Dear Colleagues,

the ELN is growing consistently with new members from all over the world. The scientific projects supported by the ELN Foundation are ongoing and the ELN is pleased to continue to support the small and larger meetings that are keys for the networking success. Two new ELN management recommendations were published in 2013: new recommendations for MDS and a third edition for CML. New pocket cards were produced for MDS and CML.

As a vehicle for support, ELN had established the ELN Foundation. To support the ELN Foundation, we initiated the ELN Foundation Circle where private companies come together with the goal to support the ELN and to support the idea of leukemia as a curable disease. We are proud that we could already win Novartis, Celgene, and Medac among others as founding members and Clara Bloomfield as the first goodwill ambassador of the ELN Foundation Circle.

In this information letter, you can read reports on activities in cytogenetics (WP 11), the impact of minimal residual disease in AML (WP 5), stem cell transplantation in elderly patients with AML (WP 14), the new MDS recommendations (WP 8), CML immunology (WP 4), morphology (WP 10), and highlights of the European Treatment and Outcome Study (EUTOS) for CML.

You will also find abstract summaries from ASH 2013 and updates of the registry of ongoing leukemia trials and meeting dates.

Since all these achievements result 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 with particular merits, there will be two ELN Merit Awards to be announced during the upcoming 11th 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. This is what ultimately will make leukemia a curable disease.

Sincerely,

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

This newsletter is financed through funding of the ESF.
Dear colleagues,

we are pleased to present you the 10th Information Letter of the European LeukemiaNet and would like to thank the contributing authors for their support. This issue nicely reflects the broad spectrum of subjects the ELN is engaged with: Topics range from basic research to diagnostics all the way to leukemia therapy.

As before, this issue contains the latest news from the ELN Foundation and EUTOS, current trials in the European Leukemia Trial Registry, and summaries of the most important clinical results from oral presentations of the 55. ASH Annual Meeting and Exposition which were selected and presented by ELN experts.

We hope you will enjoy reading.

With best regards,

Information Center

Dr. Nicola Gökbüget
Dr. Sina Hehn

WP 11 - Cytogenetics

Current and future activities in cytogenetics - a summary from WP11

Detlef Haase1, Claudia Haferlach2, Harald Rieder3, Christina Ganster1, Peter Vandenberghe4, Sophie Raynaud5, Julie Schanz1, and Alice Fabarius6 for the WP 11 members

During the WP11 meeting at the annual ELN network symposium in February 2013, new data from an international study were shown proving that the monosomal karyotype is no independent prognostic marker but is closely associated with the complexity of cytogenetic changes (Haase/Schanz). Interim results from a multicentric German registry-study of clinical features, treatment, and prognosis in patients with monosomy 7 (the largest data set world-wide) were presented by Schanz. Besides these, a variety of other WP11 projects have been discussed.

A novel hierarchical prognostic model of AML solely based on molecular mutations (C. Haferlach)

The karyotype is so far the most important prognostic parameter in acute myeloid leukemia (AML). Molecular mutations have added to prognostication in AML and were so far mainly applied to subdivide AML with normal karyotype into prognostic subsets. In order to ease AML prognostication, a prognostic model for the entire AML cohort solely based on molecular markers was developed. Therefore, 1,000 patients with cytogenetic data were investigated for the following molecular alterations: PML-RARA, RUNXI-RUNX1T1, CBFB-MYH11, FLT3-ITD, and MLL-PTD, as well as mutations in NPM1, CEPBA, RUNX1, ASXL1, and TP53. Clinical data was available in 841 patients.

Based on Cox regression and Kaplan-Meier analyses five distinct prognostic subgroups with large differences in overall survival (OS) and event-free survival were identified (Fig. 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Subgroups</th>
<th>OS at 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. very favorable</td>
<td>PML-RARA rearrangement (n = 29) or CEPBA double mutations (n = 42);</td>
<td></td>
<td>82.9 % (p &lt; 0.001)</td>
</tr>
<tr>
<td>2. favorable</td>
<td>RUNXI-RUNX1T1 (n = 35), CBFB-MYH11 (n = 31) or NPM1 mutation without FLT3-ITD (n = 186);</td>
<td></td>
<td>62.6 %</td>
</tr>
<tr>
<td>3. intermediate</td>
<td>none of the mutations leading to assignment into groups 1, 2, 4 or 5 (n = 235);</td>
<td></td>
<td>44.2 %</td>
</tr>
<tr>
<td>4. unfavorable</td>
<td>MLL-PTD and/or RUNXI1 mutation and/or ASXL1 mutation (n = 203);</td>
<td></td>
<td>21.9 %</td>
</tr>
<tr>
<td>5. very unfavorable</td>
<td>TP53 mutation (n = 80);</td>
<td></td>
<td>0 % (p &lt; 0.001)</td>
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</table>

WP 2 - ELIC
This novel model based on a molecular characterization of AML provides a very powerful model for prognostication in AML. It is applicable in younger and in elderly patients. Furthermore, the molecular characterization provides a molecular marker for the majority of patients which can be used to monitor therapy response and tailor treatment for the individual patient (Fig. 2).

Quality control for interphase-FISH diagnostics in tumor cytogenetics (QUITZ2) by round robin tests (H. Rieder)

External quality assessment is an integral part of quality control in diagnostic laboratories. 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 were sent out, instead an interpretation of a given FISH result was requested or a typical report from the participating laboratory at diagnosis of a chronic myeloid leukemia (CML) had to be sent.

In 2012, the test was integrated in the portfolio of interlaboratory testing offered by the Society of the German Professionals of Human Genetics (Berufsverband Deutscher Humangenetiker - BVDH). The respective online platform is used for uploading the reports by the participants as well as the evaluation by the reviewers. 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 2012, the diagnostic question was to evaluate whether a 5q31 deletion was present in the sample. 48 out of 50 participating centers reported the correct result that no 5q31 deletion was present. Access to the platform and to the test system is available upon registration at the BVDH (www.bvdh-ringsuche.de). However, the system is restricted to German speaking countries, so far.

Atlas of Genetics and Cytogenetics in Oncology and Haematology (C. Haferlach)
The Atlas is a peer-reviewed internet journal, encyclopaedia, and database aimed at genes involved in cancer, cytogenetics and clinical entities in cancer, and cancer-prone diseases. It is a collective effort of researchers and clinicians to give the state of the art in cancer genetics to the medical and scientific community to provide a cognitive tool for fundamental and clinical research. Readers of the Atlas are consultants at the hospital, researchers, university teachers, but it also reaches students in medicine and life sciences.

The Atlas is a hybrid formula: peer reviewed like any journal and/or easy to use like internet (hyperlinks, updates).
The lactate dehydrogenase (LDH) was significantly lower in patients with 7q-/-7 (251 U/L vs 741 U/L, p < 0.001). The bone marrow blast count, platelet count and absolute neutrophil count did not show a significant difference. The median overall survival was 53.4 months in patients with der(1;7), 23.5 months in patients with 7q-, and 13.8 months in patients with -7 (p < 0.01). The AML-free survival was not reached in patients with der(1;7), 9.6 months in patients with 7q- and 6.3 months in patients with -7 (Fig. 3).

In conclusion, MDS patients with der(1;7) show a significant better AML-free survival and OS compared to MDS patients with 7q- and -7. Although der(1;7) results in a deletion of 7q, der(1;7) needs to be prognostically classified independently from the 7q-deletion.

Relevance of secondary abnormalities in CML (A. Faborius)
Acquired genetic instability in CML as a consequence of the translocation t(9;22)(q34;q11) and the resulting BCR-ABL fusion causes the continuous acquisition of additional chromosomal aberrations and mutations and thereby progression to accelerated phase and blast crisis (BC). At least 10 % of patients in chronic phase (CP) CML show additional alterations at diagnosis. This proportion rises during the course of the disease up to 80 % in BC. Acquisition of chromosomal changes during treatment is considered as a poor prognostic indicator, whereas the impact of chromosomal aberrations at diagnosis depends on their type. Patients with major route additional chromosomal alterations at diagnosis have a worse outcome whereas patients with minor route ACA show no difference in OS and progression-free survival (PFS) compared to patients with the standard translocation, a variant translocation or the loss of the Y chromosome. However, the impact of balanced vs unbalanced karyotypes at diagnosis on prognosis of CML is not clear yet.

Clinical and cytogenetic data of 1,346 evaluable out of 1,544 patients with Philadelphia and BCR-ABL positive CP CML randomized until December 2011 to the German CML-Study IV, a randomized 5-arm trial to optimize imatinib therapy by combination or dose escalation and stem cell transplantation, were investigated. There were 540 females (40 %) and 806 males (60 %). Median age was 53 years (range: 16-88 years). The impact of additional cytogenetic aberrations in combination with an unbalanced or balanced karyotype at diagnosis on time to complete cytogenetic and major molecular remission (CCR, MMR), PFS and OS was investigated. At diagnosis 1174/1346 patients (87 %) had the standard t(9;22)(q34;q11) only and 75 patients (6 %) had a variant t(9;22). In 64 of 75 patients with t(9;22), only one further chromosome was involved in the translocation; in 8 patients two, in 2 patients three, and in one patient four further chromosomes were involved. 97 patients (7 %) had additional cytogenetic aberrations. Of these, 44 patients (3 %) lacked the Y chromosome (-Y) and 53 patients (4 %) had major or minor ACA. 36 of the 53 patients (27 %) had an unbalanced karyotype (including all patients with major route ACA and patients with other unbalanced alterations like X, del(1)(q21), del(5)(q11q14), +10, +15, +17, +p10), -21, and 17 (1.3 %) a balanced karyotype with reciprocal translocations [e.g. t(1;22); t(2;16); t(3;12); t(4;6); t(5;8); t(15;20)].

After a median observation time of 5.6 years for patients with t(9;22), t(v;22), -Y, balanced and unbalanced karyotype with ACA median times to CCR were 1.05, 1.03, 2.58 and 1.51 years, to MMR 1.31, 1.51, 4.05, 2.97 and 2.07 years. Time to CCR and MMR was longer in patients with balanced karyotypes (data statistically not significant). 5-year PFS was 89 %, 78 %, 87 %, 94 % and 69 % (Fig. 4) and 5-year OS 91 %, 87 %, 89 %, 100 % and 73 %, respectively (Fig. 5). In CML patients with unbalanced karyotype PFS (p < 0.001) and OS (p < 0.001) were shorter than in patients with standard translocation (or balanced karyotype; p < 0.04 and p < 0.07, respectively).

We conclude that the prognostic impact of additional cytogenetic alterations at diagnosis of CML is heterogeneous and consideration of their types may be important. Not only patients with major route ACA at diagnosis of CML but also patients with unbalanced...
karyotypes identify a group of patients with shorter PFS and OS as compared to all other patients. Therefore, different therapeutic options such as intensive therapy with the most potent tyrosine kinase inhibitors or stem cell transplantation are required.

**Short update of further activities (D. Haase)**
Several previous publications analyzed the prognostic impact of cytogenetic abnormalities in MDS. However, the analysis of very rare, single abnormalities was not performed in most studies due to the low number of patients showing these aberrations. Thus, large, international data collections are needed to address these questions. The planned project is based on the work of Schanz et al., where the impact of different cytogenetic abnormalities on overall and AML-free survival was updated and redefined. Using this new classification system, 91% of patients can be classified according to their cytogenetic risk. This system was integrated into the IPSS-R.10 However, rare single abnormalities that occur less than 10 times in the whole data base of 2,902 patients could not be analyzed and included into the scoring system due to the impossibility of an accurate statistic evaluation in these infrequent aberrations. Thus, the real prognostic impact of these rare findings remains unknown as yet. Perforce, they were classified into the intermediate risk group, which thus still constitutes a heterogeneous group of abnormalities with an unknown impact on prognosis.

As presented by Ganster concerning der(1;7), we will further follow the strategy to collect data from members of the ELN and other international collaborators as well as from the International Working Group for Prognosis in MDS (IWG-PM) of the MDS Foundation to elucidate the prognostic relevance of rare abnormalities in MDS. The table below enumerates the rare abnormalities which will be in the focus of our upcoming activities. Haase and Schanz furthermore have applied for a project to use the IWG-PM database of over 7,000 patients which was recently approved by the MDS Foundation. The main goal of the study is to analyze the prognostic relevance of single, rare abnormalities in MDS. By keeping in mind that rare abnormalities as a group are as frequent as del(5q) or complex abnormalities, a further prognostic clarification of these aberrations is clinically important. Certainly, this intention needs very huge international databases to overcome the problem of the infrequency of distinct rare abnormalities.

<table>
<thead>
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<th>Call for rare abnormalities</th>
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<tbody>
<tr>
<td>der(1;7)</td>
</tr>
<tr>
<td>+1q</td>
</tr>
<tr>
<td>-1/1p1</td>
</tr>
<tr>
<td>t(5q)</td>
</tr>
<tr>
<td>+11</td>
</tr>
<tr>
<td>t(11q23)</td>
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<tr>
<td>-13/13q-</td>
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Any combination of two abnormalities not including del(5q), -7, or del(7q).
Complete hematologic remission (CR) is a prerequisite for cure in acute myeloid leukemia (AML). The conventional definition of CR, based on the morphologic recognition of ≤ 5 % of leukemic blasts in the bone marrow, is not sufficient to define the quality of the response. Standard intensive therapy results in CR rates of 50-80 % (depending on age), however, the majority of patients with AML relapse within 3-5 years from diagnosis. Therefore, there is great need for more sensitive prognostic factors that can predict relapse. Currently, the most important prognostic factors for AML are based on cytogenetics and molecular abnormalities, which are assessed at diagnosis. Although these factors have been shown to be of utmost importance in risk stratification, the treatment outcome of patients within the thus-defined risk groups is still highly variable. New prognostic factors that, apart from diagnosis parameters, may include treatment and response related factors are needed.

It is now generally accepted that persistence of leukemic cells after achieving CR often referred to as minimal residual disease (MRD) is responsible for emerging relapses. MRD, defined as the persistence of leukemic cells after chemotherapy at numbers below the sensitivity detection level of routine morphology, represents the sum of the effect of all relevant cellular resistance mechanisms, pharmacokinetic resistance, dosage and compliance, and other unknown factors affecting the effectiveness of treatment. Monitoring of MRD offers early assessment of response to therapy to improve risk stratification and guide postremission therapy as well as the post treatment detection of impending relapse and could guide preemptive therapy.

Methods of MRD assessment
Several techniques were developed that enable the more sensitive quantification of minimal amounts of MRD in patients with AML in morphological remission. Methodologies for MRD detection after chemotherapy at numbers below the sensitivity detection level of routine morphology, represents the sum of the effect of all relevant cellular resistance mechanisms, pharmacokinetic resistance, dosage and compliance, and other unknown factors affecting the effectiveness of treatment. Monitoring of MRD offers early assessment of response to therapy to improve risk stratification and guide postremission therapy as well as the post treatment detection of impending relapse and could guide preemptive therapy.

PCR-based MRD detection
This technique is based on the detection of genetic aberrations, such as fusion genes and mutations specific for that particular AML. Real time quantitative reverse transcription PCR (qPCR) is the most sensitive method for the detection of MRD in AML, since 1 leukemic cell can be identified amongst 10^10-10^11 normal cells. The disadvantage of this technique, however, is that the genetic aberrances have only been identified in subgroups of AML. For many years, molecular MRD has been restricted to the major recurrent translocations (PML-RARA, AML1-ETO, CBFβ-MYH11). In this setting, qPCR has minimal background, as these aberrant transcripts are completely absent in normal cells. qPCR may also be used in patients without fusion transcript, but with other mutant phenotypes, e.g. FLT3-ITD, partial tandem duplication of MLL (MLL-PTD), and NPM1 mutations. In addition, detection of transcripts that are aberrantly overexpressed in AML (e.g. WT1 and PRAME) has been utilized for MRD assessment. Since these transcripts are not leukemia specific and are therefore limited in their utility.

Recent studies showing the importance of MRD for clinical application
The French AML Intergroup randomized a total of 198 core binding factor (CBF)-AML patients between a reinforced and a standard induction course, followed by 3 high-dose cytarabine consolidation courses. Gene mutations were screened at diagnosis while MRD levels were serially monitored for RUNX1-RUNX1T1 or CBFβ-MYH11 transcripts by real-time quantitative PCR. Despite a more rapid MRD decrease after reinforced induction, induction arm did not influence relapse-free survival (RFS) (64 % in both arms). Higher WBC, RIT, and/or FLT3-ITD/KIT gene mutations, and a less than 3-log MRD reduction after first consolidation were associated with a higher specific hazard of relapse, but MRD remained the sole prognostic factor in multivariate analysis. At 36 months, cumulative incidence of relapse and RFS were 22 % vs 54 % and 73 % vs 44 % in patients who achieved 3-log MRD reduction versus the others. The same was shown in the United Kingdom MRC AML-15 trial that also showed that MRD monitoring by quantitative RT-PCR at specific time points in CBF-AML allows for identification of patients at high risk of relapse and allows for risk stratification. The conclusion that MRD should be used for future treatment stratifications in CBF-AML patients seems justified based on these data. RNA-based quantitative RT-PCR specific for the detection of six different NPM1(mut) types was applied in 245 intensively treated AML patients. NPM1(mut) transcript levels as a continuous variable were significantly associated with prognosis after each treatment cycle. Achievement of RQ-PCR negativity after double induction therapy identified patients with a low cumulative incidence of relapse (6.5 % after 4 years) as compared with RT-PCR-positive patients (53 %); this translated into significant differences in OS (90 % vs 51 %, respectively). Multivariable analyses after double induction and after completion of consolidation therapy revealed higher NPM1(mut) transcript levels as a significant factor for a higher risk of relapse and death.

In the HOVON-SAKK AML 42a study, percentage of MRD was determined by MPFC in a setting in which MRD assessment was performed without prior knowledge of clinical management, diagnostic features, or outcome. After all courses of therapy, low MRD values distinguished patients with relatively favorable outcome from those with high relapse rate and adverse RFS and OS (Fig. 1). In the whole patient group and in the subgroup with intermediate-risk cytogenetics, MRD was an independent prognostic factor. Multivariate analysis after cycle 2,
when decisions about consolidation treatment have to be made, confirmed that high MRD values (> 0.1 % of WBC) were associated with a higher risk of relapse after adjustment for consolidation treatment time-dependent covariate risk score and early or later CR. The same prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with AML was described by the UK NCRI AML16 trial. MPFC-MRD negativity conferred significantly better 3-year survival from CR after cycle 1 (42 % vs 26 %) in MRD-positive patients with higher risk of early relapse (median time to relapse: 8.5 vs 17.1 months, respectively).

MRD assessment before myeloablative hematopoietic cell transplantation (HCT) is associated with adverse outcome in AML in first and second CR. After multivariable adjustment, risks of death and relapse were 2.61 times and 4.90 times higher for MRD+ patients (p < 0.001). MRD can also be used in the post transplant setting to guide preemptive treatment.

**Concluding remarks**

MRD assessment is of great prognostic value and will be implemented in clinical trials for guiding treatment. Fine-tuning of techniques and merging of flow and molecular genetic assays may ultimately bring us closer to the final goal of real individualized risk assessment and therapy in patients with AML. The development of a position paper on MRD in AML by WP5, 10, and 12 of the ELN could be instrumental.

**Figure 1.** OS curves for MRD- and MRD+ patients in the HOVON/SAKK AML 42a study. The upper panels are for landmarks after cycle I, cycle II, and consolidation. The lower panels are for survival after cycle II for patients with good, intermediate, and poor risk, respectively.
Role of stem cell transplantation in elderly patients with AML

Dieter Niedewiwer for the study committee®

Department for Hematology/Oncology, University Hospital, Leipzig, Germany

Up until a few decades ago, elderly patients with acute myeloid leukemia (AML) had a dismal prognosis. Attempts to control the disease with low dose chemotherapies were standard practice, curative intentions being feasible only occasionally in highly selected patients. However, in the 90ies, the introduction of age-adapted protocols with tolerable toxicities enabled the induction of complete remissions (CR) at rates similar to those achieved in younger patients with the corresponding cytogenetic abnormalities. Although this was an important step forward, the majority of patients relapsed within a few months despite consolidation and maintenance therapy. Overall survival (OS) amounted to only 10-15 % after two years. Since this time, post-remission treatment has been progressively intensified and results improved either by high-dose post-remission therapy or by allogeneic hematopoietic stem cell transplantation (HCT), which has had the highest curative potential for patients with AML.20 21 However, the toxicity of dose intensification and conventional allogeneic HCT meant that only younger patients could profit from this treatment approach. In an attempt to overcome age limits and high rates of treatment related mortality (TRM), protocols have been adapted to reduce morbidity and mortality using reduced intensity conditioning (RIC) regiments.22 23 The minimal conditioning regimen involving fludarabine and low-dose total body irradiation (TBI) followed by immunosuppression with cyclosporine and mycophenolate mofetil was associated with very low hematological and non-hematological toxicities, while enabling hematopoietic donor cell engraftment and considerable graft-versus-leukemia effects. Because of the low toxicity and very moderate neutropenia, the protocol has been tested in patients up to the age of 75 years with considerable success.24 Since December 1997, more than 3,000 transplants with low-dose TBI based regimens have been carried out in patients with a variety of hematologic malignancies, solid tumours, and non-malignant diseases.

In a study involving 122 patients with AML, those transplanted in CR1 and CR2 had better OS and leukemia-free survival (LFS) than those transplanted in later stages of the disease.25 In addition, a lower incidence of relapse and higher OS was described in patients with unrelated compared to related RIC-HCT. In patients in CR1 given related or unrelated grafts, the OS was 44 % and 63 %, respectively. At the same time, a non-relapse mortality (NRM) of 10 % and 27 % at two years was observed for related and unrelated RIC-HCT, respectively, the most frequent causes of NRM being acute and chronic graft-versus-host-disease (GVHD) (approx. 10 %) and infections in unrelated transplants (11 %). Relapse of the malignancy remained the major cause of death in AML patients. Relapse was dependent upon the stage of the disease and reached 47 % in patients with related donors and 33 % in patients with unrelated donors. The durability of remission was followed for more than eight years after RIC-HCT. This has confirmed that not only cytogenetic remissions but also long lasting molecular remissions can be induced with purely immunological effects. In comparing outcome of elderly patients with AML treated with HCT and chemotherapy, a clear advantage for HCT was observed. In the current ELN/EBMT study with the title “A randomized phase III study comparing conventional chemotherapy to low dose total body irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors as consolidation therapy for older patients with AML in first complete remission” (HCT vs CT in elderly AML), we tested the role of allogeneic HCT in a prospective comparison with chemotherapy. This type of study approach is necessary to address directly the comparative value of allogeneic HCT in this age group of patients with AML. Conventional chemotherapy offers a probability of OS in the range of 10-15 % at 2 years. Consolidation therapy with unrelated HCT may lead to an increase of OS and LFS in elderly patients with AML as shown in the phase II studies. The inclusion criteria include primary or secondary AML as defined by WHO or refractory anemia with excess of blasts in first complete remission after one or two cycles of induction therapy, karyoscopy score of ≥ 70 %, and written informed consent. Exclusion criteria involve FAB M3 and HIV positivity. The primary aim of the study is LFS, the secondary aims OS, cumulative incidence of relapse, TRM, complications, incidence of myelosuppression (absolute neutrophil count < 500/mm³ for > 2 days, platelets < 20,000/mm³ for > 2 days) after initial peripheral blood stem cell infusion, incidence of grades 2-4 acute GVHD and the incidence of chronic extensive GVHD after donor lymphocyte infusion. The study has been designed as a multicenter study involving several cooperative groups in Europe including the European Blood and Marrow Transplantation Group (EBMT) and the European LeukemiaNet (ELN) as well as AML study groups HOVON (Löwenberg, Cornelissen), OSHO (Niedewiwer), SAKK (Chalandon), ALFA (Dombret) and GOELAMS (Mohty, Blaise). Patients between 60 and 75 years with AML are registered centrally after achieving CR. During the first consolidation a related or unrelated donor (10/10) search is started. Patients without a donor are allocated to the observation arm, patients with an unrelated or related donor are randomized in a 2:1 fashion to receive either stem cell transplantation (SCT) or non-SCT treatment. The induction and consolidation as well as the non-SCT arms are study group specific. Patients with relapse in the non-SCT arm are induced into remission and scheduled for allogeneic SCT as soon as possible. There is a time limit of 5 months from diagnosis to randomization and a maximum of 4 weeks from randomization to treatment (Fig. 1).

Up until December 2012, a total of 105 patients with CR1 after 1-2 induction cycles had been registered in the clinical trial. Patients have been recruited in clinical trial centres all over the world, the top recruiting countries being Germany and The Netherlands, Austria, France, and Switzerland are joining the trial and have also started patient recruitment. Of these, 49 patients could be randomised (32 into SCT arm, 17 into non-SCT arm) and 23 patients have been enrolled into the observational arm. These patients did not qualify for randomisation because of missing donor, relapse, or other reasons. Interestingly, 52 % of the registered patients with CR1 were randomized while only 25 % did not have a suitable donor. This is quite similar to the predicted percentages. The observed toxicity profile is fully consistent with previous phase II study experience. For patients safety it was planned to trigger a d100 TRM-alarm if the critical ratio was 4/10 or 5/15. No such alarm was triggered by d100. From the current course we conclude that the concept and the rationale of the study have been validated and the study is proceeding as predicted. The safety information available to date identifies no additional risks. The next TRM analysis is planned for day 365 (one year) in spring 2013. Furthermore, the annual safety analysis has shown no change in the risk-benefit-assessment. Information on the study can be obtained from D. Niederwieser, Department of Hematology and Clinical Oncology, University of Leipzig, Johannissäule 32A, 04103 Leipzig, Germany, dietger@medizin.uni-leipzig.de

# Jon Cornelissen, Mohammad Mohy, Bob Löwenberg, Kirsten Papendorf, Hervé Dombret, Yves Chalandon, Sustrata Patel, Hildegard Greinix, Dirk Hassenclüber, Meinhard Mende

Acknowledgment: This study is supported by the “Deutsche Krebshilfe“.


Figure 1. Scheme of the study design. Note: Induction, Consolidation and non-SCT treatments will be administered as confirmed per study group protocol.

WP 14 - SCT
Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic disorders characterized by ineffective hematopoiesis, peripheral cytopenias, and increased risk of evolution into acute myeloid leukemia (AML). MDS are included in the category of myeloid neoplasms in the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, together with myeloproliferative neoplasms, myelodysplastic/myeloproliferative neoplasms, and AML.

MDS represent one of the most common hematologic malignancies in Western countries. They occur mainly in elderly people with a median age at diagnosis of 70-75 years and their incidence increases to 20-50 per 100,000 persons per year over the age of 60. This means that approximately 25,000 new cases are expected in Europe each year. Moreover, considering the progressive aging of the population in Europe, the number of MDS patients is destined to increase in the next decades making MDS one of the most challenging issues for hematologists and health care providers in the near future.

The management of patients with MDS in everyday clinical practice presents several critical issues. The diagnosis is limited by the scarce reproducibility of morphological analysis of dysplasia and by the poor specificity of dysplastic changes that make differentiation between MDS and other non-clonal conditions difficult (Fig. 1). In addition, since MDS range from indolent conditions with nearly normal life expectancy to subtypes similar to acute leukemia, clinical decision-making concerning treatment modalities and timing of interventions is problematic. Furthermore, data regarding the safety and efficacy of various therapeutic options are often based on uncontrolled clinical trials which can provide insufficient evidence to support the most appropriate management strategy.

Therefore, the European LeukemiaNet WP8 has promoted a program aiming at developing and continuously updating evidence- and consensus-based guidelines to provide clinical practice recommendations for standardized diagnostic and prognostic procedures and for an appropriate choice of therapeutic interventions in adult patients with primary MDS. These recommendations were recently published in Blood.10

The development of these guidelines was a multistep process including systematic review of the literature and formal consensus methodology. The Expert Panel included physicians experienced in MDS and active in both care of patients and clinical research from the following countries: Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, The Netherlands, Spain, Sweden, United Kingdom. A systematic review of the literature was performed and the level of evidence was rated according to the Revised Grading System for Recommendations in Evidence-Based Guidelines of the Scottish Intercollegiate Guidelines Network Grading Review Group. A list of key clinical questions was generated and rank-ordered using the criterion of clinical relevance pointing to the proper diagnostic procedures and the possible therapeutic strategies, to the possible and optimal patient subgroups, and to the risks deriving from the therapy. The Expert Panel was then invited to formulate evidence-based statements for each clinical question in an independent manner. In the field of MDS, as in other settings of hematology and oncology, most evidence was derived from uncontrolled non-randomized trials and was not of a level of detail sufficient to sustain everyday clinical decisions. Therefore, formal consensus methodology including scenario analysis was adopted to combine the best available scientific evidence with collective judgment by experts. Cost-effectiveness analysis was outside the scope of this project and has been devolved to national working groups including a broader group of individuals (physicians, consumers, funding bodies). Three consensus conferences were held to reach a definite consensus. Recommendations were formulated and ranked according to the supporting level of evidence using the criteria of the Scottish Intercollegiate Guidelines Network Grading Review Group.

Blood tests of value in the diagnostic workup of suspected MDS were identified and investigations required for the diagnosis of MDS were defined and ranked according their grade of recommendation. Classification of patients according to WHO criteria as revised in 2008 was recommended. The expert panel was unanimous in considering that the heterogeneity of the disease strongly sustains a risk-adapted treatment strategy which requires not only the evaluation of disease-related factors but also of those related to extra-hematological comorbidity. Although new prognostic scoring systems were recently proposed, therapeutic recommendations referred to patients stratified according to IPSS as the scientific evidence on the efficacy and safety of the currently available therapeutic agents was derived from clinical studies adopting this reference score. The assessment of individual risk enables the identification of fit patients with a poor prognosis who are candidates for up-front intensive treatments. In fit patients with low-risk disease who are potentially candidates for intensive therapy, delayed treatment strategies may result in longer life expectancy. However, these strategies are to be planned at the time of diagnosis and a close follow-up and an optimal management of cytopenias are mandatory in order to prevent disease complications or progression that might preclude these patients from intensive treatments. A high proportion of MDS patients is not eligible for potentially curative treatment. In these patients, therapeutic interventions are aimed at preventing cytopenia-related morbidity and improving quality of life. In this light, the implementation into clinical practice of the assessment of patient-reported outcomes was encouraged.

The inclusion of patients in clinical trials was strongly recommended in order to obtain the maximal information on safety and efficacy of new treatments. The inclusion of patients in national and international registries was also encouraged to maximize the information on the disease and on the implementation of treatment strategies in everyday clinical practice and to establish an optimal frame for biological and translational studies in the field of MDS.
20-30 years ago, chronic myeloid leukemia (CML) patients were good candidates for the allogeneic stem cell transplantation as there were no other effective treatments available and the therapy responses were better than in many other leukemia types. CML seemed to respond well to immunotherapy and relapses after transplantation were treated successfully with donor lymphocyte infusions. Since year 2000, tyrosine kinase inhibitors (TKIs) have replaced almost all other therapy types in CML as the outcome of patients has improved significantly with the TKI therapy. Today, there are several TKIs on the market and the next generation drugs seem to be always at least slightly more effective as the predecessors. However, still the majority of patients may need TKI therapy life long as the treatment does not eradicate all leukemia cells. Therefore, there has been revival of interest to other treatment options such as to immunomodulatory agents. The current treatment goal is cure and the hope is that the combination of TKIs with other therapy modalities (immunomodulating, stem cell targeting) may help patients to achieve this goal.

Already now, there are a few published studies of clinical randomized trials where one of the old immunomodulators IFN-α has been combined to first generation TKI imatinib with good treatment results showing superior treatment responses in the combination arm compared to imatinib monotherapy group. Furthermore, currently there are several clinical trials running in the European countries where IFN-α is combined to 2nd generation TKIs such as dasatinib and nilotinib. It remains to be seen whether these new combinations beat monotherapy of 2nd generation inhibitors with faster and deeper molecular responses. However, the more important question still is whether the improved therapy responses lead to increased rate of patients who are able to discontinue the therapy and be cured.

### Immunological predictive biomarkers for drug discontinuation

Recently, several studies have been published which have shown that 40-50 % of those patients who have achieved deep molecular remission (MR4.5) with TKI therapy and stayed in remission for several years can discontinue the therapy without imminent disease relapse. Interestingly, although these patients are thought to be in complete molecular remission with normal RNA based PCR methods, it has been demonstrated that all patients still have the persistence of the original CML clone after imatinib withdrawal when tested with more sensitive DNA based method. The reason why these leukemic cells do not expand is unclear but immune surveillance is a plausible explanation. In other tumor types (such as in gastrointestinal stromal tumors and mastocytoma), it has been shown that the effect of TKI therapy comes partly from the immune activating properties of TKI drugs. Similarly, T- and NK-cell activation has been observed in CML patients during TKI therapy.

Currently, there is a multinational Pan-European clinical trial in CML evaluating the possibilities of drug discontinuation in optimally responding patients (Euro-SKI study). One of the aims is to find prognostic factors which could help in the future when deciding which patients are good candidates for drug discontinuation.

In the Nordic countries, we are also running a predictive immunology biomarker substudy aiming at understanding the role of the immune surveillance in prevention of the disease relapse. In the Nordic countries, we are also running a predictive immunology biomarker substudy aiming at understanding the role of the immune surveillance in prevention of the disease relapse. In thus far published studies, increased NK-cell count has been associated with successful therapy discontinuation in both imatinib and IFN-α monotherapy treated CML patients. These patient cohorts have been relatively small however and larger ongoing Euro-SKI trial will hopefully shed more light on this issue.

### Role of immunological checkpoint modulation

The promising clinical results in solid tumors from anti-body therapy targeting key immunological checkpoint molecules, such as CTLA-4, PD-1, PD-L1, have proven correct the decade long hypothesis of the significance of acquired, reversible tumor tolerance by the adoptive immune system. Remarkably, the rational combination therapy of checkpoint inhibitors has yielded patient outcomes unheard of in the field of immunotherapy or cancer therapy in general. Several immune checkpoint modulators - mostly agonistic or antagonistic monoclonal antibodies - are in development (Tab. 1).

Many hematological malignancies are in the unique position that the tumor cells are part of the immune system and thus may be particularly well equipped for immune evasion. For example, acute myeloid leukemia cells express an array of both stimulatory (e.g. CD86, ICOSL) and inhibitory (e.g. PD-L1, PD-L2) proteins with the net effect of efficient escape from immune eradication in the bone marrow tumor microenvironment. Recently, cytotoxic T-cells from newly diagnosed CML patients were shown to express elevated levels of the immunosuppressive molecule PD-1 and the expression correlated positively with the Sokal score. Interestingly, the Philadelphia pos. (Ph+) CD34+ leukemic progenitor cells expressed high levels of PD-L1 providing one mechanism for their immune evasion and leukemic persistence. These studies indicate that a biological rational for immune checkpoint modulation exists also in leukemias. However, hematologists have been relatively conservative in adopting recent advancements in immune-oncology successful also in cancers previously thought to be non-immunoresponsive (e.g. non-small cell lung cancer). In CML, a Phase I/II study will start during 2014 with the combination of a second generation TKI (dasatinib) and a PD-1 antibody (nivolumab) in TKI-refractory patients which may pave the way to studies aiming at increasing the cure rate in CML. The more unmet clinical need for the novel immunomodulatory antibodies is in the advanced forms of CML, Ph+ acute lymphoblastic leukemia, and other acute leukemias where the prospect of significant adverse effects can be more readily accepted. As only a proportion of patients will respond to immune checkpoint modulation, the inclusion of predictive biomarker discovery programs within the clinical studies is mandatory to further understand the mechanisms of sensitivity and resistance to these novel (and expensive) drugs. It will be also very interesting to see if tumor vaccine studies (with e.g. BCR-ABL1 peptides) will experience a reappraisal now when potent tools exist for breaking the immune anergy which has been one of the major hindrances in eliciting potent anti-leukemic vaccine responses.

### Table 1. Examples of immune-checkpoint modifying drugs currently in development.

<table>
<thead>
<tr>
<th>Target molecule (function)</th>
<th>Drug</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4 (inhibitory)</td>
<td>Ipilimumab, Tremelimunab</td>
<td>Approved In development</td>
</tr>
<tr>
<td>PD-1 (inhibitory)</td>
<td>Nivolumab, MK-3475, CT-011, AMP-224</td>
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<tr>
<td>PD-L1 (inhibitory)</td>
<td>BMS936559, PDL3280A/RG7446, ME4736</td>
<td>In development</td>
</tr>
<tr>
<td>CD40 (activating)</td>
<td>Dacetuzumab, CP-870,893</td>
<td>In development</td>
</tr>
<tr>
<td>CD137 (activating)</td>
<td>Urelumab, PF-05082566</td>
<td>In development</td>
</tr>
<tr>
<td>OX40 (activating)</td>
<td>Anti-OX40</td>
<td>In development</td>
</tr>
<tr>
<td>TGF-beta (inhibitory)</td>
<td>Fresolimumab</td>
<td>In development</td>
</tr>
<tr>
<td>LAG-3 (inhibitory)</td>
<td>Anti-LAG-3</td>
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<tr>
<td>KIR2DL</td>
<td>Lirilumab</td>
<td>In development</td>
</tr>
</tbody>
</table>
Philadelphia positive ALL in the elderly: a European LeukemiaNet perspective

Philippe Rousselot

Hematologic Department, Hôpital Mignot, Le Chesnay, & University Versailles Saint-Quentin-en-Yvelines, France

The incidence of acute lymphoblastic leukemia (ALL) is decreasing in the elderly. However, the proportion of Philadelphia positive (Ph+) ALL is increasing. Over the age of 65 years, more than 55 % of all ALL cases are associated with the Philadelphia chromosome. This translates into relatively few patients over the age of 55 years diagnosed every year with Ph+ ALL in each European country. Therefore, joint efforts in order to conduct prospective clinical trials are mandatory in this population of patients.

In two thirds of the cases, the fusion BCR-ABL protein associated with the Ph+ chromosome is the p190 BCR-ABL resulting from the minor (m-BCR) breakpoint of the t(9;22)(q34;q11) translocation. The remaining cases are associated with the major (M-BCR) breakpoint and in few cases both can be evidenced. Additional chromosomal alterations have been classified in childhood Ph+ ALL and were found to represent 61 % of the cases. Reports suggest that this frequency might be higher in aged Ph+ ALL patients and may represent an adverse prognostic factor. These alterations may also reflect the genetic instability associated with the Ph+ chromosome. A three step model has been proposed: first the oncogenic stress driven by the BCR-ABL kinase, second CDKN2A/B deletion leading to P53 and RB inactivation and oncogenic permissiveness, and third IKZF1 and/or PAXS alterations resulting in a differentiation block and in the pre-B leukemic phenotype. As a result, Ph+ ALL is a complex, instable, and multilonal disease as recently demonstrated with the use of xenotransplantation models in NOD/SCID mice. The aim of therapy differs in aged patient as compare to younger patients. Allogeneic hematopoetic stem cells transplantation can only be proposed in a minority of elderly patients even using reduced intensity conditioning (RIC). Accordingly, high dose chemotherapy is not feasible for most of them and complete remission has to be achieved with low intensity therapy. Before the tyrosine kinase inhibitors (TKIs) era, the median survival of the elderly population with Ph+ ALL and treated with chemotherapy was less than 12 months. Less than 6 % of the patients were alive at 3 years as exemplified by the LALAG. The first use of imatinib mesylate in relapsing or refractory patients (all ages) was associated with a 19 % rate of complete remission (CR) and a disappointing 5 months overall survival. It was rapidly clear from these results that Ph+ ALL will remain a disease difficult to treat despite the use of targeted therapy. The GRAALL and others study groups proposed the use of high dose imatinib (800 mg/d) in combination with low intensity chemotherapy (weekly administration of vincristine and dexamethasone). We reported a 93 % CR rate and a median 13 months survival in patients failing chemotherapy demonstrating that imatinib efficacy can be greatly enhanced by the addition of steroids and non-genotoxic chemotherapy even in aged patients. A similar approach was tested by the GIMEMA in first line patients aged over 60 years using only steroids in combination with high dose imatinib (800 mg/d). All patients obtained hematologic complete remission and median survival was 20 months. The GMAALL Study Group made the comparison between induction with imatinib alone and induction with chemotherapy as front line therapy and concluded to better complete hematologic remission rates with imatinib (96 %) as compared to chemotherapy (50 %).

Based on these results, the European working group for ALL (EWALL) initiated a European joint study using a common chemotherapeutic backbone (based on low intensity and non genotoxic chemotherapy) in combination with dasatinib (EWALL-PH-01 study). Dasatinib is a more potent second generation TKI as compare to imatinib and is able to target not only BCR-ABL kinase activity but also some of the SRC kinases. The use of dasatinib was also supported by results in phase 2 and phase 3 trials showing efficacy of dasatinib in patients with Ph+ ALL with resistance or intolerance to imatinib. Response rates up to 40 % were observed leading to the approval of dasatinib for Ph+ ALL. The final results of the EWALL-PH-01 study have been presented during the 2012 ASH meeting. Induction therapy was based on the combination of dasatinib 140 mg/g (100 mg over 70 y) and weekly courses (up to 4) of vincristine and dexamethasone. Responding patients received a consolidation phase based on alternating administration of dasatinib and blocks of chemotherapy (intermediated-dose cytarabine, methotrexate (MTX) and asparaginase). Patients were then proposed to initiate a maintenance phase with dasatinib 100 mg/d one every other month in alternate with mercaptopurine/MTX orally up to 24 months followed by the continuation of dasatinib 100 mg/d alone. 71 patients were included and the median follow-up was 40 months. The CR rate was 94 %. Overall survival and relapse free survival at 3 y were 45 % and 38 %, respectively (only 5 patients were transplanted, 3 reduced intensity conditioning and 2 myeloablative conditioning). Median survival was greatly enhanced to 27 months (Fig. 2). Other key points of the EWALL-PH-01 study were to confirm the adverse prognosis given by additional chromosomal alterations and to point out the favorable outcome of the patient achieving a complete molecular response during consolidation. The molecular pattern of relapse was studied by conventional sequencing and using a BCR-ABL T315I allele-specific oligonucleotides (ASO) quantitative real-time PCR (RT-PCR) test. 60 % of the relapses were found to be associated with the T315I mutation. Moreover, we were able to detect the BCR-ABL T315I signal by ASO RT-PCR 3 to 6 months before relapse during follow-up in 11 patients and at diagnosis in 6 patients. Therefore, all patients with a detectable T315I by ASO RT-PCR relapsed.

What could be the future development of EWALL studies? First, the EWALL is running a second study, the EWALL-PH-02, similar to the EWALL-PH-01, using nilotinib (continuous administration) instead of dasatinib. Recruitment is ongoing in Germany and France. Second, the monitoring of resistance either by PCR or next-generation sequencing will allow to switch therapy before hematological relapse once a mutation is detected (for example, to start ponatinib in case of T315I). Third, novel agents such as blinatumomab in a near future, later chimeric antigen receptors (CARs) T-cells and also old medications such as interferon or PEG-interferon may be incorporated in the consolidation/maintenance schedule in order to avoid relapses. If patients over 60 years using only steroids in combination with high dose imatinib (800 mg/d). All patients obtained hematologic complete remission and median survival was 20 months. The GMAALL Study Group made the comparison between induction with imatinib alone and induction with chemotherapy as front line therapy and concluded to better complete hematologic remission rates with imatinib (96 %) as compared to chemotherapy (50 %).

Figure 1. Strategies to combine tyrosine kinase inhibitors and chemotherapy.

Figure 2. Overall survival observed in the EWALL-PH-01 study. 6 patients switched to imatinib and 3 to nilotinib post induction/consolidation. 5 patients were transplanted (3 RIC and 2 MAC; survival 9, 31, 16+, 25+, and 30+ months).
The morphology arm of WP10 is working on using medial microscopy (MM) as a new technology for morphological diagnosis. Morphological evaluation of peripheral blood (PB) and bone marrow (BM) cells through microscopic examination of properly stained smears remains a cornerstone in hematological diagnosis. Many factors contribute to a lack of standardization of this diagnostic tool such as differences in bone marrow processing procedures, staining, degree of skill in interpretation and terminology used. Starting from the French-American-British (FAB) morphological approach up to the latest WHO classification, emphasis has been rightly put to the relevance of all morphological aspects, quantitative as well as qualitative, for the recognition and classification of disease entities and for the most appropriate stratification of patients with hematological neoplasms. This is especially true for myeloid neoplasms and, above all, myelodysplastic syndromes. Microscopical examination therefore still remains a robust basis in the integrated diagnostic process of hematological diseases. Several studies are reported in the literature in which experienced morphologists have reviewed slides from different institutions: the rate of concordance is highly variable especially when the threshold is low, such as 3% of blasts or 10% of single lineage dysplastic cells. Traditionally, education, training, and accreditation systems are now challenging. The onset of traditional and online courses represents an effort to satisfy this peculiar need. The current information and communication technology era provides the opportunity of exchanging images and information via internet without geographic limitation saving time and resources. Computerized images harmonized according to their significance and technological aspects such as resolution, weight, and compression provide today the highest excellence in terms of accreditation, training, and information exchange. These systems and devices work with frozen images selected by photographs taken from optical microscope. Within this approach, the ELN Morphology Faculty of WP10 has as one of its major goals morphological consensus, concordance, and uniformity of diagnostic features. The outcome of these studies is freely available on-line through both ELN and EHA websites. The development of the new MM technology adds new and realistic opportunities. The MM is a robotic scanner microscope capable of digitalizing an entire or a selected part of a glass slide smear, using software to merge or stitch individually captured images taken at different focus into a composite digital image within a relatively short time (Fig. 1). By making the optical scanning of PB and BM smears available on the web, the virtual community involved in this knowledge process can be trained and harmonized adopting the diagnostic approach that closely reproduces the one adopted in the real life for the diagnosis of hematological patients at the optical microscope. Easy navigation, zooming, and microscopic field identification through a grid system do represent only some of the facilities in the use of this device. Within the ELN Morphology Faculty of WP10, we are now working with this MM. In February 2014, we will present and discuss the preliminary results of a pilot project including a small group of seven participants to test the compliance of this new technology. Within the ELN Morphology Faculty of WP10, we are currently working on one “morphologically critical” bone marrow smear with the aim to find a consensus on the monocytic cells according to WHO 2008 guidelines for a harmonized diagnosis.

In parallel, the flow cytometry arm of WP10 is working on both harmonization and accreditation. An important document issued recently in Cytometry Part B will be presented and discussed in the February meeting. This publication reflects the consensus position of an international panel gathered in early 2011 to assess accreditation issues in flow cytometry. ELN WP10 participated to both the meeting and redaction of its proceedings. M. C. Béné, head of WP10 being associate editor of this special issue. Prior to the ELN meeting, diffusion of this document will be provided to WP10 members in order to get feedback and an accurate agenda. Information will also be given on the harmonization and accreditation of cell populations at the optical microscope. Easy navigation, zooming, and microscopic field identification through a grid system do represent only some of the facilities in the use of this device. Within the ELN Morphology Faculty of WP10, we are now working with this MM. In February 2014, we will present and discuss the preliminary results of a pilot project including a small group of seven participants to test the compliance of this new technology. Within the ELN Morphology Faculty of WP10, we are currently working on one “morphologically critical” bone marrow smear with the aim to find a consensus on the monocytic cells according to WHO 2008 guidelines for a harmonized diagnosis.

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ABT-737 targets NRAS by inhibiting its partner BCL-2

Rose Ann Padua, Christine Chomienne, and Pierre Fenaux
Inserm U1131, Institut Universitaire d’Hematologie, Hospital Saint-Louis, Paris, France

It has been thought that the RAS oncogene is difficult to target as there are multiple redundant signaling pathways that can be engaged. We, among others, have previously supported this assumption in a mouse model of acute myelogenous leukemia (AML) post-myelodysplastic syndrome (MDS) established by crossing transgenic mice bearing NRASD12 and BCL-2. Both transgenes bind each other in a complex and co-localize in the mitochondria where BCL-2 normally resides with reduced apoptotic properties. In our article entitled “BCL-2 inhibition with ABT-737 prolongs survival in an NRAS/BCL-2 mouse model of AML by targeting primitive LSK and progenitor cells”82, we show that this BH3 mimetic inhibitor significantly prolongs life-span of these mice. Twenty six of 36 mice (72 %) completed the treatment with a median survival of 114 days compared to the untreated (n = 63, median survival of 40 days) and 10 non-completers, which had a similar survival as untreated mice. Significant improvements in clinical parameters were observed; the mice gained weight, had reduced percentage of bone marrow (BM) blasts with partial or complete clearance of tissue infiltration. However, as previously documented, myelotoxicity was observed.

Targeting the putative leukemic stem cell
In the development of the disease, the RAS/BCL-2 complex is found in the expanded primitive Sca1+/KIt+ (LSK) cells in the BM as reduced as are the progenitors. Self renewal is one of the hallmarks of a stem cell and cells from the diseased mice have been shown to be engrafted into lethally irradiated secondary syngeneic recipients. Cells from the treated mice resulted in recipients with increased survival compared to mice injected with untreated cells; this suggests an increase in normal progenitors after treatment and a reduction of leukemia initiating cells (LIC). The changes in cell lineage were reflected by the increase in differentiation and certain stem cell genes detected by gene expression profiling which may reflect the restoration of normal signatures.

Induction of apoptosis
One of the defining features of MDS-AML progression is apoptosis. Early or low risk MDS tends to be pro-apoptotic and as the disease progresses the cells acquire a reduced apoptotic phenotype. In our AML post-MDS model, young mice (2 weeks old) have pro-(late) apoptotic features in the BM measured with annexinV/7AAD and flow cytometry, reduced BM blasts; 8 % compared to > 60 % in the older diseased mice and an absence of tissue invasion. The older (4-5 weeks old) diseased mice have apoptosis levels similar to wild type mice which upon treatment with ABT-737 significantly increases late apoptosis of the BM of diseased mice with little effect on wild type mice measured by annexinV/7AAD staining and confirmed in the tissues by caspase 3 mediated apoptosis, increased uptake of technetium labeled annexin V and sequential single photon electron computed tomography (SPECT) measurement of the whole animal, and terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end-labeling (TUNEL) of liver section. The apoptosis genes were also upregulated measured by gene expression profiling. Therefore, this reagent differentially targets diseased cells to induce apoptosis, sparing normal cells, a feature which is desirable in cancer therapy.

Signaling
Despite the induction of apoptosis, the RAS:BCL-2 complex is not disrupted and moves from the mitochondria where BCL-2 normally localizes to the plasma membrane where RAS is located with decreased membrane potential after treatment. The front cover depicts the co-localization of the RAS:BCL-2 complex to the plasma membrane (Fig. 1).

Dephosphorylation of RAS signaling proteins ERK, AKT and normalization of signatures of MEK1 detected by NanoPro were also observed suggesting the restoration of normal function.

To summarize, ABT-737, a BH3 mimetic inhibitor is effective against an NRASD12/BCL-2-mediated mouse model of AML post-MDS to extend life-span and induce appropriate biological, biochemical and molecular responses, which warrants the initiation of clinical trials. At the time of writing, the BCL-2 specific derivative, ABT-199, which has reduced myelotoxicity, has been tested on CLL and lymphoma patients with promising results.

In April 2013, the European LeukemiaNet and Novartis re-
confirmed their successful public-private partnership which
was started in 2007 by prolonging the “European Treat-
ment and Outcome Study (EUTOS) for CML” for addi-
tional two years. The objectives are to evaluate (1) patients’
treatment by patient registries, (2) laboratory standar-
dization and validation according to the International Scale,
(3) educational and other activities for the spread of ex-
cellence, and (4) promotion of research across Europe for
moving along the path to cure in chronic myeloid leu-
kemia (CML).

Registration closed for new patients
In 2011, the prognostic EUTOS score was developed analy-
zing the data of the in-Study patients treated with imatinib-
therapy, which cannot be monitored by RQ-PCR using stan-
dard methodologies. At the onset of this project, most va-
riant patients across Europe were monitored solely by cy-
togenetic and hematologic analyses. A small number of la-
boratories in Europe (e.g. the Hammersmith Hospital) had
established primer/probe sets for some variants along with
plasmid calibrators but these were not standardized. As an
initial step to standardize monitoring of patients with rare
BCR-ABL variants, cDNA from patients with specific fusions
were sourced. Pilot plasmids were constructed and an ini-
tial service has been established at the Hammersmith. Fur-
ther samples were sourced to cover the principal rare va-
riants. All plasmid inserts were recloned into a common
background to facilitate the use of ABL, BCR, or GUSB as
an internal control genes. These plasmids were distributed
and quantitative PCR protocols for rare variants were de-
veloped enabling rare variant services to be established in
London, Jena, and Mannheim.

Meetings on behalf of EUTOS for CML -
Spread of Excellence
One major objective of the EUTOS Spread of Excellence
subgroup is to ensure that all physicians receive high-
quality medical education and resources that support
them in caring for patients with CML. Therefore, in October
2013, the ELN Frontier Meeting had taken place in Prague
with 650 attendees and 50 faculty members. For the first
time, the ELN handed out a device to give an easy and di-
rect interaction tool between the speakers and the audi-
torium in the sessions (Fig. 2).

Nearly 50 % of the audience attended for the first time
the ELN frontiers meeting and most had a university/re-
search background or worked in hospitals or clinics. Only
4 % of the audience worked in private practice. Although
this device was a good tool to learn about the background
of the audience, it does not substituted face-to-face inter-
action and time for discussion which was revealed by the
meeting evaluation. After five different sessions and the
appraised “meet the expert” sessions, the 2013 ELN Fron-
tiers Meeting was a great success as it provided a state-of-
the-art update on current developments in the understan-
ding of disease biology, diagnosis, treatment, and manage-
ment of CML, myelodysplastic syndromes, myeloprolifera-
tive neoplasms, and acute myeloid leukemia.

In May 2013, the established European fellow days in
Naples were organized on behalf of EUTOS for CML. This
educational meeting was carried out under the premise of
the current treatment paradigms of CML and future
perspectives. Ninety attendees discussed in five ses-
sions among other topics the resistance to initial treat-
ment and second line therapies for CML with reference to
clinical cases.

<table>
<thead>
<tr>
<th>Registry</th>
<th>Time of data collection</th>
<th>Enrolled patients, n</th>
<th>Study groups, n</th>
<th>European countries, n</th>
<th>Kind of data</th>
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<td>population-based</td>
<td>prospective 2008-2012 + yearly follow-ups</td>
<td>3,639 (1,802 with at least 1-year follow-up)</td>
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<td>newly diagnosed CML patients</td>
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<td>retro-perspective 2002-2006 + yearly follow-ups 2007-2011</td>
<td>2,414</td>
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<td>clinical studies, imatinib therapy starting within 6 months after diagnosis</td>
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<tr>
<td>out-Study</td>
<td>retro-perspective 2002-2006 + yearly follow-ups 2007-2011</td>
<td>1,547</td>
<td>8</td>
<td>7</td>
<td>national registries, imatinib therapy starting within 6 months after diagnosis</td>
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</table>
**News from ELN Foundation**

*Kristine Höfer*

**III. Med. Klinik, Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany**

**Funding by the ELN Foundation in 2012**
In 2012, the ELN Foundation asked for applications by the different workpackages. After reviewing the proposals by the board of the ELN Foundation, four different funds were granted. This article is about to present the funding projects and to give thereby a validation of the ELN Foundation work by supporting the work of the European LeukemiaNet.

**WP4: EURO-SKI (European Stop Tyrosine Kinase Inhibitor Study)**
EURO-SKI is a multicenter open label, uncontrolled trial estimating the persistence of molecular remission in chronic myeloid leukemia patients after stopping tyrosine kinase inhibitor (TKI). Main goal is the assessment of the duration of major molecular remission or better after stopping TKI therapy. Secondary goals include i) identification of clinical and biological factors affecting the persistence of complete molecular remission (CMR) after stopping TKI (e.g. level of CMR, risk score, duration of TKI treatment, type of TKI pretreatment), ii) evaluation of quality of life in patients stopping TKI, iii) evaluation of medico-economic impact of stopping TKI, iv) estimating the number of patients in CMR who are eligible for stopping TKI therapy by setting up a screening log, and v) time to recovery of CMR. Principal investigator of this study is S. Saussele together with F. X. Mahon. This study will be sponsored by the ELN Foundation with 10,000 € for one year.

**WP8: European MDS Study Coordinating office (EMSCO)**
Myelodysplastic syndromes (MDS) are relatively rare (4 new cases per 100,000 persons per year) diseases of the older population mainly presenting with anemia and cytopenia and frequently progressing to acute myeloid leukemia (AML). In order to answer critical questions in rare hematological diseases like MDS in an optimized time frame, an international collaboration and partnership between scientific study groups is required. There is a need to intensify our European partnership by performing collaborative clinical trials and translational studies within different study groups in the EU. Therefore, P. Fenaux and U. Platzbecker as members of the ELN MDS working group suggest establishing a European MDS studies coordination office (EMSCO). To identify potential hurdles, this office will start with only 2 groups: the German (GMDS-SG) and French (GFM) MDS groups and at least 1 cooperative trial before being extended to other countries and other clinical trials. The EMSCO will be sponsored by the ELN-Foundation with 5,000 € for one year.

**WP10: Workshop on morphology and flow cytometry in leukemia diagnosis and follow-up**
The workshop by WP10 will be a two-day interactive meeting on real-life cases respective to the workshop in October 2011 attended by young medical doctors. The morphology part is coordinated by M. C. Béné who will deal with cytologic analyses of bone marrow and peripheral blood smears collected as virtual slides for col- legial examination and interpretation. The flow cytometry part is coordinated by M. C. Béné who will deal with analysis strategies by using different software as a demonstration of real cases of leukemia, normal bone marrow, and minimal residual disease samples. The pros and cons of the various types of approaches in flow analysis will be discussed collectively and demonstrated. The workshop will be sponsored by the ELN Foundation with 10,000 € for one year.

**WP11: Rare abnormalities in MDS: Prognostic significance and inclusion in existing prognostic classification systems**
Recent publications have advanced the knowledge of the prognostic significance of clonal cytogenetic abnormalities in MDS. Based on an international collaboration, new prognostic subgroups were previously defined based on an international database containing 2,901 patients with primary, untreated MDS. However, the prognostic impact of 9% of abnormalities observed remained unknown due to their very low frequency. To increase the number of informative patients and expand the statistical robustness of these rare cytogenetic subgroups, the group of J. Schanz and D. Haase plan to initiate an international collaboration. Abnormalities defined as rare (n < 10) in the study mentioned above were: der (1;7), +1q, -1/1p-, t(5q), +11, t(11q23), -13/13q-, del(16q), del(17p), +21, -21, -X, and +mar. Furthermore, any other single abnormality not classified in an existing scoring system or mentioned above will be classified as a rare abnormality. By an international collaboration, the group intends to define the prognostic impact of single distinct infrequent, recurring cytogenetic aberrations observed in MDS patients. The project will help to expand the existing database and refine the cytogenetic prognostic classification system for patients suffering from MDS. The study will be sponsored by the ELN Foundation with 5,000 € for one year.

**Inauguration of the ELN Foundation Circle**
Public funding of the ELN will end in 2015 but the ELN will continue and expand its activity; therefore, the ELN Foundation was founded. On 4th and 5th February 2014, the 11th Annual Symposium of the European LeukemiaNet will be held. Researchers will – as every year – present intermediate results of their currently running research projects and clinical trials. The symposium is open to scientists from universities and the pharmaceutical industry. It is, hence, a unique platform to detect at an early stage innovations and initiate collaborations. At this symposium, the ELN is going to initiate the ELN Foundation Circle for companies as a vehicle to support to the ELN. Members of the circle will annually receive information on ELN-activities in a newsletter and can publicly mention membership in the circle. Members would expected to contribute annually about 10,000 €, small and medium size enterprises (SMEs) would pay half.
ASH abstract summaries

Acute lymphoblastic leukemia (ALL)

Nicola Gökbüget
Department of Medicine II, University Hospital Frankfurt, Germany

CD19 is an interesting target for the treatment of ALL since it is expressed on the surface of blast cells in all cases of B-precursor ALL. Several treatment approaches for this target have been reported during ASH 2013. One approach is the use of bispecific antibodies with the ability to re-direct T-cells to CD19 positive target cells leading to activation of the T-cells and serial cell-kill. After promising results in adult relapsed/refractory or ALL with minimal residual disease (MRD), a dose-finding trial with blinatumomab was performed in pediatric ALL patients (pts). The final dose was similar to the dose used in adult ALL. Also similar toxicities such as fever and cytokine release were observed. In 34 cases of heavily pretreated pts the observed complete remission (CR) rate was 32 % (#70).

Several abstracts referred to the use of genetically modified T-cells in relapsed/refractory ALL. Autologous T-cells of ALL pts are genetically modified ex-vivo with a chimeric antigen receptor (CAR) for CD19. This chimeric protein also includes different types of costimulatory or activa-
tion domains. Pts usually receive chemotherapy for immunosuppression before the transfer of the T-cells. The Philadelphia group reported 20 pts, mostly children. 18 pts had active disease or MRD. 2 pts were MRD negative at study inclusion. 82 % of the pts achieved a CR. 3 pts relapsed in bone marrow, 1 patient developed a myelodysplastic syndrome and 1 patient an extramedullary relapse. In some pts modified T-cells were detected for a long time during follow-up associated with a B-cell cytopenia (#67). Additional data with different CARs were reported from the Bethesda and the MSKCC group (#68; #69). Toxicity of CAR-T-cell therapy is usually dominated by symptoms of cytokine release. Several patients were successfully treated with the IL-6 antagonist tocilizumab and steroids.

In the management of Philadelphia positive (Ph+) ALL still limited data are available for the combination of 2nd generation tyrosine kinase inhibitors with intensive chemotherapy. A group from South Korea reported a trial with the combination of nilotinib with a standard chemotherapy backbone followed by nilotinib maintenance or stem cell transplantation (SCT). In 91 pts the CR rate was 90 %. 84 % of the pts achieved a molecular CR. 64 % of the pts received a SCT and overall survival after 2 years was 70 % (#55). In Europe, a trial with nilotinib combined with dose reduced chemotherapy in older patients is ongoing.

An increasing amount of data on additional molecular aberrations in Ph+ ALL becomes available. In an analy-
sis from the German group with a total of 96 pts treated with standard chemotherapy combined with imatinib and followed by SCT, CDKN2A/B deletions, IKZF1 deletions or PAX5 deletions were observed in 41 %, 61 %, and 39 % of the pts, respectively. CDKN2A/B deletions and IKZF1 deletions were significantly associated with survival outcome although all pts had received SCT (#231).

Several groups reported results of standard treatment of adult ALL. From the UKALL 2003 trial, results on toxicities in 1,502 children and young adults up to the age of 24 treated according to a pediatric protocol were reported. The incidence of SAEs increased significantly starting at the age limit of 10 years. Also the incidence of thrombotic events was associated with increasing age. Particularly the incidence of avascular bone necroses was high in the adolescent population. 83 % of these events were observed in pts aged between 10 and 19 years (#840). Overall, intensive pediatric-based chemotherapy is apparently associated with significant toxicities even in older children and young adults. Pts should be treated within clinical trials with close monitoring for these events.

Also the various participating groups of the European Working Group for Adult ALL (EWALL) reported results of their recent trials. Management of older ALL pts remains an important challenge. The Spanish group reported on the results of three trials in older pts (above 55 years) including Ph negative ALL (EWALL backbone) and Ph-positive ALL. The CR rates were 75 % in 40 Ph- pts and 86 % in 45 Ph+ pts. The corresponding overall survival rates at two years were 35 % and 51 % (#3869).

Infectious complications are a relevant problem associated with intensive induction therapy of ALL. The French group reported on the epidemiology of invasive aspergillosis (IA) during induction therapy of adult ALL. 3.7 % of 969 pts enrolled in a prospective trial (GRAALL-2005) developed IA during induction after a median time of 20 days. The mortality attributable to IA at 12 weeks was 17 % (#1394).

Prophylaxis of CNS relapse is an essential part of first-line treatment of ALL. The Italian group reported on the interim results of a randomised phase II study with two different types of CNS prophylaxis in adult ALL. Liposomal cytarabine (LAC) was compared to conventional triple intrathecal therapy (TIT) during induction and consolidation in a total of 141 pts. Neurologic toxicity of all grades occurred more frequently with LAC (53 %) compared to TIT (27 %). If reversible toxicities like headache and radicular pain were not considered, the incidences were 4 % vs 7 %, respectively. The overall survival was similar in both arms (54 % vs 52 % at 4 years) and prophylaxis of CNS relapse was effective (6 % CNS relapse with TIT vs 2 % with LAC (#3901)).
The German group reported results of two large consecutive trials with a focus on young adults aged between 15 and 35 years. Trial 07/2003 was compared to the previous trial 05/93. Major modifications included induction therapy (dexamethasone instead of prednisone, pegylated asparaginase instead of native E.coli asparaginase), intensified consolidation with focus on high-dose methotrexate and asparaginase, and SCT in pts with high or very high risk features including SCT. The CR rate improved from 88 % to 91 %. Remission duration was 49 % vs 61 % and overall survival 46 % vs 65 % in trials 05/93 and 07/2003, respectively. Improvements were seen in all subgroups despite early T-ALL. Further improvement was achieved by intensified asparaginase treatment and inclusion of rituximab for CD20 positive ALL. Overall excellent results were achieved with a pediatric based regimen adapted and optimised for the use in adults (#356).

In the NCRI AML16 trial, 616 pts were randomized to receive daunorubicin/cytarabine (DA) vs. DA + etoposide (ADE) with or without all-trans-retinoic acid (ATRA). The overall response rate (ORR) was 69 % and survival at 2 years was 35 %. Neither etoposide nor ATRA improved the outcome in this group of pts. Further, ATRA was associated with significantly greater early mortality (#493).

ATRA combined to anthracycline-based chemotherapy is the classical treatment of de novo acute promyelocytic leukemia (APL) but is myelosuppressive and may be associated with long-term cardiac toxicity. APL pts were compared for consolidation treatment with arsenic trioxide (ATO), ATRA and AraC as standard group. ATO or ATRA can replace AraC without increasing the relapse risk and can possibly reduce the rate of deaths in CR (2 and 2 pts vs 5 pts). Concomitantly used Idarubicin (Ida) and ATO proved as myelosuppressive as Ida-AraC cycles while myelosuppression was reduced with Ida-ATRA (#495).

In this phase 2 study, the efficacy of a combination therapy with low-dose lenalidomide plus low-dose AraC was tested in 45 pts ineligible for standard therapy in AML. Responding pts had a longer median overall survival than non-responders (428 vs 74 ds). The study aimed to identify biomarkers by global gene expression profiles. This identified 114 genes and 18 miRNAs associated with the clinical response playing roles in angiogenesis, cell cycle regulation, and immune response. Based on the expression of 5 genes, an algorithm to predict treatment response with an 87 % overall accuracy was developed (#496).

SGI-110 is a new hypomethylating agent that is well tolerated and clinically active in the treatment of AML. This randomized phase 2 study with 67 pts showed a CR and potent demethylation of ≥ 10 % equally in the 2 dose groups of 60 and 90 mg/m². Preliminary, overall remission rate of 53 % is promising and is favorably with previous results reported (#497).

**Acute myeloid leukemia (AML)**

Gert J. Ossenkoppele¹, Hanna Ebert²

¹ Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands
² Department of Medicine II, Goethe University Hospital, Frankfurt, Germany

A database on secondary AML patients (pts) out of 13 EORTC trials was pooled to characterize clinical features and to evaluate changes in survival. The outcome improved over time especially in younger pts and is in parallel with high-dose cytarabine (AraC) introduction and should be considered in therapy (#829).

Cyto- and moleculargenetic abnormalities evaluated at diagnosis are prognostic and predictive markers in AML. R. Schlenk et al. evaluated the probability of achieving complete remission (CR) and survival in relapsed AML pts in correlation to clinical characteristics, genetic abnormalities, and treatment. In a total of 3,218 enrolled pts of 5 AMLSG trials, an overall probability < 50 % to achieve a CR2 and CR3 was seen; exceptions are AML with CEBPA double mutant (mt) and core binding factor (CBF) AML. Allogeneic hematopoietic stem cell transplantation may overcame chemo-resistance (#830).

Primary failure of induction chemotherapy or disease recurrence after short remission duration remains a principal problem in AML. By analyzing 4,550 pts, the ability to predict therapeutic resistance based on routinely available clinical covariates, like molecular data on FLT3 and NPM1, is relatively limited. This finding would support the continued use of randomization to assign pts between standard and investigational therapies and argues for the integration of early treatment response to optimize prediction of therapeutic resistance (#64).

Gemtuzumab ozogamicin (GO) in AML treatment remains controversial. A meta-analysis in 3,339 pts was performed and the combined evidence shows a significant benefit in survival which more than outweighs any possible increase in early mortality (30-day(d) mortality). However, the benefit appears to be restricted to pts who have favorable or intermediate risk cytogenetics with the greatest benefit in pts with CBF leukemia. On the basis of this analysis, adding GO to induction improves survival in the majority of pts irregardless of FLT3 internal tandem duplication mutations (mts) (356).

SGI-110 is a new hypomethylating agent that is well tolerated and clinically active in the treatment of AML. This randomized phase 2 study with 67 pts showed a CR and potent demethylation of ≥ 10 % equally in the 2 dose groups of 60 and 90 mg/m². Preliminary, overall remission rate of 53 % is promising and is favorably with previous results reported (#497).
ASH Abstract summaries

For curative treatment of younger pts with AML, double induction with 2 cycles of intensive AraC/anthracycline based chemotherapy 21 ds apart is the current standard. With 387 pts, the prospective randomized trial analyzed improvement by a dose-dense regimen (S-HAM) with cycles minimized to 3 ds. The antileukemic efficacy was high with an ORR of 77 % for the whole group of unselected pts and neutropenia was reduced by more than 2 weeks. Pts receiving the 1 g/m² S-HAM regimen experienced the lowest early death rate ever reported. The concept of dose-density is able to combine high antileukemic efficacy with reduced hematological toxicity (#619).

In 69 de novo pts with AML, the safety and efficacy of decitabine combined with plerixafor was investigated and the clinical and biological effects of plerixafor on leukemia stem cells (LSCs) were evaluated. The combination of decitabine and plerixafor resulted in a high response rate with a favorable toxicity profile in poor-prognosis elderly pts (#621).

LSCs play a critical role in initiation and progression of AML. CD123+ LSCs might contribute to minimal residual disease (MRD) and disease recurrence. In this study, the expression of CD123 on CD34+ blast cells in 95 de novo AML pts showed 67 % association with persistent MRD. Expression of CD123 in enriched LSCs in 10 bone marrow (BM) samples was higher in AML samples at diagnosis (median 78.1 %) compared to normal BM (median 25.1 %) FLT3 mt AML expressed higher levels of CD123 within LSCs (median 90.9 % vs FLT3 wt median 69.5 %). Multiple signaling pathways are activated in CD123+ LSCs. An anti-CD123 single chain variable fragment antibody conjugate, SL-101, induces apoptotic cell death in CD123+ AML cell lines at low nanomolar concentrations and abrogates IL-3 mediated cytoprotection in FLT3 mt cells (#359).

The bispecific BiTE® antibody targets CD33 expressing cells and represents a strategy to specifically target and eliminate chemoresistant leukemic cells in AML. Over 99 % of patient samples expressed CD33 while a strong correlation between high CD33 and NPM1 mts was found. LSCs within the CD34+/CD38- compartment displayed CD33 at higher levels than controls. BiTE® exposure led to lysis of AML blasts even in samples with low expression levels and to efficient T-cell activation and expansion in primary AML samples (#239).

Chronic myeloid leukemia (CML)

Michele Baccarani, François Guilhot, Andreas Hochhaus, Sina Hehn

'Department of Hematology and Medical Oncology "L. and A. Seragnoli", University of Bologna, Italy
'OncologieHematologique et TherapieCellulaire, CHU de Poitiers, France
'KlinikfürInnereMedizin II, Jena University Hospital, Germany
'Department of Medicine II, University Hospital Frankfurt, Germany

Tyrosine kinase inhibitors (TKIs) targeting BCR-ABL form the basis for the treatment of patients (pts) with CML. Though second generation TKIs have been approved for the frontline therapy of early chronic phase (CP) pts, imatinib (IM) remains the reference therapy. The GIMEMA CML Working Party investigated the long-term outcome of IM in de novo early CP-CML (#258). Data of 559 pts were analysed regarding response rates, time to response, risk-dependent outcome, prognostic factors, and survival. The results provide an unbiased overview of the long-term therapeutic effects of IM.

In the ENESTnd trial, nilotinib (NIL) demonstrated clear superiority vs IM in terms of molecular response (MR) rate and depth and, less clearly, progression. 846 pts with CP-CML were randomized and follow-up for ≥ 4 yrs. More pts treated with NIL achieved an early MR (EMR; BCR-ABL ≤ 10 % at 3 months) compared to IM which correlated with improved efficacy and long-term outcomes. However, cardiac and vascular events were more common on NIL vs IM (#92).

In the PACE trial, ponatinib (PON) was investigated in 449 heavily pretreated pts with Philadelphia-positive leukemias (#650). In CP-CML, PON provided high rates of major cytogenetic response (MCyR) at 1 yr: 72 % in pts with T315I and 56 % in the others. 89 % of the pts who achieved a MCyR were still in MCyR at 2 yrs, 49 % and 36 % of pts with accelerated phase (AP) and blast phase (BP) CML, respectively, had a major hematologic response. Overall survival (OS) was 86 %, 72 %, and 21 % at 2 yrs for CP, AP, and BP CML, respectively. The most frequent drug-related SAEs were vascular, cardiovascular, and cerebrovascular (20 %). Thus, modification of the scheduled dose should be considered.

Since vascular events were reported in NIL treated pts, preclinical studies have been performed which revealed an inhibitory effect of NIL on cell migration and blood flow-recovery after induction of ischemia. NIL, but not IM, promotes the expression of pro-atherogenic cytoadhesion molecules and targets molecules related to angiogenesis. Both drugs induce the depletion of KIT+ mast cells being implicated as a major repair cell in vascular disorders (#257).
In order to optimize the prediction of outcome in CP-CML, Hanfstein et al. analyzed data of 301 pts enrolled in the German CML-Study IV regarding decline of the BCR-ABL transcript level within the first 3 months after the start of IM-based therapy (#253). Irrespective of the initial BCR-ABL transcript levels, a decrease to the 0.35-fold of the individual baseline value was identified a superior cut-off compared to EMR. Calculation of the individual BCR-ABL decline allowed for the identification of two risk groups (5-yr progression free survival (PFS) and OS: 77 % and 83 % vs 96 % and 98 % for high-risk vs good-risk, respectively).

In a study by Branford et al., who assessed the MR of 528 pts at 3 and 6 months, an optimal response at 3 months according to 2013 ELN recommendations was confirmed to be a significant predictor of survival (97 % vs 90 %), PFS (96 % vs 84 %), failure free survival (83 % vs 42 %), and major MR (89 % vs 42 % for EMR vs BCR-ABL > 10 %, respectively). Besides, the 6 months BCR-ABL assessment was found to provide important long-term prognostic information: any BCR-ABL decline below 10 % 6 months after start therapy significantly improves the outcome of pts with poor response at 3 months. Outcome for pts achieving BCR-ABL < 1 % at 6 months after a poor response at 3 months was comparable to pts with optimal responses at both timepoints (#254).

Leukemic stem cell (LSC) burden at diagnosis has a prognostic value regarding MR in CP-CML pts receiving first-line NIL (#649). In a substudy of ENEST1st, samples of 48 pts were analysed at baseline and after 1 and 3 months of NIL treatment to determine the fractions of normal hematopoietic stem cells (HSC) and LSC. High LSC burden at diagnosis correlated significantly with cytopenia and poor MR at 3, 9, and 18 months. By contrast, residual normal HSCs at diagnosis predicted for lower BCR-ABL transcript levels at 3 and 6 months. NIL therapy effectively diminishes the LSC pool during the first 3 months of treatment.

Two French cessation trials aimed to determine criteria to safely discontinue IM treatment in pts with sustained deep MR of a defined period of time in order to improve quality of life and save costs. 100 pts were enrolled in the STIM1 study. After a median follow-up of 50 months, 61 pts relapsed. 4 pts died from extra-hematological causes, 3 of them after relapse. All 58 relapsed pts alive restarted TKI treatment and 15 were proposed a second cessation. After the first discontinuation, 38 pts are still free of treatment. Of interest, the Sokal score at presentation remains the unique factor which influences the risk of relapse with significantly higher risk of relapse for high risk pts. In the follow-up STIM2 trial, 124 pts were included. A molecular relapse occurred in 48 pts. Among the 76 pts who successfully ceased IM, 41 experienced a BCR-ABL fluctuation which was not associated with a clinical relapse. Taken together, the non-treatment of CML pts in both studies saved 8.3 mio Euros (#255, #654).

Aiming for the identification of predictive biomarkers for relapse after TKI discontinuation, Ilander et al. analysed samples of 62 pts enrolled in the Euro-SKI trial (#379). No clinically and biologically significant patterns were detected but the pts who eventually relapsed had a significantly lower NK-cell count already at baseline, although the overall distribution of NK-cell counts was in a normal range. Furthermore, the cytotoxicity of NK-cells from pts who failed to discontinue TKI treatment was impaired.

**Myelodysplastic Syndrom (MDS)**

Theo de Witte1, Hanna Ebert2

1 Department of Tumorimmunology, Radboud Institute for Molecular Life Sciences, Radboud university medical center, Nijmegen, The Netherlands
2 Department of Medicine II, Goethe University Hospital, Frankfurt, Germany

New therapeutic strategies are needed to reduce disease burden and improve overall survival (OS) in MDS. Studies of NK cell function from MDS patients (pts) have shown diminished natural cytotoxicity against K562 targets. Samples from 67 MDS pts were obtained and NK cell degranulation, cytotoxicity, and cytokine production was evaluated focusing on CD16-induced NK cell function by using a bispecific killer cell engager specific for CD16 and CD33 antigen (CD16xCD33 BiKE). In summary, the data suggest that the CD16xCD33 BiKE may function not only against CD33+ MDS targets themselves but also against myeloid derived suppressor cells. This double hit approach may protect against MDS progression/transformation to acute myeloid leukemia (AML) through immune targeting and may improve blood counts by targeting MDS myeloid derived suppressor cells (phenotypically defined as CD33+/CD11b+/CD14-/HLA-DRlo/-) that contribute to ineffective hematopoiesis (#385).
The hypomethylating agent Azacitidine (AZA) reverses epigenetic silencing and is the first agent demonstrated to improve survival in pts with higher-risk MDS. Vorinostat, a histone deacetylase inhibitor, has demonstrated single agent activity in pts with MDS with responses of 20%. The response rate of pts treated with the combination of vorinostat and AZA was analyzed in three patient cohorts with MDS. Eligible pts (39 evaluable for toxicity and 33 for response) were entered into one of 3 cohorts with different combination of AZA and vorinostat. OS and complete remission (CR) rates and time to initial response are comparable among the cohorts and data suggest that the combination is superior to published results of AZA alone. Cohorts 2 (75 mg/m² d1-7, 600 mg/d d3-9) and 3 (55 mg/m² d1-7, 400 mg/d d3-9) with vorinostat administered for 7 days appear to be associated with longer response duration and OS. There was no suggestion of cumulative toxicity for either fatigue or gastrointestinal adverse events (#386).

Although anemia of IPSS Low and Int-1 (LR) MDS initially responds to erythropoietin stimulating agents (ESA) in 40-50% of pts, response is generally transient. The prognostic factors of response and OS to AZA is analyzed in this trial. The 93 pts included either received AZA with or without erythropoetin (EPO). In this prospective AZA trial in LR-MDS resistant to ESA, no significant prognostic factor for response to AZA +/- EPO was identified but a trend for better response was seen in SF3B1 mutated pts. Among mutations analyzed, only ASXL1 mutation predicted survival in univariate analysis while abnormal single-nucleotide-polymorphism (SNP) array-based karyotype (abk) predicted survival both in univariate and multivariate analysis. Thus, SNPabk and ASXL1 gene mutation analysis may become important tools to predict the long-term outcome of ESA resistant LR-MDS treated by AZA (#658).

In pts with MDS, a 20q deletion [del(20q)] is considered to define a cytogenetic subgroup and, if present as a sole cytogenetic aberration, is associated with a favorable prognosis according to the revised IPSS. Associated genetic lesions may have additional prognostic impact in MDS with del(20q). 305 pts with del(20q) were studied and a total of 210 (68.9 %) pts had “early” MDS (blasts below 5 %), and 95 (31.1 %) “advanced” MDS (i.e. RAEB-1/-2). Within groups with a sole del(20q) (n = 217), 74.2 % had early MDS, 25.8 % had advanced MDS. The cytogenetic subgroup of MDS with del(20q) has a good prognosis but may be further sub-classified by additional cytogenetic and molecular lesions: e.g. U2AF1 mutations were over-represented in MDS with del(20q) but this did not impact survival. However, ASXL1 mutations were relevant for disease progression (#657).

Specific chromosomal aberrations and somatic mutations constitute key elements of the pathogenesis of MDS different from primary AML (pAML). 707 cases of MDS and MDS-related disorders were applied to next generation sequencing (NGS), 205 cases were tested by whole exome sequencing. Comparing three MDS subcategories (lower-risk, higher-risk MDS and secondary AML [sAML]) in a cross-sectional view, RTK family, RAS family, IDH family, and cohesin family mutations were more frequently detected in the sAML group than in the MDS group. In contrast, the frequency of the DNMT family, TET2 and ASXL1 family gene mutations did not increase in the sAML cohort. RTK, IDH family and NPM1 mutations were more frequently observed in the pAML cohort and mutations of SF3B1 and SRSF2 were more common in MDS + sAML. This study continues to indicate the power of NGS in the molecular analysis of MDS. Some specific mutations are pathognomonic for specific subtypes while some may convey a prognostic rather than discriminatory value (#518).

This study describes the landscape of genetic lesions in 944 pts with various subtypes of MDS (#521). A total of 2,764 single nucleotide variants and insertions/deletions were called in 96 genes as high-probability somatic changes whereas 47 genes were considered as statistically significantly mutated. Only 6 genes (TET2, SF3B1, ASXL1, SRSF2, DNMT3A, and RUNX1) were mutated in > 10 % of the cases. This large-scale genetic and molecular profiling not only provided novel insights into the pathogenesis and clonal evolution of MDS but can also provide an invaluable tool for improved diagnosis, biologic sub-classification, and especially prognostication for pts with MDS. A prognostic molecular model classified pts into 4 risk groups showing significantly different OS (“low”, “intermediate”, “high”, and “very high risk”) with 3-year survival of 95.2 %, 69.3 %, 32.8 %, and 5.3 %, respectively (p < 0.001).

Myeloproliferative Neoplasms (MPN)

Jean-Jacques Kiladjian1, Sina Hehn2

1 Hôpital Saint-Louis et Université Paris Diderot, Centre d’Investigations Cliniques, Paris, France
2 University Hospital Frankfurt, Department of Medicine II, Frankfurt, Germany

Severe anemia with red blood cell (RBC) transfusion-dependence is common in patients (pts) with advanced MPN-associated myelofibrosis (MF). Tefferi and colleagues investigated the effect of pomalidomide on the improvement of anemia (#394). In a phase 3 trial, 252 pts stratified for age, type of MF, and intensity of RBC transfusions were randomized 2:1 to receive active treatment or placebo. There was no significant difference in response rates or durations of RBC transfusion independence. Other variables associated to the response such as median time to response, age, type of MF, and white blood count differed between pomalidomide or placebo, and pomalidomide appeared to reverse RBC transfusion dependence in some pts. These results suggest that a subset of MF pts (still to be clearly identified) could benefit from pomalidomide therapy.
In primary MF (PMF), mutations in ASXL1, EZH2, IDH1/2, and SRSF2 genes constitute an IPSS- and DIPPS-plus score independent Molecular High Risk category (MHR+) and predict for a significant reduction of median survival (OS) and leukemia-free survival (LFS). Guglielmelli et al. now provide evidence that the number of mutated MHR+ genes correlates with OS and LFS (#104).

Of 490 pts in the test cohort, 146 patients harboring one (22.8%) or more mutated “high risk” genes (6.9%) were classified as MHR+. In univariate analysis, both OS and LFS of MHR+ pts were significantly reduced compared to pts with no mutations (OS: 80.7 vs 148.9 months; LFS: 129 vs 323 months). In addition, having two or more mutated genes was significantly more detrimental for OS and LFS than having only one mutation in MHR+ pts. In multivariate analysis, MHR+ with two or more mutations was identified as an independent prognostic factor for OS and LFS in both low and high-risk IPSS categories.

Mutations in the aforementioned genes were also analyzed regarding their impact on spleen volume (SV) reduction, anemia development, and OS in pts with MPN-associated MF enrolled in the COMFORT II trial (#107). Though MHR+ did not significantly affect the chance of achieving SV reduction nor the risk of developing anemia in pts receiving the JAK-inhibitor ruxolitinib (RUX), the prognostic value of these detrimental mutations was maintained within this patient cohort. The OS of pts treated with best available therapy (BAT) was 0.58 vs 0.71 in the MHR+ cohort compared to pts without adverse mutations, respectively, and 0.79 vs 0.85 in RUX treated pts indicating a benefit of RUX in both subgroups.

In the placebo-controlled COMFORT I trial, RUX significantly improved splenomegaly, MF-related symptoms, quality of life (QoL), and survival in short- and medium-term analysis. Of 309 pts randomized in this study, all pts initially randomized to the control arm crossed over to RUX (median time to crossover: 41.1 weeks) shortly after the primary analysis or discontinued. The 3-year update of the results showed that the hazard of death for those pts decreased as they crossed over to RUX and the incidence of new onset grade 3 or 4 anemia and thrombocytopenia in pts treated with RUX declined (#396).

Two different studies investigated the impact of RUX as treatment prior to allogenic stem cell transplantation (alloSCT) in order to reduce SV and improve general performance status in patients with MF. 22 pts aged < 70 years were enrolled in the prospective JAK ALLO trial (#306). Depending on the platelet count, pts were treated with 10 or 15 mg BID RUX which was tapered and stopped before conditioning (melphalan and fludarabine) and alloSCT (HLA matched donor). After 2 months of RUX, 50% of pts showed a partial remission. Within 21 days after RUX discontinuation, 7 out of 10 pts who stopped RUX experienced severe adverse events (SAE) including febrile cardiogenic shocks prior to alloSCT, tumor lysis syndrome with acute renal failure, and two fatal SAEs due to acute grade III-IV graft-versus-host disease (GvHD) refractory to steroids. Currently, the enrollment was interrupted until safety is confirmed with longer follow-up and the protocol was amended.

In a second study, the outcomes of 22 pts treated with RUX before first or second fludarabine-based dose reduced conditioning prior to alloSCT from matched or mismatched donors were retrospectively assessed (#392). At the time of alloSCT, 86% had a clear improvement in constitutional symptoms and 73% had a response on spleen size. 4 pts developed an acute grade III-IV GvHD, one GvHD was fatal. Three other pts died due to progress to acute myeloid leukemia (sAML) and relapse, pneumonitis, and liver toxicity, respectively. Together, these 2 studies when completed may help to better evaluate the role of RUX before alloSCT in pts with MF.

RUX and other JAK inhibitors are unlikely to induce complete (CR) or partial remission (PR) in MF. In a pilot study, 18 pts with intermediate-2 or high-risk MF were treated with the telomerase inhibitor imetelstat (IME) (#662). After a median follow-up of 3.2 months, 2 pts discontinued the trial due to disease progression and unrelated death. One patient achieved a PR. 4 pts met the criteria for CR including reversal of bone marrow fibrosis and recovery of normal megakaryocyte morphology. Two CR pts became transfusion-independent and two had a complete molecular remission. Longer follow-up and a larger number of pts will indicate if IME can be a good candidate for MF therapy in the near future.
Diagnosis and treatment of primary myelodysplastic syndromes (MDS) in adults - Recommendations from the European LeukemiaNet

One main task of the ELN is to review and filter the new insights in diagnosis and treatment for the different forms of leukemia. The ELN standards are highly respected internationally and the ELN recommendations are requested all over the world.

In 2013, the proven CML recommendations were updated and condensed on the established mobile phone-sized pocket cards which can be directly ordered from the ELN.

Just in time for the 11th Annual ELN Symposium in Mannheim, the ELN is proud to present with the help and expertise of L. Malcovati the new recommendations for diagnosis and treatment of primary myelodysplastic syndromes (MDS) in adults.

We hope that this new chapter of ELN recommendations will reach a reputation as high as the CML recommendations. Analog to the CML pocket cards, the MDS pocket cards can be ordered from the ELN. There will be a link on the ELN website to the MDS pocket card order form. Up to 10 pocket cards will be ship for free.
The European Leukemia Trial Registry - ELTR (www.leukemia-trials.eu) is the first international registry dedicated specifically to leukemia trials. Currently, over 60 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).

### Ongoing studies in the ELTR (European Leukemia Trial Registry)

#### Acute lymphoblastic leukemia

**All subtypes**

- **GALL - Genotyping Analysis of Acute Lymphoblastic Leukemia**
- **de novo/non-treated**
  - ALL GRAALL 02/2005 - Treatment of Acute Lymphoblastic Leukemia (ALL) in Younger Adults
  - ALL PALG 5-2007 MRD - Optimization of the therapy of adult acute lymphoblastic leukemia according to risk factors and monitoring of minimal residual disease
  - ALL-SCT Ph negative - Role of autologous bone marrow transplantation plus maintenance therapy in acute lymphoblastic leukemia in adults.
  - HOVON 100 ALL - Clofarabine added to prephase and consolidation therapy in ALL
  - NILG-ALL 10/07 - Intrathecal DepoCyte and Lineage-targeted Minimal Residual Disease-oriented Therapy of ALL
  - UKALL 14 - Standard Chemotherapy With or Without Nelarabine or Rituximab in Newly Diagnosed ALL

- **not specified / all stages**
  - GIMEMA LAL1308 - Combination Chemotherapy in Treating Young Adult Patients With ALL
  - **relapsed/refractory**
    - CLDE225X2203 - A randomized study to evaluate the safety and efficacy of the two schedules of LDE225 in patients with acute leukemia

#### B-Precurso 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 - Blinatumomab for the Treatment of Minimal Residual Disease of B-precursor ALL (BLAST)

**relapsed/refractory**

- B1931022 - Inotuzumab Ozogamicin Versus Investigator's Choice Of Chemotherapy In Relapsed Or Refractory ALL
- MARALL - Monoclonal Antibodies in Recurrent or Refractory B Cell ALL
- MT103-211 - Phase II Trial with Blinatumomab in relapsed/refractory B-precursor 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
- EWALL-PH-02 - Study of induction and consolidation therapy with Nilotinib in combination with chemotherapy in older patients with Ph/BCR-ABL+ ALL

**relapsed/refractory**

- B1931022 - Inotuzumab Ozogamicin Versus Investigator's Choice Of Chemotherapy In Relapsed Or Refractory 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
- ASPIRE - Eltrombopag in Thrombocytopenic Subjects With MDS or AML
- 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
- OCEAN - Non-interventional trial on azacitidine in daily clinical practice in the Netherlands

**de novo/non-treated - Therapy concepts for all genotypes - All age groups**

- CLBH589G2101 - Oral Panobinostat With Chemotherapy in AML Patients < 65 Years
Ongoing studies in the ELTR
(European Leukemia Trial Registry)

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 Previously Untreated Acute Myeloid Leukemia
- 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 in patients from 60 years
- PANOBIDARA - Panobinostat, Idarubicin and Cytarabine in Patients Aged 65 Years or Older With Newly Diagnosed AML

de novo/non-treated - Therapy concepts for specific genotypes - < 60 years
- P060504 - 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
- MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS relapsed/refractory
- CLDE225X2203 - A randomized study to evaluate the safety and efficacy of the two schedules of LDE225 in patients with acute leukemia

FAB M3 (APL)
de novo/non-treated
- P050604 - Acute Promyelocytic Leukemia 2006 (APL)
relapsed/refractory
- PROMYSE - Acute PROMYelocytic Leukemia Study in Europe

Stem cell transplantation
- HCT vs CT - HCT Versus CT in Elderly AML

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

Chronic lymphocytic leukemia

All stages
- TPLL2 - Combined Immunochemotherapy in Patients With T-Prolymphocytic Leukemia
relapsed/refractory
- GIMEMA LLC0606 - Lenalidomide, Fludarabine, and Cyclophosphamide for Advanced Refraktory CLL

Chronic myeloid leukemia

All subtypes
- ENESTop - Study of Treatment-free Remission After Achieving Sustained MR4.5 on Nilotinib

Chronic phase
- CHOICES - Imatinib Versus Hydroxychloroquine and Imatinib in CML
- ENESTFreedom - Nilotinib Treatment-free Remission Study in CML
- ENESTPath - Study to Assess the Effect of a Longer Duration of Consolidation Treatment With Nilotinib on TFR in CP CML
- EPIC - Ponatinib in Newly Diagnosed 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
- CAMN107 Y 2101 - Nilotinib and LDE225 in the Treatment of Phase Chronic Myeloid Leukemia Patients Who Developed Resistance to Prior Therapy

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

All subtypes
- OCEAN - Non-interventional trial on azacitidine in daily clinical practice in the Netherlands

Intermediate II and high risk
- AML-NILG 02/06 - Remission Induction Therapy and Risk-oriented Postremission Strategy for Adult AML
- ASPIRE - Eットrombopag in Thrombocytopenic Subjects With MDS or AML
- Eットrombopag - Eットrombopag in MDS and AML with Thrombocytopenia
- 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
- HOVON 97 AML - Maintenance therapy with Azacitidine in elderly AML and RAEB/RAEB-T
- MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS
- PIRON01 - Iron overload in MDS patients

Low risk and intermedia I
- ARCADE - Darbepoetin Alfa in Anemic Low or Intermediate-1 Risk MDS
- AZA-MDS-003 - Azacitidine Plus BSC vs Placebo Plus BSC in Red Blood Cell Transfusion-dependent Anemia and Thrombocytopenia Due to Lower-risk MDS
- EPOANE - An Efficacy Study for Epoetin Alfa in Anemic Patients With MDS
- EUMDS - European Registry for Low and Intermediate-1 MDS
- GFM-Aza-Epo-2008-01 - Phase II study of Azacitidine and Epoetin Beta in low-risk and intermediate-1 MDS resistant to ESA
- HOVON 89 MDS - A Phase II study of lenalidomide with or without erythropoietin and G-CSF in low and intermediate-1 risk MDS
- PIRON01 - Iron overload in MDS patients
- SIMIDIS - Azacitidine and Beta Erythropoietin Treatment in Patients With MDS Red Cell Transfusion Dependent.

Myeloproliferative diseases

All subtypes
- I3X-MC-JHTB - LY2784544 in MPN

Essential Thrombocythaemia
- ARD12042 - Study With SAR302503 in Patients With Polycythemia Vera or Essential Thrombocythaemia
- PEGASYS - Pegylated Interferon Alfa-2a Versus Hydroxyurea in PV and ET

Myelofibrosis
- CLDE225X2116 - Safety and Efficacy of LDE225 + INC424 in Patients With MF
- JAKARTA - Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis
- JAKARTA2 - SAR302503 In MF Previously Treated With Ruxolitinib
- 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 Thrombocythaemia
- PEGASYS - Pegylated Interferon Alfa-2a Versus Hydroxyurea in PV and ET
- RELIEF - Switch Study From Hydroxyurea to Ruxolitinib for RELIEF of PV Symptoms

Stem cell transplantation

Supportive care
- BUM-GVHD - Efficacy and Safety Study of Budesonide to Treat Oral Chronic GvHD
- Isavuconazole WSA-CS-004 - Isavuconazole (BAL8557) for Primary Treatment of Invasive Aspergillosis
References

Dates/Meetings

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

28.02. - 02.03.2014
New molecular insights in emerging therapeutic strategies in Acute Lymphoblastic Leukemia (ALL)
Lisbon, Portugal

30.03. - 02.04.2014
European Group For Blood And Marrow Transplantation 40th Annual Meeting 2014
Milan, Italy

05. - 09.04.2014
105th Annual Meeting American Association for Cancer Research
San Diego, USA

9th Baltic Conference of Hematology
Vilnius, Lithuania

08. - 11.05.2014
18th ESH - EBMT Training Course on Haemopoietic Stem Cell Transplantation
Vienna, Austria

15. - 17.05.2014
European School of Haematology International Conference on Myelodysplastic Syndromes
Estoril, Portugal

30.05. - 03.06.2014
ASCO Annual Meeting
Chicago, USA

12. - 15.06.2014
19th Congress of EHA
Milan, Italy

04. - 07.09.2014
16th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy
Philadelphia, USA

3rd World Congress on Controversies in Hematology (COHEM)
Istanbul, Turkey

ELN Frontiers Meeting 2014
Berlin, Germany

23. - 25.10.2014
6th International Conference on Myeloproliferative Neoplasms
Estoril, Portugal

06. - 09.12.2014
56th Annual Meeting of the American Society of Hematology
San Francisco, USA

03. - 04.02.2015
12th Annual Symposium of the “European LeukemiaNet” and 16th Annual Symposium of the German Competence Network “Acute and chronic Leukemias”
Mannheim, Germany

22. - 25.02.2015
15th International Symposium on Acute Leukemias
Munich, Germany
Published:
European LeukemiaNet
Coordinator:
Prof. R. Hehlmann
Scientific Manager:
PD Dr. S. Saußele
Editor-in-Chief:
Dr. N. Gökbuget
Dr. S. Henn
Authors contributed to this issue:
Michele Baccarani
Gabriele Bartsch
Marie-Christine Béné
Christine Chomienne
Hanna Ebert
Alice Fabarius
Pierre Fenaux
Christina Ganster
Nicola Gökbuget
François Guilhot
Detlef Haase
Claudia Haferlach
Sina Henn
Andreas Hochhaus
Kristine Höfer
Jean-Jacques Kiladjian
Luca Malcovati
Satu Mustjoki
Dieter Niederwieser
Gert Ossenkoppele
Rose Ann Padua
Kimmo Porikka
Sophie Raynaud
Harald Rieder
Philippe Rousselet
Susanne Saußele
Julie Schanz
Gerrit J. Schuurhuis
Peter Vandenberghe
Theo de Witte
Gina Zini

Design and Realisation:
Schäfer Werbeagentur GmbH
Phone +49 6201 6049656
www.schaefer-werbeagentur.com

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Network of excellence
“European LeukemiaNet”
Purchase:
The Information Letter is available online at www.leukemia-net.org

Network Management Center:
PD Dr. S. Saußele
III. Medizinische Universitätsklinik
Pettenkoferstrasse 22
D-68169 Mannheim (Germany)
Phone: +49 621 3836962
Fax: +49 621 3836969
eMail: nmc@leukemia-net.org

Information Center:
Dr. N. Gökbuget
Medizinische Universitätsklinik II
Theodor-Stern-Kai 7
D-60590 Frankfurt (Germany)
Phone: +49 69 63016365
Fax: +49 69 63017463
eMail: elic@leukemia-net.org

Homepage:
www.leukemia-net.org

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