Dear Colleagues,

since our decision in Palermo in 2002 to establish a European leukemia network and to apply for funding as a network of excellence almost 10 years have passed. The European LeukemiaNet (ELN) has established itself and meanwhile comprises over 1000 leukemia specialists from 182 institutions in 34 countries. ELN strives for European integration and cooperation in leukemia research, recruits as a network larger patient cohorts in shorter time periods than any other group and has an impact on leukemia research and management globally.

February 2011 was the last month of EU funding within the 6th framework programme. ELN activities are now funded by the European Science Foundation (ESF). Common clinical trials and research projects, spread of excellence, partnerships, common publications, and the steadily increasing number of ELN participants are hallmarks of the ELN in 2011. Some working groups have attracted their own financing for defined projects, others have extended their activities according to the principle of subsidiarity. All these activities and the international acceptance point to sustainability and continued development of the ELN.

We are keen to maintain the ELN and our joint efforts after the end of EU funding. Besides the ESF which secures the ELN symposia and some of the networking activities until 2015, we have developed the ELN Foundation. First steps have been taken. The activities of the ELN Foundation will be intensified in the coming months to secure the future of the ELN. Detailed information can be found in this letter in the article “Two years of ELN Foundation”. Further, a sponsoring concept has been drafted which will be discussed by ELN lead participants shortly. Grants and public-private partnerships are additional components to strengthen the ELN and to support research activities in cooperation with industry. Two public-private partnerships are detailed in the articles “Highlights from the MDS field” and “Latest News about EUTOS”. Also the improvement of clinical trial infrastructure is an important topic for the ELN. The article “Clinical Trials Directive” will inform you about this topic.

This information letter no. 8 offers an overview of recent work within various ELN working groups. I wish you an interesting reading and further progress with your research projects. Cooperation is the fastest path to progress.

Sincerely,

[Signature]

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

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Editorial Network Coordinator
Editorial Information Center
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ELIC Editorial

Dear colleagues,

we are pleased to present you the 8th Information Letter of the European LeukemiaNet which was prepared thanks to the collaboration of the contributing authors. In this issue, you will find intriguing articles on basic research, new trials, and highlights of different work packages.

There has been a change of staff at the European Leukemia Information center (ELIC). Dr. Sina Hehn started in September 2011 as webmaster of the European LeukemiaNet, the German Competence Network: Acute and chronic Leukemias, and the EUtos website. Dr. Hehn studied biochemistry and did her PhD on signal transduction in FLT3-ITD positive acute myeloid leukemia. She replaces Dr. Silvia Schäfer whom we like to thank for her great engagement.

This year again, we would like to encourage all ELN members to hand in contributions representing their field of research for prospective Information Letters and to present active trials in the European Leukemia Trial Registry.

With best regards,

Information Center

Dr. Nicola Gökbüget      Dr. Sina Hehn

WP 8 - MDS

Highlights from the MDS field:
European LeukemiaNet (ELN)-WP8

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Introduction

The participants of WP8 have established a European platform for integration of myelodysplastic syndrome (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. International registries have been developed to determine incidence, disease patterns and the prognostic impact of standard treatment according to established guidelines.

WP8 has interacted with various ELN work packages for integrated activities, such as Diagnostics WP10 (immunophenotyping in diagnostic guidelines in MDS), Cytogenetics WP11 (cytogenetics in diagnostic guidelines in MDS), Acute Myeloid Leukemia (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 European Organisation for Research and Treatment of Cancer (EORTC) Leukemia Group, many national MDS study groups, with the international MDS Foundation, with the European Hematology Association (EHA), with the European School of Hematology (ESH), and with numerous pharmaceutical companies which actively support WP8 projects. Knowledge like new treatment modalities and diagnostic and therapeutic guidelines were disseminated by meetings and presentation on the ELN website. Close cooperation with national MDS study groups resulted in a well running European MDS (EUMDS) Registry Study. 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 MDS have been finalized.

Specific activities

Diagnostic guidelines: E. Hellström Lindberg and A. Porwit updated the MDS diagnostic guidelines on the basis of the new WHO classification (4th edition 2008) and revised the guidelines regarding flow cytometry. The guidelines include a work-up of suspected MDS or mixed MDS/myeloproliferative neoplasms (MPNs). The group decided to keep the MDS and AML guidelines separated because of the new WHO classification and to remove the WHO classification 2001. 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.

Flow cytometry: The group defined in its first publication the role of flow cytometry not only in the work-up of diagnosis but also its contribution in classification and prognostication of MDS. In 2009, the second workshop (MLL Munich Lab, chair A.A. 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. A newly defined scoring system has been discussed in the third international flow cytometry meeting of the WP8 on flow and MDS (London November 2010; co-chair R. Ireland). An ELN consensus guideline for flow cytometry in MDS is available and has been submitted in 2011. The diagnostics, revision of FCSS (flow cytometry scoring system), erythroid-lineage, clinical reporting and incorporate software tools for analysis/statistics were discussed during the fourth workshop in Pavia, Italy in October 2011.

**Therapeutic guidelines:**
The 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. 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. Scenario analysis of more than 50 scenarios has been developed and reviewed by the expert panels (available at the website of Haematologica). An evaluation of the web based scenario analysis by experts and non-experts (trainees) is planned in the near future.

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

Comprehensive geriatric assessment has been performed in 195 patients in Freiburg, Düsseldorf and Dresden aiming at exploring prognostically important assessment instruments and eventually defining a frailty index. Multicenter evaluation appeared feasible. Multivariate analysis revealed "Activities of daily living" (ADL) and fatigue measured with the QLO C30 questionnaire as highly prognostic for survival in the entire patient cohort. Statistical calculations are currently being performed to define a risk score. Final publication of data is planned for 2012.

**Lower risk MDS registry:**
The registry is collecting a unique data set which will prove to be very valuable for future questions and studies as well. Portugal, Poland and Denmark have joined the EUMDS Registry in 2010 and Israel is expected to enter patients in 2011. 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, FP7 EU programs), but for the time the focus will be on lower risk MDS. The follow-up time is extended to 3 years with support from Novartis. Interim data of the EUMDS Registry have been presented at the MDS Foundation biannual meeting in Edinburgh, at the annual meeting of EHA in London (Figure 1) and two posters were presented at ASh based on the first analyses of 1,000 registered patients.

**Evaluation of the prognostic value of TET-2 and EZH2 mutations in MDS**

Based on the experience of techniques used to detect and to describe the incidence and prognosis of TET2 mutation in MDS we identified a new mutation in chromosome 7 of MDS patients. In MDS deletions of chromosome 7 or 7q are common and correlate with a poor prognosis. The relevant genes on chromosome 7 are unknown. Enhancer of zeste homologe 2 (EZH2), located at 7q36.1, is frequently targeted in MDS. EZH2 functions as a histone methyltransferase. Abnormal histone modification may contribute to epigenetic deregulation in MDS. This may have therapeutic implications.

**Conclusions**

In general, MDS WP8 has been an active and productive WP within the European LeukemiaNet. We interacted with many other ELN WPs. Intensive collaboration within the European MDS study groups resulted in much progress of the European MDS Registry Study. 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. Much progress has been made for the translational studies: Using single nucleotide polymorphism (SNP) arrays 40 novel recurrent genetic loci in MDS were identified. The present steering committee of our work package has been in office for more than 6 years. The steering committee considered it to be important to continue and to extend its activities through active participation of “junior experts” in our field. Therefore, Uwe Platzbecker (Dresden), Lionel Ades (Avicenne), Arjan van de Loossrecht (Amsterdam), Luca Malcovati (Pavia) and Wolf-Karsten Hofmann (Mannheim) have joined the steering committee.

**REFERENCES**


TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression

Martin Jädersten¹, Leonie Saft², Alexander Smith³, Austin Kulasekararaj⁴, Sabine Pomplun⁵, Anette Hedlund⁶, Robert Hast⁷, Anna Porwit⁸, Eva Hellström-Lindberg⁹, and Ghulam J. Mufti¹

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Tumor protein p53 (TP53) mutation confers poor prognosis in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and is particularly prevalent in patients with complex karyotype including interstitial deletion of chromosome arm 5q (del(5q)). Despite this link to del(5q) in high-risk MDS, previous studies failed to detect TP53 mutations in low-risk patients with isolated del(5q).¹ The reasons for this may be that TP53 mutation often is a secondary hit during tumor evolution, rather than an initiating event. Also, conventional Sanger sequencing is not sensitive enough to detect subclones where the mutated allele frequency is lower than 15-20 %.

In a recent case report we described a patient with del(5q) MDS who after a two-year response to lenalidomide progressed to refractory anemia with excess blasts 1 (RAEB-1) with complex karyotype including del(17p13), containing the TP53 locus.² Immunohistochemistry (IHC) showed abundant cells with strong nuclear staining for p53, which often is indicative of accumulation of mutated p53 protein due to defect polyubiquination and degradation. Interestingly, we observed scattered cells with similar staining pattern at time of diagnosis several years earlier. Sequencing showed an inactivating TP53 mutation at time of transformation and the same mutation was seen at a lower level at diagnosis. Based on this observation, we hypothesized that subclones of marrow cells with TP53 mutation can predate overt transformation and may therefore be of prognostic relevance in low-risk MDS. To be able to detect mutational frequencies down to 1 % we utilized second generation pyrosequencing using the Roche GS FLX (454) platform, yielding an average coverage across TP53 of 1200x. DNA was isolated from unstained routine bone marrow smears or bone marrow mononuclear cells. In parallel, we performed IHC for p53 (DO-1 antibody) in order to evaluate its role as a surrogate marker for TP53 mutation.

In total, 55 MDS patients with del(5q) and IPSS Low (n = 32) or Int-1 (n = 23) from the Karolinska University Hospital in Stockholm and King’s College of Medicine in London were included.³ TP53 mutation was observed in 10 of 55 patients (18 %) at time of diagnosis or at an early stage of the disease. The median mutated clone size was 11 % (range 1-54 %), generally increasing during the course of the disease.

The IHC assessment indicated a certain degree of correlation between TP53 mutation and presence of cells strongly stained for p53 (p53++; Figure 1). All 4 patients with > 5 % p53++ cells were mutated, and 9 of 10 patients with mutation had ≥ 2 % p53++ cells. It was not expected to find an absolute correlation, since non-sense mutations may result in a truncated protein that does not accumulate or may not be recognized by the antibody, resulting in negative IHC staining. Also, wild type p53 may be overexpressed due to ribosomal stress or transition into apoptosis, although physiological levels of p53 tend to stain less intensely by IHC.

Leukemic evolution was seen in 12 of 55 patients (22 %), and the risk of transformation was higher in patients with TP53 mutation (Figure 2). Time to 25 % acute myeloid leukemia (AML) evolution was 34 and 151+ months in mutated and unmutated patients, respectively, p = 0.045. The corresponding 5 year cumulative incidence of leukemic development was 77 % and 24 %, respectively. There was also a significant association between presence of ≥ 2 % p53++ cells in the bone marrow and increased risk of leukemic transformation (p = 0.012). No significant difference was seen in overall survival, however, the study was not powered for this type of analysis.

Two mutated patients were sequenced at 4 time points during the course of the disease. Despite a partial cytogenetic response to lenalidomide in one patient, the proportion of the del(5q) clone carrying TP53 mutation gradually increased. This suggests that the TP53 mutated clone in this patient had features rendering it relatively insensitive to lenalidomide. A patient with advanced del(5q) MDS received 5-azacytidine and obtained marrow complete remission (CR). Interestingly, the proportion of TP53 mutated cells decreased during the hematological response and increased again at time of leukemic transformation, indicating that 5-azacytidine in this patient had some efficacy also on the TP53 mutated cells (Figure 3).

We conclude that TP53 mutation in low-risk del(5q) MDS is significantly associated with increased risk of AML evolution. These results were confirmed in a recent study where TP53 mutation was shown to be an independent predictor of adverse outcome also in other forms of MDS.⁴ Novel sequencing technologies have led to the identification of several other genes with prognostic value in MDS, and efforts are being made to generate improved prognostic scoring systems taking these data into account.⁵ Discovery in MDS and other tumors are likely to provide a foundation for developing an array of drugs targeting specific genetic alterations. Future incorporation of comprehensive genetic screening in the routine diagnostic work-up in patients with MDS is likely to lead to more personalized management and may ultimately improve outcome.
References


Figure 1: Immunohistochemistry (IHC) for p53 in relation to TP53 mutational status. (A) Patient with negative p53 staining and no TP53 mutation. (B) Strong p53 staining in 3% of cells at time of diagnosis, and (C) in 59% of cells at time of leukemic transformation in a patient with a gradually increasing subclone with TP53 mutation.

Figure 2: Outcome in relation to p53 status. *p53++, proportion of marrow cells with strong p53 staining by IHC.

Figure 3: Effects of treatment on TP53 mutated marrow progenitors.
Accurate diagnosis in low risk myelodysplastic syndromes (MDS) necessitates additional sensitive and specific assays which can discriminate between MDS and non-MDS cytopenic patients, in particular in those cases without karyotypic anomalies, ring sideroblasts or other major morphologic dysplastic features of granulocytes in peripheral blood films and dyserythropoiesis and dysmegakaryopoiesis in bone marrow aspirates. The WHO classification 2008 contributes to a more refined classification and prognostication of myelodysplastic syndromes. Therefore, flow cytometry (FC) can identify aberrancies in granulocytic and monocytic lineages that are not recognised by cytology (WHO). FC might be instrumental in improving the classification of MDS. FC is even considered as co-criterion when improving the classification of MDS. FC might be instrumental in refining classification and prognostication of myelodysplastic syndromes. Since flow cytometry (FC) can identify aberrancies in granulocytic and monocytic lineages that are not recognised by cytology (WHO), FC might be instrumental in improving the classification of MDS. FC is even considered as co-criterion when improving the classification of MDS.

In conclusion, standardisation of FC in MDS may further contribute to improved diagnosis, prognosis and prediction response to standard first line treatment of MDS in near future. Within the ELN we are currently focussing on FC and dyserythropoieses as well as in refining the FCSS. These issues will be addressed by performing prospective multicenter data analysis within the huge dataset of contributing participants.

References
With the introduction of tyrosine kinase inhibitors (TKI) the chronic myeloid leukemia (CML) treatment strategy has profoundly changed. Median survival improved from about 50 % to more than 90 % after 5 years. The objective of CML treatment is the normalization of hematopoiesis, the elimination of Philadelphia positive (Ph+) cells from the bone marrow and the reduction of breakpoints cluster region-abl oncogene (BCR-ABL) transcripts (major molecular remission, MMR). The current recommendation is to continue TKI treatment lifelong. However, TKI therapy is accompanied by side-effects, such as fatigue, muscle cramps and edema. Although tolerable, they impair patients’ quality of life (QoL). We still do not know the impact of TKI treatment with a very long follow up. Therefore, the ultimate future goal of CML therapy is the cure of CML. Moreover, the impact on health economy is considerable with increasing prevalence of CML patients. Yearly treatment costs with TKI amount to 40,000 € to 67,500 €. Meanwhile several studies were performed with the goal to stop TKI treatment. Discontinuation of treatment was already tried in the interferon (IFN) era. In several studies it could be demonstrated that this strategy has success in patients with CCR especially if the complete cytogenetic response (CCR) had lasted for at least 2 years before stopping IFN. RT-qPCR techniques were not sufficiently advanced, so molecular response (MR) status of these patients is unclear. In the TKI era, after several small case studies first success was reported in a pilot study with 12 patients in stable CMR for at least 2 years while under imatinib treatment. After a median follow-up of 42 months, 6 patients relapsed during the first 6 months and 6 were still in CMR. On this basis, the prospective multicenter STIM study was started and recruited patients under imatinib for at least 3 years and with a median follow-up of 42 months, 6 patients relapsed after several small case studies first success was reported in a pilot study with 12 patients in stable CMR for at least 2 years while under imatinib treatment. After a median follow-up of 42 months, 6 patients relapsed during the first 6 months and 6 were still in CMR. On this basis, the prospective multicenter STIM study was started and recruited patients under imatinib for at least 3 years and with stable CMR for at least 2 years. After a median follow-up of 30 months a molecular relapse occurred in 61 out of 100 patients with 58 relapses occurring during the first 7 months and 3 late relapses after 19 months. The overall probability of maintenance of CMR at 36 months was 39 %. All patients were sensitive to an imatinib treatment re-challenge. The probability to be in stable CMR after discontinuation was significantly better for the Sokal low-risk group as compared to intermediate and high-risk group. Using multivariate analysis, Sokal risk score and imatinib therapy duration were independent prognostic factors for prediction of molecular relapse. Taking into account the number of months without treatment, the savings within the STIM trial were estimated at 4 million Euros. Recently, it has been demonstrated that second generation TKI (dasatinib and nilotinib) may be safely discontinued in CML patients with a stable CMR. In a preliminary study, 4 of 12 patients lost major molecular response (MMR) by 6 months (median follow-up 12 months). In a recent update MMR was rapidly regained after TKI reintroduction. Some of these patients remained off therapy with weakly detectable BCR-ABL transcripts on one or more occasions.

The results of the above mentioned studies are not directly comparable and transferable into general recommendations. The main reason is that the definition of CMR is not homogenous. Results for BCR-ABL transcripts are defined according to the International Scale. Validation has been achieved, thus far, only up to a level of 1/1000 which corresponds to MMR (MR4). Most recently, the CML working group of the European LeukemiaNet agreed on a consistent definition: CMR is subdivided in MR4, MR4* and MR5*. This definition is already used for analysis in one study. The consistent CMR definition is a prerequisite to start a trial in Europe and to develop criteria for TKI discontinuation safely in CML patients. 13 laboratories work on this standardization and will be available for the planned EURO-SKI study (Figure 1). Besides, many other open questions will be answered with this trial: which level of MR is necessary, how long should the pretreatment last, has gender or combination treatment any influence etc. So far, only limited experience is available with nilotinib or dasatinib. The identification of patients who would benefit most from discontinuation of imatinib remains a key issue. Advances in CML therapy led to an expected survival prolongation of > 20 years after diagnosis. However, TKI treatment is associated with side-effects which impair patients’ QoL. The trial aims to improve the QoL by TKI discontinuation and will provide important data on the duration of the CMR status before treatment discontinuation. Considering the rapidly increasing prevalence of CML, this is of individual but also socioeconomic importance.

With the results of the EURO-SKI trial we expect to improve CML management, avoid side-effects, enhance QoL in CML patients and reduce costs and may be go farther on the path to cure of CML.

References

Figure 1: Multicenter trial estimating the persistence of molecular remission in CML after stopping TKI.
Patients’ age is one of the most important issues in treatment decisions for AML. In the AMLCG 1999 trial 1223 patients (pts) were 16-59 y and 1470 pts were 60-85 y of age. Their treatment was randomized between TAD-HAM vs HAM-HAM induction (TAD, standard dose thioguanine, cytarabine, daunorubicin 60 mg/m² x 3; HAM, high-dose cytarabine 3 g/m² x 6, mitoxantrone 10 mg/m² x 3), TAD consolidation and monthly maintenance (vs restricted to age < 60 y autologous SCT), any chemotherapy + vs - G-CSF priming. All randomization was done in one step upfront. For age adaption pts of < 60 y received routine double induction and full dose HAM while pts of 60+ y preferentially received only one course induction and HAM at 1 g instead of 3 g cytarabine/m² x 6. While there were little to no differences according randomizations, pts < 60 y and 60+ y achieved a complete remission rate (CR) of 70.2 % and 53.5 % (p < .001), overall survival (OS) at 5 y of 41.3 % and 12.9 % (p < .001) and a relapse rate (RR) of 49.0 and 72.0 % (p < .001). In order to separate the influence of age from that of other factors we focussed on pts around 60 y of age and compared the 172 pts of 57-59 y with the 261 pts of 60-62 y. According to their similar age the two groups showed similar baseline characteristics. In contrast and due to the cut-off point for age adaption at 60 y they differed considerably in treatment. Given the cumulative dosage of cytarabine as a measure of treatment intensity, the difference between the two groups was by factor 3.6. This difference, however, did not translate into a different outcome being 62 % vs 60 % CR, 28 % vs 21 % 5 y OS (p = 0.25), and 73 % vs 73 % RR at 5 y. A multivariable analysis in all pts between 16 and 85 y of age identified favorable genetics (favorable cytogenetics plus normal karyotype with NPM1 mutation but no FLT3-ITD), adverse cytogenetics, and age as main risk factors predicting CR, OS, as well as RR. Even in the younger pts of 16-60 y those below and above the median age of 47 y differed in their OS by 49 % vs 35 % (p < .001) and in their RR by 45 % vs 53 % (p < .007) (Figure 1).

We conclude that the outcome in pts with AML is substantially determined by patients’ age as an independent risk factor, but not by treatment intensity or age adaption.
A novel murine model of MPN, generated by NF-E2 overexpression, displays spontaneous transformation to acute leukemia

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The Philadelphia-negative myeloproliferative neoplasms (MPNs), polycythemia vera (PV), essential thrombocytosis (ET) and primary myelofibrosis (PMF), share among other features a propensity to transform to acute leukemia. Despite recent advances attained through the discovery of a point mutation in the Janus kinase 2 (JAK2) (JAK2V617F) in a large fraction of MPN patients, as well as various additional mutations in subgroups of MPN patients, including those in the thrombopoietin receptor (c-Mpl) and the methylcytosine dioxygenase (TET2), among others, the molecular etiology of these disorders, and their propensity for leukemic transformation, remains incompletely understood.

Several lines of evidence support the hypothesis that aberrations preceding acquisition of the most common mutation, JAK2V617F, contribute to the pathophysiology of these disorders. Firstly, the malignant clone may extend beyond the cells, which have acquired the JAK2V617F mutation. Secondly, in familial MPN, the JAK2V617F mutation does not constitute the predisposing allele, but rather is independently acquired by affected individuals. Thirdly, following transformation of JAK2V617F-positive MPN, leukemic blasts often display chromosomal aberrations present in the chronic MPN phase, but do not contain the mutant JAK2 allele. This observation strongly suggests that in these patients, the leukemic transformation occurred in a clonally expanded cell, which had not incurred the JAK2V617F mutation, hence, in a pre-JAK2V617F clone. Several different lines of JAK2V617F, TET2 and c-Mpl mutant bearing mice, generated using either bone marrow transplantation or knock-in strategies, have been reported. These murine models display many MPN features including erythroid dysplasia, thrombocytosis, leukocytosis, and display characteristic MPN bone marrow morphology including hypercellularity. NF-E2tg mice display a significant expansion of the stem and progenitor cell compartment in the bone marrow, showing increases in the more immature Kit+/Sca+/Lin- (KSL) cells as well as in the more mature Kit+/Sca-/Lin- (KL) cells. Moreover, both the common myeloid progenitors (CMPs) and the megakaryocyte erythroid progenitors (MEPs), as well as the least mature long-term engrafting hematopoietic stem cells (LT-HSCs), are significantly elevated in NF-E2tg mice. NF-E2tg mice die prematurely, displaying a loss of life expectancy remarkably similar to that observed in PV patients.

Most importantly, 10% of NF-E2tg mice spontaneously develop acute myeloid leukemia. This is remarkably similar to the percentage of PV and PMF patients that transform to acute leukemia during follow-up. Interestingly, using array-comparative genomic hybridization (array-CGH), we have demonstrated that leukemic NF-E2tg animals acquire genetic abnormalities homologous to those observed recurrently in MPN patients before and during leukemic transformation, specifically acquisition of genetic material corresponding to human trisomy 8. Due to the documented epigenetic activity of NF-E2, we examined histone modifications in the transgenic mice. Global histone 3 acetylation was markedly decreased in NF-E2tg mice, but restored upon treatment with the histone deacetylase inhibitor (HDACi) Vorinostat. At the same time, Vorinostat treatment normalized the previously elevated platelet counts of NF-E2tg mice. A clinical trial using the HDACi Givinostat (ITF2357) has recently demonstrated efficacy of these drugs in controlling thrombocytosis and erythrocytosis in MPN. Concurrently, we observed a statistically significant decrease in NF-E2 expression in Givinostat treated MPN patients. Taken together, our data establish a role for aberrant expression of the transcription factor NF-E2 in the pathophysiology of MPN. NF-E2 overexpression is sufficient to recapitulate many characteristic MPN features including thrombocytosis, leukocytosis, expansion of the stem- and progenitor compartments, characteristic bone marrow morphology, Epo-independent growth and, most importantly, a predisposition to leukemic transformation. Our data provide a molecular rationale for expanding the clinical investigation of HDAC inhibitors in the treatment of MPN patients. In addition, they support the use of NF-E2 expression as a biomarker in correlative studies accompanying these clinical trials.

References
In the past decade important progress has been made in the management of adult acute lymphoblastic leukemia (ALL). Cure rates were improved first in children and later in adults from less than 10% to 40-50% and even >50% in distinct subgroups. The progress in terms of diagnosis and treatment of ALL has stemmed mainly from systematic clinical research by a number of cooperative study groups. It is based on optimisation of chemotherapy, stem cell transplantation, supportive care integrated in risk adapted treatment strategies, and more recently complemented by approaches for targeted therapy. The European Working Group for Adult ALL (EWWAL) was founded in the framework of the European LeukemiaNet and has in the meantime 14 participating study groups. In addition, EWWAL has been accepted as an EHA (European Hematology Association) Scientific Working Group. One major aim of the EWWAL was the definition of standards for the management of adult ALL. The group decided not to follow a formal approach to define evidence based recommendations or a guideline since few randomised studies are available for adult ALL and due to new approaches for diagnosis, prognostic stratification, and treatment a guideline based on historic published data was considered as not meaningful enough. The EWWAL members therefore decided to set up an editorial board and to define a consensus process for the preparation of an expert recommendation for the management of adult ALL (Figure 1). The book is now published and gives an overview on the current strategies for management of adult ALL including approaches to rare entities and specific situations. It was distributed to the members of the European ALL study groups. Further information such as table of contents and order forms is available on the website of the European LeukemiaNet (www.leukemia.net.org - leukemias – ALL – Standards and SOP).
Clinical Trials Directive – planned amendment by the EU

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The Clinical Trials Directive 2001/20/EC which was implemented by the EU in 2001 and taken over into German law and other national European regulations until 2004 had severe negative impact on the independent academic research in Germany. This is mainly due to the fact that henceforth treatment optimisation studies and academic trials had to follow the same regulatory processes as registration trials of the pharmaceutical industry. Ethics committees, regulatory and local surveillance authorities already evinced a maximal stringent interpretation of the regulatory general framework in terms of these trials in Germany but also in other countries. In doing so, one disregards the fact that therapeutic optimisation studies do not pose an additional risk for the patients. Contrariwise, the obstruction of these trials becomes a sizable risk towards adequate and high-class therapy. Ever since, there have been numerous publications expressing massive criticism about the national and European legislation.1-6 Because of this the EU commission represented by the Industries and Enterprise Directorate-General and later by the Health and Consumers Directorate-General already called to comment on this issue publicly in 2009. Given the planned revision of the directive 2001/20/EC a public consultation process was initiated anew in 2011. Already the introduction of the consultation paper indicates that the EU commission is aware of the problems arising from the EU directive in particular the lack of European harmonisation and the inhibition of the independent clinical research. The consultation procedure was aiming to answer questions of how to precisely improve the legal provisions. For example, it was dealing with the modalities of submission to the authorities in international trials, the fillings with ethics committees, risk assessment for clinical trials, the differentiation of academic and industry-funded studies, definition of the term ‘investigational medicinal product’, patient insurances, the shared role of the sponsor in international studies, and the definition of non-interventional studies.

Representing the German Competence Network for Acute and Chronic Leukemias, the Competence Network for Malignant Lymphoma, the German Society for Hematology/Oncology and the European LeukemiaNet we submitted a statement comprising the following core messages:

1. importance of therapy-optimization studies for the care of patients with hematologic malignancies
2. bureaucratic obstacles through a complicated ethic application procedure for multicentric trials in Germany including the absurd expansion for proofs of qualification of investigators and the lack of international harmonisation
3. tight definition of interventional trials and the need for a risk adapted definition of clinical trials
4. the complex of problems concerning expensive patient insurances which in fact never take over payments
5. excessive but most of the times useless safety-reports, e.g. SUSARs.

A great opportunity for the improvement of regulatory settings lies in the risk-adapted classification of clinical trials. According to this a study having a therapeutic approach that corresponds to the standard treatment and measuring a clearly defined end-point, e.g. survival, exhibits a low risk. Thus, the regulatory requirements for such a trial should be limited to an absolute minimum. We prefer the definition of treatment optimisation studies as non-interventional trials. In this case, there would be only one approval of an ethics committee at the PI’s location, but no notification to national authorities, no patient insurance and no time-sensitive safety-management. A clear definition for this type of study needs to be worked out.

You can find the complete statement on the ELN homepage (www.leukemia-net.org - Content - International Trials - Basic information). At present, it is unclear whether the EU commission will submit the proposed draft law to an additional public consultation. Because of the time-consuming political processes in Brussels and in the EU parliament the implementation is not to be expected within the next three years.

References
European Research Initiative on CLL (ERIC)

Emili Monserrat
Hospital Clinic, IDIBAPS, Barcelona, Spain

The WP7/ERIC has a main goal to promote research on chronic lymphocytic leukemia (CLL) and similar disorders across Europe, focusing on a multi-institutional approach in basic, translational, and clinical research. With more than 300 active members, ERIC is currently focusing on a number of programs that include:
- Murine double minute 2 (MDM2) polymorphism in CLL.
- Guidelines for tumor protein p53 (TP53) mutation analysis.
- Minimal residual disease (6- and 8-color flow cytometry).
- Immunoglobulin heavy chain variable (IGHV) analysis.
- Common ERIC/European Data Set for patients with CLL.
- Phase IV Observational Study on Ofatumumab in CLL.
- Ongoing European Trial for patients with CLL and TP53 abnormalities.

To know more about these programs and their leaders and to express your interest to participate on them, please go to www.ericll.org
Two years ago the ELN Foundation was founded as a non-profit charitable organization to support the European LeukemiaNet (ELN). Since then various activities followed to increase awareness of the ELN Foundation and thereby to attract donations and grants. The publicity has been extended by the website, flyers, a publication in Haematologica and booths at important congresses in hematology like ASH, EHA or DGHO/ÖGHO/SGH.

Donations
Various pharmaceutical companies liked the idea of supporting the ELN with an unrestricted grant and donated to the ELN Foundation, so that the capital could be increased in the last two years. Companies donating to the ELN Foundation are mentioned on the ELN Foundation website if they wish: www.elnfoundation.org > Financial Support > Companies.

Book Grant
In 2011, the ELN Foundation was able to get a book grant from a pharmaceutical company. The Book Recommendations of the European Working Group for Adult ALL was realized with this grant.

Video Clips
Video clips have been created for public relations to expand the understanding and awareness of the ELN Foundation and hence for the ELN. Lead participants of the various workpackages communicated their goals and visions in video messages. You find the videos on the ELN and the ELN Foundation Homepages: www.elnfoundation.org > About us > Video clips.

Conferences 2012
In 2012, the ELN Foundation will be represented with a new design at the following meetings:
• 9th Annual ELN Symposium in Mannheim, Germany, January 31 - February 1
• German Cancer Congress in Berlin, Germany, February 22-25
• 17th Congress of EHA in Amsterdam, The Netherlands, June 14-17
• DGHO/ÖGHO/SGH-Meeting in Stuttgart, Germany, October 19-23
• ASH Annual Meeting and Exposition in Atlanta, USA, December 8-11.

Prospects
The fundraising will be enhanced after the administrative aspects have been clarified in Germany. In addition, the advertising will be expanded. It is planned to publish a new newsletter and to provide key slides for ELN and ELN Foundation promotion to all board members.

With donations to the ELN Foundation you can support the ELN.

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BLZ: 670 505 05
IBAN number: DE 68 6705 0505 0038 9098 43
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References

With donations to the ELN Foundation you can support the ELN.
The European Treatment and Outcome Study (EUTOS) for CML is a public-private partnership between the European LeukemiaNet (ELN) and Novartis Oncology Europe. Patient registries are a key objective of the EUTOS collaboration. The aim of this sub-project is to collect pan-European baseline, treatment, and outcome data in chronic myeloid leukemia (CML). The EUTOS registry project is based on the combination of different patient populations to evaluate real-world patient treatment. The aim is to collect data on (1) in-study, (2) out-study, and (3) population-based (prospectively registered) patients.

In-study

The outcome of CML has been profoundly changed with the introduction of tyrosine kinase inhibitors (TKIs) into therapy, but the prognosis of patients with CML is still evaluated using prognostic scores developed in the chemotherapy and interferon era. Therefore, one aim of the collaboration was to evaluate new prognostic models. In a recent publication a new prognostic score is described. This EUTOS score is superior to the Sokal and Euro scores both in its prognostic ability and in its simplicity. The predictive power of the score was developed and tested within the ELN/EUTOS registry (in-study) for patients treated with imatinib alone or imatinib-based regimes, frontline. The in-study registry contains the individual data for adult patients enrolled in prospective, controlled, Good Clinical Practice-operated studies between 2002 and 2006 and must be updated yearly from 2007 to 2011. The eligibility criteria for the registry were diagnosis of Philadelphia (Ph) or breakpoint cluster region-abl oncogene (BCR-ABL) positive (Ph+/BCR-ABL+) CML in chronic phase and any form of imatinib-based treatment within 6 months after diagnosis regardless of the duration of imatinib treatment. These criteria were fulfilled by 2060 patients from 5 national study groups: Germany (n = 699); Italy (the Italian Group for Adult Hematologic Diseases or GIMEMA) (n = 556); France (n = 546); Nordic (n = 140); and the Netherlands (HOVON; n = 119). Of these study groups, all 1261 patients who progressed or died within 36 months or had a minimum follow-up of 36 months, and all 1223 patients in whom cytogenetic response status had been evaluated at 18 months (acceptable interval 15-21 months) were analyzed. The latter group was divided into 2 subgroups: a learning sample of 938 patients and a validation sample of 285 patients. The EUTOS score using the percentage of basophils and spleen size (Figure 1A) best discriminated between high-risk and low-risk groups of patients, with a positive predictive value of not reaching a complete cytogenetic response (CCgR) at 18 months of 34% (Figure 1B). Five-year progression-free survival (Figure 1C) was significantly better in the low than in the high-risk group.

Figure 1: (A) EUTOS score calculation scheme; see also www.eutos.org. (B) Cumulative probability of achieving a CCgR as determined by the EUTOS risk score for all 1873 patients with a known CCgR status at any time and information on spleen size and basophil. (Gray test p < .0001; all computations in the presence of competing risks). (C) Progression free survival (PFS) calculated for all 2010 patients with follow-up (log-rank test p = .0069).
So far, 1582 patients have been registered in this part of the registry. Out-study patients are patients with a cytogenetic and/or molecular diagnosis of Ph+ and/or bCR/Abl+ CMl who have been registered for observational or institutional purposes in the databases of CMl study groups or at single referral institutions. These patients must have been diagnosed in the period 2002–2006, to ensure an adequate observation period, and must be updated for outcome and follow-up yearly from 2007 to 2011. First analyses with data of this registry are expected in 2012.

Population based registry
The population-based registry is the youngest registry, launched in July 2009. The goal is to register 2500 patients in a timeframe of about 30 months until the end of 2012. Just recently, the registration period was extended to the end of 2013. Patients (age ≥ 18) with documented Philadelphia or BCR-ABL positive CML who are newly diagnosed and resident within a specified country or one or more specified regions or districts of a country covering a maximum of 10 million people are documented. So far, 25 study groups from 24 European countries recruited 1318 CML patients. First data on epidemiology will be available in spring 2012.

Molecular monitoring
The molecular monitoring subproject of EUTOS has successfully established a network of national and regional reference laboratories. Most of these laboratories have been assigned laboratory specific conversion factors (CFs) that enable them to convert their local results to the International Scale (IS) thus providing greater comparability between centres for key therapeutic milestones, particularly major molecular response (MMR). Work is ongoing to validate the CFs and, in addition, a laboratory performance evaluation is being undertaken to assess the ability of reference laboratories to detect resistance-associated mutations. The principal aim of the 2 year extension to the molecular monitoring EUTOS subproject is to establish definitions and laboratory processes to define molecular responses at higher sensitivities, such as a reduction of BCR-Abl/Abl ratio by 4 log (MR4). Secondary aims include the establishment of processes to assess the molecular response of cases with rare variant BCR-ABL transcripts, further performance evaluation to measure the stability of established CFs, derivation of new CFs where required and facilitation of quality control for mutation testing. For further information please visit us on our website www.eutos.org.

References
Attendees of the 8th Annual Symposium of the European LeukemiaNet and the 12th Annual Symposium of the German Competence Network: Acute and chronic leukemias, 01. - 02. February 2011, 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 80 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. Furthermore, we will discuss in detail at the forthcoming meeting of the ELN which type of trials should be listed in the ELTR and whether and which efforts should be made to extend the registry. For more information please contact the European Leukemia Information Center ELIC (elic@em.uni-frankfurt.de).

ALL: Acute lymphoblastic leukemia

All subtypes
- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies
- GIMEMA ANALYSIS OF ALL - High Resolution Genome Wide-Copy Number Profiling and Pharmacogenomic Analysis in ALL by SNP Arrays
- GIMEMA LAL1308 - Young Adult ALL: Intensification of Pediatric AIEOP LLA-2000 Treatment
de novo/non-treated
- GIMEMA 0904 - Treatment of high-risk ALL and MRD-monitoring
- GRAALL 02/2005 - HyperC vs. standard induction and late intensification in Ph neg. ALL
- PALG 5-2007 MRD - Optimization of ALL therapy according to risk factors and monitoring of MRD
- PETHEMA LAL-AR-03 - Therapy of high-risk ALL
- NILG 10/07 - Study on CNS Prophylaxis With Liposome-Encapsulated Cytarabine in Association With a Lineage-Targeted and MRD-Oriented Postremission Strategy in Adult ALL
- ALL-SCT Ph-negative - Role of autologous SCT plus maintenance therapy in ALL
- MC-PEGASP.1/Adults - Randomized dose ranging trial of pegylated recombinant asparaginase
B-Precursor ALL

de novo/non-treated
- GRAALL 02/2005-R - Rituximab + induction, consolidation and late intensification in Ph neg., CD20+ ALL
- MT103-203 - Blinatumomab in B-precursor ALL With Minimal Residual Disease (BLAST)
- MT103-211 - Phase II Trial with Blinatumomab in relapsed/refractory B-precursor ALL
Ph/BCR-ABL +
de novo/non-treated
- DasaPH-01 - Study of standard induction and consolidation therapy in combination with dasatinib in Ph+ ALL
- EWALL PH-02 - Study of induction and consolidation therapy with nilotinib in combination with chemotherapy in older patients Ph+/BCR-ABL+ ALL
- GIMEMA 0201 - Imatinib in Ph+ and/or BCR-ABL+ ALL
- GENOTYPING ANA LYSIS OF ALL - High Resolution Genome Wide-Copy Number Profiling and Pharmacogenomic Analysis in ALL by SNP Arrays
- LAL1408 - Front-line Treatment of Ph+ and/or BCR-ABL+ ALL With Imatinib and Nilotinib in Elderly Patients and in Patients Unfit for Intensive Therapy and allo-SCT
- HEMOS 0106 - Phase II, 2-part Study of Tipifarnib Plus Bortezomib in the Treatment of de novo AMl unfit for Conventional Chemotherapy (>18 years) or in AMl in First Relapse
relapsed/refractory
- BMSCA 180 323 - Dasatinib plus SMO-Inhibitor in CML and Ph+ ALL
Stem cell transplantation
- AlloSCT-Clofarabine - Allo-SCT With Clofarabine, Busulfan and Antithymocyte Globulin for High-Risk AML, MDS or ALL

AML: Acute myeloid leukemia

AML all subtypes without FAB M3
- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies
- HOVON SAKK 42A - G-CSF priming in AML or refractory anemia
- HOVON SAKK 42 - Randomized induction + post induction in AML/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 tosedostat to standard induction therapy
- MDS CombiChemo - Combination Chemotherapy With or Without Gemtuzumab Ozogamicin or Tipifarnib in AML or High-Risk MDS
- NILG 02/06 - Remission Induction Therapy and Risk-oriented Postremission Strategy for Adult AML
Relapsed/refractory - >= 60 years
- HEMOS 0106 - Phase II, 2-part Study of Tipifarnib Plus Bortezomib in the Treatment of de novo AML Unfit for Conventional Chemotherapy (>18 Years) or in AML in First Relapse
Relapsed/refractory - All age groups
- AML CP4055 - A Phase I/II Study of CP-4055 in Patients With Refractory/Relapsed Hematologic Malignancies
- CLBHS8982116 - Dose-finding study of panobinostat, ara-C and mitoxantrone as salvage therapy for refractory or relapsed AML
de novo/non-treated - Therapy concepts for all genotypes - >= 60 years
  - GIMEMA AML1208 - Everolimus MICE-regimen in Treating Older Patients With Newly Diagnosed AML
  - GIMEMA AML19 - Gemtuzumab Ozogamicin in Treating Older Patients With Untreated AML
  - HOVON 81 AML - A Phase II study of Bevacizumab in addition to standard induction therapy in AML and high risk MDS
  - HOVON 97 AML - Maintenance therapy with Azacitidine in older patients with AML and refractory anemia with excess of blasts (RAEB, RAEB-T)
  - Intergroup Elderly - AML Intergroup - joint study arm for patients > 60 years
  - PANOBIDARA - Panobinostat, Idarubicin and Cytarabine in Patients Aged 65 Years or Older With Newly Diagnosed AML
  - SPARK-AML1 - Randomized Study of AZD1152 Alone and in Combination With LDAC in Comparison With LDAC Alone in de novo AML

deo novo/non-treated - Therapy concepts for specific genotypes - < 60 years
  - P060504 - Timed-Sequential Induction in CBF-AML

deo 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 AML and NPM1 gene mutation
  - AMLSG 11-08 - Phase Ib/Ila Study For the Evaluation of Dasatinib Following Induction and Consolidation Therapy as well as in Maintenance Therapy in Newly Diagnosed AML
  - AMLSG 12-09 - Phase-II trial evaluating induction therapy with idarubicin and etoposide plus 5-azacitidine and maintenance therapy with 5-azacitidine
  - ALFA-0702 - The CLARA Study from the Acute Leukemia French Association
  - LAM2006IR - Phase III Trial of Gemtuzumab Ozogamycin Associated to Intensive Chemotherapy in AML With Intermediate Risk
  - MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS

deo novo/non-treated - Not specified - <= 60 years
  - AZA-AML-001 - A Phase 3 Study of Azacitidine Versus Conventional Care Regimens in AML
  - HEMOS 0106 - Phase II, 2-part Study of Tipifarnib Plus Bortezomib in the Treatment of de novo AML Unfit for Conventional Chemotherapy (>18 years) or in AML in First Relapse (>60 years)
  - AML MEX - Trial of Mitogen-activated Protein/Extracellular Signal-regulated Kinase Inhibitor (MEK) Inhibitor
  - CP0455-205 - A Phase II Study of Elacytarabine (CP-0455) Plus Idarubicin as Second Course Remission-induction Therapy in AML
  - ALTA07 - Treatment strategy for younger patients with CD33 positive AML

FAB M3 (APL)

deo novo/non-treated
  - B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies
  - B1371001 - Pilot Study Of Tipifarnib Plus Bortezomib in the Treatment of de novo AML Unfit for Conventional Chemotherapy (>18 years) or in AML in First Relapse (>60 years)

relapsed/refractory
  - APL Arsenic Trioxide/ATRA - Acute Promyelocytic Leukemia 2006 (APL)
  - APL0406 - Combination Chemotherapy in Treating Patients With Newly Diagnosed APL

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

Supportive care
  - Eltrombopag - Eltrombopag in MDS and AML

CLL: Chronic lymphatic leukemia

de novo/non-treated
  - CLL 10 - CLL10 Study – FCR vs. BR in first line therapy of CLL
  - CLL 11 - Study of ROS072759 With Chlorambucil in Previously Untreated CLL

relapsed/refractory
  - GIMEMA LLC0606 - Pilot Trial of Fludarabine, Cyclophosphamide, and Lenalidomide for Advanced Relapsed/Refractory CLL

All stages
  - CLL 2I - CLL 2I protocol of the German-CLL Study group (DCLLSG)
  - CLL 2O - CLL 2O protocol of the German CLL-Study Group (DCLLSG)
  - CLL 7 - CLL7 Study for previously untreated patients in early stage of CLL

CML: Chronic myeloic leukemia

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

Accelerated phase
  - CML I-COME - Imatinib Concentration Monitoring Evaluation in CML

Blast crisis
  - GENOTYPING ANALYSIS OF ALL - High Resolution Genome Wide-Copy Number Profiling and Pharmacogenomic Analysis in ALL by SNP Arrays

Chronic Phase
  - CML I-COME - Imatinib Concentration Monitoring Evaluation in CML
  - CML IV - Imatinib vs. Imatinib-Interferon or Imatinib 800mg and SCT in CML
  - ENEST1st - ENEST1st Nilotinib in adult patients with newly diagnosed Ph/BCR-ABL positive CML in chronic phase
  - GIMEMA CML0408 - Nilotinib and Imatinib Mesylate in Early Chronic Phase 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
Intolerant/resistant to one TKI
- AMN2128 - Study of Multiple Doses of Nilotinib on the Pharmacokinetics of Midazolam in CML with Resistant and/or Intolerant Against at least One TKI
- BMS CA 180 323 - Dasatinib plus SMO-Inhibitor in CML and Ph+ ALL

MDS: Myelodysplastic Syndrome

**all Subtypes**
- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies

**Diagnostic/biomarker studies**
- MDS Biomarkers - Biomarkers in Patients at Risk of Developing Myelodysplastic Syndrome or Other Disorders and in Healthy Participants

**Intermediate II and high risk**
- AML MEK - Trial of Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase (MEK) Inhibitor
- HOVON SAKK-42A - G-CSF priming in AML or refractory anemia
- HOVON SAKK 42 - Randomized induction + post induction in AML/RAEB/RAEB-T
- HOVON 81 AML - A Phase II study of Bevacizumab in addition to standard induction therapy in AML and high risk MDS
- HOVON 97 AML - Maintenance therapy with Azacitidine in older patients with AML and refractory anemia with excess of blasts (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 tosedostat to standard induction therapy
- MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS
- MDS CombiChem - Combination Chemotherapy With or Without Gemtuzumab Ozogamicin or Tipifarnib in AML or High-Risk MDS
- MDS QOL II - Quality of Life and Symptoms in Patients With Newly Diagnosed MDS
- MDS Velcade Zarnestra - Bortezomib and Tipifarnib in MDS

**Low risk and intermediate-1**
- 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-005 - A Study of Lenalidomide Versus Placebo in Subjects With Transfusion Dependent Anemia in Low Risk MDS Without Del 5Q
- MDS Azacitidine-Epoetin Beta - Phase II study of Azacitidine and Epoetin Beta in low-risk and intermediate-1 MDS resistant to ESA
- SIMIDS - Azacitidine and Beta Erythropoietin Treatment in Patients With MDS Red Cell Transfusion Dependent

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

**Supportive care**
- MDS Darbepoetin alpha II - Darbepoetin in low- or intermediate-1 risk MDS with anemia
- MDS/AML Eltrombopag - Eltrombopag in MDS and AML

**Quality of Life**
- NMDSG03A Quality of Life I - Effects of anemia in elderly MDS patients, regarding quality of life and cardiac function

MPD: Myeloproliferative disease

**all Subtypes**
- B1371001 - A Study Of PF-04449913 In Select Hematologic Malignancies

**Myelofibrosis**
- JUMP (CINC424A2401) - 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**
- RESPONSE (CINC424B2301) - Study of INC424 in PV with Resistance to or Intolerance of Hydroxyurea

SCT: Stem cell transplantation


**Supportive care**
- ST Isavuconazole WSA-CS-004 - Isavuconazole (BAL8557) for Primary Treatment of Invasive Aspergillosis
Dates/Meetings

1.01. - 01.02.2012
9th Annual Symposium of the European LeukemiaNet / 13th Annual Symposium of the German Competence Network “Acute and chronic Leukemias”
Mannheim, Germany

22. - 25.02.2012
30. German Cancer Congress
Berlin, Germany

118. DGIM Congress
Wiesbaden, Germany

04. - 05.05.2012
2012 European Focus on Myeloproliferative Neoplasms & Myelodysplastic Syndromes
Lisbon, Portugal

21. - 22.05.2012
Naples Fellows Days
Naples, Italy

09. - 10.06.2012
DLH Patient Congress
Hamburg, Germany

14. - 17.06.2012
17. EHA Congress
Amsterdam, Netherlands

29.-30.06.2012
CML Study Group Meeting / 21st International CML-Workshop
Mannheim, Germany

06. - 08.09.2012
The 2nd World Congress on Controversies in Hematology (COHEM)
Barcelona, Spain

05. - 07.10.2012
ELN Frontiers Meeting 2012
Milan, Italian

Annual Conference of the German, Austrian, and Swiss Societies for Hematology and Oncology 2012
Stuttgart, Germany

54. ASH Annual Meeting and Exposition
Atlanta, USA