Dear Colleagues,

the ELN has passed the first year without substantial EU-Funding – and it is working well! The financing by the European Science Foundation (ESF) enables us to continue most ELN activities and the important small and large meetings that are key for the networking success.

Several projects funded by the ELN Foundation are ready to start within the next weeks, which points to the fact that we are able to support important scientific research as well. This emphasizes that the ELN is on a good way to longterm sustainability.

The ELN standards continue to be respected internationally and the ELN recommendations are highly requested by colleagues all over the world. For the CML recommendations, the third edition is imminent, the submission for publication is expected in March 2013. Concurrently, the extension of worldwide cooperations is increasing: due to new EU regulations, in 2012 we could welcome our first cooperative centre in the USA.

Since all these achievements are resulting from hard work of individuals and scientific groups, we want to thank all of you for your work and support in the last year. And since there are always some persons that are contributing in particular, there will be four ELN Merit Awards to be announced during the upcoming 10th Annual ELN Symposium.

I hope you will enjoy reading this information letter which tries to give an overview of recent ELN work, and I wish to encourage you to build new cooperations and invent new projects – that is what keeps the ELN alive.

Sincerely,

Prof. Dr. h. c. Rüdiger Hehlmann
Network Coordinator
ELIC Editorial

Dear colleagues,

we are pleased to present you the 9th Information Letter of the European LeukemiaNet. Since 2005, the Information Letter is prepared in collaboration with the contributing authors and the Network Management Center to inform all ELN members and the public about the excellent work of the ELN during the past months.

As before, the WP leaders were invited to suggest topics representing new advances in leukemia research or recapitulate the WP’s highlights of 2012. For the first time, this issue contains summaries of the most important clinical results from oral presentations of the 54th ASH Annual Meeting which were selected and summarized by ELN experts.

We would like to thank the current authors for their support and encourage all ELN members to hand in contributions for future Information Letters. Of course, we are also pleased about any feedback and suggestions concerning our work.

With best regards,
Information Center

Dr. Nicola Gökbüget  Dr. Sina Hehn

WP 5 - AML

Towards an integrated, risk adapted application of allogeneic stem cell transplantation for patients with AML in first complete remission

Jan J. Cornelissen1, Gert J. Ossenkoppele2 on behalf of the ELN Acute Myeloid Leukemia Working Group

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Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) from an HLA-identical sibling donor is generally recommended for patients with acute myeloid leukemia (AML) in first complete remission (CR) with intermediate or high-risk cytogenetic profile. As the benefit of alloHSCT in terms of overall survival is compromised by non-relapse mortality (NRM), it is important to weigh the most significant variables that affect the risk of relapse and variables that predict for NRM. Given the complexity of decision making, an approach that integrates different sets of risk factors was recently developed and reported by the acute myeloid leukemia working party of the European LeukemiaNet.

Risk profile of AML in CR1

Cytogenetic analysis has allowed for distinguishing categories of AML with different prognosis and risk of relapse, whereby three cytogenetic prognostic categories (favorable, intermediate, poor) have long been used. Several larger donor versus no-donor studies and their meta-analysis have shown that alloHSCT results in superior outcome in patients with poor-risk and intermediate risk AML in CR1. The reduction of relapse was estimated at approximately 50% (hazard ratio (HR) 0.4-0.5) as compared to consolidation by chemotherapy and/or autografting. Although relapse was also significantly reduced in favorable risk patients with a risk of relapse below 35%, those patients did not benefit from myeloablative alloHSCT in terms of overall survival as a NRM of approximately 20% attenuated the beneficial effect of alloHSCT in those patients. The role of alloHSCT in the new very poor-risk monosomy karyotype (MK) subcategory was also addressed. Although relapse after alloHSCT appeared high, 20% long term survival was reported and virtually no surviving patients were noted among CR patients receiving chemotherapy only or autologous transplantation. Strikingly, the relative reduction of relapse may not differ from what can be observed in other cytogenetic subtypes of AML, as was suggested by a HOVON/SAKK study.

The majority of patients with AML in first CR harbor an intermediate risk profile. While most of these leukemias lack a specific karyotypic abnormality, molecular genetic markers such as gene mutations and deregulated gene expression can be identified in the majority and may be associated with a more specific prognosis. Molecular markers currently taken into account for decision making include the NPM1 mutation, the internal tandem duplication (ITD) in the FLT3 tyrosine kinase receptor (FLT3/ITD), CEPBA mutations, EVI1 expression levels, mutations in TET and DNMT3. Although many more markers have been identified, it is especially important to identify markers associated with a favorable prognosis, as a majority of those patients may be cured with chemotherapy alone and alloHSCT may be postponed until eventual relapse, as is the current policy in the cytogenetic favorable subgroups. Indeed, a recent German study evaluating alloHSCT in molecularly defined subgroups of cytogenetically normal AML patients showed that patients with NPM1 mutation but without FLT3/ITD did not benefit from alloHSCT due to enhanced NRM, while alloHSCT appeared associated with better survival in patients with FLT3/ITD mutation or the so called triple negative patients with NPM1 and CEBPA wild-type and without FLT3/ITD.

WP 2 - ELIC

www.leukemia
Predicting counterbalancing non relapse mortality (NRM)

It has consistently been shown that age significantly predicts for outcome, an effect which is mainly due to higher NRM in patients older than 40 years1. Apart from age, other variables such as general performance, CMV serostatus, cytokine polymorphism, donor/recipien
tant gender-combination, and comorbidities significantly predict for NRM10-11. More appropriate risk assessment has become possible by developing composite risk scores, taking into account a combination of several risk factors. The European Group for Blood and Marrow Transplantation (EBMT) developed a risk score based on five criteria including disease stage, patient age, donor type, time interval from diagnosis to transplantation, and donor-recipi
tenent gender combination. The score was validated in several independent patient cohorts and confirmed over time, including AML10. An-
other composite risk-score, the hematopoiet-
ic cell transplantation (HCT) comorbidity index (CI) based on 17 comorbidities, was developed in Seattle11 and was subsequently also validated in several disease categories and other in-
titutions. Accordingly, by carefully weighing relapse risk versus NRM (Table 1, Figure 1), it may be anticipated that CR1 patients, whose AML is characterized by a relapse risk > 50 %, which may be reduced to less than 25 % by alloHSCT, may experience better disease free sur-
vival (DFS) as compared to conventional consol-
idation therapies. As a result of a number of devel-
opments including high resolution HLA typ-
ing and more efficacious infection prophylax-
is, NRM following unrelated donor alloHSCT has gradually declined and such transplants are now also offered to first CR patients12. In the recent prospective AMLHD 98A study of the German AML Study Group, equivalent ef-
Table 1. Proposed indications for alloHSCT in AML CR1, guided by diagnostic risk assessment, response to induction, and parameters predicting NRM.

Concluding remarks

The application of allogeneic HSCT in AML cur-
rently depends at one hand on the risk-profile of the leukemia and on the other hand on the risk for NRM. A continuous risk assessment in time during induction and consolidation ther-
apies is proposed, as illustrated in Figure 1 and Table 1. It may allow for a more personalized approach for AML patients in CR1, based on individual risk assessment13.
Current approaches for antibody therapy in acute lymphoblastic leukemia (ALL)

Nicola Gökgüret, Dieter Hoelzer for WP6 (European Working Group for Adult ALL)

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Outcome of adult ALL has stepwise improved over the past decade to 50 % and more in contemporary trials and this is partly due to the application of targeted therapies. Although intensive chemotherapy is the basis of all effective regimens in ALL, particularly in older patients the options for further intensification are limited. Targeted therapies may add efficacy with limited additional toxicities. The most successful example is the use of tyrosine-kinase (TK) inhibitors in Philadelphia (Ph)/BCR-ABL positive ALL.

Antibody therapy is another promising approach since ALL blasts express a number of surface markers such as CD19, CD20, CD22, CD33 or CD52, which may be utilized as therapeutic targets. Anti-CD20 antibodies have been successfully used in combination with chemotherapy in CD20 positive mature B-ALL and Burkitt’s lymphoma and in B-precursor ALL, which shows CD20 expression in 40-50 % of the cases. In both entities the addition of CD20 antibodies to standard chemotherapy has improved overall survival by more than 20 %.[1,2]

Different types of antibodies are currently under clinical investigation: Unconjugated monoclonal antibodies like Rituximab, antibodies conjugated to cytotoxins such as gemtuzumab ozogamicin, bispecific antibodies with the capability to target two different surface antigens and antibodies conjugated to radioimmunoconjugates. Currently, international trials with two antibodies have been initiated in ALL in collaboration with the European Working Group for Adult ALL (EWALL).

**Blinatumomab**

Blinatumomab is a bispecific antibody directed to CD19 and CD3. CD19 is expressed on the surface of blast cells in B-precursor ALL. The antibody attracts CD3 positive T-cells to the CD19 positive target cells and mediates thereby cell kill by the activated T-cells. After promising results in Non-Hodgkin’s lymphoma (NHL)[3] the compound was tested in ALL with persistent minimal residual disease (MRD). Persistence of MRD is a poor prognostic factor, indicates chemoresistance and is therefore an indication for stem cell transplantation (SCT).

A pilot study was conducted in 20 patients with MRD above 10⁻⁴ after intensive induction and consolidation. Blinatumomab was given as four week continuous infusion. After one cycle the molecular response rate measured by quantitative PCR of individual immunoglobulin and T-cell receptor rearrangements was 80 %.[4] Toxicity was overall manageable with lymphopenia, fever, chills, decrease of blood immunoglobulin, and hypokalemia being the most frequent ones. Fully reversible neurologic adverse events of grade III-IV were observed in 4.8 % of the cases, respectively. Nine patients had received SCT after treatment with Blinatumomab and reached a relapse-free survival of 65 %. Interestingly, four out of six patients with Ph-negative ALL and molecular complete remission (CR) after Blinatumomab remained in long-term remission for more than two years.[5]

Based on the favorable results in MRD positive ALL a trial with Blinatumomab in overt relapse of B-precursor ALL was started. Blinatumomab was administered at three dosing regimens in patients with hematological relapse including patients with relapse after SCT. The overall rate of (CR) without or without regeneration was 72 % in 36 evaluable patients. 92 % of the patients with hematological CR achieved a molecular CR measured by quantitative PCR with a sensitivity of 10⁻⁴. In the cohort treated with the final dose level, the most frequent adverse events were pyrexia (70 %), headache (39 %), tremor (30 %) and fatigue (30 %). Six patients developed fully reversible adverse events involving the CNS (seizure, encephalopathy) and four were able to resume treatment at a lower dose level[6].

Currently, two trials with Blinatumomab in B-precursor ALL are ongoing in Europe. One trial includes patients with Ph-negative ALL and MRD above 10⁻³ after intensive chemotherapy. The other trial includes patients with hematological relapse. Further information is available in the European Leukemia Study Registry (www.leukemia-trials.eu).

**Inotuzumab**

Inotuzumab ozogamicin is a CD22 antibody conjugated to the cytotoxic agent calicheamicin. CD22 is expressed in the majority of cases of B-precursor ALL. After promising results in NHL a phase II trial in relapsed/refractory ALL was initiated. The antibody was administered at 1.3 – 1.8 mg/m² i.v. every 3-4 weeks. In 49 patients the overall response rate including CRs without complete recovery of blood counts was 57 %. MRD was evaluated by flow cytometry and was negative in 63 % of the analyzed patients. The most frequent adverse events were fever (29 %), hypotension (13 %), raised bilirubin (14 %) and elevated transaminases (28 %).[7]

Based on an expected higher in vitro efficacy with more frequent exposure and a potentially lower clinical toxicity a modified regimen with weekly application was tested in 34 patients. Response rate was 53 % with weekly dosing. There was a trend towards lower incidence of bilirubin and liver enzyme increases with the weekly schedule. Response rates were higher in first versus later salvage (71 % versus 49 %) and in Ph/BCR-ABL and t(4;11) negative versus positive ALL (62 % versus 39 %).[8] A randomized world-wide trial with inotuzumab in relapsed/refractory ALL has been started (www.clinicaltrials.gov - NCT01564784).
Quality assurance in leukemia cytogenetics by web-based processing of interlaboratory tests

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External quality assessment (EQA) is an integrated part of quality control in diagnostic laboratories. In Germany, an interlaboratory test system using viable cells was established for EQA in leukemia cytogenetics in 2004. The test is based on surrogate leukemia samples which are generated by using leukemia cell lines and peripheral blood of a healthy donor. The laboratories are requested to perform a chromosome banding analysis of the surrogate sample according to routine operating procedures and to report the findings to a central review committee. By this approach, the entire process of the chromosome banding analysis is covered including cultivation of the cells, chromosome preparation, banding, and analysis as well as interpretation of the findings. The review committee consists of members of the laboratories which take part in the test and are requested to join the committee by the supervisor of the test.

To cope with the work load of the review process, an online platform was established in 2011 by the Society of the German Professionals of Human Genetics (Berufsverband Deutscher Humangenetiker - BVDH). The laboratories upload their reports and images of representative karyotypes onto the platform. The reviewers have access to the platform to assess the reports and images of the participating laboratories. Each report is evaluated independently by three reviewers with respect to the detection of target chromosome aberrations which are present in the sample, and to the correctness of the karyotype and of the formal content of the written report. All criteria for the evaluation of the reports are available in online forms in which the reviewers check the respective judgment using radio buttons. Criticisms and remarks may be added and communicated to the respective laboratory. Diverging results of the reviewers are discussed within the entire group of the reviewers via telephone conference.

Each participating laboratory receives a detailed written report of the results of the evaluation of their findings as well as a summary of the overall results of all laboratories which participated in the test. Currently, each laboratory can appraise its performance in chromosome banding analyses itself by comparison with the average performance of all laboratories. In future, it is intended that the review committee judges the results according to the pass of the test.

For quality assessment in interphase fluorescence in situ hybridization (FISH) in tumor cytogenetics, a comparable interlaboratory testing was established in 2003. Cells fixed in methanol:acetic acid from normal controls and/or (pooled) patient materials (or mixtures of both) were sent out for evaluation to participating laboratories. The participants were asked to perform the required FISH analysis and to send a report as done in routine diagnostics. The procedure covers the practical hybridization part as well as evaluation and interpretation of results. Twice no material was sent out, instead an interpretation of a given FISH result was requested or a typical report from the participating laboratory at diagnosis of a CML had to be sent. The review committee is composed of members of participating laboratories. Participants can apply to join the committee and are chosen by the supervisor of the test. In 2012 the test was integrated in the portfolio of interlaboratory testing offered by the BVDH. The respective online platform is used for uploading the reports by the participants as well as the evaluation by the reviewers. Two members of the review committee and the supervisor of the test evaluate the reports according to evaluation criteria which have been disclosed to the participants before the samples were sent out. The review committee performs two telephone conferences, one prior and one after the review process, in order to resolve questions with respect to the evaluation. The participants receive a detailed report on the review of their results as well as on the overall results of all participating laboratories. Further the reviewers provide suggestions how to improve the report if necessary. So far, each laboratory receives the number of scoring points reached. In the current test, the review committee provides the minimum number of scoring points that would be necessary to pass the test and to receive a certificate. In future, it is intended that the review committee judges the results as passed or failed.

Further details regarding the requirements to pass the tests in chromosome banding as well as in FISH analyses will be discussed during the „Tumorzytogenetische Arbeitstagung“, 6th-8th June 2013 in Braunlage, Germany.

Access to the platform and to the test system is available upon registration at the BVDH (www.bvdh-ringversuche.de). However, the system is restricted to German speaking countries, so far.
The first version of the European LeukemiaNet (ELN) recommendations for the management and the treatment of chronic myeloid leukemia (CML) were published in 2006\(^2\), when imatinib had become the gold standard of treatment. Following the introduction of second generation tyrosine kinase inhibitors (TKI) for the second-line treatment, a second version of the recommendations was published in 2009\(^3\). Both versions were fairly well received by the scientific community, became popular, were adopted worldwide and were also used by Health Agencies to evaluate the therapeutic effects of new drugs. Both versions received more than 600 citations each. The second manuscript deals with influenza both before and after stem cell transplantation\(^2\). The recent H1N1 pandemic clearly showed that severely immunocompromised patients are vulnerable to influenza with increased morbidity and mortality\(^2\). The recommendations deal with infection control, diagnosis, antiviral therapy, and vaccination. The third manuscript deals with other commu- nicable respiratory viral infections such as adenovirus infections and management of patients with chronic lymphoblastic leukemia (CLL) especially those treated with alemtuzumab. The recommendations deal with diagnostic procedures, risk factors, whom and how to monitor for adenovirus infections, and management of patients with probable or proven infections.

The second manuscript was submitted during 2013.

**WP 15 - Supportive care**

**Recommendations on the management of respiratory viral infections**

Per Ljungman on behalf of the WP 15

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The European Conferences on Infections in Leukemia (ECIL) are organized in collaboration between the WP15 of the ELN, the Infectious Diseases Working Party of the EBMT, the Immuno-compromised Host Society, and the Infectious Diseases Group of the EORTC. The aim of the ECIL meetings is to develop guidelines for diagnosis and management of infections in patients with hematological malignancies. The 4th ECIL conference was held in Juan-les-Pins in September 2011. The three main topics were respiratory viral infections, resistant bacteria, and infections in children with hematological malignancies. The work is performed by small working committees with the primary task to review published literature on the topic. These groups then produce drafts for recommendations that are discussed, revised and finally accepted by the entire group of ECIL participants. Three manuscripts resulting from the work regarding respiratory viral infections have been published recently. The first manuscript deals with adenovirus infections\(^2\). Adenoviruses are a group of viruses most significantly affecting children but also adults undergoing allogeneic stem cell transplantation although severe and fatal infections have also been documented in children with acute lymphoblastic leukemia (ALL) and patients with chronic lymphoblastic leukemia (CLL) especially those treated with alemtuzumab. The recommendations deal with diagnostic procedures, risk factors, whom and how to monitor for adenovirus infections, and management of patients with probable or proven infections.

The second manuscript deals with influenza both in patients with hematological malignancies and...
To identify potential hurdles, this office will start initially with two groups: the German (GMDS-SG) and French (GFM) MDS groups and at least one cooperative trial before being extended to other countries and other clinical trials. The proposal has been presented to the ELN steering committee which provided financial support to establish EMSCO. The GMHO, a branch of the German Society of Hematology and Oncology (DGHO) will deliver, with the help of the GMDS-SG and the GFM, logistics for this office.

The ELN MDS diagnostic and therapeutic guidelines: WP8 experts have decided to produce a combined diagnostic and therapeutic guideline document. The development of the document has been coordinated by Luca Malcovati and Eva Hellstroem-Lindberg supported by a project group of MDS experts. The MDS diagnostic guidelines have been developed on the basis of the new WHO classification (4th edition, 2008). The group introduced and revised the diagnostic guidelines regarding new insights obtained by the flowcytometry group coordinated by Arjan van de Loosdrecht. The guidelines include a work-up of suspected MDS or mixed MDS/MPNs. The current version of the diagnostic guidelines has been published on the ELN website. The therapeutic guidelines have been developed by a European expert panel and a systemic review of literature. The European guidelines for treatment of primary MDS have been finalized by an expert panel discussion of the most recent developments in MDS treatment this year. 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 entitled Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the “European LeukemiaNet” has been circulated to all experts and submission of the manuscript to Blood is expected in the first quarter of 2013.

Flowcytometry: The 5th international ELN Workshop on Standardization of Flow Cytometry (FC) in MDS was organized in Amsterdam, The Netherlands, October 26-27, 2012, hosted by Arjan van de Loosdrecht (for full report, see www.leukemia-net.org > leukemias > MDS). The FC working group in MDS has agreed that FC adds significantly to MDS characterization, diagnosis, and prognosis in the first five years of its existence within WP8 of ELN. FC may also be useful in predicting and monitoring disease during treatment with new and standard therapeutic regimens.Repeated FC assessments are strongly recommended not only in cases such as ICUS and IDUS, but also to monitor the natural course of the disease in patients with untreated low and intermediate-1 risk MDS. The same holds true for patients treated with currently available drugs, preferably within clinical trials as conducted by national and international collaborating groups. The 5th ELN Workshop further focused on widespread implementation of the diagnostic power and pitfalls in the diagnostic work-up of MDS as well establishing the prognostic value of MDS. To reach this goal several prospective trial initiatives are proposed and will be positioned within the next one to two years. The next meeting will be organized by guest-chair Dr. W. Kern from MLL Munich Leukemia Labor, Germany in the fourth quarter of 2013.

Impact of frailty index on various therapeutic approaches including supportive care, hypomethylating agents, intensive anti-leukemic therapy

Comprehensive geriatric assessment has been performed in 195 patients aged 60 years or over with newly diagnosed myelodysplastic syndromes/acute myeloid leukemia in Freiburg, Düsseldorf and Dresden. This study explored prognostically important assessment instruments and eventually defined a frailty index. 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. A simple risk assessment score has been developed based on impairment in activities of daily living. Patients with Karnofsky index below 80 %, quality of life/fatigue of 50 or over, are likely to have poor outcomes. The study is currently available online (see publications).

The ELN EU-MDS Registry: The registry is collecting a unique data set which has proven to be very valuable for clinical questions and studies as well. Serbia and Israel have joined the EU-MDS Registry in 2012. The Registry group is planning 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). The follow-up time of the first 1000 patients has been extended to five years with financial support from Novartis. Registration of new patients has continued in almost all registries with totally 1357 new patients registered in November 2012. Three studies of the EU-MDS Registry have been presented at the ASH annual meeting in Atlanta in December 2012. Theo de Witte presented the study on the impact of co-morbidities and treatment on newly diagnosed lower-risk MDS patients from the EU-MDS Registry during the MDS Foundation Symposium. Louise de Swart presented data on early mortality in 1000 newly diagnosed MDS patients with low and intermediate-1 risk MDS in the European LeukemiaNet MDS (EU-MDS) registry (abstract #3830) and Raphael Itzykson presented the prognostic relevance of the kinetics of worsening of cytopenias in lower risk MDS: a substudy from the European LeukemiaNet low risk MDS (EU-MDS) registry as an oral presentation (abstract #700). An EU-MDS Registry Academy has been planned for all participants of the EU-MDS Registry in Nijmegen, The Netherlands, January 30, 2013. All planned and ongoing studies will be presented and discussed during this academic meeting.

Implementation of the diagnostic and prognostic value of molecular mutations in MDS

The steering committee of the EU-MDS Registry has submitted a grant application to the last call of the 7th Framework Programme of the EU. This study OP-TIMA (Optimized Management of Lower Risk MDS) aims to assess in an extension of an ongoing observational study (16 countries, 2000 patients) the impact of adapted diagnosis and prognosis on survival and quality of life (QoL) of lower risk MDS patients. Objectives of OPTIMA are 1) improved survival and QoL and 2) optimized, personalized disease management. The role of biomarkers (molecular mutations) in early diagnosis, supportive care, and prognosis is assessed. OPTIMA will lead to improved supportive care resulting in improved survival and improved QoL in this aged MDS cancer population. MDS biomarker application helps to ameliorate early diagnosis, prognosis, and/or evidence based personalized care. Reﬁned MDS supportive care leads to better cost effectiveness, prevention of unnecessary expensive treatments, and appropriate application of treatment responsive patients. In addition, data obtained in the OPTIMA study can guide future prospective studies. The application has not passed the first stage of the application, but the group will apply for alternative funding in 2013.

Collaboration with other ELN WPs

MDS WP8 has interacted with many other ELN WPs. The cytogenetic WP11 has submitted a project proposal to the ELN steering committee on rare abnormalities in MDS: Prognostic signiﬁcance and inclusion in existing prognostic classiﬁcation systems. The application has been approved. The project coordinators are Julie Schanz and Detlef Haase from the Universitiy of Gottingen, Germany. Several studies have been published (refs 6 and 7) on the role of allelic stem cell transplantation in collaboration with ELN WP Stem cell transplantation (coordinator Dietger Niederrwieser) and the EBMT MDS subcommittee (coordinator: Nikolaus Kröger).

Publications 2012

WP 10 - Diagnostics

Highlights from the field of diagnosis

Marie Christine Béné on behalf of the WP 10

Immunology Laboratory, University Hospital Nancy Brabois, Nancy, France

Last year, WP10 applied for recognition as a scientific working group (SWG) of the European Hematology Association (EHA) and was granted this status. WP10 therefore had the task to organize a session, as all other SWGs, during the EHA meeting in Amsterdam. We divided the time in two parts, as per the objectives of this work-package to provide training and recommendations for both morphology and immunophenotyping. Gina Zini and Barbara Bain had an interactive series of cases with morphological tricks to which the audience participated enthusiastically. On the flow side, three presentations dealt with minimal residual disease (MRD) detection: Gerrit Schuurhuis talked about the rare typing. Gina Zini and Barbara Bain had an interest for both morphology and immunophenotyping, Giuseppe Basso presented the latest results on MRD in childhood acute lymphoblastic leukemia and Francis Lacombe showed an innovative systematized analytical strategy for the identification of MRD in acute myeloblastic leukemia.

WP10 members also had taken part to the annual meeting of the International Society of Laboratory Hematology (ISLH) in Nice (France) in May. Sessions dealing with the cellular aspects of oncohematology included the participation of Barbara Bain, Mike Loken and Arjan van de Loosdrecht. A breakfast session about the diagnosis of leukemia associated the intertwined morphological and flow point of views of Torsten Haferlach and Marie Christine Béné for a very attentive audience. In September, the French Groupe d’Etude Immunologique des Leucémies (GEIL) officially introduced the first part of a collective effort on recommendations for accreditation. This topic had already been touched upon in Mannheim at WP10 in February and will also be discussed in the 2013 meeting. At the moment, the GEIL has dealt with preanalytical recommendations (as per WP10), instruments settings and harmonization, compensations, fluorochromes choices, and proposes a top down approach of panels construction with ten and eight colors sets for acute leukemias and lymphoproliferative disorders. Along the same lines, several members participated in an international collective work about accreditation in flow cytometry, soon to be published.

Finally, at the end of October, Arjan van de Loosdrecht organized the 5th workshop on flow cytometry in myeloproliferative disorders within WP8 and with the participation of a number of WP10 members. This group has been very active in publishing the results of previous meetings, including two papers in 2012, and more work is underway.

WP10 is finally proud that its project for a training session will be receiving support from the ELN foundation. More information about this meeting will be provided in Mannheim.

WP 7 - CLL

European Research Initiative on CLL (ERIC)

Emili Montserrat

Hospital Clinic, IDIBAPS, Barcelona, Spain

The European Research Initiative on CLL (ERIC) is a scientific group whose aim is to promote clinical, basic, and translation research on CLL and related disorders across Europe and to facilitate also research joint projects at international level. ERIC was created in 2001 and subsequently established a partnership with the European LeukemiaNet and also with the European Hematology Association of which it is one of the Working Groups. ERIC has more than 300 active members from more than 20 different countries.

Currently, ERIC has four major Research Programs (ERP) embracing:

1. TP53 lesions
2. minimal residual disease (MRD) assessment and harmonization of the techniques to detect it
3. IG gene analysis
4. Clinical studies, focusing on phase I, II and IV studies; observational studies.

Below, leaders for each one of these groups, recent accomplishments and ongoing projects are briefly summarized. Further information regarding ERIC projects and how to join them can be found at www.ericll.org.

TP53 lesions

Ongoing projects:
Prospective evaluation of TP53 function, multiparametric and prospective study of the impact of novel mutation on CLL outcome.

MRD
(Rawstron A, Bötcher S, Letestu R, Ghia P, Villamor N, Hillmen P)
Ongoing projects:
Refinement of MRD assessment by using eight-colors flow-cytometry.

IG gene analysis (www.igcll.org)

Ongoing projects:
(i) Harmonizing existing methodologies;
(ii) ERIC online review board for the interpretation of IG gene sequence results (http://www.ericll.org/forumIGHVAnalysis/index.php)
(iii) IgCLL Educational Workshop on IG gene sequence analysis in CLL: the fifth such workshop is planned for fall 2013.

Clinical studies
(Moreno, C, Montillo M, Kimby E, Robak T, Del Giudice I).
Phase IV evaluation of Ofatumumab therapy for CLL (accrual finished; final data to be presented first-quarter of 2013).
Ongoing projects:
Spontaneous remission in CLL
New European regulation on clinical trials on medicinal products for human use

Nicola Gökbuget
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The Clinical Trials Directive 2001/20/EC was implemented by the European Union in 2001 and taken over into national European regulations until 2004. The directive had severe negative impact on clinical trial activities in general but particularly on the independent academic research. This is mainly due to the fact that henceforth treatment optimization studies and academic trials had to follow the same regulatory processes as registration trials of the pharmaceutical industry. Numerous publications have expressed massive criticism (see Information Letter 8/2012; www.leukemia-net.org).

After a public consultation the European Commission has now prepared a proposal for the European Parliament, which is not a directive but a regulation. First of all, this may increase the chance for more uniform application with less national aberrations throughout Europe. Furthermore, the European Commission has apparently identified many of shortcomings of the current directive and suggested a number of reasonable approaches for international trials:

- Central submission of all documents for fast authorization procedure
- Risk-adapted assessment of clinical trial applications with shortened procedures for low risk trials
- Definition of low risk (minimal interventional) trials with registered drugs and risks comparable to current standard of care
- Clearer definition of investigator responsibilities (one responsible investigator per center)
- Electronic reporting of suspected unexpected severe adverse events (SUSARs)

The new regulation may help to harmonize pre-requisites for clinical research throughout Europe. However, there is still a number of ambiguities. Specifically the ethical approval through institutional review boards (IRBs) will be in the national responsibility and the complex procedures are currently one major limitation for rapid activation of clinical trials in many European countries. Costs and tracking requirements for investigational products as well as reporting requirements to the marketing authorization holder in trials with registered drugs may potentially lead to additional efforts for academic sponsors. Finally, the new regulation will still not allow co-sponsoring of a trial. The latter was a major request of academic sponsors having difficulties to take over the full responsibility for clinical trials in other European countries.

According to the European Commission 800 million Euros per year could be saved in regulatory costs. The legislative proposal will now be discussed in the European Parliament and in the Council. The aim is that the regulation comes into effect in 2016 but it remains open which changes will be made during discussions and whether the timeline will be realized. National interests will be expressed and lobby groups have already started activities against the new regulation. Therefore study groups in the European LeukemiaNet will still have to find ways to conduct international trials according to the currently active directive and the respective national regulations.

Further information is available on www.leukemia-net.org.
Monitoring of patients with chronic myeloid leukemia (CML) includes differential blood counts, cytogenetic analysis (chromosome banding analysis from bone marrow) and molecular monitoring from peripheral blood\(^{15}\). Besides established cytogenetic milestones after 12 and 18 months of tyrosine kinase inhibitor (TKI) treatment with clear prognostic impact, new molecular milestones have recently been published by several groups. In addition to the 12 month time point, earlier molecular milestones after three and six months of treatment have been shown to impact on progression-free and overall survival\(^{36-38}\). During the last years, a significant number of researchers within the European LeukemiaNet worked on the topic of how to best harmonize monitoring of CML patients by molecular methodologies, i.e. real-time quantitative polymerase chain reaction (RQ-PCR)\(^{39-41}\). The necessity of a standardization process is obvious considering the variability of techniques being used among the estimated 300 European laboratories performing PCR of BCR-ABL mRNA transcripts. An example for heterogeneity between two laboratories using two different housekeeping genes for normalization is given here. Lab 1 uses ABL and Lab 2 performs beta-2-microglobulin (B2M) quantification. Due to the fact that B2M is expressed much higher than ABL in normal and/or leukemic cells the resulting ratio BCR-ABL/ABL would be much higher than the ratio BCR-ABL/B2M if the same sample was analyzed. These differences can either be overcome by using the same housekeeping gene in each laboratory or by allocating laboratory-specific conversion factors by performing control rounds with reference laboratories guaranteeing for stable methodologies. The latter is being performed within a European project called EUTOS for CML (European Treatment and Outcome Study) representing a cooperation between the ELN and Novartis Oncology Europe. By 2013, around 60 European laboratories have participated regular control rounds validating and revalidating their local conversion factor if a proper concordance between test and reference results was achieved. In case of harmonization problems, protocol checks and/or preceptorships in the European reference laboratory in Mannheim have been executed\(^{40}\). By successfully passing the rounds and applying the local conversion factor, each participating laboratory is enabled to report quantitative BCR-ABL results according to the International Scale (IS) representing the internationally agreed common language to compare data between laboratories and studies\(^{42}\). It is derived from a definition of a standardized baseline value of molecular response which was used for the IRIS trial (International Randomized Study of Interferon and STI571)\(^{1}\). In order to compare molecular results from the three originally monitoring laboratories, 30 samples of initially diagnosed CML patients were distributed among them. After determination of the median BCR-ABL expression level in each of the three laboratories a local conversion factor was calculated to adapt the median BCR-ABL level to a value of 100 %\(^{41}\). One of the three laboratories of the IRIS trial (Adelaide, Australia) has proven to provide stable methods since 13 years and thereby acts as the “world” reference laboratory\(^{42}\). A BCR-ABL expression value three logs below the baseline level is defined as major molecular remission (MMR) and is generally considered to equal a safe haven if achieved on TKI treatment. Current developments in terms of first-line treatment with more potent second generation TKIs raises the hope of reducing the tumor load of a higher proportion of CML patients down to 4 and 5 logs below the standardized baseline. The French STIM Study showed that patients who qualified for a discontinuation try-having achieved a 5 log reduction on imatinib - remained treatment-free without molecular relapse in about 40 %\(^{44}\). Being sensitive enough and thereby able to reliably measure in the range of a 4-5 log reduction represents a big challenge for the laboratories. A recent publication from ELN members proposes how to qualify best for the desired depths of responses\(^{45}\). It is described that a certain number of housekeeping gene transcripts should be achieved to goal for a MR\(^4\) (molecular response 4, 4 log reduction, ABL transcripts: 32000), and MR\(^3\) (4.5 log reduction, ABL transcripts: 32000), and MR\(^2\) (5 log reduction, ABL transcripts: 10000) in cases of negative BCR-ABL results. In the future, this approach will be able to inhibit false negative results which have been a problem in a number of trials using low-sensitive PCR tests. Further, if BCR-ABL is positive and sensitivity criteria are met, MR\(^4\) can be achieved by a BCR-ABL expression < 0.01 %, MR\(^3\) by < 0.0032 % BCR-ABL\(^2\), and MR\(^2\) by < 0.001 % BCR-ABL\(^2\). Current and future discontinuation trials will elucidate which depth of response will be necessary to successfully stop TKI treatment.
Acute lymphoblastic leukemia (ALL)

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Ph/BCR-ABL-positive (Ph+) ALL

In Ph+ ALL promising results were reported for older patients and autologous transplantation may be rediscovered as a treatment option for patients with negative MRD status.

Two groups reported results for Ph+ ALL from European investigator-initiated trials. Rousselot et al. (#666) presented the final results of a trial with Dasatinib in older patients (> 55 years). Dasatinib (140 mg QD) was combined with a dose reduced induction and consolidation therapy. 71 patients with a median age of 69 years were included. The complete remission (CR) rate was 94 %. After induction 54 % achieved a major MRD response (MMR) with BCR-ABL below 0.1 % and undetectable MRD in 22 %. Overall survival (OS) and relapse free survival (RFS) at 3 years was 45 % and 43 %, respectively. The T315I mutation was present in 63 % of the relapses. Patients with undetectable BCR-ABL after consolidation had a significantly better OS compared to patients with persistent BCR-ABL. These results are promising for the older patient population and further trials may be conducted based on the standard chemotherapy backbone.

Chalandon et al. (#138) reported a randomized comparison of Imatinib (800 mg/d) in combination with a dose-reduced induction (Arm A) versus a combination with the Hyper-CVAD regimen (Arm B) in younger patients (18-60 years). The CR rate was higher for Arm A versus Arm B (98 % versus 89 %) due to a higher induction mortality Arm B. The rate of MMR after two cycles was 66 % and the rate of undetectable MRD was 25 % with no difference between both arms. The OS was 53 % versus 49 % for Arm A and B, respectively. Allogeneic stem cell transplantation (SCT) was scheduled in all patients with donor whereas autologous SCT was considered in patients with MMR without donor. In patients with MMR outcome of autologous SCT compared to allogeneic SCT was not inferior with OS of 69 % versus 58 %, respectively.

The potential role of autologous SCT in Ph+ ALL was underlined by results from a CALGB trial (#816). Wetzler et al. combined Imatinib (800 mg/d) with sequential chemotherapy in younger patients (< 60 years) followed by allogeneic sibling (N=15) or autologous SCT (N=19). OS and disease free survival (DFS) were similar although relapse rate was lower after allogeneic SCT. Patients with low MRD (< 0.001) at day 120 after autologous SCT had a better outcome compared to those with higher MRD.

Giebel et al. analyzed data from the EBMT registry (#233). OS in 171 patients treated with autologous SCT was 45 %, with 54 % relapse incidence and 13 % transplant-related mortality. When different time periods were compared the leukemia free survival increased from 22 % (1996-2000), to 32 % (2001-2006) and 54 % (2007-2010) whereas the relapse incidence decreased indicating that the outcome of autologous SCT may be improved in the Imatinib era.

In a historic comparison Intermesoli et al. (#662) confirmed a better outcome in patients treated with Imatinib in combination with chemotherapy compared to a cohort from the pre-Imatinib era.

As a next-generation TK inhibitor Ponatinib is of interest for Ph+ ALL. Results were reported from the PACE trial (#163, #915). In Ph+ patients with resistant or intolerant disease (N=10) or T315I mutation (N=22) the major hematologic response rates were 50 % and 36 %, respectively. For CML in blast crisis and Ph+ ALL together the median progression-free survival was 18 weeks and the probability to remain progression free at one year was 20 %. The FDA has in the meantime granted accelerated approval for Ponatinib based on the results of the trial.

New antibodies

Promising results with two different antibodies were reported for relapsed or refractory ALL.

Topp et al. (#670) reported on a T-cell engaging bispecific CD19 antibody tested in 36 patients with relapsed/refractory ALL. The overall CR rate with or without hematologic recovery was 72 %. 92 % of responders also achieved a molecular remission defined as MRD below 0.01 %. The median OS was 9 months. One out of 13 responders with subsequent SCT relapsed compared to 8 out of 13 responders without SCT. Overall treatment was feasible; reversible CNS events were observed in 6 patients. In the final dose cohort the most frequent events were pyrexia (70 %), headache (39 %), tremor (30 %), and fatigue (30 %).

Results of a CD22 antibody conjugated to calicheamicin were reported in 83 patients, including children by O’Brien et al. (#671) comparing a single-dose to a weekly schedule. Overall response rate was 53 % for the weekly schedule (N=24) and 57 % for the single-dose schedule (N=49), with overall 17 % CR, 28 % CR without platelet recovery and 11 % CR without hematological recovery. The median OS was 5.4 months. 68 % of 28 evaluable patients became MRD negative based on flow-cytometry; the sensitivity was not defined. SCT rates were 49 % on single dose and 26 % on weekly schedule; veno-occlusive disease after SCT was observed in 23 % and 11 %, respectively. Overall toxicity appeared to be less pronounced on the weekly schedule whereas efficacy was comparable.
High-risk subgroups of ALL
Marks et al. (#663) reported the outcome of 85 pts with t(6;11) positive ALL treated in the UKALL XII/ECOG 2993 trial. The CR rate was 93 % and OS at 5 years was 35 %. Survival was inferior in 46 patients treated with chemotherapy (24 %) compared to 16 patients with sibiling SCT (56 %) or 15 with unrelated SCT (67 %).

Hoelzer et al. (#667) presented the long-term results of a prospective trial in adults with Burkitt leukemia (B-L) or lymphoma (B-Ly). The pediatric-based regimen (GMALL B-ALL/NHL 2002) combined chemotherapy with 8 doses of rituximab before the chemotherapy cycles. 229 patients with B-Ly and 134 patients with B-L were included. CR rates were 91 % and 86 %, respectively. OS in B-Ly was excellent independent of age, 91 % (15-25 years), 91 % (26-55 years) and 80 % (> 55 years). In B-OS decreased with increasing age and reached 90 %, 71 %, and 46 %, respectively. Thus, improvement of OS in older patients with B-L remains a challenge. Overall outcome was comparable to pediatric trials although chemotherapy dosages were lower.

Acute myeloid leukemia (AML)

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Treatment of acute myeloid leukemia (AML) in the elderly is still disappointing. Factors influencing complete remission (CR) rates were identified in 957 eligible elderly patients from a randomized trial investigating two study group specific regimes and a common standard arm (SA) in the German AML Intergroup study (group A: cytarabine (AraC)/mitoxantrone (M), group B: TAD/HAM, SA: AraC/ daunorubicine (Dauno)). After 90 days, CR rate was 56 % and 50 % in the study arms and SA, respectively. The type of AML (de novo or secondary), cytogenetic risk, age and WBC at diagnosis were found to be influencing CR rates (#128).

The nucleoside analogue clofarabine (Clo) has been investigated in comparison to low dose AraC (LDAC) for the treatment of unfit elderly. The CR/CRI rate was significantly better for patients receiving Clo (38 % vs. 20 %), but the treatment was related to a higher early death (ED) rate and inferior survival from relapse compared to LDAC not resulting in an overall survival (OS) benefit. The authors concluded that CR might not be a reliable surrogate for OS in elderly patients (#889).

In the UK NCRI AML16 ‘pick a winner’ trial, 806 older patients were randomized to receive Dauno/AraC vs Dauno/Clo with or without gemtuzumab ozogemicin (GO) and 2 vs 3 courses of treatment following maintenance therapy or not. The benefit of the addition of GO has been reported. All in all, DA and DClo resulted in similar outcomes and there was no significant benefit for a third course of chemotherapy in all demographic subgroups analyzed (#892).

In a phase II study Clo was also investigated in combination with idarubicin (Ida) and AraC (CIA) as first-line therapy in 59 patients ≤ 60 years. Of 57 patients evaluable, 79 % achieved CR or CR with incomplete platelet recovery (CRp). Patients aged < 40 years showed a better OS and event-free survival (EFS). Compared to Ida/AraC treatment alone (data taken from a historical group of patients), CIA treatment was associated with a significantly longer OS and EFS in all age subgroups (#43).

Patients harboring an internal tandem duplication (ITD) of the FMS-like tyrosine kinase 3 (FLT3) comprise an AML subgroup with poor prognosis. Quizartinib (AC220) is a specific inhibitor of wildtype and mutant FLT3. In a phase II trial, 333 relapsed/refractory patients with and without FLT3-ITD mutation were assigned to AC220 monotherapy or AC220 monotherapy with b-l. The first cohort included 134 elderly patients of which 69 % were FLT3-ITD positive. In the second cohort, 137 adult, heavily pretreated AML patients were included. Here, 72 % had the FLT3-ITD mutation. In both cohorts, AC220 treatment yielded in a high complete remission (CRc) rate (CR, CRI, and CRp together) for FLT3-ITD positive patients (cohort 1: 54 %, cohort 2: 44 %). Also patients who were refractory or relapsed to one or more prior chemotherapies or hematopoietic stem cell transplantation (HSCT) responded to AC220 monotherapy (#48, #673).

The German study group SAL analyzed the benefit of the multi-kinase inhibitor sorafenib in addition to standard chemotherapy (Dauno/AraC followed by HAM where required). 276 patients aged 18-60 years were randomized in this placebo-controlled SORAML trial. Of 264 patients evaluable, 56 % vs 60 % achieved CR in the placebo vs experimental arm. Sorafenib treatment resulted in a marked non-significantly EFS (1-year EFS of 50 % vs 64 %) and OS prolongation (2-year OS was 66 % vs 72 %) but was associated with a higher risk of liver toxicity and bleeding events (#144).

For AML patients fit for intensive chemotherapy but not eligible for genotype-adapted strategies, the German study group AMLSG conducted a phase II trial comparing three azacitidine (AZA)-based regimes to a standard induction therapy (Ida/AraC plus etoposide (Eto)) (AMLSG 12-09 trial). The experimental arms differed in the chronological administration of AZA towards a combination of Ida/Eto. After the randomized treatment of 104 patients, two arms were terminated as CR rates were beyond the initial expectations. A total enrollment of 100 patients in each of the remaining arms resulted in CR rates of 52 % and 59 % in the standard arm and Ida/Eto followed by AZA (AZA-after), respectively (#12).
Although LDAC is an established regime for patients ineligible for intensive remission induction therapy, the management of this patient population requires improvement. Comparing volasertib (Vol) - an intravenous Polo-like kinase inhibitor - plus LDAC vs LDAC monotherapy Maertens et al. were able to show significantly higher CR/CRI rates (31 % vs 11 %) and a trend for EFS benefit with Vol plus LDAC in a total of 87 patients with de novo AML. Remissions in the Vol plus LDAC arm were observed across genetic subgroups including adverse cytogenetic groups. Given its myelosuppressive mechanism of action, the addition of Vol led to an increased frequency of adverse events (AE) (#411).

Data from two randomized, phase III trials for patients suffering from acute promyelocytic leukemia (APL) were presented: In the Chinese APL07 trial, Zhu-Hong Zhu et al. investigated the efficacy of arsenic-containing Realgar-Indigo naturalis formula (RIF) - an oral drug - vs arsenic trioxide (ATO) in both the induction and maintenance therapy. In the induction therapy, all patients also received all-trans-retinoic acid (ATRA). Results from 242 younger patients with newly diagnosed APL showed no significant differences with respect to AE and CR rates, disease-free survival (DFS), and OS, offering now the possibility to treat APL patients with an oral regimen (#140).

The European Intergroup APL0406 trial was conducted to show the superiority of ATRA plus ATO over the standard therapy ATRA plus Idasa (AIDA) in de novo non-high risk APL for patients aged 18–70 years. 162 patients were enrolled of which 154 were evaluable for analysis. After induction, 97.4 % of all patients treated achieved CR (ATRA plus ATO: 100 %, AIDA: 95 %). ATRA plus ATO was shown to be significantly superior to AIDA in improving the 2 year EFS (97 % vs 87 %), OS (99 % vs 91 %), and frequency of AEs and tends to result in superior DFS (97 % vs 92 %) and cumulative incidence of relapse (CIR) rates (1.6 % vs 4.3 %) (#6).

**Chronic myeloid leukemia (CML)**

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Since CML became manageable after the discovery of the tyrosine kinase inhibitor (TKI) imatinib (IM), trials aim to identify treatment regimes that induce fast and deep molecular remissions which are thought to be associated with a good overall survival (OS), progression-free survival (PFS) and event-free-survival (EFS). High levels of cytogenetic and molecular responses to IM or second generation (2G) TKIs such as nilotinib and dasatinib are thought to determine a subgroup of patients (pts) who may stay in remission even after discontinuation of TKI.

In the French SPIRIT trial, 787 pts with chronic phase (CP) CML were randomized to 4 IM-based regimes: IM 400 vs. 600 mg/day vs. IM plus Cytarabine vs. IM plus pegylated Interferon α2a (Peg-IFN). After 60 months, the PFS among the four groups was quite similar with the molecular response at 3 months (BCR-ABL ≤ 10 % IS) being associated with an improvement in PFS in the IM 400 mg/day and the IM plus Cytarabine group. However, pts treated with IM plus Peg-IFN were at very low risk of progression even if their molecular response was delayed (#168).

With 1525 randomized evaluable pts with de novo CP-CML, Hehlmann and colleagues could show in the German CML-Study IV that IM dose-optimization faster induces complete molecular remission (CMR) than the other 4 regimes (comparing IM 400 mg vs. IM plus IFN vs. IM plus Cytarabine vs. IM after IFN failure vs. dose-optimized IM 800 mg). Independent of the treatment approach, CMR 4.5 at 4 years was associated with a better OS (#67).

In a retrospective approach Branford et al. analysed the molecular response of 415 pts with de novo CP-CML to identify predictors for discontinuating IM. The criterion for IM-discontinuation was defined as confirmed stable MR4.5 for at least 24 months while on IM-therapy. The time to achieve a major molecular remission (MMR), female sex, and a low BCR-ABL value at 3 months could be identified as factors that predicted the achievement of the discontinuation criterion (#165).

In line with these results is the outcome of another retrospective study investigating the improvement in prognostic accuracy by combining the RQ-PCR results for BCR-ABL at 3 and 6 months. Of 274 pts analysed, 77 % had low transcripts (< 9.8 % IS) at 3 months which was associated with a good OS and the achievement of CCyR irrespective of the transcript levels at 6 months. Only for the minority of 2 % of the pts harboring high BCR-ABL levels at 3 months but low at 6 months (< 1.67 % IS) the combined analysis may improve the prognostic classification (#68).

Another retrospective study comparing the results from four different trials showed that pts treated with dasatinib and nilotinib, and to some extent those treated with high-dose IM, have a better probability of achieving deeper responses at early time points than pts treated with standard-dose IM (#70).

With the data from the 4-year follow-up of the ENEStnd trial, Hochhaus et al. were able to show the superiority of nilotinib vs. IM in achieving earlier molecular response. Two arms of the study were analyzed for early molecular response: nilotinib 300 mg BID (n = 282) vs IM 400 mg QD (n = 283). More pts treated with nilotinib vs. IM achieved an early molecular response at 3 and 6 months (< 10 % IS), respectively (#167).
Results from the ENESTcmr (2-year follow-up) study indicate that switching to nilotinib after long-term IM therapy significantly faster led to MR4 and MR4.5 in pts with minimal residual disease (MRD, n = 104) compared to continued IM treatment (n = 103) which became even more apparent after 12 months of nilotinib treatment (#694).

The prospective monitoring of 153 CP-CML pts by Schwarz et al. by sequential evaluation of the ankle brachial index (ABI) and duplex ultrasonography revealed a significantly higher frequency of peripheral artery occlusive disease in pts on nilotinib than in pts on imatinib. This might be due to elevation of cholesterol and glucose levels or other mechanisms. Hence, caution is advised to treat pts with more than 2 major risk factors or a known history of arteriopathy with nilotinib (#914).

The feasibility of therapy discontinuation was also shown for 2G-TKIs. 34 CP-CML pts on dasatinib or nilotinib were proposed treatment discontinuation provided that (i) TKI treatment duration was ≥ 36 months and (ii) BCR-ABL transcripts were undetectable for ≥ 24 months. Pts treated with 2G-TKI as first-line therapy or after IM intolerance had a significantly higher probability of stable MMR than those with prior IM suboptimal response/resistance. 13 of 15 pts who were reintroduced to therapy regained MMR (#916).

In the French NilOPEG phase II trial, 40 CP-CML pts were treated with nilotinib plus PegINF. The combination was tolerated well despite frequent initial and transient hematologic and hepatic toxicities. This new treatment provides very high rates of molecular responses at 1 year (84 % pts in ≥ MMR) (#166).

The 2G TKI bosutinib was investigated first-line in the phase III BELA trial. 431 CP-CML pts were randomized to 2 arms: 500 mg/d bosutinib vs standard-dose IM. Bosutinib was shown to be significantly superior to IM in inducing a molecular response (BCR-ABL ≤ 10 % IS) at 3, 6 and 9 months with significantly shorter median time to MMR (#69).

Despite these progresses in CML therapy with TKI, pts with failure of TKIs or the T315I BCR-ABL mutation have limited treatment options. Ponatinib is proven to be active against wildtype and BCR-ABL mutants including T315I. In the phase II PACE trial, 449 heavily pretreated Ph+ pts resistant/intolerant to dasatinib/nilotinib or harboring BCR-ABL T315I, respectively, were assigned to six arms dependent on the stage of disease. In all cohorts, ponatinib is generally well tolerated. Response exceeded the prespecified statistical criteria for success in all cohorts. Response rates were higher in pts exposed to fewer prior TKIs and those with shorter disease duration. The mutation status had no influence on the outcome (#163, #915).

The history of disease of 512 pts with early CP-CML treated with IFNα-based therapies between 1981-95 (analyzed by Quintás-Cardama et al.) reveals that in spite of the variety of TKIs available for CML treatment, IFNα remains a therapeutically valuable agent, capable of inducing CCyR in approximately 25 % and CMR in 5 % - 7 % of pts in CP. Some pts can achieve a durable remissions on IFNα, safely discontinue therapy and remain in remission suggesting the possibility of CML cure (#918).

Myelodysplastic syndrom (MDS)

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Rafael Bejar et al. reported (#311) on gene mutations of 74 genes in 200 MDS patients who received hypomethylating treatment and 76 patients who received an allogeneic stem cell transplantation (alloSCT). P53 and DNMT3A were independently associated with poor survival after alloSCT, mainly due to a high relapse rate. Most frequently occurring gene mutations, including TET2 mutations, were not predictive for response after treatment with hypomethylating agents but CBL (14 patients) was associated with better survival and NRAS with poor survival.

The GFM (#422) enrolled 282 higher risk MDS patients in a compassionate patient named program of AZA and evaluated the prognostic impact of the new IPSS-R in these patients treated with AZA. Individual IPSS-R parameters had no significant impact on AZA response. The very high risk and high risk patients could be further subdivided by the GFM AZA scoring system in low, intermediate or high risk with a significantly different OS across those groups.

Several new prognosis indexes (PI) have been proposed: IPSS-R, WPSS-R, MD Anderson (MDA) Index, and the Spanish Group of MDS (GESMD) proposal. This Spanish study (#702) aimed to compare the four PI in 2410 patients from the Spanish registry of lower risk MDS. The new PI identified between 17 % and 46 % of patients having a median OS of around 30 months. The PI that identified the highest number of patients with shorter OS was the new IPSS-R.

This retrospective trial (#426) analysed the association between deferasirox treatment and complications of iron overload in 4226 medicare patients with MDS. Several weaknesses can be identified in this study: 1. The MDS subclassification could not be classified in 78 % of the patients. 2. The mean treatment period was short: only 35 weeks; too short to develop signs of organ toxicity due to classical iron overload. The retrospective nature and the incomplete information on the patients precludes the formulation of relevant key messages. The key take home message is that the value of a time dependent intervention can only be addressed in prospective studies (either observational or interventional) in a well defined patient population with all relevant data available from diagnosis.

This prospective observational trial (#425) describes safety, compliance, efficacy, and effect on erythroid function in 153 lower risk transfusion dependent MDS patients treated with Deferasirox (DFX). Transfusion independence occurred in 5.5 %, 15.7 %, and 19.7 % after
6, 9 and 12 months of treatment, respectively. Deferasirox seems to be effective in reducing serum ferritin levels and to lead to erythroid improvement and to transfusion need in a relevant percentage of patients.

Eltrombopag is an oral, nonpeptide agonist of the thrombopoetin-receptor (TPOR). This phase II, placebo-controlled, single blind study (#923) evaluated the safety and efficacy of eltrombopag in low and intermediate-1 risk adult MDS patients with PLT count < 30 G/l. Preliminary results suggest eltrombopag treatment is effective in raising PLT counts and in reducing the risk of bleeding.

This report (#424) is an update of a prospective, randomized trial on romiplostim, a thrombopoietic without homology of TPO, in patients with lower risk MDS and thrombocytopenia. This study has been stopped prematurely in February 2011 in view of a higher reported incidence of acute myeloid leukemia (AML): 6 % versus 2.4 % in the placebo group. The overall survival was similar in both groups: 18.0 % versus 20.5 % and the updated AML rates were 8.9 % (15 patients) and 8.5 % (7 patients), respectively. Safety concerns regarding risk of disease progression to AML are still ongoing.

This report (#421) describes an ongoing phase 1 study of the oral formulation of azacitidine (CC-486) in lower risk MDS who were RBC transfusion dependent (TD) and/or thrombocytopenic at baseline. Overall response rates (ORR) ranged from 38.5 % and 29.6 %, and RBC TI was achieved by 47 % and 33 % in the treatment and control arms, respectively. Safety concerns regarding risk of disease progression to AML are still ongoing. This dose escalation phase I trial by the German MDS application of sequential azacitidine and lenalidomide as first line therapy for higher risk MDS patients in future trials.

Myeloproliferative neoplasms (MPN)

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In order to determine the efficacy and safety of maintaining the hematocrit (HCT) values < 0.45 (arm A) vs HCT levels in the range of 0.45 - 0.50 (arm B) to prevent thrombosis in patients with polycythemia vera (PV), 365 patients with newly diagnosed or pretreated PV were randomized in the Italian CYTO-PV trial. In comparison to arm B, the incidence of major thrombotic events/cardiovascular death was significantly decreased by four-fold in arm A. These results emphasize the importance of maintaining the HCT level below 0.45 to be the main target in PV management (#4).

Ruxolitinib (RUX) is a potent inhibitor of janus kinases (JAK) 1 and 2 active against wildtype forms and JAK2 V617F mutant. Results from three trials investigating RUX in the context of myelofibrosis (MF) were presented: In the placebo-controlled phase III COMFORT-I study, RUX treatment reduced spleen volume (SV), improved MF-associated symptoms and quality of life (QoL) and trends to exhibit a survival advantage over placebo. Now long-term results from initially 309 randomized patients confirmed previous data: After a median follow-up of 102 weeks RUX provided durable reductions in SV, improvements in QoL and showed a significant (p = 0.028) benefit in overall survival (OS). The proportion of patients requiring transfusions decreased to rates similar to the control group and RUX discontinuation was unproblematic (#800).

In comparison to best available therapy (BAT), RUX was also shown to improve reduction of the JAK2 V617F allele burden (% V617F) in the phase III COMFORT-II trial. Here, 159 JAK2 V617F positive patients suffering from primary MF (PMF), post-polycythemia vera MF (PPV-MF), and post-essential thrombocytthemia MF (PET-MF) were randomized (1:2) to BAT or RUX arm. 13 % of patients in the RUX arm achieved changes ≥ 20 % V617F that were found to be gradual and progressive over the course of time and correlated to SV reduction after 72 weeks of treatment (#802).
As RUX may reduce platelet count, Moshe Talpaz et al. conducted a dose escalation study for MF patients with low starting platelet counts (50–100 × 10^9/L). A total of 50 patients with different baseline platelet counts were treated with a RUX starting dose of 5 mg BID and escalation to 10 mg BID. Titration to the effective RUX dosage of ≥ 10 mg BID preserves both hemoglobin values and platelet counts with efficacy and safety parameters consistent with the outcome of the COMFORT-I trial (#176).

Srdan Verstovsek et al. investigated RUX therapy in the context of polycythemia vera (PV). 34 patients - resistant or intolerant to hydroxyurea - were enrolled and treated for a median duration of 155 weeks. Response according to modified ELN criteria (HCT < 0.45 without phlebotomy after 4 weeks from first dose) was achieved in 97 % of patients at 24 weeks and was durable to week 48 in 79 % and week 144 in 59 %, respectively. In addition, RUX treatment reduced SV and JAK2 V617F allele burden (#804).

The histone deacetylase (HDAC) inhibitor Vorinostat (MK-0683) has been investigated in a non-randomized phase II trial. Of 63 patients (21 essential thrombocyaemia (ET), 42 PV) treated with vorinostat as monotherapy, only 49 % were followed to the end of the intervention period. Partial or complete hematological response as defined by ELN criteria was accomplished by 81 % of these patients. In ET, response was independent of the JAK mutation status. Vorinostat therapy provided a statistically significant reduction of the JAK2 V617F allele burden and SV (#803).

Midostaurin - a multi-tyrosine kinase inhibitor - is active against KIT and KIT D816V which is found in ca. 80 % of patients with advanced systemic mastocytosis (ASM). In the global phase II CPKC412D2201 trial, 40 eligible ASM patients of whom 70 % were KIT D816V/Y positive were treated with Midostaurin (100 mg BID). In these patients, midostaurin therapy was well tolerated resulting in 60 % overall response (88 % major response plus 12 % partial response) and a significant reductions in mastcell burden (#799).

In a phase II study of the telomerase inhibitor imetelstat, 13 patients with ET refractory or intolerant to at least one prior therapy were enrolled. After induction, maintenance dosing was based upon platelet count and was generally reduced with time. Imetelstat rapidly induced durable hematologic responses in all patients with 11 patients achieving a complete response (CR) after a median of 6.1 weeks. Substantial molecular response was observed in all 5 JAK2 V617F positive patients (#179).

Attendees of the 9th Annual Symposium of the European LeukemiaNet and the 13th Annual Symposium of the German Competence Network: Acute and chronic leukemias, January 31st - February 1st 2012, Mannheim, Germany.
Ongoing studies in the ELTR (European Leukemia Trial Registry)

The European Leukemia Trial Registry - ELTR (www.leukemia-trials.eu) is the first international registry dedicated specifically to leukemia trials. Currently, over 70 active European leukemia studies are listed, including investigator-initiated trials administered by study groups of the ELN or trials initiated by pharmaceutical companies and conducted in several European countries. Detailed study information and short-protocols are available for free download on the website. German national trials are listed in the German Leukemia Trial Registry at www.studienregister-online.de.

We are aware of the fact that the represented trials only reflect a part of the real study volume in Europe. This is mainly due to an incomplete announcement of newly enrolled trials to the ELTR. The ambitious goal to give a complete overview about the local and European trials on leukemia can only be achieved by joint support and continuous promotion of the ELTR by all study groups. In this matter, we would like to encourage everybody to register their new and update their listed trials. For more information please contact the European Leukemia Information Center ELIC (elic@em.uni-frankfurt.de).

Acute lymphoblastic leukemia

**All subtypes**
- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies
- GALL - Genotyping Analysis of Acute Lymphoblastic Leukemia

**de novo/non-treated**
- GRAALL 02/2005 - Treatment of Acute Lymphoblastic Leukemia (ALL) in Younger Adults
- ALL - SCT Ph-negative - Role of autologous bone marrow transplantation plus maintenance therapy in adult ALL
- LAL-AR/2003 - Therapy of high-risk ALL
- NILG-ALL 10/07 - Intrathecal DepoCyte and Lineage-targeted MRD-oriented Therapy of ALL
- UKALL 14 - Standard Chemotherapy With or Without Nellarabine or Rituximab in Newly Diagnosed ALL

**B-Precurser ALL**

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

**Molecular relapse**
- MT103-203 - Confirmatory Phase II Study of Blinatumomab (MT103) in Patients With MRD of B-precurser ALL (BLAST)

**Relapsed/refractory**
- MT103-211 - Phase II Trial with Blinatumomab in relapsed/refractory B-precurser ALL
- MARALL - Monoclonal Antibodies in Recurrent or Refractory B Cell ALL

**Ph/BCR ABL +**

**de novo/non-treated**
- ALL GRAAPH 02/2005 - Imatinib-based vs. standard imatinib containing Hyper CVAD induction in de novo Ph+ ALL
- GMALL-PH-01 - Study of standard induction and consolidation therapy in combination with dasatinib in Ph+ ALL
- LAL1408 - Ph-/Bcr-Ab1+ ALL Imatinib and Nilotinib Rotational Study

**Relapsed/refractory**
- BMS CA 180 323 - Dasatinib Combo With SMO Inhibitor (BMS-833923)

**non-B mature, non-Ph+ ALL**
- GIMEMA LAL1308 - Combination Chemotherapy in Treating Young Adult Patients With ALL

**Stem cell transplantation**
- AlloSCT-Clofarabine - Allo-SCT With Clofarabine, Busulfan and Antithymocyte Globulin for High-Risk AML, MDS or ALL

Acute myeloid leukemia

**AML all subtypes without FAB M3**
- AML-NILG 02/06 - Remission Induction Therapy and Risk-oriented Postremission Strategy for Adult AML
- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies
- HOVON 103 AML Lenalidomide - Phase II Study to assess the tolerability and efficacy of oral lenalidomide to standard induction therapy
- HOVON 103 AML Tosedostat - Phase II Study to assess the tolerability and efficacy of oral tosedostat to standard induction therapy
- UHW-AML16 - Combination Chemotherapy With or Without GO or Tipifarnib in AML or High-Risk MDS

**de novo/non-treated**
- CLBH589H2101 - Phase Ib study of Panobinostat and S-Azacitidine for MDS, CMML or AML

**de novo/non-treated - Therapy concepts for all genotypes - All age groups**
- GIMEMA AML1208 - Everolimus MICE-regimen in Treating Older Patients With Newly Diagnosed AML
- GIMEMA AML19 - GO in Treating Older Patients With Previously Untreated AML
- HOVON 97 AML - Maintenance therapy with Azacitidine in elderly AML and refractory anemia with excess of blasts (RAEB, RAEB-T)
- Intergroup Elderly - AML Intergroup - joint study arm in patients from 60 years
- SPARK-AML1 - AZD1152 Alone and in Combination With LDAC in Comparison With LDAC Alone in de novo AML
Ongoing studies in the ELTR (European Leukemia Trial Registry)

de novo/non-treated - Therapy concepts for specific genotypes - < 60 years
  - PO60504 - Timed-Sequential Induction in CBF-AML

de novo/non-treated - Therapy concepts for specific genotypes - All age groups
  - AMLSG 09-09 - Phase III study of chemotherapy in combination with ATRA with or without gemtuzumab ozogamicin in patients with acute myeloid leukemia and NPM1 gene mutation
  - AMLSG 16-10 - Protocol in Acute Myeloid Leukemia With FLT3-ITD

de novo/non-treated - Not specified - < 60 years
  - AMl AlFA-0702 - The CLARA Study from the Acute Leukemia French Association
  - LAM2006IR - Efficacy of Gemtuzumab Ozogamycin for AML With Intermediate Risk
  - MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS

de novo/non-treated - Not specified - >= 60 years
  - AZA-AML-001 - Study of Vidaza Versus Conventional Care Regimens for the Treatment of AML
  - AMl MeK - Trial of Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase (MEK) Inhibitor

relapsed/refractory
  - MEK 111759 - Phase I/II Study on the MEK Inhibitor GSK1120212 in rel./ref. Leukemias

FAB M3 (APL)
  - B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies

relapsed/refractory
  - PROMYSE - A pan-European registry for relapsed APL patients

Stem cell transplantation
  - AlloSCT-Clofarabine - Allo-SCT With Clofarabine, Busulfan and Antithymocyte Globulin for High-Risk AML, MDS or ALL
  - HCT vs CT - HCT Versus CT in Elderly AML
  - RICMAC - Dose-Reduced Versus Standard Conditioning Prior Allo SCT for MDS/sAML

Supportive study
  - Eltrombopag - Eltrombopag in MDS and AML with Thrombocytopenia

Chronic lymphoblastic leukemia

All stages
  - TPll2 - Combined Immunochemotherapy in Patients With T-Prolymphocytic Leukemia

relapsed/refractory
  - GIMEMA LLC0606 - Lenalidomide, Fludarabine, and Cyclophosphamide for Advanced Refractory CLL
  - HOMB 114242 - Ofatumumab vs Physician’s Choice in Subjects With Bulky Fludarabine-Refractory CLL

Chronic myeloid leukemia

All subtypes
  - B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies

Chronic Phase
  - GIMEMA CML0408 - Nilotinib and Imatinib Mesylate in Treating Patients With Early CP-CML
  - OPTIM DASATINIB - Phase II study to optimize the residual plasmatic level of dasatinib in chronic phase CML
  - SPIRIT 2 - Comparison of Imatinib Versus Dasatinib in Newly-diagnosed CP-CML

Imatinib resistance, -intolerance
  - C AMN107 Y 2101 - Nilotinib and LD225 in the Treatment of CML Patients Who Developed Resistance to Prior Therapy

Complete molecular remission (MR4)
  - EuroSKI - Stopping TKI in patients with CML in complete molecular remission (MR4)

Intolerant/resistant to one TKI
  - AMN2128 - Study of Nilotinib and Midazolam in CML Resistant and/or Intolerant Against One TKI
  - BMS CA 180 323 - Dasatinib plus SMO-Inhibitor in CML and Ph+ ALL
**Myelodysplastic syndrome**

*All subtypes*

- B1371001 - A Study Of PF-04449913 In Selected Hematologic Malignancies

*Low risk and intermedia I*

- EPOANE - An Efficacy Study for Epoetin Alfa in Anemic Patients With MDS
- EUMDS - European Registry for Low and Intermediate-1 MDS
- HOVON 89 MDS - A Phase II study of lenalidomide with or without erythropoietin and G-CSF in low and intermediate-1 risk MDS
- MDS Azacitidine-Epoetin Beta - Phase II study of Azacitidine and Epoetin Beta in low-risk and intermediate-1 MDS resistant to ESA
- MDS-005 - Lenalidomide Versus Placebo in Subjects With Transfusion Dependent Anemia in Low Risk MDS Without Del 5q
- MEK 111759 - Phase II/III Study on the MEK Inhibitor GSK1120212 in rel./ref. Leukemias
- SIMIDIS - Azacitidine and Beta Erythropoietin Treatment in Patients With MDS Red Cell Transfusion Dependent

*Intermedia II and high risk*

- AML MEK - Trial of Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase (MEK) Inhibitor
- AML-NILG 02/06 - Remission Induction Therapy and Risk-oriented Postremission Strategy for Adult AML
- Eltrombopag - Eltrombopag in MDS and AML with Thrombocytopenia
- HOVON 97 AML - Maintenance therapy with Azacitidine in elderly AML and RAEB/RAEB-T
- HOVON 103 AML Lenalidomide - Phase II Study to assess the tolerability and efficacy of oral lenalidomide to standard induction therapy
- HOVON 103 AML Tosedostat - Phase II Study to assess the tolerability and efficacy of oral tososedostat to standard induction therapy
- MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS
- MDS Erlotinib - Erlotinib in Higher Risk MDS
- MDS Velcada Zarnastra - Bortezomib and Tipifarnib in MDS
- MEK 111759 - Phase II/III Study on the MEK Inhibitor GSK1120212 in rel./ref. Leukemias
- ONO 1910 - Randomized Study of ON 01910.Na in Refractory MDS With Excess Blasts
- QOL II - Quality of Life and Symptoms in Patients With Newly Diagnosed MDS
- UHW-AML16 - Combination Chemotherapy With or Without GO or Tipifarnib in AML or High-Risk MDS

**Stem cell transplantation**

- AlloSCT-Clofarabine - Allo-SCT With Clofarabine, Busulfan and Antithymocyte Globulin for High-Risk AML, MDS or ALL
- RICMAC - Dose-Reduced Versus Standard Conditioning Prior Allo SCT for MDSsAML

**Myeloproliferative disease**

*All subtypes*

- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies

*Essential Thrombocythaemia*

- ARD12042 - Study With SAR302503 in Patients With Polycythemia Vera or Essential Thrombocythemia

*Myelofibrosis*

- JAKARTA - Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis
- JUMP - Expanded access study of INC 424 for PMF, PPV MF or PET-MF
- RESUME - Study of Pomalidomide in MPD-Associated Myelofibrosis with RBC-Transfusion-Dependence

*Polycythaemia vera*

- ARD12042 - Study With SAR302503 in Patients With Polycythemia Vera or Essential Thrombocythemia
- RESPONSE - Study of INC424 in PV with Resistance to or Intolerance of Hydroxyurea

**Stem cell transplantation**

- 152/2008/USper - Intrabone Infusion of Cord Blood Hemopoietic Stem Cells in Adult Patients With High Risk Haematological Malignancies

**Supportive care**

- BUM-S/GVH - Efficacy and Safety Study of Budesonide to Treat Oral Chronic GvHD
- Isavuconazole WSA-CS-004 - Isavuconazole for Primary Treatment of Invasive Aspergillosis
Dates/Meetings

05. - 06.02.2013
10th Annual Symposium of the European LeukemiaNet
Mannheim, Germany

24. - 27.02.2013
14th International Symposium on Acute Leukemias
Munich, Germany

05. - 07.04.2013
2013 European Focus on Myeloproliferative Neoplasms and Myelodysplastic Syndromes
Madrid, Spain

08. - 11.05.2013
12th International Symposium on Myelodysplastic Syndromes
Berlin, Germany

31.05. - 04.06.2013
ASCO Annual Meeting
Chicago, USA

13. - 16.06.2013
18th Congress of EHA
Stockholm, Sweden

29.09. - 02.10.2013
6th International Symposium on Acute Promyelocytic Leukemia
Rome, Italy

07. - 10.12.2013
55. ASH Annual Meeting and Exposition
New Orleans, USA

19. - 23.02.2014
31. German Cancer Congress
Berlin, Germany

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