this project are Peter Hillmen (Leeds, UK) and Barbara Eichhorst (Cologne, Germany). Within the past year negotiations with companies have been carried out to set up legal, ethical and practical requirements for the project. In collaboration with a CRO company, ICON, first steps to realize the follow up trial system have been undertaken and were presented and discussed at the last ERIC meeting in New Orleans. Currently, the group is working on solutions for the complex ethical situation regarding approval to acquire long-term follow up data on a European level, the setup of the remote trial system available for multiple countries, the governance of data flow, management and the overall system, and the maintenance of long-term confidence of investigators participating in the long-term follow-up system. Deliverable 7.28 is ongoing beyond month 91.

7.30b Promotion of ERIC for sustainability of WP7

The main goal of ERIC is to promote the development and sustainability of clinical, translational and basic research activities on CLL. In order to accomplish this goal on a long-term basis and sustain
ERIC as a European and world-wide recognized platform for CLL research, the ERIC Board initiated a strategic review process during 2010. This process kicked off with a half-day retreat of key ERIC members prior to the EHA Congress in Barcelona. From this platform the key members split into taskforces to develop strategic objectives and priorities for the following themes:

1. ERIC legal structure, board and bylaws
2. ERIC and its relationship with other organisations
3. ERIC webpage
4. ERIC Working Groups
5. ERIC visibility and marketing
6. The clinical side of ERIC
7. ERIC fundraising

Implementation of the results of the strategic review by the ERIC Board and Subcommittees continue into 2011 and beyond 2011.

Deliverable 7.28 is ongoing long-term effort beyond month 91.

Deliverable List WP7, 2010

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<td>Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups</td>
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<td>Common data safety monitoring boards in clinical trial on CLL in Europe</td>
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<td>7.11f</td>
<td>Web-based information- and communication services on CLL refined and up-dated</td>
<td>73-86</td>
<td>Ongoing</td>
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<td>86-98</td>
<td>0</td>
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<td>7.19d</td>
<td>Continued follow-up of patients with advanced CLL treated with FCR/FC – progress report</td>
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<td>86-98</td>
<td>0</td>
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<td>7.20e</td>
<td>European platform for phase I/II trials</td>
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<td>86-98</td>
<td>0</td>
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<td>Levy</td>
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87
Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved

None

List of milestones WP7, 2011

<table>
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<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
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<td>7.5</td>
<td>Spread of excellence by high-quality scientific and educational meetings and workshops</td>
<td>78, 84, 86</td>
<td>Ongoing</td>
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<td>7.23d</td>
<td>Harmonization, consensus, online support for interpretation and collection of “problematic cases” in IGHV gene mutational analysis</td>
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<td>7.24d</td>
<td>Harmonization and quality control of MRD diagnostics</td>
<td>73-86</td>
<td>86-98</td>
<td>Hallek</td>
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<td>7.26d</td>
<td>Collection &amp; investigation of functional aspects of p53 mutation</td>
<td>73-86</td>
<td>86-98</td>
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Section 3: Consortium management

The European Research Initiative on CLL (ERIC/WP7) is a continuously growing institution, which is more and more anticipated and recognized in Europe and world wide. 2010 has been an important year for ERIC as a Scientific Working Group of the European Society of Hematology (EHA): Both the Symposium and Scientific Workshop offered by ERIC at the annual EHA congress attracted increasing numbers of clinicians and scientists and stood out due to their leading specialist speakers and state-of-the-art presentations. ERIC/WP7 is continuously active in the education/spread of...
excellence on clinical and scientific topics in CLL, predominantly by the p53- and IGHV-working groups.

With the notarial registration of ERIC in 2010, the association achieved recognised legal status in Germany.

Under the new chairman Professor Emili Montserrat, transfer of the ERIC office to Barcelona was completed in 2010. Implementation of strategic development objectives will be an important focus in the upcoming months. Overall ERIC/WP7 continuous to be an active and well prospering group within the ELN and EHA, dedicated to the improvement of clinical and basic science and treatment of CLL patients in and outside of Europe.

Section 4: Other Issues

Ethical issues - none

Competitive calls – none

Section 5: WP-Performance

<table>
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<tr>
<td>Number of patients recruited into clinical trials</td>
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<tr>
<td>Number of patients included into registries</td>
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<tr>
<td>Improved predictive, prognostic or quality of life assessments</td>
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<td>Number of SOPs and consensus papers</td>
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<td>Number of meetings</td>
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<td>Number of accredited trials</td>
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</table>
Objectives and starting point of work at beginning of reporting period

The collaborators of this network have established a European platform for integration of MDS trial groups and their interdisciplinary partners. This infrastructure prevents European fragmentation and augments scientific interaction and collaboration. The platform communicates and decides about diagnostic standards, prognostic tools, new molecular targets for new treatment modalities, and guidelines for various treatment approaches. Clinical trials are initiated and performed on a European scale. In addition, international registries have been developed to determine incidence, disease patterns and the prognostic impact of standard treatment according to well established guidelines. The starting point of work at beginning of the reporting period was as follows. We had interacted with many different Workpackages of European LeukemiaNet for integrated activities: e.g. Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11 (cytogenetics in diagnostic guidelines in MDS), AML WP5 (development of a common prognostic score), Minimal Residual Disease WP12 and Gene Profiling WP13, for translational studies. WP-MDS interacted actively internationally with the EORTC Leukemia Group, several national MDS study groups (GFM-France, Nordic MDS study group, German MDS study group and the Czech MDS study group), with the international MDS Foundation (several members of the steering committee are board members of the MDS Foundation), with the European Hematology Association (EHA), with European School of Hematology (ESH), and with numerous pharmaceutical companies which actively support the MDS registry and other clinical or translational projects. Knowledge like new treatment modalities and diagnostic and therapeutic guidelines were disseminated by meetings and presentation on the ELN website.

Close cooperation with numerous European MDS study groups resulted in a well running European MDS Registry Study. All planned deliverables for this project have been fulfilled and patient inclusion started in April 2008. The second interim analysis of the EUMDS registry has been performed on the first 800 registered patients and these data have been presented at the 2010 ASH meeting. The milestone of 1000 included patients has been reached in January 2011. A clinical platform has been initiated and is being developed to create collaboration between individual national studies with the aim to reduce duplication of trials, to exchange results at an early stage and to develop common control for investigational drugs. This will allow a reduced number of patients in the control arms and comparison of the study arms in different studies using the identical control arm. Furthermore the European guidelines for treatment of primary myelodysplastic syndromes has been finalized. The aim of these guidelines is to provide clinical practice recommendations that support the appropriate choice of therapeutic interventions in adult patients with primary MDS. On top of these guidelines, a web based scenario analysis on the treatment of myelodysplastic syndromes has been developed and a training how to use this scenario has been created.
Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

8.5 Regular WP meetings

2010
1. Annual ELN Symposium, MDS WP meeting, Mannheim, 2 February; 103 registered participants
2. European MDS Registry project, Steering Committee meeting, Mannheim, February 2, 10 participants and Operational team meeting February 1; 14 participants
3. European MDS Registry project, Steering Committee and operational team meeting, Barcelona, June 9; 18 and 10 participants respectively
4. European MDS Registry project, Operational team teleconferences: March 1 (13 participants), April 6 (8 participants), May 10 (10 participants), September 6 (6 participants)
5. ELN Steering committee meeting, Barcelona, June 10; 18 participants
6. European MDS Registry project, Steering Committee meeting, at ASH congress, Orlando, December 3; 11 participants
7. ELN breakfast meeting at the Annual ASH meeting Orlando, December 5
8. ELN Frontiers meeting, Vienna, October 23-24
9. MDS Iron Forum, Rome, September 25

2011
1. Annual ELN Symposium, MDS WP meeting, Mannheim, February 1; 90 participants (68 registered)
2. European MDS Registry project, Steering Committee meeting, Mannheim, January 31 (17 participants) and Operational team meeting January 31 (13 participants)

8.6 LP reports to NMC regarding structure, trial activities and integration of national trial groups
LP reports have been sent to NMC as requested.

8.49b Maintenance of the MDS WP8 section of ELN website
The MDS WP8 section of ELN website has been updated regularly. Currently some WP8 reports and presentations have to be put on the website by ELIC.

Diagnostic Guidelines

8.25a Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website
The MDS guidelines are revised on the basis of the new WHO classification, 4th edition 2008 and presented on the ELN website. E. Hellström Lindberg and A. Porwit prepared a revised version of the guidelines: updated according to WHO and revised regarding flowcytometry, according to minutes from the previous meeting. The document was sent to all participants of the MDS WP. Many comments were received by email and E. Hellström Lindberg summarized the major comments during
the Mannheim ELN MDS WP8 meeting in 2010. The guidelines include a work-up of suspected MDS or mixed MDS/MPNs. It was proposed and agreed to keep the MDS and AML guidelines separated because of the new WHO classification. Both IPSS and WPSS are included in the guidelines (WPSS is less validated compared to IPSS). It was proposed and agreed to remove the WHO classification 2001. E. Hellstrom-Lindberg has prepared a new version of the guidelines using the comments of the MDS WP participants. These guidelines have been presented during the ELN MDS WP8 meeting in Mannheim in 2011. The new version is published on the ELN website and will be evaluated after one year.

8.25b Addition of information on Immunophenotyping in diagnostic guidelines in MDS/AML

After the start of the working group on flow cytometry in myelodysplastic syndromes in Amsterdam in 2008, the WP focussed on minimal flow cytometric criteria in the diagnosis of MDS. The group defined in its first publication [Haematologica 2009] the role of flow cytometry not only in the diagnosis but also its contribution in classification and prognostification of MDS. This report describes in detail a standard flowcytometric method dealing with sampling handling, use of antibodies as well as defining antigens involved in dys hematopoiesis primarily concerning the erythroid, granulocytic and monocytic cell lineages. In 2009, the second workshop (MLL Munich Lab, chair AA van de Loosdrecht, co-chair W. Kern) discussed in more detail the immature and maturing granulocytic and monocytic cell lineages to define those antigens expressed during differentiation which might be of relevance to distinguish normal from dysplastic hematopoietic cells. This critical multidimensional approach is needed to translate potential aberrant profiles to a numerical scoring system. A newly defined scoring system could be instrumental for diagnostic and prognostic purposes. The latter has been discussed in the third international flow cytometry meeting of the WP8 on flow and MDS which has been held in London in November 2010 (co-chair R. Ireland). An ELN consensus guideline for flow cytometry in MDS is available and will be submitted to a high-ranking international journal in 2011. Also a rationale for clinical use of flow cytometry is defined and will be submitted for publication in 2011. The diagnostics, revision of FCSS (flowcytometry scoring system), erythroid4 lineage, clinical reporting and incorporate software tools for analysis/statistics will be discussed during the fourth workshop in October 2011. WP10 will be involved in the planned meetings.

8.25f The results of the second Workshop on flow cytometry in MDS (Oct 2009 in Munich, Germany) have been submitted for publication.

The results of the second Workshop on flow cytometry in MDS has been submitted for publication. This report also contains the results of the third Workshop on flow cytometry in MDS (October 2010 in London, UK).
8.25g The third international Workshop on flow cytometry in MDS has been held on October 2010 in London, UK (host: dr. R. Ireland, chair: Dr. van de Loosdrecht)

28 Representatives from 12 countries attended this meeting (including Australia, Japan and the United States). The minimal flow cytometry criteria have been defined and have been published in Haematologica (2009). The results of this Workshop has been submitted for publication. The Flow Score has been developed as a prognostic tool. Guidelines for the Flow Score Flow will be defined and described in 2 consensus documents to be submitted in first months of 2011. Recommendations are identified for the analysis of subsets in the BM. Publications have been reported on: analysis of a minimized multiparameter panel, analysis of myelomonopoiesis and FCSS related to transfusiondependancy and progression to AML.

An ELN consensus guideline for flow cytometry in MDS is available. And a rationale for clinical use of flow cytometry has been defined (see also item 8.25b)

Therapeutic Guidelines

8.27a Yearly update of the guidelines for therapeutic procedures in MDS and presentation on the ELN website

The guidelines have been developed by a European expert panel and a systemic review of literature. The European guidelines for treatment of primary myelodysplastic syndromes have been finalized. The aim of these guidelines is to provide clinical practice recommendations that can support the appropriate choice of therapeutic interventions in adult patients with primary MDS. A final manuscript is in preparation and will be submitted to Blood in 2011.

8.27c Web based scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS

Consensus was achieved for key clinical questions and a list of treatment indications. The treatment guidelines include a summary of the diagnostic guidelines. On top of these guidelines, a web based scenario analysis on the treatment of myelodysplastic syndromes has been made and a training on how to use this is created and distributed as well.

8.27d Report on web based training program based on scenario analyses and consensus based guidelines for therapy of MDS developed by experts in this field

The final manuscript will be submitted to Blood in 2011. The next version will include international, nonEuropean experts as well.
8.29 Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians
Scenario analysis of more than 50 scenarios has been developed and reviewed by the expert panels. The recommendations for the 50 scenarios are available at the website of Haematologica.

8.29a Evaluation of web based scenario analysis experts versus trainees.
An evaluation of the web based scenario analysis by experts and non-experts (trainees) is planned for 2011.

Trials
8.31 Yearly update of a list of all trials by MDS study groups in Europe
The list of MDS trials is presented on the LeukemiaNet website. The updated list is sent to the ELIC and they will put it on the website as soon as migration to the ELTR is ready.

New List of trials and studies in Myelodysplastic Syndromes
Different risk groups:

- 5-Azacytidine II: Study of maintenance with Azacitidine in MDS patients achieving complete or partial remission (CR or PR) after intensive chemotherapy
- MDS Azacitidine: Study of Maintenance With Azacitidine in MDS Patients
- Bevacizumab: A Trial of Bevacizumab in Myelodysplastic Syndromes (Int-1, Int-2 and High Risk According to International Prognostic Scoring System (IPSS)) With Excess of Marrow Blasts
- MDS Decitabine: Study of Decitabine

Low risk and intermediate I:

- Azacitidine-Epoetin Beta: Study of Azacitidine (Vidaza) combined to Epoetin Beta (NeoRecormon) in IPSS low-risk and intermediate-1 MDS patients, resistant to ESA
- Azacitidine-Epoetin Beta II: Azacitidine and Beta Erythropoietin Treatment
- Erythropoetin: Comparison Between Erythropoietin and Erythropoietin Associated to Differentiating Therapy With Acid 13-Cis-Retinoic and Dihydroxyvitamin D3
- European Registry: European Registry for Newly Diagnosed Patients With MDS of IPSS Low and Intermediate-1 Subtypes
- HOVON 89 MDS: Study to assess the efficacy of lenalidomide with or without erythropoietin and granulocyte-colony stimulating factor in patients with low and intermediate-1 risk MDS
- MDS Lenalidomide II (pending) : A phase II tial to assess the efficacy Lenalidomide with or without Erythropoietin and G-SCF in low- and intermediate-1 MDS
- MDS Lintuzumab (temporary halt) : Monoclonal antibody therapy in treating patients with primary MDS
Intermediate II and high risk:

- 5-Azacitidine: Subcutaneous Azacitidine + best supportive care vs. conventional regimens + best supportive care
- Erlotinib: Erlotinib in high risk MDS
- HOVON 81 AML: Study to assess the tolerability and efficacy of the addition of Bevacizumab to standard induction therapy in AML and high risk MDS above 60 years.
- MDS Antithymocyte Globulin-Cyclosporine (temporary halt): A randomized trial comparing ATG + CSA with best supportive care
- MDS Clofarabine: Clofarabine in combination with a standard remission induction regimen (AraC and idarubicin) in patients 18-60 years old with previously untreated intermediate and bad risk acute AML or high risk MDS
- MDS Combi-Chemo (active): Combination chemotherapy with or without Gemtuzumab or Tipifarnib in high-risk MDS
- MDS-005 Lenalidomid: Study of the Efficacy and Safety of Lenalidomide (Revlimid) versus Placebo in Subjects with Transfusion-Dependent Anemia due to IPSS Low or Intermediate 1 Risk MDS without Deletion 5Q
- Velcade Zanestra: Bortezomib and Tipifarnib in MDS
- Vorinostat: Study of Vorinostat in Combination With Low Dose Ara-C

Monosomie 5 or del5q:

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

Supportive studies MDS

- MDS/AML Eltrombopag: Eltrombopag bei MDS und AML
- Darbepoetin-Filgrastim: Darbepoetin alpha and G-CSF vs. best supportive care
- Darbepoietin alpha II: Darbepoietin in low- or intermediate-1 risk MDS with anemia
- Romiplostim I: Evaluating the Safety of Long Term Dosing of Romiplostim (formerly AMG 531)

Diagnostic /biomarker studies MDS

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

Quality of Life
- NMDSG03A MDS Quality of life I (active): Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function
- MDS QOL II: Quality of Life and Symptoms

SCT: Stem cell transplantation
MDS
- AML RICMAC/MDSsAML: Dose reduced vs. standard conditioning + SCT in MDS or sAML
- Allo SCT after treosulfan fludarabine: Allogeneic stem cell transplantation after toxicityreduced conditioning regimen with treosulfan and fludarabine for patients with myelodysplastic syndrome (MDS) or secondary acute myeloid leukaemia (sAML) who were not eligible for a standard conditioning regimen
- StemCellTransplant II: Pilot Study of Reduced Intensity Haematopoietic Stem Cell Transplantation in Patients With Poor Risk MDS and AML Utilising Conditioning With Fludarabine, Busulphan and Thymoglobulin (FB-ATG)
- Velcade: Phase II Study of PS341 (VELCADE) in MDS
- MDS AlloSCT-Clofarabine: Allogeneic Stem Cell Transplant With Clofarabine, Busulfan and Antithymocyte Globulin (ATG) for Adult Patients With High-Risk AML/MDS or ALL

8.51d Impact of frailty index on various therapeutic approaches, supportive care, hypomethylating agents, intensive anti-leukemic therapy
The comprehensive geriatric assessment was performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. Multicenter evaluation was feasible. Multivariate analysis revealed "Activities of daily living" (ADL) and fatigue measured with the QLQ C30 questionnaire as highly prognostic for survival in the entire patient cohort. Follow-up assessments revealed that no severe deterioration in geriatric and QOL (quality of life) domains occurred within 6 months under treatment. Statistical calculations are currently being performed to define a risk score. Final publication of data is planned for 2011.
8.57 GIMEMA-ELN Qol – MDS 0108 study, Health-related quality of life and symptom assessment in patients with myelodysplastic syndromes.

The obtained data of this Quality of Life study has been published in 2009 in Expert Review Hematology, 2009 Feb; 2(1):69-80, G. Caocci, G. La Nasa, F. Efficace. Further publications are expected after completion of the full study.

MDS registry

8.54 Monthly progress reports of the prospective, non-interventional multicenter European MDS Registry (IPSS low and intermediate-1) project

Monthly reports have been sent to Novartis, the sponsor of the registry and to all participating registries. It is clear that the quality of the data is very high and informative. The registry is collecting a unique data set which will prove to be very valuable for future questions and studies as well. The accrual has risen again to an accrual of 1000 patients in January 2011 (980 per 31 December 2010). The registry continues to consider to merge the low risk MDS-registry with the high risk registry if the support will come from a Pharma consortium or other funding (outreach programs, FP-EU programs), but for the time being the focus will be on lower risk MDS. The follow-up time is extended to 3 years with support from Novartis.

8.54f First presentation on follow-up data of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) at the ASH meeting 2010

Summary from the steering committee meeting in Orlando, December 3, 2010. The EU-MDS Registry had 3 poster presentations at ASH based on the interim analyses of the first 800 patients:

1. Dr. Smith and Dr. Bowen: Population based real world of low risk MDS. European countries are participating to the registry. France, Spain, UK and Greece are major contributors. Cytogenetic data are available in 93% of the patients. Epo levels are low in majority of patients: <100U/l in 68% of the patients. The basal EPO-levels have no significant relationship to Hb-levels.

2. Dr. Stauder: Quality of Life at base line. The Hb-levels show no correlation with age in contrast to nonMDS elderly people. Patients having problems with daily activities have a decreased median Hblevel: 9.5 vs 10.4 g/dl when no problems with daily activities. The Sorror score (co-morbidity index) showed a clear relationship with EQ-5D Visual Analogue scale.

3. Drs. de Swart: Disease management during the first 18 months. About 35% of the patients have received EPO with or without G-CSF. 303/800 Patients were transfusion dependent. Transfusion dependency and high ferritin levels in transfusion dependent patients were independent prognostic factors for survival and progression-free survival.
8.54g Second interim analysis (800 patients) entered in the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1)
The statistician, Dr. Smith, has created the second interim analysis on the first 800 registered patients. She has presented the analysis at the steering committee meetings in Orlando (December 2010) and Mannheim (January 2011).

8.54h Inclusion of next patients to 1000
In February 2011 the milestone of 1000 included patients has been reached.

8.54i Extension of follow-up, 2-5 years
The follow-up period has been extended from 2 to 3 years.

8.54j Extension to more registries (new countries)
Portugal, Poland and Denmark have joined the EUMDS Registry in 2010. Israel has joined the steering committee in 2010. Israel is expected to enter patients in 2011.

8.54k Extension of Registry after 1000 patients
Continuation of the support of Novartis after the first 1000 patients is under discussion. Several participating countries in the Registry have committed themselves to continue the Registry with local funding.

8.73-8.79 A prospective, non-interventional multicenter European high-risk MDS Registry
The steering committee discussed the progress of the development of this registry during the ELN annual meeting in Mannheim 2010 and at the EHA congress in London 2010. A consortium of sponsors are being invited to support the study. The CRFs and the web-based reporting will be adapted from the low risk registry system developed by the University of York. Merging of the low risk and high risk registries is foreseen after completion of the low risk MDS registry project.

Translational research

8.80 and 8.80a: Iron Pathophysiology and imaging of iron overload: side studies of the low risk MDS registry study.
The protocol has been finalized by the steering committee in May 2009. The contract of the sponsor has been signed in October 2009. Collection of necessary samples has already been performed for more than 300 patients. In 6 countries (34 sites) samples have been collected: UK, GR, NL, SW, CZ, RU. In total samples of 810 different visits are collected. Already 37 patients have completed the substudy (= 5 samples collected). The samples will be transported to the UMCN in The Netherlands and laboratory analysis of the samples will be performed before the end of 2011.
8.81 Side study of Low Risk MDS Registry: Cytomorphologic sub-study. Meeting in Düsseldorf planned June 2010
The aim of this cytomorphologic substudy is to assess the reproducibility of diagnosis. Methods have already been defined: review of randomly selected slides from all participating countries; reviewer panel includes both „experts“ as well as physicians in training; description of results and correlation with original findings and calculation of degree of discrepancy using k-test. The side study and progress of the protocol and logistics have been presented and discussed during the EUMDS-steering committee meeting and the ElN-WP8 meeting in Mannheim in 2011. The final protocol of this review is expected in April 2011.

8.82 Side study of Low Risk MDS Registry: Geriatric Assessment: presentation at EHA 2010, Barcelona
B. Deschler presented the effects of different treatment regimens on the various geriatric assessment tools and the quality of life in elderly MDS patients. Careful geriatric assessment evokes awareness of relevant changes in elderly MDS/AML that otherwise might be unnoticed (Deschler et all, abstract 0464 Haematologica 2010; 95: 189).

8.83 Evaluation of the prognostic value of TET-2 mutations in MDS
Based on the experience of techniques used to detect and to describe the incidence and prognosis of TET-2 mutation in MDS (S. Langemeijer et al Nat Genet. 2009;4:838-42) we identified a new mutation in chromosome 7 of MDS patients (G. Nikolski, et al. Nature Genetics 2010; 42: 665–667). In MDS deletions of chromosome 7 or 7q are common and correlate with a poor prognosis. The relevant genes on chromosome 7 are unknown. EZH2, located at 7q36.1, is frequently targeted in MDS. Analysis of EZH2 deletions, missense and frameshift mutations strongly suggests that EZH2 is a tumor suppressor. As EZH2 functions as a histone methyltransferase, abnormal histone modification may contribute to epigenetic deregulation in MDS. This may have therapeutic implications.

8.84 Evaluation of the prognostic value of TET-2 mutations in AML
Ten-Eleven-Translocation 2 (TET2) gene mutations and deletions have been detected in myelodysplastic syndromes, acute myeloid leukemias (AML) and other myeloid malignancies. TET2 mutations are found in 8–19% of adult AML and the expression of TET2 is high in granulocytes as compared with other hematopoietic and non-hematopoietic cells, where it is increased during myeloid differentiation. S. Langemeijer described novel TET2 mutations in 3.8% of pediatric AML. Despite the lower incidence compared with adult AML, this observation may be instrumental for the design of novel targeted therapies in pediatric acute myeloid leukemia (Leukemia. 2011;25:189-92).
8.59 ESH-EHA Scientific Workshop on Experimental Haematopoiesis and Therapeutics 2010. (MRD, Gene Profiling, Immunophenotyping, Cytogenetics, in AML and MDS)

The scientific Workshop took place at Frankfurt during September 16-18, 2010. Altogether 27 distinguished speakers from 10 different countries including the US and Australia. The topics ranged from normal and leukemic stem cell biology to new molecular pathways including epigenetic biology in leukemia, myelodysplastic syndromes and myeloproliferative disorders.

Table 8.1: List of deliverables WP8, 2010 and 2011.

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<th>Deliverable Name</th>
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<td>Hellström-Lindberg</td>
</tr>
<tr>
<td>8.25b</td>
<td>Integration of immunophenotyping in diagnostic guidelines in MDS</td>
<td>73-86</td>
<td>86 ongoing</td>
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<td>6</td>
<td>Hellström-Lindberg, Van de Loosdrecht</td>
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<tr>
<td>8.25g</td>
<td>The third international workshop on flow cytometry in MDS was held on 30-31 Oct 2010 in London, UK (host: Dr. R. Ireland; chair: AA van de Loosdrecht)</td>
<td>70</td>
<td>82</td>
<td>2</td>
<td>4</td>
<td>Van de Loosdrecht</td>
</tr>
<tr>
<td>Therapeutic Guidelines</td>
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<tr>
<td>8.27a</td>
<td>Yearly update of the guidelines for therapeutic procedures in MDS and presentation on the ELN website</td>
<td>73-86</td>
<td>86</td>
<td>1</td>
<td>6</td>
<td>Malcovati, Cazzola</td>
</tr>
<tr>
<td>8.27c</td>
<td>Web-based scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS</td>
<td>73-86</td>
<td>86</td>
<td>1</td>
<td>4</td>
<td>Malcovati, Cazzola</td>
</tr>
<tr>
<td>8.27d</td>
<td>Report on web based training program based on scenario analysis and consensus based guidelines for therapy of MDS developed by experts in this field</td>
<td>78</td>
<td>86</td>
<td>1</td>
<td>2</td>
<td>Malcovati, Cazzola</td>
</tr>
<tr>
<td>8.29</td>
<td>Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians</td>
<td>78</td>
<td>78</td>
<td>1</td>
<td>4</td>
<td>Malcovati, Cazzola</td>
</tr>
<tr>
<td>8.29a</td>
<td>Evaluation of web-based scenario analysis experts versus trainees</td>
<td>78</td>
<td>86</td>
<td>1</td>
<td>3</td>
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<td>Trials</td>
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<td>8.31</td>
<td>Yearly update of a list of all trials by MDS study groups in Europe</td>
<td>73-86</td>
<td>86</td>
<td>2</td>
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<tr>
<td>8.57</td>
<td>GIMEMA-ELN QoL - MDS 0108 study Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes. Obtain additional key data to further facilitate clinical decision-making in MDS patients.</td>
<td>78</td>
<td>78</td>
<td>2</td>
<td>3</td>
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<td><strong>MDS registry</strong></td>
<td><strong>8.54</strong> Monthly progress reports of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) project</td>
<td>73-86</td>
<td>73-89</td>
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<td>De Witte</td>
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<td><strong>8.54f</strong> First presentation on follow-up data of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) at the ASH meeting 2010</td>
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<td><strong>8.54g</strong> Second interim analysis (800 patients) entered in the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1)</td>
<td>79</td>
<td>85</td>
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<tr>
<td><strong>8.54h</strong> Inclusion of next patients 600 to 1,000</td>
<td>73-86</td>
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<tr>
<td><strong>8.54i</strong> Extension of follow-up, 2-5 years</td>
<td>78</td>
<td>86</td>
<td>2</td>
<td>3</td>
<td>De Witte, Bowen</td>
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<td><strong>8.54j</strong> Extension to three more registries (new countries): Portugal, Poland and Denmark</td>
<td>73-76</td>
<td>80</td>
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<td>2</td>
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<tr>
<td><strong>8.54k</strong> Extension of registry after 1000 patients</td>
<td>86</td>
<td>Ongoing</td>
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<td>De Witte, Bowen</td>
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<td><strong>Translational Research</strong></td>
<td><strong>8.59</strong> ESH-EHA Scientific Workshop on Experimental Haematopoiesis and Therapeutics 2010. (MRD, Gene Profiling, Immunophenotyping, Cytogenetics in AML and MDS)</td>
<td>78</td>
<td>80</td>
<td>2</td>
<td>3</td>
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<td><strong>8.80</strong> Side study of Low Risk MDS Registry: Iron pathophysiology.</td>
<td>78</td>
<td>86</td>
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<td><strong>8.80a</strong> Side study of Low Risk MDS Registry: Imaging of iron overload</td>
<td>75</td>
<td>86</td>
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<td>4</td>
<td>De Witte</td>
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<td><strong>8.82</strong> Side study of Low Risk MDS Registry: Geriatric Assessment: presentation at EHA 2010, Barcelona</td>
<td>78</td>
<td>78</td>
<td>0</td>
<td>4</td>
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<td><strong>8.83</strong> Evaluation of the prognostic value of TET-2 mutations in MDS</td>
<td>76</td>
<td>86</td>
<td>0</td>
<td>4</td>
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<td><strong>8.84</strong> Evaluation of the prognostic value of TET-2 mutations in AML</td>
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<td>86</td>
<td>0</td>
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<td>Jansen</td>
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Table 8.2 List of milestones WP8, 2010 and 2011

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<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
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<td>8.25</td>
<td>Publication of the results of the second Workshop on flow cytometry in MDS (Oct 2009 in Munich, Germany)</td>
<td>73-86</td>
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<td>8.54m</td>
<td>Second presentation on follow-up data of the prospective, non-interventional multi-center European MDS Registry (IPSS Low and Intermediate-1) at the ASH meeting 2010</td>
<td>104</td>
<td>73-86</td>
<td>Bowen</td>
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<td>8.75</td>
<td>Establishment of a high-risk European MDS registry: Setting up central IT structure</td>
<td>78-86</td>
<td>86</td>
<td>Bowen</td>
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<tr>
<td>8.83</td>
<td>Evaluation of the prognostic value of TET-2 mutations in MDS</td>
<td>76</td>
<td>86</td>
<td>Jansen</td>
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</tbody>
</table>

Section 3: Consortium management

In general, we speculate that MDS WP8 has been an active and productive WP within the European LeukemiaNet, as indicated by this report and the website content of WP8. We have interacted with many different Workpackages of European LeukemiaNet for integrated activities: e.g. Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11, (cytogenetics in diagnostic guidelines in MDS), AML WP5 (integration of diagnostic guidelines in AML and MDS, shared criteria of response for AML and MDS) and Gene Profiling WP13 (Multi-Center Microarray Study for the Molecular Classification of Leukemia).

The cooperation with WP11 and WP13 is coordinated within the COST action (coordinator: Dr Ken Mills) and Eugesma (coordinated by Dr Rose-Ann Padua) They organised two Working group meetings each attended by ~95 participants from 20 countries. Cost (Action) and Eugesma participants organized two major FP7 applications:

- MATRIX involving participants from WG’s 1, 2, 3 & 4
  - Resistance in AML and MDS
  - Selected from 460 Stage I applications for Stage II
- DCDVAACL, a one-stage application, from WG4
  - Innovative Therapeutic Approaches and Interventions (DNA Vaccines)
  - One-stage application – currently in EU review

Close cooperation of many European MDS study groups resulted in much progress on the European MDS Registry Study (see Annex Section 3, WP8 (del. 8.53e). The inclusion started April 1st 2008. At the end of December 2009, the overall recruitment was 650 patients in 12 countries.

The study entitled “Prognostic significance and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes (MDS) is progressing well. This
International multicenter observational study “GIMEMA-ELN QoL - MDS 0108” aims to obtain additional key data to further facilitate clinical decision-making in MDS patients. This initiative fits very well in our deliverables on developing a frailty index for treatment decision-making for older patients with MDS or AML. Therefore, this study is incorporated in our LeukemiaNet activities.

Finally, much progress was made for the translational studies: Using SNP-arrays 40 novel recurrent genetic loci in MDS were identified (del.8.57). This resulted in three high ranking papers (see: 8.83 and 8.84).

The present steering committee of our workpackage has been in office for more than 6 years. The steering committee felt it important to continue and to extend its activities through active participation of “junior experts” in our field. The steering committee discussed the extension of the steering committee with young investigators during the ESH-EHA MDS postgraduate course, in Mandelieu France. Uwe Platzbecker Dresden), Lionel Ades (Avicenne), Arjan van de Loosdrecht (Amsterdam), Luca Malcovati (Pavia), Wolf-Karsten Hofmann (Mannheim) and Martin Jadersten (Huddinge) have been invited as steering committee members. We shall identify the topics which the junior steering committee members will coordinate.

Section 4: Other Issues
Ethical issues – none,
Competitive calls -none

Section 5: WP-Performance

<table>
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<th>Performance indicators</th>
<th>Status</th>
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</thead>
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<tr>
<td>Number of clinical trials started and/or completed</td>
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</tr>
<tr>
<td>Number of patients recruited into clinical trials</td>
<td>Not reported</td>
</tr>
<tr>
<td>Number of patients included into registries</td>
<td>The inclusion started April 1st 2008. In February 2011, the overall recruitment was 1000 patients in 12 countries.</td>
</tr>
<tr>
<td>Improved predictive, prognostic or quality of life assessments</td>
<td>See del. 8.25b Yearly update of the guidelines for diagnostic standards in MDS and presentation on the ELN website. The MDS guidelines were adapted on the basis of the new WHO classification, 4th edition 2008 and presented on the ELN website. See del. 8.25b Addition of information on Immunophenotyping in diagnostic guidelines in MDS/AML. This concerns a cooperation of WP8 and WP10 (Diagnostics). The second International ELN Workshop on standardization of flow cytometry in MDS in Munich, October 2009 was very successful. A general consensus protocol developed during the first Workshop has been published and became operational in the beginning of 2009. See del. 8.51d Frailty index for treatment decision-making for older patients with MDS or AML. The comprehensive geriatric assessment was performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. This index has been validated in a group of patients with myeloid malignancies candidates for allogeneic stem cell transplantation. In addition, this model is tested prospectively in the study entitled “Prognostic significanc and longitudinal assessment of patient-reported quality of life and symptoms in high risk myelodysplastic syndromes (MDS). An international multicenter observational study” GIMEMA-ELN QoL - MDS 0108 which has started in 2008.</td>
</tr>
<tr>
<td>Performance indicators</td>
<td>Status</td>
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<td>----------------------------------------</td>
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</tbody>
</table>
| Degree of harmonization of trials      | Multiple deliverables regarding harmonization of trials have been fulfilled and the results are presented on the ELN website:  
See del. 8.25b Guidelines for diagnostic standards.  
See del. 8.25b Immunophenotyping in diagnostic guidelines, a cooperation of WP8 and WP10 (Diagnostics). A general consensus protocol developed during the first Workshop has been published (see pdf 8.5) and became operational in the beginning of 2009. See del. 8.27c Webbased scenario analysis by the experts for development of evidence and consensus based guidelines for therapy of MDS (see attachment 8.13)  
See del. 8.29 Development of a web-based training program using virtual patients to exercise the therapeutic guidelines and supervised by experts and European clinicians http://mds.haematologica.org  
See del. 8.31b We updated the list of all trials by MDS study groups in Europe.  
See del. 8.32 Every year an inventory on new drugs/treatments is made, by asking all participants of the MDS WP for input regarding this issue. Furthermore, new drugs/treatments is discussed at several MDS WP8 meetings. If necessary an investigator meeting on a particular new drug/treatment is organized. |
| Number of SOPs and consensus papers    | 4                                                                                                                                                                                                      |
| Number of publications                 | 56                                                                                                                                                                                                     |
| Number of meetings                    | 11                                                                                                                                                                                                     |
| Number of accredited trials           | See 8.31b                                                                                                                                                                                             |


9 **CMPD (WP09)**

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

9.5 Regular WP meetings

WP9 participants met 3 times in 2010 during International congresses: in Mannheim on February, in Barcelona on June 10 (EHA meeting), and in Orlando on December 5 (ASH meeting). Written minutes of those meetings were provided to WP9 members, and are available upon request.

9.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group

Minutes of meetings were sent to the NMC.

9.26e Phase II study of imatinib therapy in PV patients – (recruitment closed, progress report)

The recruitment was completed in June 2009.

Primary objective: To determine the antiproliferative effects of imatinib on the major parameters of the increased myeloproliferation in patients with PV, utilizing a dose escalation schedule.

The main endpoint of the study is the response rate to the therapy (reduction of the phlebotomy rate, of platelet count, of white blood cell count, of spleen size) after one year of treatment.

Secondary objectives: To determine the rate and severity of side effects of the therapy; to determine the PV-related complications and symptoms (thrombosis, bleeding, microvascular disturbances, pruritus) under therapy with imatinib.

Main inclusion criteria: Newly diagnosed or pretreated patients with PV according to the WHO criteria. Patients ≥18 years of age no upper age limit.

Main exclusion criteria: Postpolycythemic myelofibrosis. Secondary acute leukemia. Pretreatment with $^{32}$P. Other malignant disease requiring therapy or with life expectancy of less than one year.

**Treatment:** Imatinib starting dose of 400mg daily. During follow up, the dose will be adapted to response and tolerability (stepwise dose escalation to 600mg and 800mg or reduction to 300mg in adaptation to blood counts, spleen size and side effects).

**Results:**

Included patients: 34 patients (17f / 17 m) from 9 German centers

Median age (64 (44 – 84) years

Previous therapy: phlebotomy (n = 17), cytoreductive therapy (n = 13)

Median duration of imatinib therapy: 13 (0,1 – 35) months

Response rate of at least one parameter (erythrocytosis, leukocytosis, thrombocytosis, splenomegaly): observed in approximately 60% of patients.
9.28e Advancement in a registry of pregnancies in ET (ongoing)

There is an ongoing registry of pregnancies in MPD patients, with forms available on the ELN website, chaired by M. Griesshammer (Minden). At last evaluation, 143 pregnancies were reported in 71 patients, implemented by hematologists from 6 different EU countries. The majority of patients had ET (57/71), but several pregnancies in PV (10 patients) and PMF (4 patients) patients were also reported. Pregnancy outcome could be evaluated in 125 pregnancies. Live birth rate was 70%, including 63% of full term normal deliveries, a rate significantly higher than previously reported (about 50% in the literature). Spontaneous abortions remained the main complication, occurring in 28% of pregnancies. Maternal complications were low, but clearly higher than in “normal” pregnancies: preeclampsia (4%), major bleeding (5%), venous thromboembolism (4%). Implementation of this registry will allow better knowledge and recommendation for management of pregnancies in MPD patients.

9.30e Advancement in a randomized clinical trial of 2 phlebotomy regimens in low-risk PV start of trial (still recruiting patients)

**Patients:** PV diagnosed according to WHO criteria, age > 18 years.

**Randomization:** between standard target hematocrit at less than 45%, and the experimental arm with a target hematocrit between 45 and 50%. The study aim is to recruit 500 PV patients in each arm.

**Primary endpoint:** To demonstrate that, in patients with PV and treated at the best of recommended therapies (i.e., low-dose aspirin when indicated and adequate control of standard cardiovascular risk factors), long term, aggressive cytoreductive therapy aimed at maintaining HCT < 45% (either with phlebotomy and/or HU) is more effective than cytoreductive therapy aimed at maintaining HCT in the range 45-50% (either with phlebotomy and/or HU) in reduction of:
- CV deaths plus thrombotic events (stroke, acute coronary syndrome [ACS], transient ischemic attack [TIA], pulmonary embolism [PE], abdominal thrombosis, deep vein thrombosis [DVT], and peripheral arterial thrombosis).

**Secondary endpoints:** The events included in the PEP, arterial and venous thrombosis, major and minor thrombosis as well as hospitalization for any reason, hospitalization for CV reason, malignancy, and PV-related malignancy (progression to myelofibrosis, myelodysplastic or leukemic transformation) will be analyzed separately to assess the full benefit/risk profile of experimental treatments.

**Recruitment** has started in May 2008. As of January 2011, 343 patients were registered and 300 were randomized. The study is still ongoing.

9.31e Advancement in a registration study of high-risk ET patients treated with Anagrelide – (recruitment closed, progress report)

The Exels study is a non-interventional, multicenter, European observational study of a large cohort of at-risk ET patients on cytoreductive therapy. The study was a prerequisite for the registration of
Xagrid® (anagrelide) as an orphan drug by EMEA. 125 centres in Europe have now completed the recruitment of 3600 patients. The inclusion was closed in April 2009. The patients will be followed for 5 years, and the first patient to complete the study will do so in March 2010.

The patients are followed with 6-monthly data collections regarding disease complications, toxicity, drug use, efficacy of therapy, death and pregnancy. Reports to the DSMB every 6 months have not shown any new safety concerns.

The analysis of collected data shows that the treatment pattern is rather homogenous throughout Europe with a couple of exceptions. Hydroxyurea is first line treatment except in patients under 50 years of age, where anagrelide is more common.

The cohort consists of two large treatment groups, hydroxyurea (around 2000 patients), anagrelide (around 900 patients) as well as more than 150 patients with combination therapy and about 150 treated with interferon. Pipobroman is used only in a couple of countries in Europe.

The number of events is still too low to allow statistical comparison of various treatment groups. A total of 101 thrombohemorrhagic events were reported at the latest data-cut in September 2009.

This study, which is sponsored by Shire, the manufacturer of Xagrid, now encompasses a large cohort of ET patients, and results are expected to include frequency of thrombosis, bleeding, transformation to myelofibrosis and leukaemia as well as safety data. Final reports will be due after the completion of the last patient in 2014, and an interim report will be produced after the September 2011 data cut.

Publications on demography, treatment patterns in Europe, treatment in elderly ET patients are forthcoming during 2011 and 2012.

9.34e Protocol for a multicenter study of vorinostat in CMPDs (started in 2009, still recruiting patients)

The COSMYD protocol "Safety and Efficacy of Vorinostat in the Treatment of Polycythemia Vera and Essential Thrombocythemia" - a multicenter study enrolling patients from centers within the COSMYD-group (UK, Holland, Sweden and Denmark).

This is an investigator-driven study in several countries within the European LeukemiaNet. H.C. Hasselbalch is the representative of the Sponsor for this Study – University of Copenhagen, Department of Hematology, Herlev Hospital – and Professor Mary Frances McMullin, Belfast City Hospital, is the representative for the UK – sites in the study. The study has now concluded enrolment of the target cohort of 60 patients. H.C. Hasselbalch has been currently involved in monitoring timely enrolment of patients and several News Letters have been forwarded to the participating centres. Preliminary data are encouraging. An abstract on preliminary results has been forwarded to EHA, London June 2011. Since vorinostat seems to have a striking effect, including a marked reduction in huge splenomegaly in one of the patients HCH has elaborated a protocol aiming at enrolling 20 patients with myelofibrosis and large splenomegaly. This study will be conducted in Denmark only. Furthermore, an application has been forwarded to extend the study period in order to obtain long-term
efficacy and safety data on vorinostat in the treatment of patients with Ph-negative chronic myeloproliferative neoplasms. This study will be conducted in UK only.

9.36b Survey and harmonization of assay methods for JAK2-V617F (ongoing)
This deliverable refers to a project in common with WP12, MRD. In this year, we have performed additional experiments to characterize different published quantitative assays for JAK2V617F mutation, and we have now resolved that three of the initial 8 assays present acceptable characteristics of reproducibility and specificity. These are being used in current experiments. In collaboration with Ipsogen, that is involved in WP12, we have also performed a RQ assay using different plasmid preparations of JAK2 wild-type and V617F-mutated, as well as progressive dilutions of JAK2V617F mutated HEL cells. The data have been centrally collected and analyzed, and they have been discussed at the WP12 meeting held in Orlando, December 2010. Furthermore, the laboratory of A. Vannucchi has prepared and distributed to all participant laboratories progressive dilutions of a different JAK2V617F-mutated cell line, UKE-1, both as cell dilutions in normal mononuclear cells and as dilutions of purified DNA. Analysis of these preparations has been accomplished by most of involved laboratories, and overall results are planned to be presented in Mannheim, February 2012. Finally, this WP has interacted with the MPN&MPNr-Euronet action COST action BM-0902, coordinated by Dr Sylvie Hermouet, which aims at the standardization and dissemination in Europe of molecular techniques for the study of MPN.

9.37b Registry of IFN-treated MPD patients (started in 2010)
Last year, H.C. Hasselbalch forwarded a proposal for a deliverable "A Registry of Patients with Polycythemia Vera, Essential Thrombocythemia and Primary Myelofibrosis treated with Alpha-Interferon within European LeukemiaNet". This was further discussed during the ELN annual meeting in Mannheim.

“The Nordic Long-Term IFN-Efficacy Study in Patients with Polycythaemia Vera and Essential Thrombocythemia”
On the initiative of H.C. Hasselbalch this study aims at collecting a large cohort of patients with ET and PV being treated long term with pegylated Interferon-alpha2. The impetus for this study is the observation in several Danish Patients that long-term treatment with IFN-alpha is able to induce a state of “minimal residual disease “ with normalisation of the bone marrow and “complete molecular remission“ with JAK2V617F mutation load below 1 %, even after discontinuation of IFN-alpha2 for up to 24 months (operational cure?). A total of 75 Danish patients have been enrolled and additional Danish patients are expected to be included in the study. An interim analysis will hopefully be presented at ASH 2011.
9.38 A pilot study of efficacy and safety of erlotinib in PV and ET (to be started in 2010)

"Erlotinib in the Treatment of Polycythemia Vera and Essential Thrombocythemia. A Pilot Study of Efficacy and Safety"

The study has been delayed owing to lack of financial support in the Clinical Research Unit. The protocol is expected to be activated at the Department of Oncology-Hematology, Roskilde Hospital, University of Copenhagen, within the next 6 months. It is a Pilot Study which will include a total of 10 patients. Based upon the experience in the pilot study it will be decided whether to extend the study to other centres.

Status April 12, 2011: Unfortunately, this study – ready to include patients – had to be cancelled due to the retraction of the manufacturer of erlotinib.

9.39 Study of MPD leukemic transformations (publication in progress)

Transformation to acute myeloid leukemia (AML) is a known complication of myeloproliferative neoplasia (MPN). Recent studies have reported the high incidence (53%) of JAK2 negative blasts from transformed JAK2V617F-MPN. We collected blasts and mature myeloid cells from BM of 40 newly diagnosed patients with AML secondary to MPN and analyzed the JAK2 status before and after leukemic transformation by ASO-PCR and (QRT)-PCR assay. At the time of MPN, JAK2V617F was detectable in 28 of 40 patients. No cytogenetic abnormalities or MPL and JAK2-exone 12 mutations were detected at this stage. A significantly shorter (p= 0.02) time to progression was found in previously JAK2 mutated MPN patients. In our cohort of patients we found that JAK2V617F mutation was still present at the blast transformation in both compartments: CD34+ cells and CD15+ cells in 26 of 28 JAK2 mutated MPN (92%). Two of 28 patients (7%) developed JAK2V617F negative AML starting from a mutated PV with a mean TTP of 5.14 yrs. No differences (p= 0.3) in the allele burden were found comparing MNCs from chronic phase with MNCs of leukemic transformations or comparing GRA with blasts in AML phase. CONCLUSIONS: In our work, the loss of JAK2V617F mutation during AML progression is a rare event (7%).

9.40 Myeloproliferative Neoplasms: Management recommendations of the ELN

New project achieved in 2010: Definition of resistance / intolerance to hydroxyurea in PV and PMF

The ELN WP9 decided to review recent data regarding therapy, standard monitoring procedures, and definitions of responses and to produce recommendations aimed at contributing to the optimization and standardization of management of the three Ph-negative classical MPNs. An expert panel of 21 experts, including several experts from the USA, was selected for their expertise in research and clinical practice of management of MPNs. Using a consensus process, the expert panel produced updated recommendations, that were published in the Journal of Clinical Oncology.

Publications: See Annex Section 3, WP9.
### List of deliverables WP9, 2010

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<th>Deliverable Name</th>
<th>Date due</th>
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<td>Regular WP meetings</td>
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<tr>
<td>9.6</td>
<td>LP reports to NMC regarding structure, trial activities and integration of national leukemia trial group (1 page, bullet point style)</td>
<td>79,86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Kiladjian</td>
</tr>
<tr>
<td>9.26e</td>
<td>Phase II study of imatinib therapy in Pv patients – (recruitment closed, progress report)</td>
<td>78</td>
<td>78</td>
<td>0</td>
<td>2</td>
<td>Lengfelder</td>
</tr>
<tr>
<td>9.28e</td>
<td>Advancement in a registry of pregnancies in ET (ongoing)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>3</td>
<td>Griesshammer</td>
</tr>
<tr>
<td>9.30e</td>
<td>Advancement in a randomized clinical trial of 2 phlebotomy regimens in low-risk PV start of trial (still recruiting patients)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>3</td>
<td>Barbui Finazzi</td>
</tr>
<tr>
<td>9.31e</td>
<td>Advancement in a registration study of high-risk ET patients treated with Anagrelide – (recruitment closed, progress report)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Birgegard</td>
</tr>
<tr>
<td>9.34e</td>
<td>Protocol for a multicenter study of vorinostat in CMPDs (started in 2009, still recruiting patients)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Hasselbalch</td>
</tr>
<tr>
<td>9.36b</td>
<td>Survey and harmonization of assay methods for JAK2-V617F (ongoing)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>5</td>
<td>Vannucchi</td>
</tr>
<tr>
<td>9.37b</td>
<td>Registry of IFN-treated MPD patients (to be started in 2010)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>3</td>
<td>Kiladjian Hasselbalch</td>
</tr>
<tr>
<td>9.38</td>
<td>A pilot study of efficacy and safety of erlotinib in PV and ET (to be started in 2010)</td>
<td>73-86</td>
<td>Nd</td>
<td>0</td>
<td>0</td>
<td>Hasselbalch</td>
</tr>
<tr>
<td>9.39</td>
<td>Study of MPD leukemic transformations (publication in progress)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Rinaldi</td>
</tr>
<tr>
<td>9.40</td>
<td>Myeloproliferative Neoplasms: Management recommendations of the ELN</td>
<td>73-86</td>
<td>83</td>
<td>0</td>
<td>8</td>
<td>Barbui</td>
</tr>
</tbody>
</table>

### List of milestones WP9, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP9 CMDP</td>
<td></td>
<td></td>
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<tr>
<td>9.36b</td>
<td>Survey and harmonization of assay methods for JAK2-V617F</td>
<td>73-86</td>
<td>86</td>
<td>Vannucchi</td>
</tr>
<tr>
<td>9.40</td>
<td>Myeloproliferative Neoplasms: Management recommendations of the ELN</td>
<td>73-86</td>
<td>82</td>
<td>Barbui</td>
</tr>
</tbody>
</table>

### Section 4: Other Issues

Ethical issues - none

Competitive calls - none
### Section 5: WP-Performance:

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Number of clinical trials started and/or completed</td>
<td>4</td>
</tr>
<tr>
<td>Number of patients recruited into clinical trials</td>
<td>About 1500</td>
</tr>
<tr>
<td>Number of patients included into registries</td>
<td>About 500</td>
</tr>
<tr>
<td>Improved predictive, prognostic or quality of life assessments</td>
<td>2</td>
</tr>
<tr>
<td>Degree of harmonization of trials</td>
<td>0</td>
</tr>
<tr>
<td>Number of SOPs and consensus papers</td>
<td>1</td>
</tr>
<tr>
<td>Number of publications</td>
<td>48</td>
</tr>
<tr>
<td>Number of meetings</td>
<td>5</td>
</tr>
<tr>
<td>Number of meta-analyses</td>
<td>0</td>
</tr>
<tr>
<td>Number of accredited trials</td>
<td>0</td>
</tr>
</tbody>
</table>
10 Diagnostic platform (WP10)

Objectives and starting point of work at beginning of reporting period

The major goals this year were to publish information on morphology and consensual flow recommendations for leukemia diagnosis which was indeed the case.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

10.5 Regular WP meetings, telephone conferences

WP10 participants met at the ELN annual meeting in Mannheim. Some of the team met also at the EGIL meeting in Berlin in March, at the MDS meeting in Munich in October and at the EHA European School in Cascais in November 2010.

10.6 LP reports to NMC regarding structure, activities and integration of national groups

Reports have been forwarded to the ELN management as requested.

10.11f Ongoing European quality control rounds on (morphological) leukemia diagnostics on the ‘reference center level’

The morphology faculty completed a comprehensive and published study, available also on line on the ELN website.

10.18e Ongoing extension of internet library of microscopical pictures (incl. immunocytoology), case reports, leukemia diagnostics

All of the activities of WP10 that are posted on the website of the ELN are potentially useful for self-training or as teaching material. This seems, from feedback in Mannheim, to be indeed well used. Pr Gina Zini obtained from the ELIC interesting data on the use of our pages. The participation of WP10 to educational sessions especially within the European School of Hematology should also be mentioned. WP10 applied this year to be one of the EHA SWGs.

The internet library of powerpoint presentations on leukemia diagnostics that was established (www.leukemia-diagnostics.org).

10.22e Interaction with other groups in diagnostic for design of algorithms

Interaction is fruitfully ongoing on the MDS topic, with published and submitted papers (see Annex section 3, WP10).

10.24e Specific project on microarray for preDC leukemia with WP13-continued

Published joint paper and ongoing discussions about pDC ALL.
10.25 European workshop on Minimal Residual Disease strategies in immunophenotyping

Review paper published and planned meeting in October with MRD as the major flow topic.

10.26 Ongoing cooperation with WP9 on MDS immunophenotyping

See 10.22

*Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved*

**Table 10.2: List of Deliverables WP10, 2010**

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Delivery/Achieve date</th>
<th>Actual/Fo recast delivery date</th>
<th>Estimated indicativ e person months</th>
<th>Used indicative person months</th>
<th>Responsible lead participant/ investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP10</td>
<td>Diagnostics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.5</td>
<td>Regular WP meetings, Telephone conferences</td>
<td>78,80</td>
<td>78, 79, 80, 83, 86</td>
<td>0</td>
<td>2</td>
<td>Béné</td>
</tr>
<tr>
<td>10.6</td>
<td>LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style)</td>
<td>79,86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Béné</td>
</tr>
<tr>
<td>10.11f</td>
<td>Ongoing European quality control rounds on (morphological) leukemia diagnostics on the ‘reference center level’</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Zini</td>
</tr>
<tr>
<td>10.18e</td>
<td>Ongoing extension of internet library of microscopical pictures (incl. immunocyto) , case reports, leukemia diagnostics</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Link Hastka</td>
</tr>
<tr>
<td>10.22e</td>
<td>Interaction with other groups in diagnostic for design of algorithms</td>
<td>66-78</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>Béné</td>
</tr>
<tr>
<td>10.24e</td>
<td>Specific project on microarray for preDC leukemia with WP13-continued</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>3</td>
<td>Béné</td>
</tr>
<tr>
<td>10.25</td>
<td>European workshop on Minimal Residual Disease strategies in immunophenotyping</td>
<td>80</td>
<td>86, ongoing</td>
<td>0</td>
<td>4</td>
<td>Béné</td>
</tr>
<tr>
<td>10.26</td>
<td>Ongoing cooperation with WP9 on MDS immunophenotyping</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Béné</td>
</tr>
</tbody>
</table>

**Table 10.3: List of milestones WP10, 2010**

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP10</td>
<td>Diagnostics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.18e</td>
<td>Ongoing extension of internet library of microscopical pictures (incl. immunocyto), case reports, leukemia diagnostics</td>
<td>73-86</td>
<td>On line</td>
<td>Link Hastka</td>
</tr>
<tr>
<td>10.25</td>
<td>European workshop on Minimal Residual Disease strategies in immunophenotyping</td>
<td>80</td>
<td>Planned for October 2011</td>
<td>Béné</td>
</tr>
<tr>
<td>10.26</td>
<td>Ongoing cooperation with WP9 on MDS immunophenotyping</td>
<td>73-86</td>
<td>Papers pending next meeting end of 2011 in Pavia</td>
<td>Béné</td>
</tr>
</tbody>
</table>
Section 3: Consortium management

Management of the WP10 is going smoothly, with a lot of electronic communication. New members are joining. It is sometimes required to renew call for papers revision or documentation but the electronic way chosen costs only time. Cooperation with other programs is effective with WP8, WP13 and WP12. Contacts have been made with the clinical WP and will be reinforced.

Section 4: Other Issues

Ethical issues-none
Competitive calls-none

Section 5: WP10-Performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establishment of European reference panels</td>
<td>done</td>
</tr>
<tr>
<td>Organization of interdisciplinary consensus conferences</td>
<td>done</td>
</tr>
<tr>
<td>Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes</td>
<td>done</td>
</tr>
<tr>
<td>Organization of quality control rounds</td>
<td>Done, new round in progress</td>
</tr>
<tr>
<td>Establishment of European telemicroscopical networks</td>
<td>ongoing</td>
</tr>
<tr>
<td>Set up of internet forum</td>
<td>done</td>
</tr>
<tr>
<td>Training courses and improvement of teaching facilities with new technologies</td>
<td>done</td>
</tr>
<tr>
<td>Number and quality of publications within the network</td>
<td>12</td>
</tr>
</tbody>
</table>
11 Cytogenetics (WP11)

Objectives and starting point of work at beginning of reporting period

- Intensify harmonization of cytogenetic techniques between laboratories based on consensus protocols and practical training in other laboratories.
- Establish working groups on distinct cytogenetic questions
- Improve analysis of large and complex cytogenetic data sets

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives

11.5 Regular WP meetings

- WP meeting at the annual network symposium in Mannheim, 3.-4. February 2010
- 4th Work Group meeting and 5th Management Committee meeting Munich of COST and ELN, held at the Munich Leukemia Laboratory, Munich 18.-19. October 2010
- WP meeting at the annual network symposium in Mannheim, 2.-3- February 2011

11.6 LP reports to NMC regarding structure, activities and integration of national cytogenetics groups:

LP reports were prepared in time.

11.10f Further presentation of difficult cases

For questions regarding cytogenetic methods, nomenclature, FISH-probes, and help in difficult cases technical support was continuously offered in the WP11 website and an email address to contact experts of the field was presented.

11.16f Further identification of new recurring chromosome aberrations by analyzing large cytogenetic databases

The online Cytogenetic Data Analysis System (CyDAS.org) was continued for the analysis of large cytogenetic data sets.

11.17f Continuation of data collection on rare abnormalities

New cases with rare chromosome aberrations were collected in collaboration with the Atlas of Genetics and Cytogenetics in Oncology and Hematology which is edited by Dr. Huret such as t(8;9)(p12;q33); t(1;21)(p32;q22).
11.18f Continuation of identification and analysis of cryptic and complex chromosome aberrations by using new cytogenetic methods

SNP microarray analysis revealed cytogenetically cryptic 17q11 deletion encompassing the NF1 gene in 6 out of 37 AML with CBFB-MYH11 positive AML. Based on this finding a new project on the identification of NF1 deletions using interphase FISH in other myeloid malignancies was started. 889 myeloid malignancies were analyzed by FISH for NF1 deletions. NF1 deletions occur in 7.3% of de novo AML, 4% of CMML, 1.2% of MDS and 5.1% of MPN and therefore are a frequent and important alternative genetic mechanism for activating the RAS pathway in adult myeloid malignancies. As the majority of NF1 deletions are not detectable by chromosome banding analysis due to the small size of the deletion, FISH analysis is required. Furthermore, in 58% of cases with NF1 deletion as detected by FISH a NF1 mutation was observed in the remaining allele.

Two novel cytogenetically cryptic EVII rearrangements were characterized by SNP arrays and sequencing.

By combining SNP arrays, banding analysis and sequencing a novel acquired deletion of RAD51 could be identified in a case of MDS with isolated del(5q) by chromosomal banding analysis.

11.20f Continuous development and provision of additional methods

An additional interlaboratory test of the chromosome banding analysis procedure using viable leukemia cells involving 46 laboratories was initiated. An AML cell line carrying typical chromosome aberrations was used. The results are still pending.

11.23d/e Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Spain

A publication on cytogenetic findings of 2124 MDS patients of Germany and Austria appeared in December 2007 in BLOOD (Haase et al., Blood, 2007). The data collection and merging of the databases are still in progress:

Up to date, 3856 cases of primary and secondary MDS were collected of whom 2901 patients received no disease-altering therapy. The patients included are coalesced from the IMRAW- (Greenberg et al.; n=816), the German-Austrian (n=2011), and the Spanish (Solé et al.; n=975) databases. Additionally, 53 patients from an ICWG-cooperative project, supported by the MDS-Foundation, were included. Based on the 2901 primary, untreated patients mentioned above, a new comprehensive cytogenetic scoring system was designed. Dr. Schanz from Prof. Haases group wrote the manuscript regarding this project, statistic evaluation has been performed by Heinz Tüchler, Vienna. The manuscript has been submitted to JCO, was reviewed and is now under revision.

Dr. Schanz from Prof. Haases group also has performed a multicentric analysis on 2855 MDS patients that indicates an underestimation of poor risk cytogenetics in the IPSS. The manuscript has been submitted and was just accepted for publication in JCO (see Schanz et al, Annex section 3, WP11).

The data collection and merging of the databases is still in progress.
11.25d Cytogenetically unrelated clones in MDS
A recent update of this project yielded 95 cases with MDS cytogenetically unrelated clones which were collected from 11 different national and international (Greece, USA, Sweden, Japan, Spain, France) laboratories. The incidence, based on the international database described in 11.23c, is 0.7%. The most frequent combination was a clone with 5q deletion and a clone with trisomy 8 (43%). Overall, trisomy 8 is overrepresented in independent clones. The median survival of all patients with unrelated clones was 26.2 months, which has to be classified as an intermediate prognosis. Combinations of 5q-/+8 and isolated 5q- showed no statistically significant difference in survival (median survival: 42.7 months). Patients with a trisomy 8 clone and a clone with any other aberration showed an adverse progress (median survival 20.5 months). Combinations of 5q-/+8 had, in comparison to cases with +8 plus a clone with any other aberration, to a significant better survival (p=0.004).
Data have been presented recently at the annual meeting of the German Society of Hematology and Oncology, October 2010. A manuscript is in preparation.

11.26b Provide data for the establishment of a European external quality assessment to EUROGENTEST
The pilot Cytogenetic External Quality Assessment (CEQA) Scheme in Hematology of the EUROGENTEST has been established.

11.27b Administration of WP11 website and spreading of excellence by promotion of web-based information
The contents of the WP11 site were kept up to date by the WP11. E.g., the minutes of the annual Symposium were integrated.
## Table 11.1: List of Deliverables WP11, 2010

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Delivery/Achieve date</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months</th>
<th>Used indicative person months*)</th>
<th>Responsible lead participant/investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5</td>
<td>Regular WP meetings</td>
<td>78,86</td>
<td>78, 86</td>
<td>0</td>
<td>10</td>
<td>Fonatsch, Haferlach C.</td>
</tr>
<tr>
<td>11.6</td>
<td>LP reports to NMC regarding structure, activities and integration of national cytogenetics groups (1 page, bullet point style)</td>
<td>79,86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Fonatsch</td>
</tr>
<tr>
<td>11.10f</td>
<td>Further presentation of difficult cases</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Rieder Haferlach C</td>
</tr>
<tr>
<td>11.16f</td>
<td>Further identification of new recurring chromosome aberrations by analyzing large cytogenetic databases</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Rieder</td>
</tr>
<tr>
<td>11.17f</td>
<td>Continuation of data collection on rare abnormalities</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Haferlach C Rieder Fonatsch</td>
</tr>
<tr>
<td>11.18f</td>
<td>Continuation of identification and analysis of cryptic and complex chromosome aberrations by using new cytogenetic methods</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Rieder Haferlach C Fonatsch</td>
</tr>
<tr>
<td>11.20f</td>
<td>Continuous development and provision of additional methods</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Fonatsch Rieder</td>
</tr>
<tr>
<td>11.23d</td>
<td>Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Spain</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>Haase</td>
</tr>
<tr>
<td>11.25d</td>
<td>Cytogenetically unrelated clones in MDS</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Haase Haferlach C Fonatsch</td>
</tr>
<tr>
<td>11.26b</td>
<td>Provide data for the establishment of a European external quality assessment to EUROGENTEST</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Rieder Dastugue</td>
</tr>
<tr>
<td>11.27b</td>
<td>Administration of the WP11 website and spreading of excellence by promotion of web-based information</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Rieder</td>
</tr>
</tbody>
</table>
List of milestones WP11, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
</tr>
</thead>
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<tr>
<td>WP11 Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.23e</td>
<td>Continuous collection of cytogenetic and clinical data of MDS patients from Germany, Austria and Spain</td>
<td>73-86</td>
<td>86</td>
<td>Haase</td>
</tr>
<tr>
<td>11.26b</td>
<td>Provide data for the establishment of a European external quality assessment to EUROGENTEST</td>
<td>73-86</td>
<td>86</td>
<td>Rieder, Dastugue</td>
</tr>
</tbody>
</table>

Section 3: Consortium management
Cooperation with other workpackages is effective especially with WP6, WP8, WP9 and WP13.

Section 4: Other Issues
Ethical issues-none
Competitive calls-none

Section 5: WP-Performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establishment of European reference panels</td>
<td>in progress</td>
</tr>
<tr>
<td>Organization of interdisciplinary consensus conferences</td>
<td>COST meeting in cooperation with WP8 (MDS) took place</td>
</tr>
<tr>
<td>Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes</td>
<td>first consensus protocol published in Genes Chromosomes Cancer</td>
</tr>
<tr>
<td>Set up of internet forum</td>
<td>done</td>
</tr>
<tr>
<td>Number of rare abnormalities for which the prognostic impact could be clarified</td>
<td>1</td>
</tr>
<tr>
<td>Number of new recurrent abnormalities identified</td>
<td>2</td>
</tr>
<tr>
<td>Number and quality of publications within the network 2010</td>
<td>57</td>
</tr>
<tr>
<td>Implementation of technology transfer</td>
<td>in progress</td>
</tr>
<tr>
<td>Improved techniques with better results</td>
<td>in progress</td>
</tr>
</tbody>
</table>
Objectives and starting point of work at beginning of reporting period

A coordinated and integrated working group was successfully established to develop new assays to increase the proportion of patients with myeloid leukemias/myeloproliferative disorders (MPDs) who could potentially benefit from minimal residual disease (MRD) monitoring using real-time quantitative PCR (RQ-PCR) approaches. Key objectives over the last year have been to continue to improve standardization of established assays (i.e. BCR-ABL, JAK2 V617F in collaboration with WP4 and WP9, respectively), the evaluation of novel RQ-PCR assays (i.e. Wilms’ Tumor gene (WT1) and nucleophosmin (NPM1) mutation) and the validation and implementation of a computer software reporting package to improve standards of reporting of RQ-PCR data to clinicians, which also serves to facilitate comparison of results between laboratories.

While development of RQ-PCR assays for fusion genes associated with myeloproliferative disorders enables sequential MRD assessment to guide therapy with tyrosine kinase inhibitors (Jovanovic et al, Blood 2007; Metzgeroth et al, Br J Haematol 2008; Score et al, Leukemia 2009; Müller et al, Leukemia 2009; Hochhaus et al, Leukemia 2009), in acute myeloid leukemia (AML) we have been exploring a number of approaches whereby MRD detection could lead to improved management and clinical outcome. For leukemia-specific markers that afford relatively high levels of assay sensitivity (i.e. leukemic fusion genes e.g. PML-RARA, NPM1 mutation) it is possible to use MRD monitoring to pinpoint those patients destined to fail first-line therapy, thereby allowing the administration of additional treatment in first remission – this approach has been evaluated initially in acute promyelocytic leukemia (APL) (Grimwade et al, J Clin Oncol 2009). For AML cases lacking a leukemia-specific molecular marker, MRD monitoring relies upon flow cytometry to detect a leukemia-associated aberrant phenotype or RQ-PCR analysis of genes that are highly expressed in the blast population (e.g. WT1). In this situation, evidence to date suggests that MRD assessment is best suited to investigate the degree of leukemic blast reduction during early phases of therapy and its relationship to subsequent risk of relapse (reviewed Freeman et al, Semin Oncol 2008; Béné & Kaeda, Haematologica 2009; Grimwade et al, Curr Opin Oncol 2010; Smith et al, Blood Rev 2011). We have recently shown that determination of depth of response to induction chemotherapy using an optimized ELN WT1 assay provides an independent prognostic factor in AML suggesting that it could be used to enhance risk stratification (Cilloni et al, J Clin Oncol 2009; Grimwade & Hills, Hematology Am Soc Hematol Educ Program 2009). Development of optimized protocols for flow cytometric detection of MRD has been a focus of attention for the “Diagnostic Platform” workpackage (WP10) and we have established a joint program to investigate the optimal approach for MRD-directed therapy in AML cases lacking a leukemia-specific molecular target. Prospective parallel analysis of flow cytometry and optimized RQ-PCR assays is now being evaluated by ELN MRD laboratories within the context of large scale clinical trials. These studies will establish the extent to which MRD assessment affords additional prognostic information as compared to conventional risk factors, facilitating the
development of enhanced risk stratified treatment approaches to AML and providing more insights into the role of autologous or allogeneic transplantation in first remission.

Progress towards objectives – tasks worked on and achievements made with reference to planned objectives:

12.5 Regular WP meetings

Instrumental to the progression and development of the experimental program for WP12 over the course of the last year has been the provision for regular meetings. WP12 meetings were linked to international hematology meetings: LeukemiaNet Annual Symposium, Mannheim (2nd February 2010 & 1st February 2011) and the European Hematology Association (EHA), Barcelona (10th June 2010). A separate EUTOS BCR-ABL molecular monitoring group meeting was held on 9th June 2010 in Barcelona.

12.6 LP reports to NMC regarding structure, activities and integration of national groups

Minutes from each WP12 meeting are drawn up by the lead participant and submitted to ELN NMC following approval by the membership of WP12. Updates from international BCR-ABL standardization meetings chaired by Prof Cross are fed back to the relevant national groups, such as the UK network of molecular diagnostic laboratories (meeting 25th June, 2010), the German Kompetenznetz “Akute und chronische Leukämien”, the Italian and the Nordic networks.

12.10c Evaluation of expression levels of target genes in diagnostic material

Prior to this reporting period, WP12 projects had established through application of optimized RQ-PCR assays that leukemic fusion genes e.g. **FIP1L1-PDGFRA** in hypereosinophilic syndrome (Jovanovic et al, Blood 2007; Reiter et al, Haematologica 2007) and **PML-RARA** in acute promyelocytic leukemia (Grimwade et al, J Clin Oncol, 2009) exhibit significant variation in expression in diagnostic samples (~ 3-log range), which impacts significantly upon sensitivity of assays to detect MRD. Over the course of this year WP12 participants have continued to focus on the analysis of **NPM1** mutations and **WT1**, which afford the opportunity to evaluate response to therapy using a molecular marker in a substantial proportion of AML cases.

**NPM1**: RQ-PCR assays have been developed for the commonest **NPM1** mutations (types A, B & D) by Prof Saglio’s group (Gorello et al, Leukemia 2006) and evaluated more widely within WP12. In addition, RQ-PCR assays that have been shown to be mutant specific have been developed for a number of rarer mutations, including Types G, H, I, J, N, Om, S and previously unreported mutations. Analysis of diagnostic samples has shown that the **NPM1** mutant allele is highly expressed, typically affording assay sensitivities of 1 in $10^5$ (Figure 12.1).
Figure 12.1: Normalized $NPM1$ mutant transcript level in diagnostic and follow-up samples from patients recruited to the UK National Cancer Research Institute (NCRI) AML17 trial. $NPM1$ mutant transcripts were highly expressed at diagnosis, typically allowing detection of MRD at a sensitivity of 1 in $10^5$ in follow-up samples. Abbreviations: d, diagnosis, pc, post-course; m, months.

$WTI$: This is an interesting potential target for MRD detection in that it has been reported to be over-expressed in approximately 70% of AML and is being investigated as a target for immunotherapy in this disease. In a project led by Daniela Cilloni and Giuseppe Saglio involving 11 WP12 laboratories, 9 published or “in-house” $WTI$ assays were systematically analyzed in parallel prior to this reporting year, leading to the selection of an assay located within exons 1 and 2, which was confirmed to be RNA specific and afforded greatest sensitivity. The selected “ELN $WTI$” assay also has the distinct advantage that it is located in a region of the gene that is rarely subject to mutation in AML. Indeed $WTI$ mutations which occur in ~10% of normal karyotype AML typically involve exons 7 and 9, where many published $WTI$ RQ-PCR assays are located thereby giving rise to the potential for “false negative” results. A full length $WTI$ plasmid was developed in conjunction with Ipsogen, Marseille and included in an “ELN $WTI$ kit” including primers and probe for the ELN $WTI$ assay, $ABL$ control gene assay (Europe Against Cancer) and respective plasmid standards. ELN $WTI$ kits were centrally distributed to participating laboratories for evaluation in large numbers of AML and non-leukemic samples (620 pre-treatment AML samples and 204 control PB, BM and PBSC samples). This allowed us to establish thresholds for background levels of expression of $WTI$ in normal PB and BM (upper limit 50 and 250 copies/ $10^4 ABL$ copies, respectively). This relatively high background level of expression limits the sensitivity of $WTI$ RQ-PCR assays to detect residual disease as compared to use of leukemia-specific markers (e.g. mutant NPM1, $PML-RARA$), suggesting that $WTI$ is most appropriately used to measure kinetics of disease response during early phases of therapy rather than
for serial MRD monitoring to track impending relapse. Based upon the differential expression of *WT1* in AML blasts and normal PB and BM, PB was considered to provide the preferred sample source allowing at least a 2-log reduction in transcripts to be discriminated in approximately half of AML patients.

No significant difference in *WT1* expression level as determined by the ELN assay was observed in AML cases harboring mutations in exons 7 and 9 of the gene as compared to those with wild type *WT1* (p=0.2). However, sequence analysis of a series of 32 cases of AML in which the ELN assay suggested a low level of *WT1* transcript expression (<250 copies/10^4 ABL copies), showed that they were enriched for mutations in exons 1 and 2 that disrupted primer and/or probe binding sites. The QC rounds and results of the final validation of the selected ELN *WT1* assay were recently published (Cilloni *et al*, *J Clin Oncol* 2009). The optimized ELN *WT1* assay has now been taken forward to assess MRD in multicenter clinical trials including the UK NCRI AML17 trial as a tool to enhance risk stratification and in the Epicept study (EPC2008-02) to evaluate response to histamine dihydrochloride and IL-2 as maintenance therapy in AML (12.15d).

12.11d Establish the additional proportion of leukemic patients that can be monitored using novel targets

The major focus of this work was the development of optimized RQ-PCR assays for detection of *WT1* and numerous different *NPM1* mutations, thereby substantially extending the proportion of AML patients that can be monitored for disease response beyond the range of fusion gene assays developed in the Europe Against Cancer program, which are applicable to only ~25% of AML.

*NPM1*

Over the course of the last year significant progress has been made, with the Munich, Ulm, Lille and UK groups providing strong evidence that *NPM1* mutations provide highly promising MRD targets that could allow the development of individualized treatment approaches in a significant proportion of AML patients. The Munich Leukemia Laboratory developed assays for 17 different *NPM1* mutation types based on the Lightcycler platform to analyze 252 AML cases (Schnittger *et al*, *Blood* 2009). Relapses were predicted by failure to reduce *NPM1* mutant level by more than 3 logs or by more than a 1 log rise in the mutant level. In this study *NPM1* mutant level was the most important predictor of relapse in multivariable analysis considering age and FLT3-ITD status. In a study led by Jan Krönke, the Ulm group has undertaken MRD detection in over 1600 samples from 245 adult AML patients (aged 16-60 years) with NPM1 mutations (Krönke *et al*, *J Clin Oncol* 2011, in press). MRD positivity following the second induction and at the post-consolidation timepoint were both predictive of subsequent risk of relapse. On longitudinal monitoring, median time from PCR positivity to relapse was 3 months; in some patients the time from molecular conversion to relapse was very prolonged and
the Lille group (Aline Renneville & Claude Preudhomme, unpublished data) has shown that very late relapses (up to 12 years from diagnosis) with stability of the \textit{NPM1} mutation can occur.

Since it is anticipated that \textit{NPM1} MRD monitoring data will increasingly be used to guide patient therapy, a major focus of WP12 has been to establish predictive thresholds, evaluate the optimal sample type for monitoring (PB vs BM), investigate the kinetics of disease relapse, and consider the stability of the \textit{NPM1} mutation as an MRD target. The Ulm group have reported that a threshold of 200 \textit{NPM1} mutant copies/10^4 \textit{ABL} copies to be an informative threshold for relapse. While, detailed mathematical modelling of the raw data provided from the Munich study, performed by Hans Ommen (Aarhus, Denmark), has suggested that \textit{NPM1} mutant levels above a threshold of 5 x 10^{-5} relative to \textit{ABL} are indicative of MRD (Ommen \textit{et al}, \textit{Blood} 2010). To investigate the optimal sample source for MRD monitoring, 174 paired PB and BM follow-up samples have been analyzed using the Gorello assays for Type A, B and D mutations by the Lille group. Good concordance was observed in \textit{NPM1} MRD results obtained with the two sample sources, with bone marrow typically affording ~0.5log greater sensitivity. Kinetics of disease relapse have been investigated in the Munich data set, showing that speed of relapse is significantly more rapid in the group with coexistent FLT3-ITD mutations than in \textit{NPM1}^\text{mut} cases with wild type FLT3 (Schnittger \textit{et al}, \textit{Blood} 2009; Ommen \textit{et al}, \textit{Blood} 2010). A key aim of WP12 is to establish optimal MRD monitoring schedules to predict disease recurrence and allow time for pre-emptive therapy to be delivered to prevent clinical relapse. Applying the mathematical model which is independent of assay sensitivity, the relationship between sampling interval and likelihood of relapse detection in \textit{NPM1} mutant AML in relation to other molecular subsets was defined. Thus, taking a 3 month bone marrow sampling interval as an example, the median time from molecular positivity to hematological relapse was 120 days for \textit{NPM1}^\text{mut} AML as compared to 200 days for \textit{CBFB-MYH11}+ patients, 90 days in \textit{RUNXI-RUNXIT1}+ cases, but as short as 45 days in \textit{PML-RARA}+ patients (Ommen \textit{et al}, \textit{Blood} 2010). Application of the mathematical model to the Munich data set showed that 6 monthly and 4 monthly BM examinations are required to achieve a relapse detection frequency of at least 90% with a window of at least 60 days to hematological relapse in \textit{NPM1c+/FLT3-ITD-} and \textit{NPM1c+/FLT3-ITD+} AML, respectively. Optimal MRD sampling frequencies are currently being prospectively validated in multi-center clinical trials such as the UK NCRI AML17 trial.

The stability of the \textit{NPM1} mutation as an MRD marker has also been considered. The Munich group reported stability of the \textit{NPM1} mutation in 84 of 84 paired diagnostic and relapse samples (Schnittger \textit{et al}, \textit{Blood} 2009). The Lille group have also found that the \textit{NPM1} mutation is stable based on an analysis of 55 paired diagnostic and relapse samples (Aline Renneville, Claude Preudhomme unpublished data). However, the Ulm group have observed occasional cases in which the \textit{NPM1} mutation is lost at “relapse”, including cases with acquisition of trisomy 8, \textit{RUNX1} mutation and \textit{MLL-PTD}, which most likely reflect development of t-AML rather than relapse of the original clone (Krönke \textit{et al}, \textit{J Clin Oncol} 2011, in press). These studies support the notion that \textit{NPM1} mutation is a
primary lesion in the pathogenesis of AML, but also serve to highlight the importance of comprehensive molecular and cytogenetic characterization of patients with “relapsed” AML.

The Munich \textit{NPM1}\textsuperscript{mut} assays involve use of a mutation-specific forward primer and common reverse primer, which do not amplify the mutation-specific plasmid standards originally developed by Ipsogen to be used in conjunction with the Gorello assays. Therefore, in collaboration with Ipsogen (Marseille), a set of universal plasmid standards for the commonest mutation types (A, B & D), accounting for ~90% of cases that can be used in conjunction with all RNA- and genomic DNA-based assays has been developed. These have been evaluated within WP12, showing good performance profile and will allow for standardized reporting of \textit{NPM1} MRD data across different RQ-PCR platforms.

\textbf{WT1:}

As part of the validation process the optimized ELN \textit{WT1} assay has been tested in samples derived from a cohort of 142 AML patients with high level \textit{WT1} expression at diagnosis (>20,000 \textit{WT1} copies/ \textit{10}^4 \textit{ABL} copies) treated with standard anthracycline and cytarabine-based therapy (Grimwade & Hills, \textit{Hematology Am Soc Hematol Educ Program} 2009; Grimwade \textit{et al}, \textit{Curr Opin Oncol} 2010). In this informative group, greater \textit{WT1} transcript reduction after induction predicted reduced relapse risk (hazard ratio, 0.54 per log reduction; 95% CI, 0.36 to 0.83; \textit{P}=0.004) that remained significant when adjusted for age, WBC count, and cytogenetics (Figure 12.2). Failure to reduce \textit{WT1} transcripts below the threshold limits defined in normal controls by the end of consolidation also predicted increased relapse risk (\textit{P}= 0.004).

\textbf{Integrated approaches to MRD detection:}

This aim is being addressed in conjunction with WP10, with current data indicating that virtually all AML patients can be subject to assessment of MRD using flow cytometry- and/or RQ-PCR- based approaches (reviewed Béné & Kaeda, \textit{Haematologica} 2009; Grimwade \textit{et al}, \textit{Curr Opin Oncol} 2010). A major aim of WP10 is to achieve greater collaboration between groups performing flow cytometry within the context of national clinical trials. Vincent van der Velden (Rotterdam) has been comparing RQ-PCR and flow cytometric approaches for MRD detection in pediatric AML (van der Velden \textit{et al}, \textit{Leukemia} 2010). Moreover, Gerrit Schuurhuis has led a national Dutch study prospectively evaluating flow cytometry-based MRD detection to predict outcome in AML and which is comparing flow data with molecular approaches to MRD detection using RQ-PCR. This theme is also being developed in the UK NCRI AML17 trial which commenced in April 2009 in which RQ-PCR (using EAC and ELN standardized assays) and flow-cytometry are being evaluated prospectively in parallel to establish whether early MRD assessment provides greater discriminatory power than current conventional criteria to identify those patients most and least likely to benefit from allogeneic transplantation in first remission.
Figure 12.2: Kinetics of minimal residual disease response following induction therapy are predictive of subsequent relapse risk in AML. The predictive value of MRD assessment by standardized ELN WT1 RQ-PCR assay was determined in a cohort of 142 AML patients treated with conventional anthracycline and cytarabine based treatment. Analysis was undertaken in AML cases with WT1 expression exceeding $2 \times 10^4$ copies/ $10^4$ ABL copies in pre-treatment samples, allowing the detection of at least a 2-log reduction in WT1 transcripts following induction, taking into account the background level of expression observed in normal hematopoietic tissues. The patient cohort included 91 cases reported previously (Cilloni et al, J Clin Oncol 2009) combined with a further 51 cases treated in the MRC AML15 trial (samples kindly provided by John Yin and Michelle Sale, Manchester Royal Infirmary and analyzed at Guy’s Hospital, London, UK).

**FIP1L1-PDGFRA:**  
A further focus of WP12 has been to develop RQ-PCR assays to direct molecularly targeted therapies in myeloproliferative disorders, in collaboration with WP9. Indeed the structure of WP12 has enabled our group to continue to collect clinical material from patients with relatively rare conditions such as FIP1L1-PDGFRA+ hypereosinophilic syndrome which we have found to account for ~10% cases of persistent unexplained eosinophilia (Jovanovic et al, Blood 2007), enabling us to gain further biological insights into this subset of disorders, complementing the work of WP9 (Burgstaller et al, Leukemia 2007; Reiter et al, Haematologica 2007; Metzgeroth et al, Br J Haematol 2008; Walz et al, Leukemia 2009). Indeed, in a study led by Prof Nick Cross, we also showed that genomic DNA based RQ-PCR assays for the FIP1L1-PDGFRA fusion can detect MRD following imatinib therapy with significantly greater sensitivity than RNA-based assays (Score et al, Leukemia 2009). The ELN is ideally suited to the conduct of such studies, which would not have been feasible at the national level.
12.13c Development of standardized protocols for MRD assessment (from bedside to clinical report)

**BCR-ABL:**

In order to achieve this aim, WP12 has linked up with the international standardization efforts for RQ-PCR analysis and reporting of BCR-ABL results in chronic myeloid leukemia (CML), led by Prof Nick Cross. This ongoing effort will establish key principles that will be relevant to development of standardized protocols for other MRD targets. The BCR-ABL related work within WP12 has focused on the development of accredited reference reagents as a means to facilitate the implementation of the International Scale (IS) for MRD determination in CML. Following a series of successful pilot experiments and control rounds we commissioned ECACC (European Collection of Cell Cultures) to grow 40 litres of HL60 cells in Autumn 2008, from which we made four mixtures of K562/HL60 to approximate 10%, 1%, 0.1% and 0.01% on the IS. These mixtures were prepared as rapidly as possible and transported to the National Institute of Biological Standards and Control (NIBSC) for aliquoting into ampoules and freeze drying, yielding approximately 3000 vials per dilution. Following initial successful in house evaluation of the freeze dried material we performed a field trial in January-March 2009 that aimed to establish IS values for each dilution. Laboratories were selected that had validated conversion factors (CF), with at least three laboratories for each of the three internationally accepted control genes: ABL, BCR and GUSB. A total of 10 laboratories were involved (6 from the EU) using 4 different protocols and 8 different RQ-PCR platforms. Each lab received 3 vials at each of the four dilution levels. RNA was extracted from each vial and reverse transcribed twice on different days yielding 24 datapoints/lab. The amounts of RNA extracted, absolute copy numbers of control gene, BCR-ABL/control gene before and after conversion were calculated and the mean for the laboratories used to calculate the IS values for each dilution (Figure 12.3).

In addition, the performance of the freeze dried materials was evaluated by homogeneity and stability testing. The coefficients of variation of 17 randomly selected freeze dried vials for each dilution were similar to the variation seen in 17 aliquots of non-freeze dried material and also patient replicates, confirming batch homogeneity. In accelerated degradation studies, the amounts of extractable RNA fell significantly when the vials were maintained at >20°C for 10 months, but the BCR-ABL/ABL ratios were distorted only in samples that had been maintained at 45 degrees or higher (Figure 12.4).

The documentation describing these experiments was submitted by NIBSC to the World Health Organisation (WHO) in July 2009 and following assessment of the evidence, the materials were approved as primary reference reagents in November 2009. The supply of these reagents will be limited to companies and reference laboratories that are able to generate the secondary reference materials that will actually be used by testing laboratories. This work was presented at EHA 2010 (White et al., Haematologica 2010;95; Suppl2:84-85) and recently published (White et al., Blood 2010;116:e111-7).
Figure 12.3: BCR-ABL QC results of freeze dried cell dilution analysis for the 6 laboratories that used ABL as the control gene. Top panel: before conversion; bottom panel: after conversion using local CFs. The mean of the converted values were assigned as IS values to each dilution.

Figure 12.4: Stability of BCR-ABL transcripts in freeze dried cells in accelerated degradation studies. Left panel: absolute copy numbers for each of the four dilutions extracted from vials of freeze dried cells that had been maintained at 7 different temperatures for 10 months. Right panel: Values plotted as BCR-ABL/ABL ratios.

In addition to the work above, the EUTOS group has focused very productively on the establishment of conversion factors (CFs) for at least one laboratory per country or region following the protocol developed by the Adelaide laboratory. An evaluation concerning the stability of CFs over time has been presented at ASH 2010 (Müller et al., Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 893). A control round to assess the ability of laboratories to detect resistance-associated mutations was
performed and results presented at ASH 2010 (Ernst et al., Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 894).

QC1: The first QC round involved distribution of dilutions of HEL and K562 cells, which harbor JAK2-V617F and wild type JAK2 alleles respectively, which were tested in 4 laboratories using the three best-performing published wild type and mutant assays (Larsen, Lippert & Nussenzveig), that were taken forward from previous experiments conducted within WP12 (that led to the elimination of 3 published assays, shown to exhibit suboptimal performance). The Larsen mutant assay was found to be the most efficient and afforded greater sensitivity, as compared to the Lippert and Nussenzveig assays. There was limited crossover of the Larsen mutant assay when tested on K562 cells (100% wild type JAK2), but much more crossover with the Lippert assay. The wild type JAK2 assays showed significant crossover as evidenced by amplification of the mutant allele in HEL cells, which was less marked with the Nussenzveig and Lippert assays than with the Larsen assay.

QC2: The second round involved 8 laboratories (Florence, Freiburg, Cambridge, Paris, Bern, London, Nantes, Bordeaux) and investigated 8 JAK2 assays (4 V617F mutant assays [Larsen, Lippert, Nussenzveig & Bern (Oppliger) “in house” assay]; 3 wild type assays [Larsen, Lippert & Nussenzveig]; total JAK2 [Oppliger “in house” assay]) and parallel amplification of independent control gene assays (albumin [BIOMED] and cyclophilin A [Pallisgaard “in house”]) to control for variations in template in each reaction. Plasmid standards for the wild type JAK2, mutant JAK2 and control gene assays were developed by Ipsogen, Marseille on behalf of WP12 and were found to perform well (Figure 5 and Table 1). Genomic DNA extracted from serial dilutions of HEL in K562 cells and K562 dilutions in HEL cells, reaction mixes for each RQ-PCR assay and plasmid standards for wild type and mutant JAK2 and the independent control genes were prepared and centrally distributed by Nicolas Maroc, Ipsogen. A standardized format for performing the QC exercise was distributed to the participating laboratories and data were returned to Nicolas Maroc and David Grimwade/Jelena Jovanovic (Guy’s Hospital, London) for centralized analysis. The identities of the JAK2 mutant and wild type assays were blinded to all participants by Ipsogen, and which were not revealed until after the results of the analyses had been completed. The design of the QC exercise that included HEL and K562 cells which harbor only mutant and wild type JAK2 alleles respectively allowed the specificity of the wild type assays to be assessed, in conjunction with assessment of the specificity and sensitivity of the mutant assays. Despite the different platforms (ABI7300, ABI7000, ABI7500 n=2, ABI7900 n=2, LC480, RG6000) and consequent differences in run conditions, marked concordance in the results obtained with all of the respective assays between the laboratories was observed, highlighting the validity of the exercise to draw firm conclusions.
In accordance with previous QC rounds, both the wild type and mutant Nussenzveig assays exhibited poor amplification plots and markedly inferior efficiency (median slopes -3.69 & -3.77, respectively). The Lippert wild type assay exhibited greater specificity than the Larsen wild type assay, in accordance with previous QC rounds. The Oppliger and Larsen mutant assays were found to be the most specific, yielding Ct values >40 when applied to neat K562 cells in the majority of laboratories, irrespective of platform. Taking into account the detection limit of RQ-PCR assays (taken as Ct value of 40 according to the Europe Against Cancer [EAC] program consensus) and the level of background amplification observed for the mutant assays in neat K562 cells, the level of sensitivity of the mutant assays was determined in serial dilutions of HEL in K562 cells (taking detection limit as 1 Ct below background amplification).

**Figure 12.5:** Development of plasmid standards for independent control genes to normalize MRD data for DNA-based Q-PCR assays.

**Table 12.1:** Comparison of performance of wild type (WT) and mutant (MUT) JAK2 assays in QC exercise conducted in 8 laboratories. The values provided are slopes reported for plasmid standard curves generated with centrally distributed reagents; assays with maximal efficiency exhibit a slope value of -3.3. Data for the independent control gene assays Albumin (ALB) and Cyclophilin (CYC) are also shown.

Design A: Lippert assay
Design B: Bern (Oppliger) “in house” assay. For this assay the “WT” data relate to total JAK2 (i.e. wild type and mutant)
Design C: Nussenzveig assay
Design D: Larsen assay
The mutant assays differed in their sensitivities (Table 2), with the Oppliger assay capable of detecting an estimated 0.008% mutant JAK2, the Larsen assay detected 0.08-0.008%, the Lippert assay was consistently less sensitive – 0.08% and the Nussenzveig assay the least sensitive due to inferior efficiency (0.8%). These data are in accordance with those of previous experiments showing that the Larsen assay exhibited better performance than the Lippert assay, with both assays being superior to the Nussenzveig assay.

**Table 12.2:** Determination of relative sensitivity of 4 assays to detect JAK2-V617F mutant allele in serial dilution of HEL cells in K562 cells in QC exercise conducted in 8 laboratories. The sensitivity quoted for each assay (0.8%-0.008%) by each laboratory takes into account the detection limit of RQ-PCR assays (taken as Ct value of 40 according to EAC) and the level of background amplification observed for the mutant assays in neat K562 cells (taking detection limit as $\leq 1$ Ct below background amplification).

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<th>Cassinat (ABI 7500 fast)</th>
<th>Oppliger (ABI 7900)</th>
<th>Tobal (ABI 7900HT)</th>
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**QC3:** The third round involved evaluation of 5 assays which were blind tested by 6 participating labs on serial dilutions of HEL in K562, as well as against plasmid standards. All materials were prepared and centrally distributed by Ipsogen. JAK2 V617F mutant level was quantified relative to total JAK2 and albumin (standardized BIOMED assay). The JAK2 V617F assays tested were those with a good performance profile in previous QC rounds (i.e. Larsen assay, Oppliger “in house” assay & Lippert assay). In addition, two further “in house” assays were tested – provided by Bert van der Reijden and Jean Gabert. An aliquot of DNA from each HEL cell line dilution was subject to pyrosequencing to check mutant percentage. Concordance of data between the labs was generally very good, despite deployment of 6 different Q-PCR platforms (4 ABI platforms, LC480 & RG6000). The Nijmegen assay showed poorer performance and it was agreed that this was likely due to assay conditions, since the assay performs much better in the “in house” setting. In accordance with previous QC rounds, the Oppliger “in house” assay performed well, affording greatest sensitivity and showing good concordance of results across platforms.

**QC4:** Taking into account reports that in a recent US QC study conducted by Erasmus Schneider (Albany, New York) that the Nussenzveig assay performed well “in-house” in relation to the Ipsogen MutaQuant kit (Lippert assay) when used to test samples mimicking JAK2-V617F allele loads
observed in the diagnostic setting, a further QC study was conducted. This involved testing of serial dilutions of K562 and HEL cell lines and plasmid controls dispatched to the London, Florence, Bordeaux and ARUP laboratories (Todd Kelley & Joseph Prchal, Salt Lake City – where the Nussenzveig assay was established). The Oppliger, Larsen, Lippert and Nussenzveig assays were tested using reagents centrally distributed by Nicolas Maroc from Ipsogen and where possible “in-house” reagents were used on the test materials in parallel. This QC round again showed that the Larsen and Oppliger assays afford greatest sensitivity to detect JAK2-V617F, exhibiting better performance than the other two assays. In accordance with these data, the Larsen assay actually performed better in Eric Lippert’s laboratory, than his own assay when using centrally distributed or in house reagents. There were discrepant results with the Nussenzveig assay, which performed much better “in-house” in the ARUP laboratory than in the other laboratories when using centrally distributed reagents with published conditions for the assay. This will be addressed in a further QC round to be conducted in Spring 2011, which should allow a final decision to be made regarding the optimal assay at the EHA meeting in June 2011. It is anticipated that this assay will be of value for routine diagnostics, given that a 1-2% level of the mutant allele may be clinically relevant in the diagnosis of myeloproliferative neoplasms, as well as for accurately measuring treatment response, including tracking of disease following allogeneic transplant.
12.14c Validation of “leukemia-specific” targets by determination of expression levels in normal peripheral blood, bone marrow and regenerating bone marrow

The development of novel RQ-PCR assays requires confirmation that they are RNA-specific and determination of background levels of amplification due to non-leukemic cells. RNA-specificity was previously confirmed in novel assays designed to amplify \textit{FIP1L1-PDGFRA} fusion transcripts in chronic eosinophilic leukemia (Jovanovic \textit{et al}, \textit{Blood} 2007). In AML we have shown that levels of background amplification in \textit{NPM1} mutation assays due to the wild type allele are too low to compromise assay sensitivity.

Since \textit{WT1} is expressed in normal hematopoietic progenitors and is therefore not a leukemia-specific target we have previously undertaken extensive analyses using centrally distributed ELN \textit{WT1} kits to establish reference ranges for levels of expression of \textit{WT1} transcripts in normal blood (n=118, median 0.01 \textit{WT1} copies/10$^4$ \textit{ABL} copies, 0.01-47.6), marrow (n=61, median 19.8, 0-213), and peripheral blood stem cells (n=25, median 6.1, 0-39) (Figure 6, left panel). Sequential analysis of PB and BM samples from 15 AML cases with low \textit{WT1} expression (<250 copies) showed no significant modulation in transcript level on regeneration after chemotherapy (Figure 6, right panel), indicating that in \textit{WT1}+ AML, transcript levels detected in follow-up samples reliably reflect disease status.

![Figure 12.6: Evaluation of standardized ELN \textit{WT1} assay for MRD detection in AML](image)

Left panel: Relative expression of \textit{WT1} (\textit{WT1} copies/10$^4$ \textit{ABL} copies) in pre-treatment PB and BM samples from AML patients relative to control PB, BM and peripheral blood stem cell (PBSC) samples derived from normal volunteers. Median values denoted by a horizontal bar.

Right panel: Comparison of \textit{WT1} transcripts between diagnosis and follow-up samples taken on regeneration following intensive chemotherapy in patients lacking over-expression of \textit{WT1} in leukemic blasts. These data provide evidence that \textit{WT1} expression is not modulated on regeneration following chemotherapy, supporting its use as a valid MRD target.
Prospective detection of *PML-RARA* transcripts to direct treatment of acute promyelocytic leukemia patients:

A key premise is that molecular detection of MRD using RQ-PCR can reliably predict relapse, thereby allowing early treatment intervention which could potentially avert full-blown relapse and improve overall chances of cure. There was preliminary evidence from the GIMEMA and PETHEMA groups to support this notion in acute promyelocytic leukemia (APL), although this had not been evaluated prospectively in multi-center clinical trials using RQ-PCR. In a project led by David Grimwade, this was addressed in collaboration with Alan Burnett and Francesco Lo Coco in WP5 (AML) in the UK Medical Research Council (MRC) AML15 trial. First-line treatment involved ATRA and anthracycline-based chemotherapy, with RQ-PCR used to identify patients with persistent disease or molecular relapse to direct pre-emptive therapy with arsenic trioxide prior to transplantation, with type of transplant (autologous vs allogeneic) being dependent upon molecular response as well as donor availability. Over 6,000 samples were prospectively analyzed by RQ-PCR from 303 patients, including over 2,000 paired BM and PB samples. The majority of samples were analyzed by Jelena Jovanovic, who was jointly supported by ELN WP12 and charitable funding (Leukaemia & Lymphoma Research). MRD monitoring according to the recommended schedule (3 monthly BM examination – based upon the data acquired concerning maximal assay sensitivity and kinetics of disease relapse) successfully identified the majority of patients subject to relapse and provided the most powerful predictor of relapse free survival (RFS) in multivariable analysis (HR 17.87, 95% CI 6.88-46.41, p<0.0001), far superior to presenting WBC (HR 1.02, CI 1.00-1.03, p=0.02) which is currently widely used to guide therapy. In patients who were predicted to experience relapse on the basis of MRD monitoring, early treatment intervention with arsenic trioxide prevented progression to overt relapse in the majority, associated with 73% relapse free survival at 1 year (Grimwade *et al*, *J Clin Oncol* 2009).

Applying the strategy of sequential MRD monitoring to direct pre-emptive therapy within AML15 was associated with a cumulative incidence of clinical relapse (CIR) of only 5% at 3 years. This was lower than the 12% rate of CIR (p=0.02) observed in the previous MRC AML12 trial involving patients treated with combination MRC chemotherapy with extended ATRA, but in which MRD monitoring was not performed (Figure 7). While it is recognized that AML12 represents a historical control group, treatment was less intensive in half the patients in AML15 who were randomized to receive the PETHEMA schedule. The lower relapse rate in AML15 could not be accounted for by differences in the distribution of Sanz risk groups, the rate or relative timing of relapses between MRC and PETHEMA treatment schedules.
Based on comparison of survival of patients treated with MRC chemotherapy in the successive trials, with RQ-PCR assays costing an average of $5,370 per patient and assuming a life expectancy of 25 years for patients successfully salvaged, MRD monitoring was found to be most cost-effective in high risk patients (WBC >10) with a 10% survival benefit at 5 years giving $2,415/quality adjusted life year (QALY) compared to those with WBC<10 (1% survival benefit at 5 years giving $25,600/QALY). This prospective multi-center study has been very helpful in establishing the most appropriate MRD monitoring schedules in APL, that have been taken into account in the British Committee for Standards in Haematology (BCSH) AML guidelines (Milligan et al, Br J. Haematol 2006) and International APL guidelines developed by an expert working group convened by ELN and led by Prof Miguel Sanz on behalf of WP5 (Sanz et al, Blood, 2009). The role of MRD monitoring in the management of APL has recently been reviewed (Grimwade & Tallman, Leuk Res 2011).

**Figure 12.7:** Evaluation of minimal residual disease (MRD) monitoring and pre-emptive therapy to reduce rates of frank relapse in PML-RARA+ acute promyelocytic leukemia (APL) in the Medical Research Council Acute Myeloid Leukaemia 15 (MRC AML15) trial. Cumulative incidence of clinical relapse was compared between patients with APL treated with extended all-transretinoic acid (ATRA) and anthracycline-based chemotherapy in the MRC AML12 trial, in which MRD monitoring and pre-emptive therapy were not routinely undertaken, and the MRC AML15 trial, in which this was performed. The ADE/ADE/MACE/MiDAC schedule from AML12 was given to half the patients in MRC AML15, and the remaining patients were randomized to receive the less intensive PETHEMA schedule involving ATRA and anthracycline mono-chemotherapy. A significant reduction in relapse rate was observed in AML15, which was apparent across risk groups defined by presenting white blood count (WBC) (10 \( \times \) 10^9/L) or Sanz risk group.

Analysis of RQ-PCR profiles in APL has served to highlight important principles that enable the development of optimized schedules for MRD detection, suitable for guiding therapy according to the needs of the individual patient. This is becoming increasingly relevant with interest in investigation of de-intensified treatment protocols for APL, placing greater reliance on MRD monitoring to identify patients who need additional therapy to secure cure of their disease. RQ-PCR using the standardized assay is being used prospectively to guide the management of APL patients in a number of multi-
center European studies being conducted by the GIMEMA, DSIL, AMLSG and UK NCRI groups evaluating the use of chemotherapy-free schedules comprised solely of molecular-targeted therapies (i.e. arsenic + ATRA) as compared to conventional ATRA+anthracycline-based therapy. The results of the MRC AML15 trial have also helped inform the International Pediatric APL trial (ICC-APL01) in which treatment reduction is being investigated in low-risk disease and which uses MRD monitoring to guide treatment approach.

12.23 Development and enhancement of computerized RQ-PCR reporting systems:
This project has been led by Peter Hokland (Aarhus) in collaboration with a Danish software house – Langtved Data, with the aim of developing a program to report RQ-PCR results from any platform in a standardized manner (see Figure 8), since this could have a major benefit in management of patients. A beta version of the program was generated in Spring 2005. Further modifications to the program were made following a users’ group meeting and intermittent system review.

Figure 12.8: MRD reporting program software overview
A) The software accommodates raw data from a broad range of qPCR hardware (carousel/plate/microplate principle). B) Two standard modes of MRD calculation, ‘absolute’ and ‘relative’ quantification, as well as two different ways of assessing assay sensitivity can be employed – based on control gene copy number or ΔCt as reported (Grimwade et al, J Clin Oncol 2009). C) A number of different MRD graphs (solid lines) and sensitivity graphs (hatched lines) can be produced, e.g. a) peripheral blood (PB) and bone marrow (BM) in either separate or b) combined graphs, c) with up to three different target genes (TG) in one graph, and d) inclusion of a fixed threshold line (in bold), e.g. for illustration of the normal expression level for WT1 assessments. Graph colors and styles are editable. D) A premade report template allows for fast and easy completion and printing of e) a PDF report to the referring department, or f) a list of all results from a given patient (exportable to Excel).
The software program was installed in September 2006 for evaluation in two laboratories in London (Guy’s Hospital and King’s College Hospital) using ABI platforms (ABI7700/7900) and in the Munich Leukemia Laboratory which employs Lightcycler technology. Installation was successful; however, a number of minor operational issues were identified regarding the display of sensitivity values for follow-up samples, selection of a reference standard and export of data from the Lightcycler platform. These prompted further modifications to the program and an installation guide and “User manual” were prepared by Mette Østergaard and Charlotte Guldborg Nyvold.

The reporting program has been installed and tested in 8 WP12 laboratories (Aarhus, Copenhagen, Frankfurt, Istanbul, London [King’s College & Guy’s Hospital], Turku & Vejle). The capacity of the program to allow reporting of MRD data in a standardized fashion irrespective of RQ-PCR platform was evaluated through a QC exercise that was coordinated by Charlotte Nyvold (Aarhus). This involved centralized distribution of leukemic cDNA samples (provided by Aarhus), RQ-PCR primers/probes and plasmid standards (provided by Ipsogen, Marseille) to the 8 laboratories (3 labs with some experience of the MRD reporting program, 5 labs in which the program had just been installed and were testing it for the first time).

Figure 12.9: Generation of standardized MRD reports using ELN Reporting Program
Complementary DNAs derived from diagnostic and follow-up samples from (inv)16 related AML were dispatched to laboratories participating in the QC exercise, analyzed using centrally distributed assay reagents (CBFB-MYH11, WT1, ABL) and reported in a standardized fashion using the ELN MRD reporting program. Good concordance was observed between normalized MRD results obtained using the Europe Against Cancer CBFB-MYH11 (green line – labs 2, 4 & 5; blue line – labs 1 & 7) and ELN WT1 (blue line – labs 2, 4 & 5; green line – labs 1 & 7) assays. Good concordance was also observed in the reports generated with the program, although differences in the scale of the y-axis reflect normalization to 100 or 10^4 ABL copies.
Serial samples were provided from a CML patient (5 consecutive samples + cDNA from the K562 cell line as a reference) and also from an AML patient (5 consecutive samples), to be monitored by \textit{CBFB-MYH11} and \textit{WT1} assays in parallel (using the standardized EAC and ELN assays, respectively). Data were normalized to the \textit{ABL} control gene. Between the participating laboratories, 4 platforms were used (ABI 7500/7900, Mx3000 & Lightcycler 480). Relative quantification based on $\Delta\Delta$Ct (compared to the diagnostic sample and K562 for the CML sample) and absolute quantification (comparison to plasmid standards) methods for RQ-PCR data reporting were evaluated. For the \textit{BCR-ABL} samples, remarkable intra- and inter-laboratory concordance was observed in the results irrespective of whether data were reported relative to the diagnostic sample, to the K562 cell line, or whether absolute quantification based on plasmid standards was used. A high degree of concordance was also observed between laboratories in the reporting of \textit{WT1} and \textit{CBFB-MYH11} data, when using diagnostic levels as reference or absolute quantification (Figure 9). Moreover, very close concordance was observed between the \textit{WT1} and \textit{CBFB-MYH11} MRD profiles in each laboratory; although, there were some discrepancies where particular labs had adopted different cut-off thresholds to define samples as PCR positive (e.g Ct <41 and Ct <45) or had normalized target gene expression to different numbers of \textit{ABL} copies (e.g. per 100 or per 10e4 copies).

The QC exercise usefully revealed some minor teething problems in the installation and use of the program; these included difficulties in uploading data to the program, generating certain report types and failure of some labs to use recommended settings. These issues were easily rectified following advice provided by Aarhus or Langtved Data. The QC exercise clearly highlighted the potential of the program to facilitate greater standardization in reporting of MRD data between laboratories and the revised program is now used routinely for reporting of all MRD results by the APL reference laboratory at Guy’s Hospital, London, including all samples from the UK NCRI AML17 trial.

In the current reporting year a further QC study was conducted involving 5 laboratories with established \textit{BCR-ABL} conversion factors, required to analyze a series of CML samples, and report MRD data using the program according to the International Scale. This was confirmed to lead to greater concordance in the MRD results, suggesting that the reporting program could be a useful tool in achieving greater standardization in the reporting of RQ-PCR data between laboratories (Østergaard & Nyvold \textit{et al}, \textit{Leukemia} 2011, in press). It is anticipated that the MRD reporting program, which is available free of charge to all ELN members, will be disseminated even more widely. Measures are being put in place for Langtved Data to provide a user help desk to support the program, covered by a service charge (~€2,200 per annum). The legal agreement regarding the future of the program, service agreement, escrow and intellectual property issues has been drawn up between Langtved Data and the ELN Management Center.
12.21c Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines


12.22c Analysis of gender specific issues

A major source of interest to the group is the male preponderance of FIP1L1-PDGFRA associated leukemia. Andreas Reiter is leading the project to define the genomic anatomy of the chromosomal rearrangement underlying this condition which may provide some insights into the sex bias associated with this disease and which could be pertinent to the pathogenesis of other subsets of leukemia. Recently, his group analyzed FIP1L1-PDGFRA junction sequences from 113 patients at the mRNA (n=113) and genomic DNA (n=85) levels (Walz et al, Leukemia 2009). Transcript types could be assigned in 109 patients as type A (n=50, 46%) and type B (n=47, 43%), which were created by cryptic acceptor splice sites in different introns of FIP1L1 (type A) or within PDGFRA exon 12 (type B). A new transcript type was identified – type C (n=12, 11%) in which both genomic breakpoints fell within coding sequences creating a hybrid exon without use of a cryptic acceptor splice site. The location of genomic breakpoints within PDGFRA and the availability of AG splice sites determine the transcript type and restrict the FIP1L1 exons used for the creation of the fusion. Stretches of overlapping sequences were identified at the genomic junction site, suggesting that the FIP1L1-PDGFRA fusion is created by illegitimate non-homologous end-joining. Statistical analyses provided evidence for clustering of breakpoints within FIP1L1 that may be related to DNA- or chromatin-related structural features. The variability in the anatomy of the FIP1L1-PDGFRA fusion has important implications for strategies to detect the fusion at diagnosis or for monitoring response to treatment.

In a related study, current detection methods for FIP1L1-PDGFRA were evaluated by developing a means to rapidly amplify genomic breakpoints (Score et al, Leukemia 2009). Two hundred and two cases were screened and genomic junctions detected in all samples previously identified as RT-PCR positive (n=43). Genomic fusions were amplified by single step PCR in all cases, whereas only 22 (51%) were single step RT-PCR positive. Importantly, FIP1L1-PDGFRA was detected in two cases that initially tested negative by RT-PCR or fluorescence in situ hybridization. Absolute quantification of the fusion by real-time PCR from genomic DNA (gDNA) using patient-specific primer/probe combinations at presentation (n=13) revealed a 40-fold variation between patients (range, 0.027-1.1 FIP1L1-PDGFRA copies/haploid genome). In follow up samples, quantitative analysis of gDNA gave 1-2 log greater sensitivity than RQ-PCR of cDNA. Minimal residual disease assessment using gDNA showed that 11 of 13 patients achieved complete molecular response to imatinib within a median of 9
months (range, 3-17) of starting treatment, with a sensitivity of detection of up to 1 in $10^5$. One case relapsed with an acquired D842V mutation. Detection of FIP1L1-PDGFRα from gDNA is thus a useful adjunct to standard diagnostic procedures and enables more sensitive follow up of positive cases after treatment.

Deviations from the workprogram and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved.

Not applicable

Table 12.3: List of deliverables WP12, 2010

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months(*)</th>
<th>Used indicative person months(*)</th>
<th>Lead contractor</th>
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<tr>
<td>WP12</td>
<td>MRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12.5</td>
<td>Regular WP meetings</td>
<td>73,78,85</td>
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<td>15</td>
<td>15</td>
<td>Grimwade, Hochhaus, Reiter</td>
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<tr>
<td>12.6</td>
<td>LP reports to NMC regarding structure, activities and integration of national groups (1 page, bullet point style)</td>
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<td>5</td>
<td>3</td>
<td>Grimwade</td>
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</tr>
<tr>
<td>12.11d</td>
<td>Establish the additional proportion of leukemic patients that can be monitored using novel targets</td>
<td>66</td>
<td>done</td>
<td>8</td>
<td>8</td>
<td>Grimwade, Saglio Preudhomme</td>
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<tr>
<td>12.15d</td>
<td>Evaluation of validated RQ-PCR assays in national clinical trials</td>
<td>78</td>
<td>done</td>
<td>15</td>
<td>10</td>
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<tr>
<td>12.21c</td>
<td>Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines</td>
<td>78</td>
<td>ongoing</td>
<td>4</td>
<td>1</td>
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<tr>
<td>12.22c</td>
<td>Analysis of gender specific issues</td>
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<td>done</td>
<td>2</td>
<td>2</td>
<td>Reiter</td>
</tr>
<tr>
<td>12.23</td>
<td>Installation and implementation of Q-PCR reporting program within ELN member laboratories</td>
<td>66</td>
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<td>4</td>
<td>Grimwade, Hokland</td>
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<tr>
<td>12.24</td>
<td>Evaluation of MRD monitoring to predict relapse and direct donor leucocyte administration following allogeneic transplant</td>
<td>78</td>
<td>ongoing</td>
<td>8</td>
<td>2</td>
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</tr>
<tr>
<td>12.25</td>
<td>Conduct of QC exercises for mutation targets</td>
<td>66</td>
<td>done</td>
<td>2</td>
<td>2</td>
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<tr>
<td>12.26</td>
<td>Compare sensitivity and specificity of published JAK2 V617F Q-PCR assays to establish best-performing assay</td>
<td>72</td>
<td>ongoing</td>
<td>6</td>
<td>3</td>
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<tr>
<td>12.27</td>
<td>Compare performance of reference gene assays for JAK2 V617F quantification</td>
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<td>done</td>
<td>2</td>
<td>2</td>
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<tr>
<td>12.28</td>
<td>Develop plasmid standards for JAK2 V617F and selected reference gene assay</td>
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<td>Hermitte</td>
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<td>12.29</td>
<td>Comparison of RNA- and DNA-based Q-PCR assays for NPM1 mutations</td>
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<td>1</td>
<td>Grimwade</td>
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*) if available
Table 12.4: List of milestones WP12, 2010

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<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
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<td>WP12</td>
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<tr>
<td>12.13c</td>
<td>Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report)</td>
<td>66</td>
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<td>Grimwade Hochhaus Cross Hokland</td>
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<tr>
<td>12.15d</td>
<td>Establish prognostic significance of validated Q-PCR assays in national clinical trials</td>
<td>66</td>
<td>66</td>
<td>Grimwade Saglio</td>
</tr>
<tr>
<td>12.23</td>
<td>Service implementation of ELN MRD reporting program</td>
<td>66</td>
<td>66</td>
<td>Grimwade</td>
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<td>12.26-8</td>
<td>Establish optimal assay for quantification of JAK2 V617F mutant allele load</td>
<td>72</td>
<td>91</td>
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Section 3: Consortium management

Not applicable

Section 4: Other Issues

Ethical issues - none
Competitive calls - none

Section 5: WP-Performance

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<th>Performance indicators</th>
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<tr>
<td>Development of consensus protocols for the diagnostic work up to identify MRD targets in leukemia</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Organization of quality control rounds</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Set up of internet forum</td>
<td>In progress</td>
</tr>
<tr>
<td>Number and quality of publications within the network</td>
<td>16 published papers, 7 abstracts</td>
</tr>
<tr>
<td>Number of researchers in exchange programs</td>
<td>0</td>
</tr>
<tr>
<td>Implementation of technology transfer</td>
<td>In progress</td>
</tr>
<tr>
<td>RQ-PCR assays for rare fusion gene transcripts, leukemia associated mutations and for novel overexpressed genes</td>
<td>4</td>
</tr>
<tr>
<td>Evaluation of validated RQ-PCR assays in national clinical trials</td>
<td>In progress</td>
</tr>
<tr>
<td>Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report)</td>
<td>Done</td>
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<tr>
<td>Development of optimized sensitive validated assays for MRD detection</td>
<td>Done</td>
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</table>
**13 Gene profiling and Next Generation Sequencing (NGS) (WP13)**

*Objectives and work within reporting period*

WP13 is an established and still growing working group of MDs and PhDs who were first interested in using gene expression profiling both for investigating basic research topics and the application of microarrays in a clinical setting. Since 2010 next generation sequencing is of high interest for the same members and mainly takes over the focus of WP13. Both tasks are strongly supported by biostatisticians. Microarray data as well as NGS data very recently were collected within the ELN network and involved respective subgroups in WP13 as well as other WPs in close collaborations. The DACH and the MILE studies are published and data is public available in GEO.

In parallel, all biostatistical platforms have been upgraded in 2010 and expanded to NHS data sets: GAP is freely available for all ELN members, and not restricted to the MILE subgroups. In the ELN GAP database, data can easily be stored, exchanged and analyzed within the participating WPs (see below and a new data base was placed on the same homepage together with WP13 and COST members (see below).

Many publications were published in 2010 using parts of the MILE data set and form the MDS paper (K. Mills, Blood 2009) and more are upcoming and started to be performed in WP13 (see below).

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**13.1e Expand of WP information and communication structures**

The GAP database in Münster was further improved and includes now much more multiple statistical packages for analysis of gene expression microarray data (for details see [http://imiblinux05.uni-muenster.de](http://imiblinux05.uni-muenster.de)). This is all only possible due to the strong support of this outstanding statistic group (Head Prof. Dugas) within and through the WP13. Furthermore the new Leukemia Atlas was posted in 2/2011 and is sponsored in part by the ELN. Also several highly ranked biostatistical papers were published together:

Toolbox for 454 data: use cases

- Detection of fusion genes by targeted NGS

[Grossmann et al., Leukemia. 2011 Jan;]

Toolbox for 454 data: use cases

- Amplicon sequencing:
  Monitor amplicon coverage and
  Annotate/Filter detected variants

[Kohlimann et al., J Clin Oncol. 2010 Aug; 28(24)]
Due to strong efforts from members of WP13 (Mills, Dugas, Haferlach) the EU funded a new project bridging ELN WP13 and other future activities and leading to shared meetings, data and personnel and lab exchanges (see below):

**Activities at the European Level**

- **EuGESMA**
  European Genomics and Epigenomics Study on MDS and AML
  (coordinator: Ken Mills, Belfast)
- **Workgroup Informatics**
  Italy (Silvio Biocino, Cesare Furlanello)
  Spain (Javier Des las Rivas, Lara Nonell)
  France (Chimène Morelhon)
  Finland (Jaakko Hallmen, Leo Lathi)
  Poland (Maciej Wywroz)
  Germany (Martin Dugas)

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**Review: Integrative data analysis**

- Topic: Detection of genes that are regulated by copy number variations
- Quantitative comparison of 8 methods based on simulated data and on real data sets
- Cooperative work from 3 EU countries
  - Finland (Leo Lathi, University of Aalto)
  - Germany (Martin Schafer, University of Dortmund; Hans-Ulrich Klein, Martin Dugas University of Münster)
  - Italy (Silvio Biocino, Univ. of Modena and Reggio Emilia)
- Submission 02-2011
The most important paper published by WP13 was:

**MILE Study**

Clinical Utility of Microarray-Based Gene Expression Profiling in the Diagnosis and Subclassification of Leukemia: Report From the International Microarray Innovations in Leukemia Study Group

Teresa Haferlach, Alexander Kohlmann, Lechla Wieczorek, Giuseppe Basso, Germaine Te Kronnie, Marie-Claude Bédé, Marta De Vos, Gusta M. Hernandez, Wolf-Karsten Hoffmann, Ken L. Mills, Amanda Gilles, Serena Ciavarelli, Stella A. Shurtleff, Thomas J. Kipps, Laura Z. Rassenti, Eileen Y. Yeoh, Peter R. Papenhausen, Wei-min Liu, F. Mickey Willams, and Ilse Fey

**ABSTRACT**

**Purpose**

The Microarray Innovations in Leukemia study assessed the clinical utility of gene expression profiling as a single test to subtype leukemias into conventional categories of myeloid and lymphoid malignancies.

**Methods**

The investigation was performed in 11 laboratories across three continents and included 3,394 patients. An exploratory retrospective stage I study was designed for biomarker discovery and subsequent validation.

**Results**

The gene expression profiling-based diagnostic accuracy was validated in a prospective second stage study of an independent cohort of 1,191 patients.

**Conclusion**

Gene expression profiling is a robust technology for the diagnosis of hematologic malignancies with high accuracy. It may complement current diagnostic algorithms and could offer a reliable platform for patients who lack access to today's state-of-the-art diagnostic work-up. Our comprehensive gene expression data set will be submitted to the public domain to foster research focusing on the molecular understanding of leukemias.

Haferlach T et al., J Clin Oncol. 2010;28: 2529-37

Further WP13 publications included:

**WP13 Publications**

Gene expression-based classification as an independent predictor of clinical outcome in juvenile myelomonocytic leukemia.


Gene expression profiling in AML with normal karyotype can predict mutations for molecular markers and allows novel insights into perturbed biological pathways.


A very recent paper from ELN WP13 and COST was published 3/2011:

**WP13 Publications**

Gene expression profiling identifies a subset of adult T-cell acute lymphoblastic leukemia with myeloid-like gene features and over-expression of miR-223.

**Molecular Genetics of Adult Acute Myeloid Leukemia: Prognostic and Therapeutic Implications.**
Marcucci G, Haferlach T, Döhner H.
J Clin Oncol. 2011 Jan 10., e-pub

A deep-sequencing study of chronic myeloid leukemia patients in blast crisis (BC-CML) detects mutations in 76.9% of cases.
Leukemia. 2011 Jan 28. e-pub
The WP13 then started to focus on NGS and established a 454 hematology focus group that first met in May 2010 in Munich. From this group a first proof-of-principle study was initiated, performed and presented as a poster at the ASH 2010; the manuscript was submitted for publication on 3/26/2011.
To combine all activities and open up new areas of interest the WP13 met with COST and EuGESMA in October 2010 in Munich:

**Joint ELN WP13 – EuGESMA Meeting**

Meeting from Monday 18th October - Tuesday 19th October 2010, Munich

Chairs: Ken Mills (COST) and Torsten Haferiach (ELN, WP13)

- 80 participants
- 21 countries
- ~50% early stage researchers
- 24 presentations
- 5 break-out work groups
- Strengthen networks

New collaborations initiated: SNP and mutational analyses; epigenetics
This meeting led to the following subgroups and activities since 10/2010 and with increasing output and cooperation in 2011:

**Activities 2011+: IRON Study Phase II**

List of centers with interest in participation (>20 laboratories, 10 countries):

| Dr. Christian Gabriel | Linz | AUSTRIA | T-ALL |
| Prof. Peter Vandenbergh | Leaven | BELGIUM | AML |
| Dr. Bernardo Garicochea | Porto Alegre | BRASIL | AML |
| Prof. Claude Preudhomme | Lille | FRANCE | AML |
| Prof. Christian Thiede | Dresden | GERMANY | AML, MDS, MPN |
| Prof. Brigitte Schlegelberger | Hannover | GERMANY | CML, MPN, MDS |
| Prof. Andreas Hochhaus | Jena | GERMANY | MDS |
| Prof. Wolf-Karsten Hofmann | Mannheim | GERMANY | AML, MDS, ALL, MPN, CLL |
| Prof. Torsten Haferlach | Munich | GERMANY | AML, MDS, CLL, Lymphoma |
| Dr. Lars Bullinger | Ulm | GERMANY | B-ALL, T-ALL, Myelofibrosis, AML |
| Dr. Orsola Spinelli | Bergamo | ITALY | ALL, AML, CML |
| Prof. Giovanni Martinelli | Bologna | ITALY | ALL, MPN |
| Prof. Enrico Tagliabue | Modena | ITALY | childhood AML and ALL, JMML, ALL |
| Dr. Giovanni Cazzaniga | Monza | ITALY | ALL, CLL |
| Prof. Giuseppe Basso | Padova | ITALY | ALL |
| Prof. Robin Fea | Rome | ITALY | ALL, CLL |
| Prof. Allen Yeoh | Singapore | SINGAPORE | ALL |
| Prof. Jesus M Hernandez | Salamanca | SPAIN | ALL, MDS, ALL, CLL |
| Dr. Joop H Jansen | Nijmegen | THE NETHERLANDS | MDS, MPN |
| Prof. Peter Valk | Rotterdam | THE NETHERLANDS | AML, MDS, Lymphoma |
| Dr. Jade Fitzgibbon | London | UK |

Supported by ROCHE the first tools to be investigated using NGS performed on 454 FLX or Junior instruments are the following:

**IRON: Assay-on-Demand Plates**

- **Design proposal #1:**
  - TET2 (complete coding region, 27 amplicons)
  - CBL (Ring + linker domain, exons 8 and 9)
  - KRAS (exons 2 and 3)
  - 3 patients per plate

- **Design proposal #2:**
  - RUNX1 (complete coding region, 7 amplicons)
  - 12 patients per plate

Roche Applied Science intends to launch these products in second half of 2011
For better maintenance WP13 included an increasing number of industry partners to make all these future activities in NGS and GEP including also SNP arrays possible:

All these new activities will closely cooperate with WP13 in the ELN to spread information in the upcoming years.

13.5 Regular WP meetings
One regular WP meeting for all WP13 members, combined in part with WP11, had been organized in Heidelberg in February 2010. Furthermore, some members of WP13 - mostly representing members also of the European part of the MILE study - met together with WP10, 11 and 12 in Munich in May 2010 and in October 2010 for new activities together with COST and EuGESMA (see above).

13.6 LP reports to NMC regarding structure, activities and integration of national GEP groups
- Ongoing exchange of information regarding GEP and NGS data management and analysis strategies with ELN and COST and EuGESMA partners
- Regular updates to the European biostatistical data analysis platform (GAP) and new Leukemia Atlas in Münster based on input from ELN participants available for all WP13 partners, also making new data sets public (see above)

13.10e Develop new biostatistical approaches and expand the centralized data base
See in detail above.

13.11e Detect further new subgroups of leukemia according to gene expression profiles
As part of a collaboration between Dresden, Munich and Ulm on AML with normal karyotype over 250 cases predefined by NPM1, MLL-PTD, FLT3-ITD, CEPBA and WT1 status were analyzed with
HG-U133 Plus 2.0 microarrays. Data are published in Leukemia in 2010; see in detail 13.1d above. Another manuscript addressing FLT3 signatures is ready to be submitted (L. Bullinger et al.).

13.12e Further evaluation of new genes for therapeutic and diagnostic purposes
Studies by Müller-Tiedow began in 2009 and manuscript will be circulating soon.

13.16d Further evaluation of new biostatistical methods
Has been published or made publically available in 2009 and 2010/11 (see 13.1d) and is still ongoing, now strongly expanding to next-generation sequencing data.

13.18e Find new diagnostic markers and MRD markers with WP10, 11, 12
No further input in 2010.

13.19e Define new entities in AML with WP5 with respect to prognosis in intermediate risk group
Done, paper by Kohlmann et al. Leukemia 2010 and ongoing with same data set (Bullinger et al. manuscript to be submitted soon).

13.21 Use broadly data of WP13 studies and MILE study for all ELN members
See for new tools implemented in 2009 and 2010: (http://imiblinux05.uni-muenster.de/), see above.

13.22 Include SNP data and further projects of WP13 members
See 13.21

13.23 Set up a NGS working group
Done, see above

13.24 Use already available NGS data for new analyses and develop new biostatistic approaches
Ongoing and already published in part, see above.

Deviations from the work program and corrective actions taken: identify the nature and the reasons for the problem, identify contractors involved
Not applicable.
### Table 13.1: List of all Deliverables WP13, 2011

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months*)</th>
<th>Used indicative person months*)</th>
<th>Lead contractor</th>
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<tbody>
<tr>
<td>WP13 Gene profiling</td>
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<td></td>
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<td></td>
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<tr>
<td>13.1e</td>
<td>Expand of WP information and communication structures</td>
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<td>13.4f</td>
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<td>13.5</td>
<td>Regular WP meetings</td>
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<td>13.6</td>
<td>LP reports to NMC regarding structure, activities and integration of national GEP groups (1 page, bullet point style)</td>
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<td>Dugas</td>
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<tr>
<td>13.12e</td>
<td>Further evaluation of new genes for therapeutic and diagnostic purposes</td>
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<td>2</td>
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</tr>
<tr>
<td>13.16d</td>
<td>Further evaluation of new biostatistical methods</td>
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<td>86, ongoing</td>
<td>0</td>
<td>4</td>
<td>Dugas</td>
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<tr>
<td>13.18e</td>
<td>Find new diagnostic markers and MRD markers with WP10, 11, 12</td>
<td>73-86</td>
<td>86, ongoing</td>
<td>0</td>
<td>3</td>
<td>Haferlach Grimwade Foa Bene</td>
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<tr>
<td>13.19e</td>
<td>Define new entities in AML with WP5 with respect to prognosis in intermediate risk group</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Haferlach Döhner Thiede</td>
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<td>13.21</td>
<td>Use broadly data of WP13 studies and MILE study for all ELN members</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Haferlach Dugas</td>
</tr>
<tr>
<td>13.22</td>
<td>Include SNP data and further projects of WP13 members</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
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<td>Haferlach Dugas</td>
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<td>13.23</td>
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<td>13.24</td>
<td>Use already available NGS data for new analyses and develop new biostatistic approaches</td>
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<td>86, ongoing</td>
<td>0</td>
<td>4</td>
<td>Haferlach Kohlmann Dugas</td>
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</table>

* if available
List of milestones WP13, 2010

<table>
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<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
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<tr>
<td>WP13</td>
<td>Gene profiling</td>
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<td></td>
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</tr>
<tr>
<td>13.16d</td>
<td>Further evaluation of new biostatistical methods</td>
<td>73-86</td>
<td>86, ongoing</td>
<td>Dugas</td>
</tr>
<tr>
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<td>Find new diagnostic markers and MRD markers with WP10, 11, 12</td>
<td>73-86</td>
<td>86, ongoing</td>
<td>Haferlach, Grimwade, Foa, Bene</td>
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<tr>
<td>13.19e</td>
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<td>86</td>
<td>Haferlach, Dugas</td>
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<tr>
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<td>Include SNP data and further projects of WP13 members</td>
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<td>86</td>
<td>Haferlach, Dugas</td>
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<td>73-86</td>
<td>86, ongoing</td>
<td>Haferlach, Kohlmann, Dugas</td>
</tr>
</tbody>
</table>

Section 3: Consortium management

Workshop together with WP10 and WP8 and COST and EuGESMA were held in Munich in May and October 2010.

Participants of WP13 further played a major role at important international and national conferences on microarray data and NGS data in leukemia and chaired several sessions or presented their individual data in talks or as posters.

Section 4: Other Issues

Ethical issues - none

Competitive calls – none

Section 5: WP13-Performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establishment of European reference panels</td>
<td>See published papers</td>
</tr>
<tr>
<td>Organization of interdisciplinary consensus conferences</td>
<td>See published papers</td>
</tr>
<tr>
<td>Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes</td>
<td>See published papers</td>
</tr>
<tr>
<td>Organization of quality control rounds</td>
<td>done</td>
</tr>
<tr>
<td>Number and quality of publications within the network</td>
<td>See 13.1.d</td>
</tr>
<tr>
<td>Implementation of technology transfer</td>
<td>In further progress</td>
</tr>
<tr>
<td>Number of difficult cases presented in the expert forum</td>
<td>n.d.</td>
</tr>
<tr>
<td>Number of new cooperations between network participants</td>
<td>New cooperations in WP13 and with COST and EuGESMA and 454 hematology focus group</td>
</tr>
</tbody>
</table>
Stem cell transplantation (WP14)

Objectives and starting point of work at beginning of reporting period

Many important deliverables were obtained in WP14 during 2010. This was possible through regular working party meetings and continuing the important work started previously with the EBMT/ELN network. As in previous years, the stem cell transplant survey was performed in Europe and worldwide, but also the harmonization process between Europe and the US was continued, providing valid information on changes in indications, frequencies among the different countries but also among diseases. In this regard a global survey was continued in 2007/2008.

The main aim consisted in connecting the activities of the different disease-oriented WP of the ELN with the WP hematopoetic cell transplantation (HCT) but also in improving procedure related issues.

In AML, the first randomized study comparing transplant vs. non-transplant treatment and involving the major AML study groups has started in January 2010 and 19 patients were already included. The second study on reduced intensity conditioning for patients with related donors in comparison to non-transplant treatment has included now more than 130 patients. Analysis on molecular risk factors and their role for patients with or without SCT were initiated in retrospective analysis. The possibility to use a common arm in Europe raised considerable discussions and has still to be developed in more detail. In MDS the significance of reduced intensity conditioning in comparison to conventional SCT is being studied in the RICMAC study.

In ALL, phase II protocols for older patients using allogeneic HCT after reduced intensity conditioning have been initiated. The results are very encouraging and justify a prospective protocol investigating the role of allogeneic HCT in high risk patients. Especially in high risk patients, an advantage of reduced intensity conditioning regimen seems apparent. More patients are required, however, to set up a randomized study.

In CML, analyses on SCT outcome after second generation TKI are very important. In addition, indication for SCT has to be defined considering the improvements and definition of risk factors of the last years. Therefore outcome of patients with low risk Gratwohl score has been analyzed. A prospective study investigating the role of Dasatinib in patients relapsing after SCT has been finalized and the results of Donor Lymphocyte updated.

In T-PLL, the survival of patients after autologous and allogenic SCT was updated and a prospective registration audit initiated.

In regard to multiple myeloma the NMMA 2000 study has been accepted as publication in JCO. For patients relapsing after autologous HCT a randomized study comparing Velcade, Thalidomide and Steroids with Thalidomide and steroids has recruited already more than 240 patients and will be presented at the EBMT 2011 as best abstract.
Procedure related questions:
A significant improvement in reducing complications after STC was obtained in the pediatric randomized study for VOD prevention. Defibrotide was able to reduce VOD but also the incidence of GvHD. This work received the VanBekkum Award in March 2010 and the manuscript has been submitted to the NEJM.

In addition standardization and spreading of excellence was pursued by training courses and by standardizing indications for SCT. The DMSO prospective audit is proceeding as expected and complications registered. A standardization of DMSO concentration is urgently needed. Also the standardization of GvHD treatment is making progress. As a first step, the current practice has been evaluated and a manuscript written. Subsequently recommendations have to be established. Accreditation of stem cell transplantation centers is making considerable progress in Europe. The outcome of second stem cell transplantation has been analyzed in detail.

WP SCT report 1+2/4 2010
Nothing has changed in Europe regarding prospective investigator driven studies after the directive 2001. Despite many meetings at the European Level in Bruselles and London and participation to consultations nothing really improved. Insurance fees are especially high in Germany, founding is restricted to individual member states (e.g. DFG) and national authorities request increasingly more bureaucracy, making clinical studies almost impossible.
Despite all this problems we managed to have approval for the AML study and even foundings from a national cancer aid society. Using this generous financial support and other financial means we were able to start the AML EBMT study for elderly patients. Many other studies could not be started. Many new studies have a moratorio. The majority of the analysis concentrate on retrospective analysis of registry data, which are still important and valuable, but not able to replace prospective studies. In addition observational audits were started within the EBMT.
As described in the minutes, the results achieved during this period were otherwise impressive. More than 25.000 new SCT performed in 2010 were entered in the registry (total >380.000). The RICMAC study recruited patients in four European Countries and the mmvar study completed accrual. The annual EBMT meeting in Vienna attracted more than 4000 persons around the globe to discuss and present the newest achievements in SCT.

WP SCT report 3/4 2010
During this period further activities on deliverables and non-deliverables were continued. In this period the global survey for 2007-2008 was completed and an increase of more than 40% in certain regions in the world noted (e.g. Asia Pacific Region). Now, all transplant activity around the world is registered with the WBMT, the world blood and marrow transplantation network (a federation of the 18 societies involved in stem cell transplantation around the world) on an annual basis. This powerfull tool can be used to recognize differences in frequencies, indications and tendencies from one continent
or even country to the other. New studies were discussed and collaboration within Europe intensified. Procedure related questions were addressed in order to reduce relapse or treat relapse.

**WP SCT report 4/4 2010**

The main aim of this period was to intensify the cooperation with other working groups of the ELN like WP AML and WP CML. The study on defibrotide was updated and the results presented at ASH. Some of the observational studies were completed (e.g. DMSO; second generation TKI before SCT) or the protocols finalized (Dasatinib for relapse after SCT in CML) and retrospective studies updated (second SCT).

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**14.5 Regular WP meetings:**

8 meetings were held during 2010 including joint WP meetings with WP 4 and WP5

- EBMT CLWP/ELN; Hotel Merian, Basel, Switzerland, January 22-23, 2010
- ELN Meeting, Mannheim, February 1-3, 2010
- EBMT annual meeting, Vienna, March 21, 2010
- EHA/ELN FIRA, Gran Via Conf. Center, Barcelona, June 10, 2010
- Subcommittee chair meeting in Leiden 17/06/10
- EBMT CLWP/ELN; “La Distillerie”, Mons, Belgium, September 17-18, 2010
- Subcommittee chair meeting in Leiden 12/11/10
- ELN Meeting WP5/WP14 JW Marriott Orlando Grande Lakes December 05, 2010

**14.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups**

Reports have been sent to NMC.

**14.14f Report of study patients to registry**

Information on 386887 SCT in 329096 patients are now available in the EBMT Registry and describe patients with autologous and allogeneic SCT (241805 and 144565 respectively; 517 unknown type), transplants from related and unrelated donors (86631 and 42499 respectively; 784 unknown type), from cord blood, bone marrow and peripheral stem cell grafts (6233, 97115 and 288046 respectively; of which 5940 have more than one type of source and 4134 are of unknown source).

The EBMT Registry also allows the registration of other type of cell therapy procedures such as mesenchymal cells, whether performed for similar or new indications, and whether performed by themselves or in association with haematopoietic stem cell transplantation. Currently there are 464
patients for which such procedures have been registered, including 408 mesenchymal cells therapy and 59 dendritic cells therapy.

14.42d Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning (EBMT study)
The study has been started in January 2010 and more than 17 patients were registered till January 2011. The study is proceeding as planned with the Nederlandes and Germany involved. Switzerland and France did not start yet for administrative reasons, but center initiations are planned in April. The goal of including 210 patients is expected to be reached in 2 years from now.

14.45c Allogeneic reduced intensity conditioning transplantation versus conventional conditioning in MDS (RICMAC) Study start
The RICMAC is a European EBMT-trial comparing a dose-reduced conditioning versus a standard myeloablative conditioning regimen followed by allogeneic SCT in patients with myelodysplastic syndrome or secondary acute myeloid leukaemia. Accrual is ongoing and has substantially improved this year. 72 of the planned 140 patients are randomized so far.

14.46d MMVAR Study to treat relapse in myeloma after autologous SCT
246 patients entered the study and recruitment stopped. The following abstract was submitted to the EBMT meeting in Paris 2011 and a manuscript is in preparation. The abstract will receive the prestigious Van Bekkum award.

**Bortezomib(Velcade®)-Thalidomide-Dexamethasone (VTD) is superior to Thalidomide-Dexamethasone (TD) in patients with multiple myeloma (MM) progressing or relapsing after autologous transplantation**

In 2006, the EBMT and the IFM initiated a prospective, randomized, parallel-group, open-label phase III, multicenter study, comparing VTD (arm A) with TD (arm B) for MM patients in first progression/relapse after at least one autologous transplantation. TTP was the primary end point. Treatment was: bortezomib 1.3 mg/m2 as an i.v bolus on days 1, 4, 8 and 11, followed by a 10-day rest period (days 12 to 21), for 8 cycles (6 months) and then on days 1, 8, 15 and 22, followed by a 20-day rest period (days 23 to 42), for 4 cycles (6 months). In both arms, thalidomide was administered at 200 mg/day for 1 year and dexamethasone at 40 mg/day orally for 4 days every 3 weeks for 1 year. Response was assessed by EBMT criteria. Adverse events were graded by the NCI-CTCAE, Version 3.0. Results: On 01/07/10, a first interim analysis based on 246 patients and 134 events was performed. The trial was then stopped because of superiority of VTD over TD. We report an updated analysis as of 02/12/10. 267 patients (135 in arm A, 132 in arm B) had been enrolled in the study and 157 events had been observed. The median age was 61 years (range 29-76) The stage according to the ISS was I in 56 %, II in 27 %, III in 17 %. The number of previous autologous transplants was one in
71 vs 69 patients and two or more in 64 vs 63 patients, in arms A and B respectively. The median follow-up was 27 months. The median TTP was 19.5 vs 13.8 months respectively in arms A and B, with a cumulative incidence of relapse/progression at 2 years of 56% vs 71% (p=0.0011). The median PFS was 18.6 vs 12.7 months with a cumulative incidence at 2 years of 37% vs 23% (A vs B, p=0.0011). The OS in the first two years was 72% vs 68% (p=0.18). The probability of achieving CR and CR+PR during the first year was 32% vs 12% and 90% vs 69% with VTD and TD (p=0.0001, and p=0.0001). In the VTD and TD arms, the mean number of treatment cycles for the first 8 cycles were 6.25 vs 6.88 and for the 12 cycles, 7.56 vs 9.93 respectively. Treatment was discontinued due to toxicity in 48 patients (VTD= 36, TD=12). 33 patients died during the treatment period (VTD= 14, TD= 19). The incidence of thrombo-embolic events >= grade 3 was similar in the two arms (6.6% vs 5.2%, p=ns, VTD vs TD) while >= grade 3 thrombocytopenia was higher with VTD (16% vs 7%, p=0.025). Conclusion: VTD resulted in significantly longer TTP and PFS in patients relapsing after ASCT with an acceptable toxicity. Protocol EU-DRACT number: 2005-001628-35.

14.47d Related allo-SCT after Reduced Intensity Conditioning versus Best Standard of Care in elderly patients with AML in CR1 (Brune)

This is an academic study, comparing reduced intensity transplants (RICT) with standard of care in AML. Based on the availability of an HLA identical sibling, patients in their first remission are allocated to a RICT group or a control group. Primary endpoint is survival and the study is supported by the Canadian BMT Group and several funds. PI is Mats Brune Göteborg, Sweden.

At this point, >130 pts have been enrolled from centers in Canada, Norway, Finland, Germany, New Zealand and Sweden. The study has been open also to patients with unrelated donors.

14.48d AlloSCT after tyrosine kinase inhibitors (TKI) in CML

The retrospective study on second generation TKI use prior to allo-transplant is in its final analysis. A total of 19 centres (11 EBMT centres, 8 non EBMT centres) participated. 56 pts. with CML have been identified. At SCT, 37% of the patients were in accelerated or in blast phase, 36% in CP2 and 27% in first chronic phase. In two pts primary graft failure occurred. At 24 months the estimated non-relapse mortality was 33% and the relapse incidence 15%. The conclusions of the study were that allotransplants remain a reasonable treatment option for pts. with CML after TKI treatment. Results are promising if pts are transplanted while still in 1st CP. These results have to be confirmed in a larger prospective study. There were differences in outcome after SCT depending on the TKI used before SCT.

The prospective non interventional study (ONIS) has been started. 57 centres have registered, expecting to recruit 422 pts. At this time 46 pts. have been included. For 29 pts data are available. 1/3 were transplanted in 1st CP, 80% were beyond 1 year after diagnosis and 75% had an unrelated donor. No graft failure was observed. The NRM amounted 14% and the RR 7%.

158
14.49d Role of unrelated allogeneic SCT after autologous SCT in comparison to second autologous SCT in multiple myeloma (NMMA 2005, start study).

The study did not start because of lack of fundings. Several talks were undertaken with pharmaceutical companies to obtain grants. The interest is high especially for maintenance therapy after SCT, but no definitive decision about funding was given.

14.50d Study investigating the role of Kepivance for treating Mucositis after autologous SCT (350 patients)

Study is complete and a manuscript submitted to JCO. The study was presented at different meetings. In a high-dose melphalan setting, palifermin compared to placebo did not show an effect on oral mucositis or related patient’s burden.

This RCT aimed to study the efficacy of palifermin when administered in two different dosing regimens in a chemotherapy-only conditioning setting, to reduce maximum severity of oral mucositis (OM), patient-reported outcome (PRO) and health care burden including medical resource use, significant infections and duration of hospitalization. The efficacy of palifermin relative to placebo was investigated with palifermin given either pre/post-HDM or pre-HDM in patients with MM undergoing ASCT at 39 European centres. Oral cavity assessment (WHO grades (0/1, 2, 3 or 4)), patient reported outcome (PRO) questionnaires (Oral Mucositis Daily Questionnaire [OMDQ], Functional Assessment of Cancer Therapy Esophageal [FACT-E], European Quality of Life Utility Scale [EQ 5D], Mucositis Chronic Symptoms Questionnaire [MCSQ]) were used until 30 days post transplant or hospital discharge. 281 patients (mean age 56, ±SD= 8 years) were enrolled; 109 patients were randomized to pre-HDM, receiving palifermin (60 µg/kg/day) iv for 3 consecutive days before HDM and 115 subjects were randomized to pre/post-HDM receiving palifermin on 3 consecutive days before HDM and on 3 consecutive days after ASCT. 57 patients were randomized to receive placebo. There was no statistically significant difference in the primary endpoint maximum severity of OM between placebo and palifermin administered pre/post-HDM or pre-HDM. Severe OM (WHO grade 3 and 4) occurred in 37% (placebo), 38% (pre/post-HDM) and 24% (pre-HDM) of the patients. No difference was observed between placebo and palifermin pre/post-HDM, nor pre-only-HDM with respect to PRO assessments or medical resource use i.v. anti-infective drugs or non-opioid drug use, whereas use of opioids was somewhat lower in the palifermin treated arms (eg. 77, 67 and 64%, respectively). A higher incidence of febrile neutropenia and more significant infections were reported in the pre/post-HDM versus placebo group (eg. 51% and 26%). The lack of efficacy of palifermin in this study might be explained by the timing of the palifermin post-dose relative to the development of OM. Usually, OM develops about 10-14 days after start of conditioning. HDM is an exceptionally short (one day) conditioning regimen leading to an interval of two days from start of conditioning to day of transplant and start of post dose, compared to about a week for all common conditioning regimens. This has influenced the outcome of the trial, as the post dose of palifermin should be timed relative to the development of OM. To conclude, palifermin did not show an effect on OM in the
HDM setting, most likely due to the timing interval influenced by the short, one day course of HDM. Consequently, palifermin was not able to reduce OM or patient’s burden related to OM after HDM conditioning used to prepare patients before ASCT.

**14.55c Comprehensive survey outside Europe (Alois Gratwohl)**
The WBMT, has collected information from >1,350 transplant centers over all continents on the numbers of HSCT by indication and donor type for 2007 and 2008. A preliminary analysis was presented at the cIBMTR meeting in Honolulu (Hawaii) February 2011. The transplant rates are increasing and the reporting standardized. A manuscript will be written in summer 2011.

**14.56d Integration of risk factor profiling into risk adapted therapy pilot AML HOVON/SAKK <60 years (Alois Gratwohl)**
This analysis is still being performed and will be finalized in 2011.

**14.59c Guidelines for secondary allotransplantation after relapse (retrospective analysis)**
This megafile analysis involves 1631 patients undergone second SCT between 1994-2005 (all malignant disorders with emphasis on transplantation complications and NRM). The relevant clinical questions involve the donor (same or other donor), sibling or MUD, BM or PBSC and which intensity of conditioning? The factors affecting results were identified as: disease type, phase of disease, age, EBMT score, interval between the transplantations, conditioning, same or other donor, sibling vs. MUD and year of transplantation. The analysis will be finalized and presented during one of the meetings in 2011. A manuscript will be prepared as well.

**14.60c Prospective feasibility study phase II Dasatinib for relapse in CML after allo (Olavarria)**
Regulatory approval has been obtained and the study is open for recruitment in four countries (UK, Germany, Switzerland and France). Currently, no more countries are planned but additional countries may potentially be added in the future (Hungary is expected).
This Phase II efficacy study analyzes the role of dasatinib in patients with chronic and accelerated phase chronic myeloid leukemia relapsing after allogeneic blood or bone marrow transplantation. Patients > 18 years of age with Ph+ CML, whose disease is relapsed after transplant from an HLA-identical sibling or an HLA-matched unrelated donor (MUD) and have not responded to withdrawal of immunosuppressive treatment where this is possible, are entered. The primary objective is to assess the efficacy of dasatinib therapy in chronic and accelerated phase BCR-ABL (+) CML patients that undergo molecular, cytogenetic or hematological relapse following SCT. The secondary objectives determine the impact of dasatinib therapy on patient survival after relapse post-SCT and the incidence of any subsequent need for ‘rescue’ DLI and the safety of dasatinib in this clinical context using this specific dose regimen. The study is recruiting very slowly and the interest of the centers low. If the recruitment will not improve, the study will be closed.
14.61c T-PLL after autologous and allogeneic SCT (Wieslaw Jedrzejczak)
It is the largest group ever evaluated with this disease (54 patients). A first draft was written and the possibility to increase patient’s number considered (adding more patients from Claire Dearden). The analysis is now restricted to allogeneic only. A final draft is in preparation, which should be submitted in summer 2011.

14.62c Prospective registration audit for T-PLL (Wieslaw Jedrzejczak)
Prospective study is very close to meet the original planned number of 50 patients. Last information was 47 patients and an analysis is expected within May 2011.

14.65b Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling (Guglielmi)
500 patients were analyzed. 16% had molecular relapse, 30% cytogenetic relapse, 42% chronic hematological relapse and 12% accelerated relapse. The response rate was 68% with a median time to response of 7.5 mts. The GvHD rate amounted 44% with a median onset of 3 months after donor lymphocyte infusion. The relapse rate after response was seen only in 16 patients a median of 19 months after response. A manuscript is planned.

14.66b Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal (Wieslaw Jedrzejczak)
Recommendations are written and are waiting for submission after the retrospective analysis would be accepted for publication

14.67b Cytogenetic high risk AML: results of a biological randomized study in patients under the age of 60 a
The analysis was published in Leukemia 2009 and showed the important role of allogeneic SCT in high risk patients. The results determine the approach to patients with high risk leukemia and favour SCT as soon as CR is reached.

14.68b DMSO prospective audit (Curly Morris)
An increased risk of side effects is expected with the use of DMSO, especially with the highest doses (side effects are NCI definitions). There are huge center variations in the side effects observed. Some unexpected observations: apparently, DMSO would have a protective effect in young lymphoma patients and on the contrary more side effects seem to be present in old MM patients? The role of the different factors and their interactions can now be analyzed. A manuscript will be prepared.

14.69b ATG-depending outcome in MUD patients transplanted for CML (F. Schleuning)
This analysis is written up for a manuscript and will be submitted.
14.70b Prophylaxis and treatment of GvH-D: an EBMT survey (B. Hertenstein, T. Ruutu)

Reports from 81 EBMT centres from 23 countries are available to document the heterogeneity of GvHD prophylaxis and treatment strategies, to form a platform for efforts to standardize transplantation methods and to help in planning clinical trials. A manuscript has been written Clear recommendations on indications for allogeneic haematopoietic stem cell transplantation have been established. In contrast, the techniques used have remained poorly standardized. Reported outcomes vary markedly, and it would be important to know, to what extent this is due to differences in treatment procedures. EBMT performed in 2010 a survey among its member centres about their strategies in preventing and treating graft versus host disease (GvHD). Seventy-nine centres from 23 countries participated. The survey showed marked variability in the GvHD prophylaxis and treatment strategies applied in the centres. Even superficially similar methods differed in relevant practical details. It is likely that these differences have a bearing on the outcome of allogeneic transplantations. The present findings underline the need for standardization and prospective controlled studies in GvHD prevention and treatment. The aim is to set recommendation for prophylaxis and treatment of GvHD.

14.71b Analysis of non-disease related complications after HCT (T. Ruutu)

M. Stern is working on an analysis on GvHD as surrogate marker for GvL on relapse using the CLWP megafile. The following questions should be answer a.) How do different diseases compare? b.) How do different transplant settings compare c.) Are there differences between unrelated and related sibling transplantations d.) Are there differences between TCD and non-TCD grafts?

A further topic is the topical tacrolimus for chronic cutaneous GvHD. The recruitment will start in March 2010 and will end October 2011. The Follow-Up time of this study will be six months after recruitment. The target will be to recruit 100 patients to this study.

Finally the role of comorbidity on stem cell transplantation will be defined in detail. This study will be a prospective study, which is now in a very preliminary status. No update is available on this evaluation.

14.72b Randomized study on VOD in pediatric patients n=360 (Corbacioglu)

The manuscript has been submitted to NEJM

Hepatic veno-occlusive disease (VOD) is a leading cause of morbidity and mortality after hematopoietic stem-cell transplantation (HSCT).

In this international, randomized, controlled, open-label trial, we compared defibrotide (Gentium S.p.A.) prophylaxis with no prophylaxis in pediatric HSCT patients at high risk for developing VOD. The primary endpoint was the incidence of VOD by Day+30 post-HSCT, adjudicated by a blinded, independent review committee. Secondary endpoints included graft-versus-host disease (GVHD), VOD-related organ failure and mortality.
A total of 356 patients met the inclusion criteria and gave informed consent to be randomized to the i.v. defibrotide arm (n=180) or the control arm (n=176). VOD was reported in 22 patients (12%) in the defibrotide arm and in 35 patients (20%) in the control arm (competing risk, P=0.05; Kaplan-Meier, P=0.05). The incidence and severity of acute GVHD were significantly reduced (P=0.005 and P=0.003, respectively) in the allogeneic recipients. VOD-associated organ failures were lower in the defibrotide arm with a significant reduction in the incidence of renal failure (1% vs. 6%, P=0.02). A significantly higher Day+100 mortality was observed in patients with VOD (25% vs. 6%; P<0.001). Although mortality after VOD diagnosis was lower in the defibrotide arm (4 vs. 10 patients, P=0.1), overall mortality was similar in the two arms. There was no difference in the incidence of adverse events between arms (87% vs. 88%).

Defibrotide reduced the incidence of VOD by 40%, as well as the incidence and severity of acute GVHD, and has a good safety profile. (ClinicalTrials.gov number, NCT00272948.)

14.73a Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD (Mary Eapen and Vanderson Rocha, on behalf of CIBMTR, Eurocord and ALWP of EBMT)
Data support the use of UCB as first line therapy for adults with acute leukemia, especially when transplant is urgently needed or when an HLA-matched unrelated adult donor is lacking. The manuscript is currently being written.

14.74 Non interventional studies (Passweg). Manuscript ready
The possibility to enter patients in non-interventional studies has been exploited by J. Passweg. Using this possibility patients are treated according to established treatment modalities, but outcome can be still evaluated.

14.75 CML RIC vs. standard (Crawley).
The manuscript is in preparation.

14.76 Allo-SCT in T315I mutation (W Wiesław Jędrzejczak) data collection
We have collected 23 reports with T513I mutations. There was recently extensive correspondence between members of the WP since additional 40 patients were collected in another country. The data are now collected and will be analyzed for a manuscript.

14.77 Punctal plugs for dry eyes after allotransplantation. M van Gelder
The protocol has been finalized and 8 patients of the 48 are included. The study will be advertised in a forthcoming newsletter.

14.78 Graft failure after reduced intensity conditioning. B Hertenstein
The paper was rejected by Haematologica and is now being prepared for submission to BMT.
14.79 Cytokine gene polymorphism  A Dickinson/ J Norden. Manuscript submission
The manuscript has been published:

BACKGROUND: Non-HLA gene polymorphisms have been shown to influence outcome after allogeneic hematopoietic stem cell transplantation. Results were derived from heterogeneous, small populations and their value remains a matter of debate.

DESIGN AND METHODS: In this study, we assessed the effect of single nucleotide polymorphisms in genes for interleukin 1 receptor antagonist (IL1RN), interleukin 4 (IL4), interleukin 6 (IL6), interleukin 10 (IL10), interferon (IFNG), tumor necrosis factor (TNF) and the cell surface receptors tumor necrosis factor receptor II (TNFRSF1B), vitamin D receptor (VDR) and estrogen receptor alpha (ESR1) in a homogeneous cohort of 228 HLA identical sibling transplants for chronic myeloid leukemia. Three good predictors of overall survival, identified via statistical methods including Cox regression analysis, were investigated for their effects on transplant-related mortality and relapse. Predictive power was assessed after integration into the established European Group for Blood and Marrow Transplantation (EBMT) risk score.

RESULTS: Absence of patient TNFRSF1B 196R, absence of donor IL10 ATA/ACC and presence of donor IL1RN allele 2 genotypes were associated with increased transplantation-related mortality and decreased survival. Application of prediction error and concordance index statistics gave evidence that integration improved the EBMT risk score.

CONCLUSIONS: Non-HLA genotypes were associated with survival after allogeneic hematopoietic stem cell transplantation. When three genetic polymorphisms were added into the EBMT risk model they improved the goodness of fit. Non-HLA genotyping could, therefore, be used to improve donor selection algorithms and risk assessment prior to allogeneic hematopoietic stem cell transplantation.

14.80 Organ transplantation after allogeneic SCT. Manuscript ready.  C Koenecke
The manuscript has been published with the following title:

To analyze the outcome of solid organ transplantation (SOT) in patients who had undergone allogeneic hematopoietic stem cell transplantation (HSCT), a questionnaire survey was carried out within 107 European Group of Blood and Marrow Transplantation centers. This study covered HSCT between 1984 and 2007 in Europe. Forty-five SOT in 40 patients were reported. Fifteen liver, 15 renal, 13 lung, 1 heart and 1 skin transplantations were performed in 28 centers. Overall survival (OS) of patients after SOT was 78% at 5 years (95% confidence interval [CI], 64% to 92%). OS at 5 years was 100% for renal, 71% (95% CI, 46% to 96%) for liver and 63% (95% CI, 23% to 100%) for lung transplant recipients. The 2-year-incidence of SOT failure was 20% (95% CI, 4% to 36%) in patients with graft-versus-host disease (GvHD) and 7% (95% CI, 0% to 21%) in patients without GvHD before
SOT. The relapse incidence for underlying malignant diseases was 4% at 5 years (95% CI, 0% to 12%). In summary, this study shows that selected patients receiving SOT after HSCT have a remarkably good overall and organ survival. These data indicate that SOT should be considered in selected patients with single organ failure after HSCT.

14.81 HLA-identical siblings: Impact on cytogenetics and outcome (Francesco Onida).
Cytogenetics (CG) represent one of the most important prognostic factors in MDS. However, it is uncertain whether the negative effect of poor CG could be counteracted by allo-HSCT as a curative strategy in patients with MDS. With the aim of evaluating the impact of cytogenetics in patients with primary MDS undergoing allogeneic transplant from HLA-identical siblings, the MDS subcommittee of the CLWP has performed a retrospective analysis on 510 patients who underwent this transplant strategy from 1981 to 2006 and were reported to EBMT with full cytogenetic data. This study provides evidence that poor risk cytogenetics as classified by the IPSS have strong prognostic impact on outcome of patients undergoing allo-HSCT from HLA-identical siblings for MDS. However, the overall outcome after alloSCT compared to the outcome of nontransplant approaches, makes alloSCT the treatment of choice for this group of patients. The manuscript is currently under its last finalization and will be submitted within next month of April.

14.82 Survey in Europe (annual) A. Gratwohl
The EBMT activity survey 2009: trends over the past 5 years. Bone Marrow Transplant. 2011 Feb 28. [Epub ahead of print] has been accepted for publication.
Six hundred and twenty-four centers from 43 countries reported a total of 31,322 hematopoietic SCT (HSCT) to this 2009 European Group for Blood and Marrow Transplantation (EBMT) survey with 28,033 first transplants (41% allogeneic, 59% autologous). The main indications were leukemias (31%; 92% allogeneic), lymphomas (58%; 12% allogeneic), solid tumors (5%; 6% allogeneic) and non-malignant disorders (6%; 88% allogeneic). There were more unrelated than HLA-identical sibling donors (51 vs 43%) for allogeneic HSCT; the proportion of peripheral blood as stem cell source was 99% for autologous and 71% for allogeneic HSCT. Allogeneic and autologous HSCT continued to increase by about 1000 HSCT per year since 2004. Patterns of increase were distinct and different. In a trend analysis, allogeneic HSCT increased in all World Bank Categories (P=0.01, two sided; all categories), autologous HSCT increased in middle- (P=0.01, two sided) and low-income (P=0.01, two sided) countries. EBMT practice guidelines appeared to have an impact on trend, with a clear increase in absolute numbers within the categories 'standard' and 'clinical option' for both allogeneic and autologous HSCT (P=0.01, two sided; for both allogeneic and autologous HSCT) and a clear decrease in autologous HSCT for the 'developmental’ and 'generally not recommended’ indications (P=0.01, two sided). These data illustrate the status and trends of HST in Europe.Bone Marrow Transplantation advance online publication, 28 February 2011; doi:10.1038/bmt.2011.11.
14.83 Accreditation in Europe

A study led by Alois Gratwohl (Basel, CH) looked at the effects of implementing quality management in transplant programmes on patient outcome. Their conclusions pointed to a strong correlation between quality management and improvements in patient outcome. Prof. Gratwohl presented the study at the EBMT meeting in Vienna and an article was accepted for publication in the Journal of Clinical Oncology and is expected in print in Spring 2011.

The review process to prepare the 5th edition of the FACT-JACIE Standards commenced in June 2010 with a meeting in Barcelona. The draft text will go to public consultation in April 2011 and release of the final text is expected at the end of 2011.

At the 2010 EBMT Annual Meeting in Vienna, the 2nd Quality Management Meeting took place as part of the congress programme. This proved very successful with approximately 150 attendees participating in a varied programme with opportunities to ask questions and share experience. The meeting has now become a regular part of EBMT Annual Meetings.

In 2010, 11 training courses and other events were run on the initiative of national societies or individuals with JACIE support or directly by JACIE. A total of 73 participants received training either as inspectors, preparing their centre for accreditation or internal audits.

The number of trained inspectors continues to grow and now stands at over 230 from 19 countries.

Accreditation Programme Status:

a. 20 new applications received and 17 applications for reaccreditation.
b. 30 audits were performed (17 first-time and 5 reaccreditation)
c. 21 centres were accredited for the first time and 5 were reaccredited.

Total centres/facilities registered: 230
Centres in progress: 68
Centres inspected: 206
Accredited: 102
Countries: 17
**Figure 14.1:** Reaccreditation applications per year.

**Figure 14.2:** Completed inspections per year.

**Figure 14.3:** JACIE awarded accreditations by year.
14.84 Outcome in centers with JACIE accreditation manuscript ready A. Gratwohl

The manuscript has been accepted by the Journal of Clinical Oncology:

INTRODUCTION OF A QUALITY MANAGEMENT SYSTEM AND OUTCOME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

The comprehensive quality management system “JACIE” was introduced to improve quality of care in hematopoietic stem cell transplantation (HSCT). The justification for these investments remained open. We therefore tested the hypothesis that the introduction of JACIE improved patient survival stepwise and more than expected by calendar time alone.

Data on 41,623 allogeneic (39%) and 66,281 autologous (61%) HSCT for an acquired hematological disorder performed between 1999 and 2007 by 421 teams in Europe were used to assess outcome of patients transplanted in teams at baseline (> 3 years prior to application or no application), during preparation (3 years prior to application), during application (time from application to accreditation) and after JACIE accreditation. The analysis was clustered by team, stratified for donor type, disease, year of HSCT, conditioning and Gross National Income per capita of the respective country. Patient’s risks were adjusted for by the EBMT score.

Outcome improved stepwise from baseline up to JACIE accreditation. This improvement was systematic and robust for patients after allogeneic HSCT, quantified for relapse free survival compared to baseline by a HR of 0.96 (0.90-1.03; p = 0.22) for preparation, 0.95 (0.88-1.03; p = 0.20) for application, and 0.86 (0.78-0.95; p = 0.01) for the accreditation (test for trend: p=0.01). Improvement from baseline was of similar order of magnitude after autologous HSCT (HR for accreditation 0.83, 0.74-0.93; p<0.01).

These findings support the hypothesis that introduction of a comprehensive clinical quality management system is associated with improved outcome of patients after HSCT.
### Table 14.1: Deliverables WP14, 2010 and 2011

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Stem cell transplantation</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months*)</th>
<th>Used indicative person months*)</th>
<th>Lead contractor</th>
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<tr>
<td>14.5</td>
<td>Regular WP meetings</td>
<td>76,78, 84,86</td>
<td>76,78,84,86</td>
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<td>2</td>
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<tr>
<td>14.6</td>
<td>LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)</td>
<td>79,86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Niederwieser</td>
<td></td>
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<tr>
<td>14.14f</td>
<td>Report of study patients to registry</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Brand</td>
<td></td>
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<tr>
<td>14.42d</td>
<td>Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning. Start study</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Niederwieser, Löwenberg, Sierra, Dombret, Cornelissen, Verdonck, Gratwohl, Rocha</td>
<td></td>
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<tr>
<td>14.45c</td>
<td>Allogeneic reduced intensity conditioning transplantation versus conventional conditioning in MDS (RICMAC) Study start</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Kröger deWitte</td>
<td></td>
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<tr>
<td>14.46d</td>
<td>MMVAR Study to treat relapse in myeloma after autologous SCT (40 patients)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Gahrton</td>
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<tr>
<td>14.47d</td>
<td>Related allo-SCT after Reduced Intensity Conditioning versus Best Standard of Care in elderly patients with AML in CR1 (Brune)</td>
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<td>86</td>
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<td>2</td>
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<tr>
<td>14.48d</td>
<td>AlloSCT after TKI in CML</td>
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<td>Schleuning, Guilhot</td>
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<td>14.49d</td>
<td>Role of unrelated allogeneic SCT after autologous SCT in comparison to second autologous SCT in multiple myeloma (NMMA 2005, start study).</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Niederwieser, Gahrton, Gratwohl,</td>
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<td>Study investigating the role of Kepivance for treating Mucositis after autologous SCT (350 patients).</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Niederwieser, Blijlevens, deWitte,</td>
<td></td>
</tr>
<tr>
<td>14.55c</td>
<td>Comprehensive survey outside Europe (publication)</td>
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<td>86</td>
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<td>2</td>
<td>Gratwohl, Niederwieser</td>
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<td>14.56d</td>
<td>Integration of risk factor profiling into risk adapted therapy pilot AML. HOVON/SAKK &lt;60 years</td>
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<td>2</td>
<td>Gratwohl</td>
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<td>Prospective feasibility study phase II Dasatinib for relapse in CML after allo</td>
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<td>Olavarria, Schleuning (2)</td>
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<td>14.61c</td>
<td>T-PLL after autologous and allogeneic SCT (44 patients)</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Jedrzejczak</td>
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<td>14.62c</td>
<td>Prospective registration audit for T-PLL</td>
<td>73-86</td>
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<td>Jedrzejczak</td>
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<tr>
<td>Deliv. No.</td>
<td>Deliverable Name</td>
<td>Date due</td>
<td>Actual/Forecast delivery date</td>
<td>Estimated indicative person months*</td>
<td>Used indicative person months*</td>
<td>Lead contractor</td>
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<td>Long term outcome of CML patients treated with DLI after allogenic SCT from an HLA-identical sibling</td>
<td>73-86</td>
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<td>Guglielmi</td>
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<td>Recommendation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal</td>
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<tr>
<td>14.67b</td>
<td>Cytogenetic high risk AML: results of a biological randomized study in patients under the age of 60 a</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Basara (Leipzig)</td>
<td></td>
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<tr>
<td>14.68b</td>
<td>DMSO prospective audit</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Morris</td>
<td></td>
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<tr>
<td>14.69b</td>
<td>ATG-depending outcome in MUD patients transplanted for CML</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Schleuning</td>
<td></td>
</tr>
<tr>
<td>14.70b</td>
<td>Prophylaxis and treatment of GvH-D: an EBMT survey</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Hertenstein</td>
<td></td>
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<tr>
<td>14.71b</td>
<td>Analysis of non-disease related complications after HCT</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Ruutu</td>
<td></td>
</tr>
<tr>
<td>14.73</td>
<td>Effect of Stem Cell Source on Transplant Outcomes in Adults with AL: A Comparison of Unrelated BM, PBSCT and CD</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Rocha</td>
<td></td>
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<tr>
<td>14.74</td>
<td>Non interventional studies (Passweg). Manuscript ready</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Passweg</td>
<td></td>
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<tr>
<td>14.75</td>
<td>CML RIC vs. standard (Crawley). Manuscript ready</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Crawley</td>
<td></td>
</tr>
<tr>
<td>14.76</td>
<td>Allo-SCT in T315I mutation (Wiesław Jędrzejczak) data collection</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Jędrzejczak</td>
<td></td>
</tr>
<tr>
<td>14.77</td>
<td>Punctal plugs for dry eyes after allotransplantation. M van Gelder</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Van Gelder</td>
<td></td>
</tr>
<tr>
<td>14.78</td>
<td>Graft failure after reduced intensity conditioning. B Hertenstein</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Hertenstein</td>
<td></td>
</tr>
<tr>
<td>14.79</td>
<td>Cytokine gene polymorphism A Dickinson/ J Norden. Manuscript submission</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Dickinson, Norden</td>
<td></td>
</tr>
<tr>
<td>14.80</td>
<td>Organ transplantation after allogeneic SCT. Manuscript ready, C Koenecke</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Koenecke</td>
<td></td>
</tr>
<tr>
<td>14.81</td>
<td>HLA-identical siblings: Impact on cytogenetics and outcome (Francesco Onida). Manuscript ready</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Onida</td>
<td></td>
</tr>
<tr>
<td>14.82</td>
<td>Survey in Europe (annual) A. Gratwohl</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Gratwohl</td>
<td></td>
</tr>
<tr>
<td>14.83</td>
<td>Accreditation in Europe</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>EOIN</td>
<td></td>
</tr>
<tr>
<td>14.84</td>
<td>Outcome in centers with JACIE accreditation manuscript ready A. Gratwohl</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Gratwohl</td>
<td></td>
</tr>
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### Table 14.2: List of milestones WP14, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP14</td>
<td>SCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.42</td>
<td>Randomized study in patients with AML over the age of 60 a studying the role of SCT with reduced intensity conditioning</td>
<td>78</td>
<td>Started recruitment, recruitment will last 2-3 years.</td>
<td>Niederwieser, Löwenberg, Sierra, Dombret, Cornelissen, Verdonck, Gratwohl, Rocha</td>
</tr>
<tr>
<td>14.57</td>
<td>Autologous SCT for CML (30 patients reported to the EBMT). Evaluation</td>
<td>78</td>
<td>86</td>
<td>Heim, Gratwohl</td>
</tr>
<tr>
<td>14.58</td>
<td>Outcome of patients with low risk Gratwohl score CML</td>
<td>78</td>
<td>Ongoing</td>
<td>Heim, Gratwohl</td>
</tr>
<tr>
<td>14.61b</td>
<td>T-PLL after autologous and allogeneic SCT (44 patients)</td>
<td>78</td>
<td>ongoing</td>
<td>Jedrzejczak</td>
</tr>
<tr>
<td>14.65</td>
<td>Long term outcome of CML patients treated with DLI after allogeneic SCT from an HLA-identical sibling</td>
<td>78</td>
<td>Ongoing</td>
<td>Guglielmi</td>
</tr>
<tr>
<td>14.66</td>
<td>Recommandation for allogeneic and autologous stem cell transplantation in T-PLL: An EBMT/ERIC proposal</td>
<td>78</td>
<td>Ongoing</td>
<td>Jedrzejczak</td>
</tr>
<tr>
<td>14.70</td>
<td>Prophylaxis and treatment of GvH-D: an EBMT survey</td>
<td>78</td>
<td>86</td>
<td>Hertenstein</td>
</tr>
<tr>
<td>14.71</td>
<td>Analysis of non-disease related complications after HCT</td>
<td>78</td>
<td>86</td>
<td>Ruutu</td>
</tr>
<tr>
<td>14.72</td>
<td>Randomized study on VOD in pediatric patients n=360</td>
<td>78</td>
<td>Delivery of the manuscript</td>
<td>Corbaciouglou (Ulm)</td>
</tr>
<tr>
<td>14.73</td>
<td>Effect of Stem Cell Source on Transplant Outcomes in Adults with AL. A Comparison of Unrelated BM, PBSCT and CD (manuscript ready)</td>
<td>78</td>
<td>86</td>
<td>Rocha</td>
</tr>
</tbody>
</table>

### Section 4: Other Issues

Ethical issues - none  
Competitive calls - none

### Section 5: WP-Performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinical trials</td>
<td>12</td>
</tr>
<tr>
<td>Number of patients registered in the survey</td>
<td>50000</td>
</tr>
<tr>
<td>Number of metaanalyses</td>
<td>7</td>
</tr>
<tr>
<td>Development of standardization and guidelines</td>
<td>done</td>
</tr>
</tbody>
</table>
15 Supportive care/anti-infection prophylaxis and treatment (WP15)

Project objectives and major achievements during the reporting period

The work with guidelines has continued during the period. One paper was submitted for publication in Bone Marrow Transplantation and two other papers are in final stages of preparation. In addition collaboration has been initiated with the Infectious Diseases Society of America (IDSA) regarding update of vaccination guidelines in patients with leukemia and other hematological malignancies. This work was presented at the IDSA meeting in Vancouver October 2010.

15.5 Regular WP meetings

The WP has held meetings at the ELN meeting in Mannheim in February, at the EBMT meeting in Vienna in March, and in Paris in October.

15.6 LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups

No new activity.

15.22e Initiation of a protocol to use KGF immune reconstitution after allo-SCT: Use of the established platform for an actually performed prospective trial

The protocol is finalized but the sponsor did not want to fund the prospective study. Thus, the protocol is currently on hold.

15.27d Develop common protocols for molecular diagnosis of fungal infections by PCR

This topic has been developed into an international collaboration (EAPCRI; European Aspergillus PCR Initiative).

15.29d Arrange courses in infectious diseases in stem cell transplant recipients

A training course was held in Paris September 23-25 with approximately 30 participants.

15.30b Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines

Collaboration has been initiated with IDSA regarding guidelines for vaccination of patients with hematological malignancies and after stem cell transplantation. These have been presented at the IDSA meeting in Vancouver, Canada in October 2010 and the manuscript is in the final stages of preparation. From the 3d ECIL meeting, one manuscript has been published, one manuscript has been submitted and two are in the final stages of preparation from the 3d ECIL meeting. Slide sets regarding the recommendations have been published on the ELN website. A 4th European Conference regarding Infections in Leukemia is in planning for September 2011 updating previous guidelines (slides not published on the ELN website), and covering new topics.
**Table 15.1:** List of deliverables WP15, 2010

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months</th>
<th>Responsible lead participant/investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP15</td>
<td>Supportive care, anti-infection prophylaxis and treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.5</td>
<td>Regular WP meetings</td>
<td>86</td>
<td>73,75,80</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>15.6</td>
<td>LP reports to NMC regarding structure, trial activities and integration of national leukemia trial groups (1 page, bullet point style)</td>
<td>79,86</td>
<td>86</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>15.22e</td>
<td>Initiation of a protocol to use KGF immune reconstitution after allo-SCT: Use of the established platform for an actually performed prospective trial</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15.27d</td>
<td>Develop common protocols for molecular diagnosis of fungal infections by PCR</td>
<td>86</td>
<td>86 ongoing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15.29d</td>
<td>Arrange courses in infectious diseases in stem cell transplant recipients</td>
<td>78</td>
<td>80</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15.30b</td>
<td>Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 15.2:** List of milestones WP15, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP15</td>
<td>SCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.27d</td>
<td>Develop common protocols for molecular diagnosis of fungal infections by PCR</td>
<td>86</td>
<td>86 ongoing</td>
<td>Einsele Maertens</td>
</tr>
<tr>
<td>15.30</td>
<td>Develop guidelines for prevention of infections in stem cell transplant recipients not covered in previous guidelines</td>
<td>73-86</td>
<td>86</td>
<td>Einsele Ljungman Cordonnier</td>
</tr>
</tbody>
</table>

**Section 3: Consortium management**

All deliverables and milestones that had to get revised timetables as described in 2010. The two subcommittees have continued to function. One subcommittee handles the specific topic of infections in stem cell transplant recipients. This subcommittee is lead by Hermann Einsele. The second subcommittee did the planning for the 3rd European Guidelines meeting and is now working on the publications and is planning the 4th meeting.. This group is chaired by Catherine Cordonnier and incorporates representatives for the ELN, the EBMT, the ICHS, and the EORTC.

**Section 4: Other Issues**

Ethical issues - none
Competitive calls - none

**Section 5: WP-Performance**

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>European guidelines for anti-infection prophylaxis and therapy in neutropenic patients</td>
<td>Finalized and expanded</td>
</tr>
</tbody>
</table>
With regard to the major objectives as stated in the original grant application many years ago, most of them have been achieved in the field of CML. This is partly due to the fact that there had been already a close collaboration among the premier European CML study groups since 1992. But a major reason why comparable achievements were missing for a long time for the other leukemia entities was lack of funds. Initially a considerably higher funding (actually 4 times as much as finally awarded) was expected and planned for. To establish a registry requires considerable and enduring activities over a long time without the hope of immediate rewards like presentations and publications. This in combination with lack of funds is certainly not a good starting point. Over time and certainly influenced by the constant flow of presentations of the CML Registry, the situation has changed. Thus an ELN-MDS-Registry has been initiated with the support of Novartis which will become productive once a sufficiently sized sample has been recruited and observed for an adequate period of time.

Quite recently similar first activities have been started for AML, too. Guided by the German AML Study Groups and U. Mansmann (IBE, University of Munich) planning and design activities have started. A decisive factor for the outcome of these activities is of course the access to funding.

Considering that the establishment of European Leukemia Registries is pioneer work there are considerable achievements. In this context one should not forget that the legal situation with regard to registries, clinical and epidemiological research and data confidentiality issues differs from country to country and is thus rather complicated, and difficult to overcome.

**Objectives and starting point of work at beginning of reporting period**

There were one major objectives for the current reporting period:

- to expand and update the European CML-registry which collects data about the epidemiology and the clinical management of patients with CML in the various member states of the EU.

Considerable progress has been achieved.

**European CML-registry**

The three sections (in-study, out-study, and population-based) of the EUTOS CML-Registry have been successfully established. With 2389 eligible CML-patients in the in-study and 1582 patients in the out-study section even more patients than initially expected could be recruited.

The prospective population-based section took a bit longer to get started as many difficulties had to be solved to get the research plan agreed upon by all participants and to get the data collection started. Thus the majority of the 24 participating countries began with data collection in 2010 only.
Considering this background the reporting of 731 eligible patients should be considered as a success too. Altogether data of 4703 eligible CML-patients have been registered in the reporting period.

The collaboration between the Scientific Headquarter in Bologna, the Management Center in Mannheim and the Central Data Center in Munich worked very well. Although the workload at the CDC is heavy we managed to get good relations with all participants and there is a constant flow of queries, responses, and questions and answers.

Typically registers take years before they get productive in the sense of analysing data, providing presentations and submitting manuscripts. The major reason is that a research plan has to be prepared and agreed upon and all the country-wise different laws and regulations have to be identified and complied with. The CDC has provided numerous reports both for the sponsor and for the various committees and boards of EUTOS. We are proud that a manuscript has been finalized about a new prognostic model which allows to predict CCgR at 18 months using two variables only (Hasford et al., Blood in press, see section 3 WP17).

The major challenge in the coming period is to safeguard that all patients are monitored according to the research plan and that the registry receives proper follow-ups.

*Progress towards objectives – tasks worked on and achievements made with reference to planned objectives*

**17.5 Regular WP meetings**
WP meetings took place at the annual ELN meeting in Mannheim (1/2010), Barcelona (EHA 6/2010), Mannheim (CML 7/2010)). Most often these WP meetings were joint meetings of WP17 and WP4.

**17.6 LP reports to NMC regarding structure, activities and integration**
There were regular reports to the NMC regarding structure, activities and integration.

**17.13c Collect data for prognostic model analyses and meta-analyses (European CML registry)**
Data of more than 3900 patients from Austria, Czech Republic, Denmark, Finland, France, Germany, Israel, Italy, Norway, Poland, Romania, Russia, Spain , Sweden and Switzerland have been checked and included in the registry.

**17.14c Quality control of incoming data**
Quality control of incoming data is a prerequisite of any data evaluation. There are plausibility checks of each variable, concerning completeness, minimum and maximum, valid numbers, valid dates etc. Furthermore there are two-dimensional plausibility checks concerning more than one variable. Finally
comparisons between centres are being conducted to find outliers, which can be due to misinterpretations or erroneous documentation.

There will be send queries to the centres to complete the documentation and improve the quality of the data. The results of the quality control of incoming data are being presented to all participants. This activity has to continue as long as the registry collects data.

There were considerable problems due to many languages used to describe and explain the variables and items, and the ‘translation’ to English took some extra time. But we are confident now that we have solved this problem. It is very helpful for us to get the documentation in the Excel template sheets that are provided by us, the participants can cross-check their documentation by filling in them so the number of queries can be reduced.

17.15d Spreading of Excellence by promotion of web-based information, educational training courses etc.

- A major point of basically all presentations was to encourage the physicians in the audience to treat elderly patients with modern treatments like Imatinib.
- In May, Joerg Hasford and Markus Pfirrmann participated in the “European investigators in CML” meeting, in Prague. Hasford and Pfirrmann met most European coordinators of studies in CML. The occasion was used to promote the CML registry. In addition results of our analyses were presented and discussed.
- In July Joerg Hasford presented results at the annual CML-Symposium in Mannheim

17.16d Update of the CML registry

As already mentioned in 2008 and 2009, we tried hard to update the information in the registry. In the last quarter, many study groups provided updates so that we can proceed with the analysis plan.

17.17b Gender specific issues

- To analyse the influence of gender is an obligate issue in each analysis. Gender and age are considered as potential prognostic variables in each standard evaluation of leukaemia studies and therefore compulsory. But it is planned to check for sex-specific disease-, treatment-, and outcome characteristics, too. Due to the fact that most data provided by the study groups consisted of baseline data, our plans of first analyses could not yet be fulfilled with the registry.

17.21b Analysis and Validation of prognostic models

Due to the delays in updating the data and the comparable few events (e.g. death, relapse) seen under Imatinib, we could not yet analyse prognostic factors. We hope to progress in 2009.
Table 17.1: List of Deliverables WP17, 2010

<table>
<thead>
<tr>
<th>Deliv. No.</th>
<th>Deliverable Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Estimated indicative person months*)</th>
<th>Used indicative person months*)</th>
<th>Lead contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP17</td>
<td>Biometry of Registry, Epidemiology, Metaanalyses and Prognosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.5</td>
<td>Regular WP meetings</td>
<td>78,84,86</td>
<td>78,84,86</td>
<td>0</td>
<td>2</td>
<td>Hasford</td>
</tr>
<tr>
<td>17.6</td>
<td>LP reports to NMC regarding structure, activities and integration (1 page, bullet point style)</td>
<td>79,86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Hasford</td>
</tr>
<tr>
<td>17.13d</td>
<td>Collect data for prognostic model analyses and epidemiological and treatment survey</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>Hasford</td>
</tr>
<tr>
<td>17.14d</td>
<td>Quality control of incoming data-continued</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>6</td>
<td>Hasford, Müller</td>
</tr>
<tr>
<td>17.15e</td>
<td>Spreading of excellence by promotion of web-based information, educational training courses etc</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>2</td>
<td>Simonsson, Hasford, J Guilhot, Baccarani</td>
</tr>
<tr>
<td>17.16e</td>
<td>Update of CML-Registry</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td>4</td>
<td>Hasford, J Guilhot, Baccarani, Simonsson</td>
</tr>
<tr>
<td>17.17c</td>
<td>Analysis of gender specific issues</td>
<td>76</td>
<td>86</td>
<td>0</td>
<td>1</td>
<td>Hasford</td>
</tr>
<tr>
<td>17.21c</td>
<td>Analysis and Validation of prognostic models</td>
<td>73-86</td>
<td>86</td>
<td>0</td>
<td></td>
<td>Hasford</td>
</tr>
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</table>

*) if available

Table 17.2 List of milestones WP17, 2010

<table>
<thead>
<tr>
<th>Milestone No.</th>
<th>Milestone Name</th>
<th>Date due</th>
<th>Actual/Forecast delivery date</th>
<th>Lead contractor</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP17</td>
<td>Biometry of Registry, Epidemiology, Metaanalyses and Prognosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.21c</td>
<td>Analysis and Validation of prognostic models</td>
<td>73-86</td>
<td>86</td>
<td>Hasford</td>
</tr>
<tr>
<td>17.22c</td>
<td>Estimates of incidence of CML and treatment survey</td>
<td>73-86</td>
<td>86</td>
<td>Hasford</td>
</tr>
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</table>

Section 4: Other Issues

Ethical issues – none, Competitive calls – none

Section 5: WP-Performance

<table>
<thead>
<tr>
<th>Performance indicators</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of core data sets</td>
<td>done (for CML, MDS)</td>
</tr>
<tr>
<td>Number of clinical trials performed with standardized common data sets</td>
<td>CML trials</td>
</tr>
<tr>
<td>Number of involved countries</td>
<td>24</td>
</tr>
<tr>
<td>Number of involved/registered patients</td>
<td>4703</td>
</tr>
</tbody>
</table>
Annex - Plan for using and disseminating the knowledge

16 **Section 1: Exploitable knowledge and its use**

Is not relevant and not the primary aim of the network.

17 **Section 2: Dissemination of knowledge: WP-Meetings**

**WP-Meetings WP1**

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 450 participants from EU and non EU countries

- WP-meetings, EHA, Barcelona, June 2010
  Attendance: Approximately 210 participants from EU countries

- ELN ASH Breakfast Meeting 2010, Orlando, December 05th, 2010
  Attendance: Approximately 180 participants from European countries

**WP-Meetings WP2**

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 60 participants EU countries

- Internal Workshop of the ELN for Quality of life and late effects in Hematologic Social Malignancies, Mannheim, 1 February 2011
  Attendance: Approximately 90 participants EU countries

- Workshop in Mannheim about European Clinical Trials Directive: Suggestions for modification and practical approaches, Mannheim, 1 February 2011
  Attendance: Approximately 40 participants EU countries

**Road Map Initiative for Clinical Research in Europe:**

- 18 January 2010: Meeting in Barcelona (Spain): Risk based approach organised by ECRIN
- 19 January 2010: Meeting in Barcelona (Spain): Research Ethic Committees and Ethical Review in Europe organised by ECRIN
- 8 February 2010: Meeting in Brussels (The Netherlands): Towards a better Future for Pharmacovigilance in Clinical Trials organised by EORTC
- 17 March 2010: Meeting in Brussels (The Netherlands): Designing the Future Conditions for Clinical Research in Europe by EFGCP

**WP-Meetings WP3**

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 45 participants from EU and non EU countries

**WP-Meetings WP4**

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 100 participants from EU and non EU countries
- **Annual ELN Symposium, EUTOS Meeting, Mannheim, February 3rd**
  Attendance: Approximately 75 participants from EU and non-EU countries

- **EI-CML meeting, Spineto, Italy, May 2010**
  Attendance: Approximately 40 participants from EU

- **WP meeting, EHA, Barcelona, June 4**
  Attendance: Approximately 50 participants from EU

- **CML symposium, Heidelberg July 2**
  Attendance: Approximately 120 participants from EU and non-EU

- **ELN Frontiers meeting, Wien, September 2010**
  Attendance: 400 participants from EU

- **ESH-ELN joined CML meeting, Bordeaux, September 2009**
  Attendance: 300 participants from EU

- **ELN Breakfast meeting at ASH, Orlando, December 5**
  Attendance: Approximately 55 participants from European countries

- **EUTOS registry meeting WP4, ASH, New Orleans, New Orleans December 05**
  Attendance: Approximately 10 participants from EU countries

**WP-Meetings WP5**

- **Annual ELN Symposium, Mannheim, February 2nd**
  Attendance: Approximately 60 participants from EU and non-EU countries

- **6th Symposium of the AML Intergroup, Reisensburg February 11 2011**
  Attendance: Approximately 25 participants from EU and non-EU countries

- **WP meeting, EHA, Barcelona, June 10**
  Attendance: Approximately 50 participants from EU

- **AML Intergroup Meeting, Frankfurt, 05/2010**
  Attendance: Approximately 20 participants from EU countries

- **AML Intergroup Meeting, Frankfurt, 09/2010**
  Attendance: Approximately 20 participants from EU countries

- **ELN Breakfast meeting at ASH, Orlando, December 5**
  Attendance: Approximately 20 participants from European countries

**WP-Meetings WP6**

- **Annual ELN Symposium, Mannheim, February 2nd**
  Attendance: Approximately 45 participants from EU and non-EU countries

- **EWALL, Milano June 2010**
  Attendance: Approximately 20 participants; EWALL internal meeting

- **EWALL, Frankfurt, November 2010**
  Attendance: Approximately 20 participants from EU countries

- **ASH, Orlando, December 2010**
  Informal meeting during the ELN breakfast meeting; approximately 10 EWALL members
WP-Meetings WP7

- 19th ERIC Meeting at the 6th Annual Symposium of the ELN, Mannheim, February 02, 2010
  Attendance: Approximately 45 participants from EU and non EU countries
- 23rd ERIC Meeting at the European Hematology Association (EHA) Congress, Barcelona, Thursday 10th June 2010.
  Attendance: Approximately 55 participants from EU and non EU countries ERIC/EHA
- 24th General Meeting of ERIC Members, Orlando, 5th December 2010
  Attendance: Approximately 50 participants from EU and non EU countries
- 21st General Meeting of ERIC Members, Orlando, December 05th, 2010
  Attendance: Approximately 50 participants from EU and non EU countries

WP-Meetings WP8

- Annual ELN Symposium, MDS WP meeting, Mannheim, 2 February; 2010
  Attendance: 103 participants from EU
- European MDS Registry project, Operational team meeting, Mannheim, February 1, 2010
  Attendance: 14 participants
- European MDS Registry project, Steering Committee meeting, Mannheim, February 2, 2010
  Attendance: 10 participants
- European MDS Registry project, Operational team meeting, Barcelona, June 9, 2010
  Attendance: 18 participants
- European MDS Registry project, Steering Committee meeting, Barcelona, June 9, 2010
  Attendance: 10 participants
- European MDS Registry project, Operational team teleconferences, March 1, 2010
  Attendance: 13 participants
- European MDS Registry project, Operational team teleconferences, April 6, 2010
  Attendance: 8 participants
- European MDS Registry project, Operational team teleconferences, May 10, 2010
  Attendance: 10 participants
- European MDS Registry project, Operational team teleconferences, September 6, 2010
  Attendance: 6 participants
- ELN steering committee meeting, ASH congress, Orlando, December 3 2010
  Attendance: 11 participants
- ELN breakfast meeting, ASH congress, Orlando, December 5 2010
- ELN Frontiers meeting, Vienna, October 23-24 2010
- MDS Iron Forum, Rome September 25, 2010
- Annual ELN Symposium, MDS WP meeting, Mannheim, 1 February; 2011
  Attendance: 90 participants from EU
- European MDS Registry project, Steering Committee meeting, Mannheim, January 31, 2011
  Attendance: 17 participants
- European MDS Registry project, Operational team meeting, Mannheim, February 1, 2010
  Attendance: 13 participants
WP-Meetings WP9

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 60 participants from EU and non EU countries
- European Hematology Association (EHA) Congress, Barcelona, June 10th
  Attendance: 15 participants from European countries
- ELN Breakfast meeting, ASH, Orlando, December 5th
  Attendance: 20 participants from European countries

WP-Meetings WP10

- Annual ELN Symposium, Mannheim, February 2nd 2010
  Attendance: Approximately 60 participants from EU and non EU countries
- EGIL meeting in Berlin, March 2010
  Attendance: Approximately 10 participants from EU and non EU countries
- MDS meeting, Munich, October 2010
  Attendance: Approximately 15 participants from EU and non EU countries
- EHA European School in Cascais, November 2010
  Attendance: Approximately 15 participants from EU countries

WP-Meetings WP11

- Annual ELN Symposium, Mannheim, February 2nd
- EHA, Barcelona, June 10th 2010
  Attendance: Approximately 30 participants from EU countries
- Annual ELN Symposium, Mannheim, February 1st 2011
  Attendance: Approximately 8 participants from EU and non EU countries

WP-Meetings WP12 (2010-2011)

- Annual ELN Symposium, Mannheim, February 2nd 2010
  Attendance: Approximately 85 participants from EU and non EU countries
- EHA, Barcelona, June 10th 2010
  Attendance: Approximately 20 participants from EU countries
- Annual ELN Symposium, Mannheim, February 1st 2011
  Attendance: Approximately 70 participants from EU and non EU countries

WP-Meetings WP13

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 60 participants from EU and non-EU countries
- MILE study - met together with WP10, 11 and 12 in Munich in May 2010
  Attendance: Approximately 60 participants from EU and non-EU countries
- MILE study - met together with WP10, 11 and 12 in Munich in May 2010
  Attendance: Approximately 60 participants from EU and non-EU countries
One regular WP meeting for all WP13 members, combined in part with WP11, had been organized in Heidelberg in February 2010. Furthermore, some members of WP13 - mostly representing members also of the European part of the MILE study - met together with WP10, 11 and 12 in Munich in May 2010 and in October 2010 for new activities together with COST and EuGESMA (see above).

WP-Meetings WP14

- EBMT CLWP/ELN; Hotel Merian, Basel, Switzerland, January 22-23, 2010
  Attendance: n.a.
- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 80 participants from EU and non-EU countries
- EBMT annual meeting, Vienna, March 21, 2010
  Attendance: Approximately 70 participants from EU and non-EU countries
- WP5/WP14 meeting at EHA/ELN FIRA, Gran Via Conf. Center, Barcelona June 10, 2010
  Attendance: Approximately 50 participants from EU and non-EU countries
- Subcommittee meeting in Leiden, June 17 2010
  Attendance: Approximately 30 participants from EU and non-EU countries
- EBMT CLWP/ELN; “La Distillerie”, Mons, Belgium, September 17-18, 2010
  Attendance: Approximately 70 participants from EU and non-EU countries
- CLWP Subcommittee chair meeting in Leiden November 13 2010
  Attendance: Approximately 30 participants from EU and non-EU countries
- ELN Breakfast meeting, ASH, WP5/WP14 JW Marriott Orlando, December 05, 2010
  Attendance: Approximately 40 participants from EU and non-EU countries

WP-Meetings WP15

- Annual ELN Symposium, Mannheim, February 2nd
  Attendance: Approximately 10 participants from EU and non EU countries
- EBMT meeting in Vienna March 2010
  Attendance: Approximately 30 participants from EU and non-EU countries
- EBMT meeting in Paris October 2010
  Attendance: Approximately 30 participants from EU and non-EU countries

WP-Meetings WP17

- Annual ELN Symposium together with WP4 and WP5, Mannheim, February 2nd
  Attendance: Approximately 100 participants from EU and non EU countries
- EI-CML Meeting, Spineto, Italy, May 2010
  Attendance: Approximately 40 participants from EU countries
- 18th International CML Workshop, 2 July 2010, Heidelberg
  Attendance: Approximately 120 participants from EU and non EU countries
- ELN-Frontiers meeting, CML Educational, September 2010, Vienna
  Attendance: Approximately 400 participants from EU and non EU countries
• ELN Breakfast meeting together with WP4, ASH, Orlando, December 05, 2010
  Attendance: Approximately 40 participants from EU and non-EU countries
• EUTOS registry meeting WP4, ASH, Orlando, December 05, 2010
  Attendance: Approximately 10 participants from EU countries
### Presentations / Spread of excellence

**Table Annex 1:** (Press release (PR), oral presentations (OP), organization (O), Exhibition (E), Congress/Symposium (CS), Poster (PO), email, Website (www), Workshop (WS))

<table>
<thead>
<tr>
<th>WP</th>
<th>Planned/actual Dates</th>
<th>Type</th>
<th>Event</th>
<th>Type of audience</th>
<th>Countries addressed</th>
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<td>Tannheimer Tal, Vortrag: “Historische und aktuelle Entwicklung der CML-Therapie”</td>
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<td>AACR Meeting, European LeukemiaNet, enabling personalized Leukemia diagnosis in Europe and beyond, Washington</td>
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<td>ECPC Cancer Summit, Brüssel: The European LeukemiaNet: Cooperative research to cure leukemia</td>
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<td>Orlando, ASH</td>
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<td>Meeting in Barcelona (Spain): Risk based approach organised by ECRIN</td>
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<td>Meeting in Barcelona (Spain): Research Ethic Committees and Ethical Review in Europe</td>
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<td>CML GOLS The revised ELN recommendations CML GOLS, Dresden</td>
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<td>Workshop „Modern diagnostic and treatment approach to CML“; OP: On the path to cure CML. New developments, Kiew</td>
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<td>International Meeting on CML: Updated ELN recommendations for the management of CML, Genua</td>
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<td>Novartis 6th Nilotinib Global Investigators Meeting: The treatment of patients with newly diagnosed CML: A decade of progress, Rome</td>
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<td>European fellows educational day: EUTOS for CML. An innovative collaboration between ELN and Novartis, Naples</td>
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<td>Imidex: Current best practice for management of accelerated/blastic phase CML, Chicago, ASCO</td>
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<td>Treatment optimization by high-dose imatinib: Randomized comparison of imatinib 800 mg versus imatinib 400 mg ± IFN in newly diagnosed BCR-ABL positive chronic phase (CP) CML: The German CML-study IV, ASCO</td>
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<td>EHA 2010: Treatment optimization by high-dose imatinib: Randomized comparison of imatinib 800 mg vs. imatinib 400 mg vs. imatinib 400 mg ± IFN in newly diagnosed BCR-ABL positive chronic phase (CP) CML with regard to MMR at month 12: The German CML-study IV</td>
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<td>4</td>
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<td>OP</td>
<td>1. World Congress Controversies in Hematology: Should first line imatinib treatment be optimized by combination with IFN or by higher imatinib dose? Rome</td>
<td>Physicians and Scientists</td>
<td>European</td>
<td>150</td>
<td>Hehlmann</td>
</tr>
<tr>
<td>4</td>
<td>10.06.2010</td>
<td>OP</td>
<td>EHA: “Randomized clinical trial for the optimization of imatinib therapy by combination, dose escalation and transplantation. Designed first interim analysis of the German CML Study IV”</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>2000</td>
<td>Hehlmann</td>
</tr>
<tr>
<td>4</td>
<td>2.-3.7.10</td>
<td>OP</td>
<td>international CML-Workshop, EUTOS Meeting: CML Study IV</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>120</td>
<td>Hehlmann</td>
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<td>4</td>
<td>9.7.10</td>
<td>OP</td>
<td>Rotary-Kurpfalz: European LeukemiaNet – europäische Antwort auf das Leukämieproblem</td>
<td>Public</td>
<td>National</td>
<td>70</td>
<td>Hehlmann, Saußele</td>
</tr>
<tr>
<td>4</td>
<td>23.-27.9.10</td>
<td>CS</td>
<td>ESH-Symposium, Washington</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>300</td>
<td>Hehlmann, Müller</td>
</tr>
<tr>
<td>4</td>
<td>2.-5.10.10</td>
<td>OP</td>
<td>DGHO, Mannheim, Vortrag: CML IV</td>
<td>Physicians and Scientists</td>
<td>Germany</td>
<td>300</td>
<td>Hehlmann</td>
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<td>4</td>
<td>2.-5.10.10</td>
<td>OP</td>
<td>DGHO, Berlin, Vortrag: CML IV</td>
<td>Physicians and Scientists</td>
<td>Germany</td>
<td>150</td>
<td>Saußele, Müller</td>
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<td>4</td>
<td>20.-25.10.10</td>
<td>OP</td>
<td>ELN Frontiers 2010, Vienna: The concept of cure and the path to cure</td>
<td>Physicians and Scientists</td>
<td>European</td>
<td>550</td>
<td>Hehlmann</td>
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<td>1/4</td>
<td>21.10.10</td>
<td>PR</td>
<td>EUTOS-Press event</td>
<td>Physicians and Scientists</td>
<td>European</td>
<td>50</td>
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<td>4</td>
<td>27.-28.10.10</td>
<td>OP</td>
<td>Society of Hematology, Romania: Current options for first line treatment of CML and impact on prognosis</td>
<td>Physicians and Scientists</td>
<td>European</td>
<td>200</td>
<td>Hehlmann</td>
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<td>4</td>
<td>7.-8.12.10</td>
<td>OP</td>
<td>Mission Inn, Orlando: Treatment optimization in CML by tolerability adapted high dose imatinib</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>50</td>
<td>Hehlmann</td>
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<td>4</td>
<td>17-23.1.10</td>
<td>OP</td>
<td>Fortschritte in der Hämatologie: Historische und aktuelle Entwicklung der CML-Therapie</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>50</td>
<td>Hehlmann</td>
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<tr>
<td>4</td>
<td>2.-7.12.10</td>
<td>OP</td>
<td>Orlando, ASH, OP: How to optimize TKI treatment Dose? Schedule? Interferon? Superior CMR-Rates with Tolerability-Adapted Imatinib 800 mg vs. 400 mg vs. 400 mg + IFN in CML: The German Randomized CML-Study IV</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>2000</td>
<td>Hehlmann</td>
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<tr>
<td>5</td>
<td>01.02.-03.02.10</td>
<td>OP</td>
<td>European LeukemiaNet Symposium, Mannheim, Germany</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>ca. 400</td>
<td>Büchner</td>
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<td>Type of audience</td>
<td>Countries addressed</td>
<td>Size of audience</td>
<td>Partner(s) responsible/involved</td>
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<tr>
<td>5</td>
<td>12.02.10</td>
<td>OP</td>
<td>AML Intergroup Meeting, Reisensburg, Germany</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>40</td>
<td>Büchner</td>
</tr>
<tr>
<td>5</td>
<td>26.03.2010</td>
<td>OP</td>
<td>Amonafide Advisory Board Meeting, London, GB</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>20</td>
<td>Büchner</td>
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<tr>
<td>5</td>
<td>03.05.10</td>
<td>OP</td>
<td>AML Intergroup Meeting, Frankfurt, Germany</td>
<td>Physicians and Scientists</td>
<td>Germany</td>
<td>20</td>
<td>Büchner</td>
</tr>
<tr>
<td>5</td>
<td>10.06.10</td>
<td>OP</td>
<td>European LeukemiaNet Meeting at EHA, Barcelona, Spain</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>40</td>
<td>Büchner</td>
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<tr>
<td>5</td>
<td>19.08.2010</td>
<td>OP</td>
<td>AML Register Meeting, München, Deutschland</td>
<td>Physicians and Scientists</td>
<td>Germany</td>
<td>8-10</td>
<td>Büchner</td>
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<tr>
<td>5</td>
<td>14.-15.09.2010</td>
<td>OP</td>
<td>Advisory Board Meeting, Barcelona, Spain</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>50</td>
<td>Büchner</td>
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<tr>
<td>5</td>
<td>18.-20.09.2010</td>
<td>OP</td>
<td>Raissa Gorbacheva Memorial Lecture, St. Petersburg, Russia</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>100</td>
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<tr>
<td>5</td>
<td>01.-05.10.2010</td>
<td>OP</td>
<td>DGHO Satellite Symposium Berlin, Germany</td>
<td>Physicians and Scientists</td>
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<td>Büchner</td>
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<tr>
<td>5</td>
<td>10.-12.10.2010</td>
<td>OP</td>
<td>XXXIII World Congress of ISH, Jerusalem, Israel</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>ca. 500</td>
<td>Büchner</td>
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<td>5</td>
<td>15.10.2010</td>
<td>OP</td>
<td>Turku XII Stem Cell Symposium, Turku, Finnland</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>100</td>
<td>Büchner</td>
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<td>5</td>
<td>18.10.2010</td>
<td>OP</td>
<td>AML Intergroup Meeting, Frankfurt, Germany</td>
<td>Physicians and Scientists</td>
<td>Germany</td>
<td>20</td>
<td>Büchner</td>
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<td>5</td>
<td>22.-24.10.2010</td>
<td>OP</td>
<td>ELN Frontiers Meeting, Vienna, Austria</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>200</td>
<td>Büchner</td>
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<tr>
<td>5</td>
<td>05.12.2010</td>
<td>PO</td>
<td>ASH Annual Meeting, Orlando, USA</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>100</td>
<td>Büchner</td>
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<tr>
<td>5</td>
<td>02.12.2010</td>
<td>OP</td>
<td>ELN Breakfast Meeting at ASH, Orlando, USA</td>
<td>Physicians and Scientists</td>
<td></td>
<td>25</td>
<td>Büchner</td>
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<td>6</td>
<td>1.2.-2.2.11</td>
<td>OP</td>
<td>European Leukemia Network Netzwerksymposium Kompetenznetz Leukämien EWALL WP6</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>40-100</td>
<td>Bassan, Holowiecki, Hoelzer, Ribera, Hunault, Gökbüget, Ottmann, Iacobucci, Martinelli</td>
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<tr>
<td>6</td>
<td>06.2010</td>
<td>WS</td>
<td>first workshop of the newly founded EHA-EWALL working group (EHA meeting in Barcelona)</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>100</td>
<td>Bassan Dombret Gökbüget Foa Fielding Ribera</td>
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<tr>
<td>6</td>
<td>EHA Education Session 12/2010</td>
<td>OP</td>
<td>Ottmann O.G.: Treatment of Ph+ adult ALL</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>2500</td>
<td>Ottmann</td>
</tr>
<tr>
<td>6</td>
<td>EHA Education Session 12/2010</td>
<td>OP</td>
<td>MRD oriented treatment in PH-adult ALL</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>1500</td>
<td>Ribera</td>
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<td>6</td>
<td>ASH Education Session 12/2010</td>
<td>OP</td>
<td>Treating the &quot;Older&quot; Adult With Acute Lymphoblastic Leukemia</td>
<td>Physicians and Scientists</td>
<td>International</td>
<td>3500</td>
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<td>Type of audience</td>
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<td>7</td>
<td>02.02.10</td>
<td>CS</td>
<td>Annual Symposium of the European LeukemiaNet, Mannheim</td>
<td>clinical + basic researchers</td>
<td>International</td>
<td>45</td>
<td>Hallek</td>
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<tr>
<td>7</td>
<td>05.12.09</td>
<td>CS, WS, OP, PO</td>
<td>ERIC/ELN Breakfast Meeting at the 52th Annual Congress of the American Society of Hematology, Orlando, USA</td>
<td>clinical + basic researchers</td>
<td>International</td>
<td>50</td>
<td>Hallek</td>
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<td>8</td>
<td>02.02.10</td>
<td>CS</td>
<td>Annual ELN Symposium, MDS WP meeting, Mannheim</td>
<td>clinical + basic researchers</td>
<td>European</td>
<td>95</td>
<td>De Witte</td>
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<tr>
<td>9</td>
<td>03.02.10</td>
<td>CS, WS</td>
<td>Annual ELN Symposium</td>
<td>clinical + basic researchers</td>
<td>European</td>
<td>30</td>
<td>Barbui</td>
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<td>9</td>
<td>10.06.2010</td>
<td>OP</td>
<td>WP meeting at the EHA Congress in Barcelona</td>
<td>clinical + basic researchers</td>
<td>European</td>
<td>35</td>
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<td>9</td>
<td>05.12.10</td>
<td>OP</td>
<td>WP meeting at the ASH in Orlando, US</td>
<td>clinical + basic researchers</td>
<td>International</td>
<td>20</td>
<td>Barbui</td>
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<td>10</td>
<td>03.02.10</td>
<td>CS</td>
<td>Annual ELN Symposium</td>
<td>clinical + basic researchers</td>
<td>European</td>
<td>20</td>
<td>Béné</td>
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<tr>
<td>12</td>
<td>20.05.2010</td>
<td>OP</td>
<td>British Medical Journal Masterclass for Physicians Haematology, London</td>
<td>clinical + basic researchers</td>
<td>UK</td>
<td>150</td>
<td>Grimwade</td>
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<tr>
<td>12</td>
<td>28.06.2010</td>
<td>OP</td>
<td>Advances in Haematology Research 2010, The Christie Hospital, Manchester</td>
<td>clinical + basic researchers</td>
<td>UK</td>
<td>100</td>
<td>Grimwade</td>
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<tr>
<td>12</td>
<td>02.09.2010</td>
<td>OP</td>
<td>Haematological Malignancies Conference, Institute. of Physics, London</td>
<td>clinical + basic researchers</td>
<td>UK</td>
<td>50</td>
<td>Grimwade</td>
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<tr>
<td>12</td>
<td>03.- 05.09.2010</td>
<td>OP</td>
<td>Controversies in Haematology meeting, Rome</td>
<td>clinical + basic researchers</td>
<td>international</td>
<td>200</td>
<td>Grimwade</td>
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<tr>
<td>12</td>
<td>16.- 18.9.2010</td>
<td>OP</td>
<td>“Molecular Pathogenesis of Leukemia, Insights &amp; Challenges”, Frankfurt</td>
<td>clinical + basic researchers</td>
<td>European</td>
<td>75</td>
<td>Grimwade</td>
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<td>12</td>
<td>27.9.2010</td>
<td>OP</td>
<td>Acute Leukaemia Day, Birmingham</td>
<td>clinical + basic researchers</td>
<td>UK</td>
<td>100</td>
<td>Grimwade</td>
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<tr>
<td>12</td>
<td>03.10.2010</td>
<td>OP</td>
<td>DGH0 meeting, Berlin</td>
<td>clinical + basic researchers</td>
<td>international</td>
<td>80</td>
<td>Grimwade</td>
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<tr>
<td>12</td>
<td>25.10.2010</td>
<td>OP</td>
<td>Advances in the Management of Haematological Malignancies, Birmingham</td>
<td>clinical + basic researchers</td>
<td>UK</td>
<td>30</td>
<td>Grimwade</td>
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<td>12</td>
<td>29 Nov 2010</td>
<td>OP</td>
<td>NCRI Paediatric AML</td>
<td>clinical + basic researchers</td>
<td>UK</td>
<td>30</td>
<td>Grimwade</td>
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<td>13</td>
<td>02.02.10</td>
<td>WS</td>
<td>WP meeting for all WP13 members, combined in part with WP11, in Mannheim, Germany</td>
<td>Research + Clinical</td>
<td>International</td>
<td>70</td>
<td>Haferlach</td>
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<td>13</td>
<td>9-11.5.10</td>
<td>WS</td>
<td>IRON workshop in Munich for NGS testing</td>
<td>Research + Clinical</td>
<td>International</td>
<td>60</td>
<td>Haferlach</td>
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<tr>
<td>13</td>
<td>17-19.10.10</td>
<td>WS</td>
<td>WP13 members representing the European met together with WP10, and COST group for NGS future in Munich</td>
<td>Research + Clinical</td>
<td>International</td>
<td>90</td>
<td>Haferlach / Mills</td>
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<td>Event</td>
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<td>6.12.10</td>
<td>PO</td>
<td>Poster on IRON study at ASH Orlando</td>
<td>Research + Clinical</td>
<td>International</td>
<td>ASH</td>
<td>Kohlmann / Haferlach</td>
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<td>14</td>
<td>12.10</td>
<td>CS</td>
<td>ELN meeting WP5/WP14 Orlando</td>
<td>Research + Clinical</td>
<td>International</td>
<td>Niederwieser</td>
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<td>15</td>
<td>02.10</td>
<td>WP</td>
<td>WP meeting at the ELN symposium in Mannheim, Germany, and in Paris.</td>
<td>Clinicians and basic researchers</td>
<td>international</td>
<td>20</td>
<td>Ljungman</td>
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<td>03.10</td>
<td>WP</td>
<td>WP meeting at the EBMT meeting in Vienna,</td>
<td>Clinicians and basic researchers</td>
<td>international</td>
<td>100</td>
<td>Ljungman</td>
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<td>09.10</td>
<td>WP</td>
<td>WP meeting at the EBMT meeting in Juan-les-Pins</td>
<td>Clinicians and basic researchers</td>
<td>international</td>
<td>50</td>
<td>Ljungman</td>
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<td>15</td>
<td>10.10</td>
<td>WP</td>
<td>WP meeting at the EBMT meeting in Paris</td>
<td>Clinicians and basic researchers</td>
<td>international</td>
<td>15</td>
<td>Ljungman</td>
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<tr>
<td>17</td>
<td>02/2011</td>
<td>OP</td>
<td>ELN Symposium Mannheim</td>
<td>Physicians and Scientists</td>
<td>European</td>
<td>100</td>
<td>J. Hasford</td>
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<td>17</td>
<td>04/2010</td>
<td>OP</td>
<td>Cancers in the Elderly, Rome</td>
<td>Physicians</td>
<td>European</td>
<td>500</td>
<td>J. Hasford</td>
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Section 3: Publishable results

WP1 (NMC) and WP2 (ELIC)

1-1 N. Gökbüget, D. Hoelzer, S. Saussele, R. Hehlmann (Editors). WP2 in cooperation with WP1, 01/2011: 7th ELN Information Letter.

1-2 ELN Booth, EHA, Barcelona 06/2010

1-3 ELN Booth, DGHO, ÖGH, SGH, Berlin, 10/2010

1-4 ELN Booth, ELN-Frontiers, Vienna, 10/2010

1-5 ELN Booth, ASH, Orlando, 12/2010

1-6 Steering Committee 2010, Minutes

1-7 Steering Committee 2011, Minutes

1-8 ELN Assembly minutes 2010


1-10 Poster on the ELN Registry at the German Hematology Oncology Congress (DGHO) in Berlin 2010.


WP2 (ELIC) Publications:

**International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)**


**International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)**


WP3 (CICS) Publications:

**International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)**


WP4 (CML)

**International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)**


Catellani S, Pieri I, Gobbi M, Poggi A, Zocchi MR. Imatinib Treatment Induces CD5+B Lymphocytes and IgM Natural Antibodies with Anti-Leukemic Reactivity in Patients with Chronic Myelogenous Leukemia. Plos One 2011; 6(4):Article No.: e18925.


Abstracts (with a reference to the European LeukemiaNet):


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


Fava C, Saglio G. Can We and Should We Improve on Frontline Imatinib Therapy for Chronic Myeloid Leukemia? Seminars in Hematology 2010; 47(4):319-26.


Saglio G, Hochhaus A, Goh YT, Masszi T, Pasquini R, Maloisel F, et al. Dasatinib in Imatinib-Resistant or Imatinib-Intolerant Chronic Myeloid Leukemia in Blast Phase After 2 Years of Follow-Up in a Phase 3 Study


Salomon O, Tohani T, Trakhtenbrot L, Metivier R, Kneller A, Berkowitz M, et al. BCR-ABL transcripts are not detected in cord blood or the peripheral blood of the newborn child whose mother developed chronic myeloid leukemia while pregnant. Leukemia Research 2010; 34(2):E78-E81.


Sobrinho-Simoes M, Wilczek V, Score J, Cross NCP, Apperley JF, Melo JV. In search of the original leukemic clone in chronic myeloid leukemia patients in complete molecular remission after stem cell transplantation or imatinib. Blood 2010; 116(8):1329-35.


Abstracts oral presentations


chiral myeloid leukemia: First line treatment with Nilotinib 800 mg daily results in unprecedentedly high rate of rapid, "deep" and stable molecular responses - Results of a phase 2 trial of the GIMEMA CML working party. AACR Meeting Abstracts 2010. Abstract n. 1805.


Abstracts poster presentations


International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)

5-1  Minutes from the Reisensburg Meeting, February 6, 2009


5-3  Haferlach T. Die Zukunft der Diagnostik akuter Leukämien. Reisensburg Meeting Feb. 2010


Abstracts (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


5-82 Stelljes M, Beelen D, Braess J, et al. Allogeneic transplantation as postremission therapy for cytogenetically high risk acute myeloid leukemia (AML); Landmark analysis from a single prospective multicenter trial. Haematologica 2011, in press


WP6 (ALL)

*International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)*


International publications that are the not a direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


WP7 (CLL))

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)

International publications that are the direct result of the European LeukemiaNet
(without a reference to the European LeukemiaNet)


WP8 (MDS)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


WP9 (CMPD)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


WP10 (Diagnostics)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


WP11 (Cytogenetics)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


11-10 Coyaud E, Struski S, Dastugue N, Brousset P, Broccardo C, Bradtke J: PAX5-AUTS2 fusion resulting from t(7;9)(p11.2;p13.2) can now be classified as recurrent in B cell acute lymphoblastic leukemia. Leuk Res 2010;34:323-325.


11-20 Flach J, Dicker F, Schnittger S, Kohlmann A, Haferlach T, Haferlach C: Mutations of JAK2 and TET2, but not CBL are detectable in a high portion of patients with refractory anemia with ring sideroblasts and thrombocytopenia. Haematologica 2010;95:518-519.


Lundin C, Horvat A, Karlsson K, Olofsson T, Paulsson K, Johansson B: t(9;11)(p22;p15) [NUP98/PSIP1] is a poor
abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia
chemotherapy in patients aged 60 years or older with acute myeloid leukaeemia: a web-based application for

Gross Chromosomal Rearrangements in Leukemia. Plos One 2010; 5(9):Article Number: e12855.

Fort MP, Legros L, Eclache V, Mahon FX: Loss of the Y chromosome in Philadelphia-positive cells predicts a poor

Lundin C, Horvat A, Karlsson K, Oflofsson T, Paulsson K, Johansson B: t(9;11)(p22;p15) [NUP98/PSIP1] is a poor
prognostic marker associated with de novo acute myeloid leukaeemia expressing both mature and immature surface

abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia
2011;25:110-120.

Pierini V, Brandimarte L, Vignetti M, Foa R, Mecucci C: Rescue of genomic information in adult acute
lymphoblastic leukaemia (ALL) with normal/failed cytogenetics: a GIMEMA centralized biological study. Br J
Haematol 2010;149:70-78.

Haferlach T: Multilineage dysplasia (MLD) in acute myeloid leukemia (AML) correlates with MDS-related
cytogenetic abnormalities and a prior history of MDS or MDS/MPN but has no independent prognostic relevance: a
comparison of 408 cases classified as "AML not otherwise specified" (AML-NOS) or "AML with myelodysplasia-related

N, Cabrol C, Bernard OA: Chromosomal abnormalities in transformed Ph-negative myeloproliferative neoplasms are
associated to the transformation subtype and independent of JAK2 and the TET2 mutations. Genes Chromosomes
Cancer 2010;49:919-927.

a single predominant tyrosinase-specific T-cell clone associated with disease control in a patient with metastatic

Okamoto R, Ogawa S, Nowak D, Kawamata N, Akagi T, Kato M, Sanada M, Weiss T, Haferlach C, Dugas M,
Ruckert C, Haferlach T, Koellerl HP: Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide
polymorphism oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. Haematologica
2010;95:1481-1488.


11-52 Schnittger S, Haferlach C, Ulke M, Alpermann T, Kern W, Haferlach T: IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis in adults younger than 60 years and unmutated NPM1 status. Blood 2010;116:5486-5496.


WP12 (MRD)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)

International publications to which the European leukemia Network has made a contribution

(without a reference to the European leukemia Network)


12-30 Schnittger S, Haferlach C, Ulke M, Alpermann T, Kern W, Haferlach T. IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavorable prognosis in adults younger than 60 years and unmutated NPM1 status. Blood 2010; 116(25):5486-96.


Abstracts


12-38 Lengfelder E., Francesco Lo-Coco, Pau Montesinos, David Grimwade, Lionel Ades, Bhuvan Kishore, Maria Pagoni, Safaa M. Ramadna, Massimo Breccia, Alexandra Holowiecka, Anne Pradel, Maria Cristina Sauerland, Pierre Fenaux,


WP13 (Gene profiling)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)


WP14 (SCT)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet):


14-7 Chalandon Y, Passweg JR, Schmid C, Olavarria E, Dazzi F, Simula MP, et al. Outcome of patients developing GVHD after DLI given to treat CML relapse: a study by the chronic leukemia working party of the EBMT. Bone Marrow Transplantation 2010; 45(3):558-64.


WP15 (Supportive care/anti-infection prophylaxis and treatment)

International publications that are the direct result of the European leukemia Network (with a reference to the European leukemia Network)


International publications that are the direct result of the European LeukemiaNet (without a reference to the European leukemiaNet)


WP17 (Biometry of Registry, Epidemiology, Metaanalyses and Prognosis)

International publications that are the direct result of the European LeukemiaNet (with a reference to the European LeukemiaNet)


Abstracts with reference to the ELN:


International publications that are the direct result of the European LeukemiaNet (without a reference to the European LeukemiaNet)