Dear Colleagues,

starting in June 2015 after the end of funding by the European Science Foundation, the ELN will be supported by a new finance concept. Thanks to the ELN Foundation, the ELN Foundation Circle, and support from new projects of ELN participants, we will be able to continue with scientific projects, the annual ELN-Symposium, and working groups for recommendations. More than that: with the new funding concept arise new prospects to foster core activities within the ultimate goal: making leukemias curable.

This information letter again reflects the broad range of subjects within the ELN: Besides news from the different work packages, you can read reports about the results of several registries: EUMDS, the EUTOS for CML, and the ELN CML Pregnancy registry. New EU-Regulations and their consequences for academic research are a topic as well as a rare leukemia subgroup, chronic myelomonocytic leukemia (CMML). And last but not least you will find abstract summaries from ASH 2014 as well as updates of the registry of ongoing leukemia trials.

We are looking forward to seeing many of you during the upcoming 12th Annual ELN Symposium in Mannheim in February 2015. This is our yearly opportunity to meet, to exchange, to build new cooperations, and to invent new projects. And this is also the occasion where we acknowledge that there are always some persons that are contributing in particular and who will be honoured with the ELN Merit Award.

The team of the Network Management Center Mannheim and

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

Dear colleagues,

we are pleased to present you the 11th Information Letter of the European LeukemiaNet. Since 2005, the Information Letter is prepared in collaboration with the contributing authors and the Network Management Center to inform all ELN members and the public about the excellent work of the ELN during the past months.

This issue mainly focuses on non-acute myeloid diseases, but it also covers the latest projects of the Cytogenetics work package and the Central Information and Communication Service (CICS). Furthermore, we report on the new EU-regulation on clinical trials. Details are still not clear but it may present another tremendous challenge for the initiators of academic studies.

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

With best regards,
Information Center

Dr. Nicola Gökbüget
Dr. Sina Hehn

Clinical endpoints for drug treatment trials in BCR-ABL1-negative classic MPNs

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The discovery of somatic mutations, primarily JAK2V617F and CALR, in classic BCR-ABL1-negative myeloproliferative neoplasms (MPNs) has generated interest in the development of molecularly targeted therapies. In exploiting the clinical research with drug treatments, the MPN community is facing the issue of testing a high number of new agents with studies whose design and methodology should be clearly agreed and outcomes should measure clinically relevant benefits for the patients. Thus, there is increasing pressure to rethink drug development in a new framework for clinical research.

A working group, comprised of members from the European LeukemiaNet (ELN) and the International Working Group for MPN Research and Treatment (IWG-MRT), has recently published consensus-based recommendations regarding trial design, patient selection, and definition of relevant endpoints for the main therapeutic key questions in MPNs [1]. The Panel selected a series of key therapeutic issues relevant to clinical research in MPNs (Tab. 1).

The most challenging area is that of developing new drug therapies in MPNs. The prognostic categories in MPN were deemed appropriate to portray disease severity and to adequately represent patients to enrol in phase I clinical trials. The Panel recommended that predicting potential toxicity from preclinical data should be informative for exclusion criteria of patients from study, thus minimizing the risk of toxicity and early trial attrition.

The use of “seamless” designs, in which a phase I protocol defines an expansion to phase II a priori (phase I/II trials) was discouraged since the maximum tolerable dose (MTD) is not necessarily the maximum effective dose: thus, with the extension phase, information on dose effectiveness could be misleading. Moreover, in the absence of predictive molecular biomarkers reflecting tumor and host biology, the efficacy results may be misleading for the planning of subsequent studies.

The Panel claimed the criterion “need of therapy” as selection criterion for phase II trials is appropriate for essential thrombocythemia (ET) and polycythemia vera (PV) patients. However, the criterion was judged too general for myelofibrosis (MF) where treatment is addressed to a variety of disease manifestations that are not feasible targets for the time horizon of phase II trials. For this reason, selection of the MF patients population in phase II trials should focus on contrasting major disease manifestations, excluding rare or life threatening complications.

The Panel stressed the importance that dose titrations or dose randomization designs should be included in the phase II studies with the expectation to allow the administration of doses lower than MTD while increasing efficacy. Under the assumption that in phase II trials the primary endpoint should act as a surrogate for a clinically relevant time-to-event endpoint, panelists critically appraised the acceptability of surrogate endpoints that represented a limited response. They convened that the use of “overall response” (complete plus partial remission), even though not validated for its surrogacy for a time-to-event endpoint, was the only adequate endpoint for phase II trials.
Phase III trials with agents having the potential of modifying the natural history of the disease are not experimentally affordable in PV and ET, where the measurable outcomes occur in a time range of decades. Testing a novel agent for MF should include all patients in need of therapy for the disease, i.e. presenting disease symptoms, manifestations, or complications. Patients with intermediate or high-risk disease, or low-risk disease but with a significant degree of splenomegaly are appropriate target populations. For phase III trials in MF, the primary endpoint should be a time-to-event endpoint that is relevant to the patients, such as overall survival (OS), or progression free survival (PFS). Analysis of time-to-event typically requires a large sample size and long follow-up time in order to identify statistically significant as well as clinically meaningful differences between treatment arms. For this reason, the Panel discussed and weighted in the context of MF patients, the shortcomings of using surrogate endpoints to reduce the cost and shorten the duration of phase III trials. None of the candidate surrogate endpoints, molecular response, pathological response, patient reported outcomes (PROs), or overall response was deemed to have adequate validation to be used in phase III trials for new drug development. Recently, pharmaceutical drug development has indicated the challenge of multiple co-primary endpoints, and regulators have recommended multiple co-primary endpoints for assessing the response of new drugs in an array of chronic and disabling disorders. Since the natural history of MF is described by elements of different origin, either related to the progression of the disease, or to therapies or unrelated to both, the Panel indicated that the combination of OS and PFS may better capture the effect of new agents on disease course.

There remain several challenges in the advancing in clinical research in MPNs. First, it should be established whether disease biomarkers, either molecular (gene mutations), inflammatory (cytokines) or PROs, meet the surrogacy principle for survival, so that they could be used as primary endpoints. Biomarker validation is a subtle process that may deserve specific clinical trials or may be achieved in clinical trials as secondary endpoints. Second, a more precise molecular classification of MPNs might become clinically practical and substitute for the clinico-pathological classification in the near future and this might improve trial design. Specific molecular studies with the techniques of next generation sequencing and wide genome screening may meet clinical needs in the future.

<table>
<thead>
<tr>
<th>Population</th>
<th>Primary endpoint</th>
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<tr>
<td>Phase I trials</td>
<td>Patients with high-risk prognostic categories</td>
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<tr>
<td>Phase II trials</td>
<td>Patients in need of therapy for ET and PV</td>
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<tr>
<td>Phase III trials</td>
<td>Patients in need of any therapy for the disease</td>
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<td>Phase III trials</td>
<td>Previously untreated patients with IPSS score 0 (low-risk disease)</td>
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<tr>
<td>Phase III trials</td>
<td>Patients in need of therapy for splenomegaly</td>
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<tr>
<td>Phase III trials</td>
<td>Patients in need of therapy for anemia</td>
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<tr>
<td>Phase III trials</td>
<td>PV patients or ET patients with high-risk of thrombosis or low risk of thrombosis with JAK2 V617F mutation or vascular risk</td>
</tr>
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</table>

Table 1. Recommendations for patient population and primary endpoints in clinical trials in Ph-neg MPNs. Legend: Ph-neg = Philadelphia negative; MPN = myeloproliferative neoplasm; PV = polycythemia vera; ET = essential thrombocythemia; MF= myelofibrosis; IPSS = International Prognosis Scoring System
Survival and prognosis in patients with first-line imatinib under particular consideration of death due to CML

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The introduction of imatinib led to 8-year overall survival probabilities above 80 % [2,3]. Many patients died of causes other than chronic myeloid leukemia (CML) [3]. However, investigators are particularly interested in the probabilities of dying of CML in order to assess the efficacy of imatinib treatment. Furthermore, to be able to use risk-adapted therapy, they would like to differentiate risk groups with regard to these probabilities.

The In-study section of the European Treatment and Outcome Study (EUTOS) provided data on 2,290 adult patients with Philadelphia chromosome-positive chronic-phase (CP) CML which allowed analyses on probabilities of dying of CML. Between 2002 and 2006 these patients were enrolled in six prospective, controlled clinical trials. Only death after recorded disease progression was regarded as “death due to CML”. Following the recommendations of the European LeukemiaNet [4], progression was defined by the observation of accelerated phase or blast crisis.

At 8 years, the overall survival (OS) probability of the 2,290 patients was 89 % [95 % confidence interval (CI): 87-90 %]. Adjusting the OS probabilities by population data which was matched to our sample by country, sex, year of and age at start of imatinib treatment (downloaded from the Human Mortality Database, www.mortality.org) and using the method of Pohar-Perme [5], an 8-year relative survival probability of 96 % [95 % CI: 93-97 %] was estimated. Cause of death was due to CML in 44 % of 208 cases. Based on our sample and treating other causes of death as competing risks, the 8-year cumulative incidence probability (CIP) of dying of CML was 4 % [CI: 4-5 %]. With regard to all three established prognostic scores [4], 2,205 patients were evaluable. The Sokal, the Euro and the EUTOS score identified 499 (23 % of 2,205), 222 (10 %), and 232 (11 %) high-risk patients, respectively. Their corresponding 8-year CIP of dying of CML was 7 % [95 % CI: 5-10 %], 12 % [95 % CI: 8-17 %], and 9 % [95 % CI: 5-13 %].

Using the regression model of Fine and Gray, higher age, more blasts, a bigger spleen size enlargement, and low platelet counts were associated with a significant increase of the CIPs of dying of CML. To find cutoffs for risk group definition, a combination of bootstrap resampling, the minimal P value approach, and kernel density estimation was applied to the resulting linear predictor of the four factors of the new prognostic score. While the CIPs of the low- and intermediate-risk patients were neither significantly different with the Sokal nor with the Euro score, three risk groups with pairwise significantly different CIPs were identified for the new score.

For a fair comparison between all four scores, independent data is collected. The results were presented at the 56th ASH Annual Meeting and Exposition [6].

Incidence of CML in Europe - an estimation from the EUTOS population-based registry

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The European Treatment and Outcome Study (EUTOS) population based registry is the first pan-European prospective study of the incidence of chronic myeloid leukemia (CML) in Europe using uniform definitions and requiring a definite diagnosis of Philadelphia-chromosome positive (Ph+) and/or BCR-ABL1-positive (BCR-ABL+) CML (Fig. 1). A robust and updated estimate of the incidence of CML is important for health care planning and for proper management of the disease.

The population-based registry aimed to document all newly diagnosed adult patients with Ph+ and/or BCR-ABL+ CML at any stage in whole countries or specified regions within countries of Europe. The registration period varied between 12 and 60 months in the different countries, from January 2008 to December 2012. Raw and standardized incidences were calculated for the countries and regions and adjusted to the registration period. For countries observed statewide, population data from the United Nations database were used. For partially observed countries, the study groups provided the population figures of the specified regions. For standardisation, the Old Europe Standard Population was used.

There were altogether 92,526,127 people living in the observed areas and the total number of newly diagnosed CML-patients with information on age and sex was 2,904, of those 2,887 were ≥ 20 years old. Registration time ranged from 12 to 60 months (median 39 months). 54 % of patients were male, the median age was 56 years (male 55 / female 57). The raw incidence for the whole registration area was 0.99 per 100,000 inhabitants per year (1.12 in males / 0.88 in females) and ranged from 0.69 in Poland to 1.39 in Italy. The standardised incidence was 0.96 per 100,000 inhabitants per year (1.10 in males / 0.82 in females) ranging from 0.7 in Austria, Poland and the UK to 1.28 in Italy. Incidence was higher in males than in females in all age groups and almost all countries. For both sexes, the yearly incidence rose from a minimum of 0.39 new cases per 100,000 inhabitants (0.47 in males, 0.29 in females) in very young adults (20-29 years old) to 1.52 (2.08 in males, and 1.18 in females) in senior adults of 70 years and more. No regional clustering of high or low incidences could be seen. Extrapolating from the raw incidence calculated in the 20 countries from 92.5 million people to all of Europe, the number of newly diagnosed patients with Ph+ and/or BCR-ABL+ CML should approximate 6,370 per year [7]. Raw and standardized incidences from the EUTOS registry fit in well with earlier findings of study groups from countries like the UK [8,9], Sweden [10], Germany [11], and France [12] that range between 0.7 and 1.1 per 100,000 inhabitants.
Gene amplifications (amp) are rarely but recurrently occurring abnormalities in myeloid neoplasia. Their most common cytogenetic manifestations are double minutes (dmin), homogenously staining regions (hsr) and unidentified marker chromosomes. Usually, gene amplifications result in significant multiplication of oncogene expression. Although trisomies and tetrasomies also cause oncogene over-representation, gene amplification is defined as the occurrence of more than four copies of a region. Frequently affected regions in myeloid neoplasia include the genes MYC (located in 8q24), MLL (located in 11q23), and RUNX1 (located in 21q22.3). However, further or other genes might be involved as the amplified region often is not restricted to the oncogene locus or amplifications do not include known oncogenes at all. Therefore, we aimed to characterize the molecular architecture of amplifications in myeloid neoplasia in more detail. We identified regions with copy numbers $\geq 3$ in eight patients (3 x myelodysplastic syndrome (MDS), 2 x acute myeloid leukemia (AML) following MDS, 3 x AML) and characterized them by using chromosomal banding, multicolour fluorescence in situ hybridization (M-FISH), interphase FISH, and SNP array (SNP-A) analysis. Two AML cases with MYC-containing dmin were included in our study. In one case, amplification of MYC was the single abnormality (Fig. 1); in the other case, it occurred together with trisomy 4. In both cases, SNP-A analysis revealed a 4.3 Mb amplified region in 8q24.13q24.21. The genes MYC and TRIB1 were affected in both patients. Previously, an overexpression of TRIB1 but not of MYC was described in 8q24 amplicons [13]. Furthermore, we analyzed amplifications of chromosome 11 in three patients (2 x AML after MDS, 1 x MDS RAEB-2). Two patients with complex abnormal karyotypes showed an MLL amplification in the form of an hsr(11q23). The third patient with AML showed an isolated del(5q) in banding analysis, but SNP-A analysis revealed a 3.7 Mb amplification of 11q24.3q25 with involvement of ETS1, but not MLL. Finally, amplifications on chromosome 21 were observed in three patients (2 x MDS, 1 x AML). Two patients showed complex aberrant karyotypes that included amplification of RUNX1 on ring-chromosomes and marker-chromosomes, and on multiple marker chromosomes, respectively. The third patient just showed dup(21)(q21q22) and r(21)(p11q22). RUNX1 was not included in the 3.6 Mb amplified region in this case, but SNP-A analysis revealed that ERG was one of the amplified genes. Gene amplification was described to be associated with rapid disease progression and short survival. Frequently, gene amplification occurs in the presence of complex karyotypes with at least three abnormalities which are generally associated with poor prognosis in AML and MDS. Oncogene amplification might promote the neoplastic transformation event resulting in complex karyotypes. MYC amplifications also occur as single aberration or in combination with trisomy 4 and there is evidence that prognosis of these patients is not as poor as MYC amplifications within a complex karyotype [14]. Given the low incidence of gene amplifications in AML (about 1 %) and MDS (<1 %) [15], a reliable evaluation of the prognosis of oncogene amplification in MDS was not achieved as yet. Neither has the involvement of oncogenes or oncogene combinations been deciphered in a comprehensive fashion although in single cases typical oncogenes do not seem to be involved in the amplification process. Therefore, we would like to suggest collecting clinical data of patients with oncogene amplifications as single aberrations or together with a second aberration within the WP 11 project “rare abnormalities” in order to answer this question conclusively. Beyond that, a delineation of stored samples of such cases by SNP-A analyses and M-FISH would be desirable.

If you are interested in this project please contact Dr. nat. techn. Christina Ganster (E-mail: christina.ganster@med.uni-goettingen.de).

**Figure 1.** MYC-amplification. Representation of chromosome 8 and double minutes by banding analysis (a), multicolor FISH (b), and interphase FISH (two cells left) and metaphase FISH (one cell right) with a probe hybridizing to the MYC-gene (c). Schematic representation of chromosome 8 (result of SNP-A analysis with allele peaks and smooth signal (copy number)). The position of the MYC-gene is shown by the vertical dashed line (d).
Tyrosine kinase inhibitors (TKIs) in clinical practice have dramatically changed the prognosis of patients with chronic myeloid leukemia (CML). CML patients diagnosed in chronic phase can reasonably have excellent disease control, good quality of life and a normal life expectancy. Therefore, it became mandatory to address issues of fertility and pregnancy. Management of CML during pregnancy is a matter of continuous debate. The cases of pregnancy are rare, practical experience is limited. Preventing of CML progression and fetus safety are the main issues. Accumulating the information and careful analyses of therapy approaches for CML during pregnancy can provide an objective picture and renew our knowledge. As the cases of pregnancy in CML observed in many countries are rare, it is reasonable to unite the data from as many centers as possible.

Two observational retrospective and prospective multicenter studies to register all female pregnancies/male conception in the TKI era have been launched in the end of 2012 in Italy (GIMEMA) and Russia (Hematology Research Center, Moscow). In 2013, we suggested to create a common Pregnancy Registry within the ELN, defined a circle of the countries willing to participate and developed the collecting databases. A summary of the data in case report forms of the registry was provided to the potential participants.

The common synopsis of the ELN CML Pregnancy Registry has been written in February 2014 (Tab. 1). New reviews dealing with how to manage a planned and/or unplanned pregnancy in CML patients have been recently published [16,17]. A detailed updated information for 54 completed pregnancy cases (70 % ended with successful delivery) in CML females from the Russian database has been presented at EHA 2014 [18], and 63 cases from the GIMEMA registry were presented at ASH 2014 [19]. There were also abstract publications for pregnancy cases from Czech Republic [20], Ukraine [21], and Uzbekistan [22] in 2013-2014.

ELN members from different countries are encouraged to harvest data following their specific institutional review board regulations. A protocol is available in English from GIMEMA to consult. A database in English in Excel format will be ready soon to collect basic information on female/male pregnancy/conception. We hope that the gathered information can help us to develop the rules and recommendations for the safe pregnancy planning and our patients will have the opportunity to live really normal lives.

### Table 1. ELN CML Pregnancy Registry. Trial design, object and purposes.

<table>
<thead>
<tr>
<th><strong>Trial design</strong></th>
<th>Multicenter study, observational, retrospective and prospective</th>
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<tbody>
<tr>
<td><strong>Object</strong></td>
<td>Registration of all pregnancies/conceptions in female and male CML patients and their managing</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td><strong>Main goal:</strong> To describe patients with CML in terms of pregnancy/conceptions outcome and managing</td>
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<td></td>
<td><strong>Secondary goals:</strong></td>
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<td></td>
<td>CML therapy managing</td>
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<td></td>
<td>Disease status before and after pregnancy</td>
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<td></td>
<td>Proportion of spontaneous abortions</td>
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<td>Proportion of foetal abnormalities</td>
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<td></td>
<td>Terms and quality of delivery</td>
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<td></td>
<td>Follow up of the newborns up to the age of 3</td>
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</table>

Ekaterina Chelysheva1, Elisabetta Abruzzese2

1 FSBI Hematology Research Centre of Ministry of Healthcare, Moscow, Russian Federation
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The European MDS Registry (EUMDS) started as an observational pan-European study aiming to prospectively collect longitudinal data from a large number of lower-risk myelodysplastic syndromes (MDS) patients in April 2008. The registry has evolved into a valuable source containing data on diagnostics, demographics, clinical parameters, health-related quality of life, disease-management and outcome of around 1800 newly diagnosed MDS patients across 141 centres in 17 countries (Fig. 1). The EUMDS population has a median age of 74.4 years, a maximum follow-up of 6.5 years and a median survival of 4.6 (95% confidence interval 4.3 to 4.9 years). Two hundred ten (12%) patients have progressed to acute myeloid leukemia/high-risk MDS.

Ongoing activities

The system is fully operational and inclusion is ongoing at an annual rate of 200-300 new cases. The concept of EUMDS has been validated annually since 2011 [23], including re-classifying cytogenetic data to allow more precise prognostication of patients (Fig. 2) [24] and the collection of data on early interventions, making it possible to evaluate the impact of erythroid stimulating agents (ESA) and transfusions on survival and health-related quality of life. These and other interim studies have been presented at international meetings. Currently, three studies are at an advanced stage of analyses and manuscripts finalization, including the description of the first 1000 patients, impact of ESA treatment, and pathophysiology of iron accumulation. The latter concerns the analysis of iron parameters including labile iron molecules NTBI (non-transferrin bound iron) and LPI (labile plasma iron) in the first 100 patients, that was presented at the recent ASH meeting. Early this year, this analysis will be extended to the entire cohort of 300 patients. Advanced statistical methods are implemented to analyse the impact of transfusions and chelation. For three more studies analyses are ongoing and for several new research questions studies are being designed or additional data is being collected.

Developments

The registry is constantly evolving through prolonged cooperation with Novartis Oncology and other funding partners, including FP7. Besides elongation of the inclusion and follow-up time, diagnostic methods will be extended with the implementation of molecular techniques and flow cytometry through the TRIAGE-MDS project, funded by FP7 and the MDS-RIGHT project recently approved for a Horizon2020 Grant (January 2015). The MDS-RIGHT project envisions to improve diagnostics, prognostication, and (disease specific) outcome assessment evaluation of quality of life, and to build a platform contributing to the communication and sustainability of MDS health care. Moreover, this project aims to increase the feasibility to identify MDS as the cause of anemia in the huge elderly, anemic population.
About CMML
Chronic myelomonocytic leukemia (CMML) is a rare chronic leukemia (1.5/100,000 inhabitants per year) which is usually observed in the elderly (mean age ~70 years). It is however also the most common myelodysplastic/myeloproliferative syndrome according to the WHO classification [25], affecting 2 to 3-fold more men than women. Based on CMML-specific prognostic models and available meta-analyses, the median overall survival for CMML patients is around 20 months but can be as short as 5 months for patients with high-risk scores including leukocyte count, blast excess and severe anemia [26-30]. Therefore, CMML represents a rare hematologic disease with a poor prognosis. Rates of transformation into acute myeloid leukemia (AML) vary from 15 % to 50 % in the literature, also depending on disease risk, and are higher in cases with proliferative features including leukocytes > 13 Gpt/L, myelemia, and splenomegaly. Many CMML patients are impaired in daily functioning by anemia, infection and bleeding as well as weight-loss, night sweats, loss of appetite, and abdominal pain due to splenomegaly. Auto-immune phenomena such as vasculitis, arthritis, and pleural effusions can add additional medically relevant problems.

The need for better treatment options for proliferative type CMML
While azacitidine is registered for non-proliferative type CMML (WBC < 13 Gpt/L), available treatment options for CMML have previously been limited to allogeneic stem cell transplantation on the one end of the spectrum and hydroxyurea on the other end. Allogeneic transplantation remains the only potentially curative option, but is only feasible for a minority of patients and is associated with considerable transplant-associate risks. For proliferative CMML patients unable to undergo allogeneic transplantation, hydroxyurea has been used for many years, and although overall response rates to hydroxyurea are high, achievement of complete remission is rare. In a randomized trial in advanced CMML, hydroxyurea proved superior to VP16, but with a modest median overall survival for hydroxyurea-treated patients of 20 months [31]. The main side effect of hydroxyurea treatment is myelosuppression, while ulcerative skin lesions are rare side effects. Improvement in therapies for CMML remains challenging due to the lack of clinical trials investigating the disease as its own clinical entity. Currently, most proliferative CMML cases are treated with hydroxyurea and supportive care rather than disease-modifying options because most current therapies do not alter the course of the disease.

DACOTA TRIAL for advanced proliferative CMML by the GFM, FISM and GMDS study groups

Pierre Fenaux1, Valeria Santini2, Sonya Faber3, Uwe Platzecker4

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The hypomethylating agent decitabine has been approved by the FDA in the US for the treatment of myelodysplastic syndromes (MDS) on the basis of a randomized phase III trial, in which CMML patients were included [32]. However, the number of CMML patients in this trial was very small. Several phase II trials using decitabine specifically in CMML patients have also been reported [33-35]. The previously published trial by Braun et al. [36] demonstrated a response rate of nearly 40 % with an acceptable toxicity profile. Most patients were treated on an outpatient basis. In summary, the outcome for patients with CMML is generally poor and there is an unmet medical need for better treatment options. Decitabine has emerged as a promising new drug, which has already been extensively studied in MDS and tested in smaller phase II trials for CMML. The drug is safe, well tolerated and effective. However, it is critical at this point to carry out a randomized trial prospectively evaluating decitabine in comparison to standard treatment with hydroxyurea, especially in terms of survival benefit.

The genetic basis of CMML - a starting point for individualized therapy
Recent breakthroughs in CMML have revealed that over 90 % of the patients carried at least one somatic mutation in 9 recurrently mutated genes. Many of these genes code for components of the splicing machinery and genes coding for epigenetic factors [37,38]. Several of the accompanying translational research projects to be carried out in this trial are based on clarifying some of the questions raised by these recent discoveries.

The translational aspects of this investigator initiated clinical trial (IIT) therefore have the potential for better delineating prognostic factors of response and overall survival and should provide important results regarding tailoring of epigenetic therapy to certain molecular subgroups of CMML.

Thierry Arber, et al. A Randomized Phase III Study of Decitabine (DAC) with or without Hydroxyurea (HY) versus HY in Patients with Advanced Proliferative Chronic Myelomonocytic leukemia (CMML) was designed in cooperation between French, German and Italian MDS study groups and is supported by EMSCO, the European MDS Study Coordination Office (www.emsco.eu).

The coordinating committee thanks Janssen for providing the study drug and for its support. Sponsor: Groupe Francophone des Myelodysplasies (GFM)
PI: P. Fenaux (France), Co-PIs: V. Santini (Italy), U. Platzecker (Germany)
The MDM-portal (Medical Data Models, available on https://medical-data-models.org) is currently the largest international open access metadata repository for medical forms [39,40] (Fig. 1). The overall objective of the MDM-portal is to develop an infrastructure not only for leukemia research, but for medical research in general and for routine healthcare. The problem: Electronic forms for documentation of patient data are an integral part within the workflow of physicians. A huge amount of data is collected either through routine documentation forms for electronic health records (EHRs) or as case report forms (CRFs) for clinical trials. This raises major scientific challenges for healthcare, since different health information systems are not necessarily compatible with each other and thus information exchange of structured data is hampered. Software vendors provide a variety of individual documentation forms according to their standard systems, which function as isolated applications. Furthermore, free availability of those forms is rarely the case. Currently, less than 5% of medical forms are freely accessible. Based on this lack of transparency harmonization of data models in health care is extremely cumbersome, thus work and know-how of completed clinical trials and routine documentation in hospitals are hard to be re-used.

The proposed solution: Open access to medical documentation forms, enabling researchers to view, discuss, download and export forms in most common technical formats. All these functions are served by the MDM-portal. Already now the portal contains more than 9,000 system-independent forms with more than 300,000 data elements available in up to 26 languages. It contains forms in CDISC ODM format (www.cdisc.org) (Operational Data Model) supporting several export functions. A focus of the system are leukemia-related forms (Fig. 2), for example several full CRF sets for acute myeloid leukemia and chronic myeloid leukemia are available. Features already included:

- Create medical forms with our ODM editor providing multilingual support of forms
- Add semantic annotations to your form elements with decision support for Unified Medical Language System (UMLS, developed by U.S. National Library of Medicine, National Institute of Health)
- Import existing medical forms by:
  - Using original ODM files (copyright and legal issues need to be respected)
  - Using our MS Excel template to create your own ODM files in MS Excel
- Re-use existing forms through our search function
- Select and compare multiple forms based on semantic annotations
- Export any ODM file into other formats for user-specific processing to
  - ADL to use a form in openEHR
  - CDA for easy information exchange or imports into systems that require CDA
  - CSV to comfortably edit a form
  - PDF to easily print them
  - R for smooth analytical usage in R
  - SPSS to work with statistic tools
  - SQL to import the form’s structure into your SQL database
  - XLSX to edit a form in MS Excel

Leukemia centers use regularly a large variety of medical documentation forms, both for research and routine healthcare (~2,000 data elements per center). Open access to all these forms and data models will improve quality of CRFs and EHR forms and speed up the process of creating documentation forms by sharing best practice and avoiding to “re-invent the wheel”.

In this matter, we would like to encourage all leukemia researchers to register and add forms and discuss existing forms. For further information please contact: imi@uni-muenster.de.
The new clinical trial EU-Regulation (EU-Reg) was established to form a harmonised approach on application and conduct of clinical trials (CT) within the EU. The application of the EU-Reg is conditional on the conduct of an audit by the European Medicines Agency (EMA) of the EU portal (EU-P) and the EU database (EU-DB) showing full functionality of the system (Fig. 1). After intensive public consolidation, also including the ELN as representative for multiple national study groups in the academic field within Europe, the EU-Reg now came into effect on June 16th 2014 and thereby repeals the Directive on CTs 2001/20/EC.

Many of the public suggestions were considered, whereas some aspects still remain unclear or depict a massive challenge of independent academic research. One major advantage is probably the central submission for international clinical trials, the indirect recommendation to use English language and the clear timelines for each step of the approval. This is probably mainly helpful for trials conducted by pharmaceutical industry with a large organisational body available.

A definition of low-risk trials, so called low-interventional (low-int) trials, was included and it is stated that less stringent rules regarding informed consent, monitoring, traceability of investigational medicinal products (IMPs), contents of the master file, and damage compensation will be applied. Low-int trials are CT that fulfill the following conditions:

- The IMPs, excluding placebos, are authorised.
- According to the CT protocol, the IMPs are used in accordance with the terms of the marketing authorisation or the use of IMP is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the member states concerned.
- The additional diagnostic or monitoring procedures do not pose more than a minimal risk or burden to the safety of the subject compared to normal clinical practice in any member state concerned.

However, many aspects are still not clear and also the corresponding national regulations have to be awaited. Problems for academic trials could specifically arise from the following parts of the process:

- Tight timelines given, e.g. to respond to questions or to include additive national regulations.
- Mandatory electronic reporting of SUSARs through the EU-P could be a problem for academic studies if specific software would be required.
- The definition of low-int trials was specified as detailed above, but less stringent rules were not specified and the assignment of low-int trials is probably a task of the reference member state.

It remains open whether submission of national trials through the EU-P is mandatory and whether or not this is really an improvement for these trials.

- The approval of investigator qualification could comprise tremendous workload. The EU-Reg states that investigator's qualifications need to be demonstrated. Investigators are defined as persons responsible for the conduct of CTs. In addition, the term 'principal investigator' (PI) is defined as the responsible leader of a team of investigators. It seems to be most likely that as a consequence, qualification documents need to be collected for both investigators and PIs. Reporting of individual qualification would include CVs, training in good clinical practice (GCP) and experience in the conduct of CTs and patient care. In Germany, these processes include most recent signed CVs, regular updates in GCP, in some cases annually, complete and detailed listing of CT experience and financial disclosure. Within the application of the EU-Reg, the exact specifications of these certificates remain unclear. Without a clear definition of requirements this approach might rise up to an enormous workload on study centres and investigators. It may also lead to continuous considerable variability between countries. Also, it remains unclear who will assess these qualifications.

- In addition, the current organisational structure for example in Germany includes a lead investigator as leader of study sites in multicentre trials, which is not destined any more in the EU-Reg. Especially in the academic field, this omission might turn out to be difficult with respect to the management in CTs.

Although it is destined to perform a review of an ethics committee (EC), details of assessment in the application process remain up to the law of the member states concerned and might be completely different with respect to the extent and contents of review as well as additional fees.

In general, it is also not clear until now, which fees will arise and if academic initiated trials will be free of charge or supported.

- Alleviations of the patient insurance and replacement by a national programme may not be realized in many countries.
- Intensification affects also the publication of data. After the end of a trial and irrespective of the outcome, a summary of the results of the CT together with a summary that is understandable to a layperson needs to be published in EU-DB within one year. Additionally, within the informed consent, the subject should be informed about the availability of this summary, and, to the extent possible, when the summaries become available. On a voluntary basis, the sponsor can also share raw data.

The EU-Reg depends on the functionality of the EU-P and EU-DB. In line with this, the EU-Reg will apply 6 months after the publication in the Official Journal of the EU but not before May 28th 2016. This long period of transition is necessary to adapt national regulations and for study centres to adapt their existing organisational systems in the conduct of CTs. For ongoing CTs, the commencement of the EU-Reg can apply after another 3 years. However, it remains unclear in which way long-term trials exceeding this timeframe need to be adjusted to the requirements of the EU-Reg or even need to be transferred into the EU-DB.

By creating a harmonised approach of one CT application for all member states, with one decision and one fee for each member state and within a narrow timeframe, the EU-Reg represents a challenging innovation on national regulation and action including ECs.

For the development of novel therapies in academic research in a multinational and multicentre approach this might be helpful, but only if the organisational burden for these independent investigator initiated trials is kept to a minimum. For the transitional period, study centers and sponsors, especially in the academic field, need to adapt standard operating procedures, quality control, and training as on the long term the administrative effort is hoped to be less. Still, it remains questionable how the different nations will act on the requirements and how the current processes that have been already established can persist.

![Figure 1. Specifications for the EU portal and EU database.](image-url)
Acute lymphoblastic leukemia (ALL)

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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. 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 with Blinatumomab in relapsed/refractory ALL the preliminary results of a large confirmative trial in MRD (minimal residual disease)-positive ALL were reported. These patients usually have a high risk of relapse and are candidates for a stem cell transplantation (SCT). This was the first international European trial with an MRD based entry criterion and corresponding MRD based response criteria. Patients with MRD ≥ 10−1 after intensive induction/consolidation or salvage treatment after relapse were included. The primary endpoint was complete MRD response after one cycle consisting of 4 weeks continuous infusion with Blinatumomab. 113 patients with a median age of 45 (18-76) years were evaluable and 78 % achieved a complete MRD response. Most frequent severe adverse events were fever, tremor, and CNS events like tremor, aphasia, or encephalopathy. Responses were observed in all subgroups independent of stage of disease or MRD level and other factors (#379). Long-term results will show whether the favourable response data are correlated to long-term outcome.

Several abstracts referred to the use of genetically modified T-cells. Autologous T-cells of ALL patients are genetically modified ex vivo with a chimeric antigen receptor (CAR) for CD19. This chimeric protein also includes different types of costimulatory or activation domains. Patients usually receive immunosuppression before the transfer of T-cells. The Philadelphia group reported results on 30 patients with pediatric CD19+ ALL. 25 had measurable disease (cytologic relapse or MRD positivity) whereas 5 patients were MRD negative before treatment. Response data (90 % complete remission (CR)) were reported for the whole group independent of the disease status before treatment. The median follow-up was 8 (6-26) months. 16 patients had continuous CR. Interestingly, modified T-cells were detected in the CSF in 17 of 19 tested patients (#380). The New York group reported results on 24 adult patients with a median age of 56 (23-74) years. 12 were included in cytological relapse and 10 with positive MRD. The median follow-up was 7 (1-34) months. Response data were reported independent of disease status at study entry (91 % CR and 90 % MRD-CR). 77 % of the patients were transferred to SCT. 6 patients were free of disease for more than 1 year whereas 5 patients relapsed (#382). Both groups reported relevant rates of cytokine release syndrome which were controlled with IL6-directed therapies. Larger, prospective multicenter trials with CAR-T-cells in clearly defined patient populations are in preparation. Two European groups reported treatment results for T-lymphotropic lymphoma (T-LBL). T-LBL is a rare subtype of non-Hodgkin lymphoma (NHL) and is combined with ALL by the WHO classification. Patients are usually treated according to protocols for ALL. The German GMALL group reported results of 149 patients treated according to two different protocols between 2004 and 2013. The median age was 31 (17-62) years. The response rate (best response) after induction/consolidation I was 73 % (CR, CRu) with 23 % additional partial remissions (PRs). Overall survival (OS) after 5 years was 65 % with no difference between patients with CR, CRu, or PR. The omission of mediastinal irradiation did not lead to higher relapse rates. PET analysis in a subset of patients revealed that none of the CRu patients was PET positive whereas 45 % of the PR patients had a positive PET result. There was a trend to an unfavourable outcome for patients with early-T-subtype, older age and later response (#370). The French GRAALL group reported results on 131 patients with T-LBL and a median age of 33 (18-59) years treated according to an ALL protocol between 2004 and 2012. Patients were candidates for SCT in CR1 if no CR/CRu was achieved after 1st induction. The overall CR rate was 91 % and the OS at 5 years was 66 %. Molecular analyses were performed in a subgroup of patients (n = 49). Patients with molecular high-risk features (no Notch1/FBXW7 mutations but mutations in N/K-RAS or PTEN deletions) had a poorer outcome. SCT was performed in 17 patients with late response and had no impact on outcome (#371). It became evident in both studies that conventional NHL-type risk factors are probably not relevant for T-LBL and that indications for SCT in first CR cannot be defined.

Antibodies to CD22 are another interesting approach for the management of B-precursor ALL. The MD Anderson Cancer center reported a first-line trial in older ALL patients (≥ 60 years) with dose reduced chemotherapy and Inotuzumab, a CD22 antibody conjugated to Calicheamicin. 26 patients were evaluable and 96 % achieved a CR. Overall 10 % of the patients relapsed and 19 % died in CR. The OS after 1 year was 81 %. Major toxicities were infections and thrombocytopenias (#794). Results are promising but larger patient numbers and a longer follow-up are required to evaluate this treatment approach.

In older patients with Ph/BCR-ABL positive (Ph+) ALL results of a study conducted by the European Working Group for Adult ALL (EWALL) were reported. Nilotinib was combined with a dose-reduced chemotherapy backbone. 36 patients with a median age of 66 (66-85) years were evaluable. The CR rate was 97 % with no early mortality. Overall 4 patients relapsed and OS at 2 years was 67 %; the rate of SCT seems to increase in this age group since 7 of 36 CR patients were transferred to SCT (#798). Data on MRD response will be essential to compare this study to the previous EWALL study with Dasatinib and a similar chemotherapy backbone.
Finally, the Italian GiMEMA group reported results of a trial in younger patients with Ph+ ALL. Induction was based on steroids and Dasatinib. Further treatment was adapted to response. Patients were candidates for SCT in case of available donor and persistent molecular disease whereas patients with molecular response were candidates for continuous Dasatinib treatment. 60 patients with a median age of 42 (19-59) years were included. The CR rate was 97 % and the OS at 2 years was 69 %. Interestingly, there was a trend towards slower molecular response and higher relapse rate in patients with p210 positive ALL (#797). The debate on the optimal TK-inhibitor, the need for intensive chemotherapy and the indications for SCT in Ph-positive ALL is ongoing.

**Chronic lymphocytic leukemia (CLL)**

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A number of important contributions on CLL were presented. What follows is a short, and inevitably incomplete, summary of key-points from some of the more relevant abstracts.

Programmed death-ligand 1 (PD-L1), which is expressed on many cancer and immune cells, is an important component of cancer immunity. Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation and secretion of cytotoxic mediators, and prevents apoptosis. Hanna et al. (#717) demonstrated in WT mice that early PD-L1 blockade effectively controls CLL development and enables complex effector function of myeloid and T-cells, thus restoring anti-tumor immune responses; Mc Clanahan et al. (#716) shown that PD-L1 expression on spleen B-cells from both WT and non-leukemic TCL1 mice was strongly induced by micro RNAs (miRs) -21 and -29, comparable to the effect of direct TLR7 and TLR9 binding by specific agonists. PD-L1 expression was highly correlated with the expression of CD69 and CD86. These observations suggest that aberrant PD-L1 expression on CLL is likely to be a result of adaptive immune resistance mediated by tumor cells-derived miRNAs.

NF-kB signaling is particularly important in B-cell malignancies. Mansouri et al. (#297) presented a NGS study of 18 NF-kB genes in a discovery cohort of 124 CLL patients subsequently validated in an independent cohort. Mutations were identified in 35 of 124 patients in the discovery series. IkB genes, which encode for cytoplasmic inhibitor proteins, accounted for 57 % of mutations, with IkBε (encoded by NFKBIE) being the most frequent. Notably, these mutations can be observed also at diagnosis at low clonal levels. NFKBIE deletions were also found in 2 % to 5 % of B-cell lymphomas.

A “subclones war” characterizes CLL. TP53 mutations present at subclonal level at diagnosis have been shown to ultimately convey poor prognosis. The same authors (Rossi et al. #295) showed that, in contrast to TP53, mutations of BIRC3, SF3B1, and NOTCH1 at subclonal level at diagnosis do not correlate with patients’ outcome, emphasizing once more the major role of TP53 mutations in CLL prognosis.

The B-cell antigen receptor (BCR) is the key to survival and proliferation of CLL cells. Drennan et al. (#830) investigated in 222 patients if variations of BCR sIgM levels correlate with clinical features, CLL B-cells phenotype, and genetic lesions. High sIgM levels were associated with a more aggressive disease even when IGHV unmutated and mutated cases were investigated separately. High sIgM CLL correlated with higher CD20, CD38, ZAP70, and CD22. Genetic analysis revealed that CLL subsets harboring trisomy 12 or del(17p)/TP53 mutations had significantly higher sIgM levels. This study supports the critical role of sIgM in CLL-associated anergy, documents the dominant role of sIgM levels on cell signaling and CLL progression, and suggests influences of genetic aberrations on sIgM levels.

Regarding treatment, several abstracts updated information on signal transduction inhibitors (ibrutinib,idelalisib). Although not yet with a meaningful follow-up, several studies show a progression free survival (PFS) and an overall survival (OS) of around 80-90 % at 3 years; remarkably, the effectiveness of these agents seems to be independent of the genetic risk (i.e. del(17p)/TP53 mutations). Signal transduction inhibitors as well as BCL2 antagonists are likely to become an important landmark in the history of CLL therapy. However, optimal treatment combinations, mechanisms accounting for resistance to therapy, clinical behavior of patients failing to these agents, and long-term toxicity need to be ascertained.

Eichhorst et al. (#19) presented the final results of the GCLLSG CLL 10 trial comparing fludarabine, cyclophosphamide, and rituximab (FCR) to bendamustine plus rituximab (BR) in the first-line treatment of fit patients. The complete remission (CR) rate was significantly higher with FCR (40.7 % vs. 31.5 %) and the median PFS was also better with FCR (53.7 vs. 43.2 months), although the latter difference was concentrated in patients with unmutated IGHV genes. No differences in PFS were observed in patients ≥ 65 years old. Importantly, no significant differences in OS at 3 years were observed (90.6 % vs. 92.2 %). While FCR remains the standard therapy in very fit patients, some elderly fit patients might benefit from BR.

Two independently conducted randomized trials (Greil et al. #20 and van Oers et al. #21) have shown that maintenance treatment with anti-CD20 monoclonal antibodies (rituximab and ofatumumab, respectively) resulted in a longer PFS. CLL could add therefore to the list of B-cell malignancies in which maintenance therapy is useful. However, before entering prime time there are many issues to be clarified: best dose and schedule, treatment duration, and toxicity (mainly infections); also whether maintenance therapy should be guided by minimal residual disease status. These studies open the door to further trials using other anti-CD20 monoclonal antibodies or other agents (e.g. lenalidomide, signal transduction inhibitors).
In summary, the abstracts on CLL presented at ASH 2014 (339 in total) did reflect the increasing interest and constant progress in this disease. CLL biological diversity and its molecular pathogenic pathways are rapidly unfolding. In addition, new targeted treatments will hopefully continue increasing life expectancy of patients with this form of leukemia.

**Chronic myeloid leukemia (CML)**

Jan Geissler, Giora Sharf, Andreas Hochhaus

Since the introduction of imatinib (IM), chronic myeloid leukemia (CML) treatment has gone through a revolution. In 2008, the first early results of 2nd generation drugs were presented which were often the last hope, other than stem cell transplant, for those patients that developed resistance or intolerance against IM.

Today, survival of patients with CML in chronic phase has become similar to that of the general population across all age groups. This was evidenced by a presentation of the EUTOS project which aggregated data from clinical trials with IM conducted by 6 European CML study groups: Within 8 years, only 4 % of patients died because of CML, while 7 % had passed away for CML unrelated causes (#153). The 5-year data of dasatinib (DASA) (#152) and 6-year data on nilotinib (NILO) 1st line (#454) demonstrate increasing rates of good responses, while we learn how best to handle co-morbidities and side effects. Hence, CML research largely focuses on optimizing treatment, on the prognostic importance of achieving the 10 % BCR-ABL milestone after 3 months of treatment, on the conditions to consider treatment-free remission, on improving quality of life, on handling side effects and comorbidities, on increasing adherence – and eventually on how to cure this disease.

Treatment-free remission or stopping treatment in stable deep molecular remission (MR) has probably been the most reported topic at this year’s ASH. The EURO-SKI trial, being the largest ongoing stop study, has just completed recruitment of 800 participants. An interim analysis of 200 patients with a minimum follow-up of 12 months was presented (#151). The study aims to define prognostic markers to increase the rate of patients in durable deep MR after stopping tyrosine kinase inhibitor (TKI) treatment, evaluate molecular monitoring procedures, and assess quality of life. Other than in earlier trials, the prerequisite for TKI discontinuation is MR² (≤ 0.01 % BCR-ABL) for more than 1 year on a minimum 3 years of TKI treatment. Therapy is restarted when major molecular response (MMR, BCR-ABL ≤ 0.1 %) is lost. The 200 patients on EURO-SKI had a median treatment duration of 8 years and 5 years of MR² before stopping TKI.

As a result of stopping, 111/200 patients (56 %) remained therapy-free after stopping TKIs and 89 relapsed. Like in the STIM study, most relapses occurred quickly within the first 6 months. Amongst those 89 patients that relapsed, 76 regained MMR and 70 returned to MR³. There have been no progressions to advanced phases. In terms of prognostic factors for relapse, the duration of prior TKI treatment and deep MR before stopping seemed to have a positive influence. Debates are still going on how to manage and prevent the “therapy withdrawal syndrome” with pain in muscles, joints or bones, sweating, skin problems, depressive episodes, tiredness, or weight loss. The estimated drug-related savings to healthcare systems in the 8 EURO-SKI countries was estimated to be 7 million Euro.

To better understand whether specific characteristics of a patient’s individual immune system has an influence on the risk of relapse after stopping, a EURO-SKI sub-study investigated how the immune system keeps a residual CML under control and whether TKIs influence the immune system (#812). The findings suggest that relapsing patients have a lower proportion and absolute number of NK-cells at the time of TKI discontinuation. The presentation raised the question whether the measurement of those might help to predict relapse.

In the education session, Michael Mauro concluded that achieving “treatment-free remission seems feasible” and that “concern over long-term risk of attempting treatment free remission has not increased”, albeit in a tightly monitored framework. This is supported by the data from 4 STOP studies presented at ASH this year. Tight monitoring within a clinical study, very sensitive PCR diagnostic in the best labs with a reliable sensitivity to measure MR⁴⁻⁵, and immediate re-initiation of therapy when PCR rises above MMR seems to provide a considerably safe framework to stop treatment. Depending on study and re-start criteria, the proportion of patients remaining in deep MR varies between 40-60 %. Both the ENESTnd studies (NILO 1st line) and DASISION studies (DASA 1st line) suggest more than half of patients on 2nd generation TKI achieves MR⁴⁻⁵ within 5-6 years and only half of them would relapse when stopping treatment - meaning approximately every fourth patient may safely stop CML treatment.

Ponatinib (PON), a 3rd generation TKI, is the only drug effective against T315I and some other mutations and seems to work very effectively in many patients after failure of IM, DASA, and NILO. The presentation by Müller et al. provided an update on the PACE phase II study, analysing the achievement of responses to PON at early time points (#518). Participants of this study had experienced a failure of DASA or NILO or developed a T315I mutation before they enrolled in this study. 60 % of the patients had at least three prior TKI treatments. 80 % of patients were resistant to NILO or DASA and 15 % were intolerant to both drugs. The median time since diagnosis was 7 years and the median follow-up was 38 months. After 12 months of PON therapy, 56 % of patients achieved a complete cytogenetic response and 39 % a MMR. The two-year overall survival was 90 % of those that achieved < 1 % BCR-ABL vs. 84 % of those with BCR-ABL ≥ 1 % after 3 months of PON therapy. Achieving an MMR early in treatment with PON seemed to improve outcomes. This means that even after failing 2nd generation TKIs, a significant proportion of patients achieves good responses on PON. Early monitoring of response might help to decide whether continuing with the therapy or switching to bone marrow transplant might be the preferred option for the individual patient.
A presentation by Lipton et al. described the phase III EPIC trial which investigated PON as a 1st line treatment in comparison to IM (#519). Even though the study was suspended in 10/13, the safety and efficacy data up to the point of study termination, by which patients received on median 5 months of PON, has been presented. 36 % of patients on PON had to reduce the dose (initially 45 mg/d) due to side effects. 57 % had to interrupt treatment. However, 94 % of PON patients vs. 68 % of IM patients achieved < 10 % BCR-ABL at 3 months, and 15 % of PON patients, as opposed to none of the IM patients, achieved even an MR4.5 within that short time frame. However, there was clearly a higher incidence of severe adverse events with PON. Most critical were vascular events, which 7 % of the PON and less than 1 % of the IM patients experienced.

Fixed starting doses of 45 mg/d were used in all recent PON studies, but the option of treatment interruptions and dose reductions in those trials coupled with multiple assessments of molecular responses enabled now to explore dose-response relationships. With regards to the association of doses and side effects, an analysis of 671 PON patients of different studies (#4546) demonstrated that PON dosing level is associated with many side effects including blood clotting and narrowing of blood vessels. The data supports approaches to reduce the average dose level, such as starting at lower doses and/or reducing dose when response is achieved, to reduce toxicity while keeping high efficacy of the treatment. For patients with resistance or intolerance on other TKI and for patients harboring the T315I mutation, PON is an important treatment option. It however seems that the trials that led to approval of PON have aimed too high in terms of dosing, focusing too much on best efficacy against CML while taking not enough time to scrutinize toxicity. The mechanisms that cause these side effects are still poorly understood. Cardiovascular risk factors will be watched more closely now, e.g. high blood pressure, diabetes, and previous cardiovascular events. The PON data reflects benefit-risk discussions. It provides a good basis for dose-ranging trials which might investigate dynamic dosing schemes for still effective treatment with reduced side effects.

Myelodysplastic syndrome (MDS)

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The emerging new technologies over the last decade have significantly improved our understanding of the biology of MDS and have led to new targets with novel therapeutic approaches. The work by Fink et al. (#4) was selected for plenary scientific session. Lenalidomide (LEN) treatment decreased Casein kinase 1A1 (CSNK1A1) protein levels in human cell lines in a dose-dependent manner without altering CSNK1A1 mRNA levels. CSNK1A1 increases ubiquitination and decreases protein abundance following LEN treatment. This gene is encoded in the del(5q) commonly deleted region and is thus a potential LEN target in del(5q) MDS. Interestingly, the same group (Scheider et al. #1892) generated a murine model for conditional, heterozygous inactivation of Rps14 providing in vivo evidence that Rps14 haploinsufficiency contributes to the erythroid differentiation defect in del(5q) MDS by reduced protein synthesis and p53 induction in late-stage erythroblasts. Liu et al. (#526) showed that HSPA9 (gene located at 5q33.1) knockdown may contribute to TP53 activation and increased apoptosis observed in del(5q)-associated MDS. In patients (pts) without 5q-, treated with LEN in a prospective trial, Chesnais et al. (#533) failed to demonstrate the presence of a mutation related to the resistance to LEN. However, a low expression level of NPM1 associated with an A/A polymorphism of CRBN was highly predictive of treatment failure by LEN in this group. According to Meggendorfer et al. (#4608) two thirds of pts with 5q- had other mutations, being the genes more frequently mutated DNMT3A and TP53 (18 %) as well as SF3B1 (17 %). Kotini et al. (#524) developed an interesting model based on the generation of induced pluripotent stem cells (iPSCs) from bone marrow hematopoietic cells of two MDS pts, demonstrating that del(7q) abnormality confers a profound loss of hematopoietic potential, mediated through haploinsufficiency of one or more genes. Alkhatabi et al. (#1885) studied miR-595, localized to 7q36.3, demonstrating that haploinsufficiency of miR-595 in pts with -7/7q del is important in pathogenesis of reduced erythropoiesis and a reduction in myeloid and erythroid progenitor populations. The effects are mediated via the ribosomal protein RPL27A.

Several papers explored the genes involved in the splicing machinery. Shiozawa et al. (#826) showed a relationship between the presence of SF3B1 mutations and the presence of more splicing changes, mainly in genes involved in heme biosynthesis, cell cycle progression, and DNA repair while mutations in SRSF2 and U2AF1 were related to an alternative exon usage, and ZRSR2 mutations were associated with retentions of U12 introns. Shirai et al. (#827) generated a mutant U2AF1 mouse model leading to an altered hematopoiesis and changes in the pre-mRNA splicing.

In summary, new and exciting data about the molecular abnormalities in MDS will provide the biological basis for new therapies.

Anemia remains the main problem in pts with lower-risk MDS (LR-MDS). These pts are offered, in addition to RBC transfusions, erythroid stimulating agents (ESA) and LEN, especially if they carry the 5q- abnormality. But, what about non-responding patients?

Platzecker et al. (#411) presented the preliminary results of a phase 2, dose-finding study with ACE-536, a recombinant fusion protein containing modified activin receptor. ACE-536
binds to TGF-β ligands, inhibits Smad2/3 signaling and promotes late stage erythroid differentiation unrelated to ESA effects. Two of the 7 pts with low transfusion burden (LTB, < 4 u/8 wk) increased their Hb > 1.5 g/dL within 8 weeks, and 6 pts achieved transfusion independence (TI). 6/19 pts with high TB (HTB) demonstrated decreased TB. Komrokj et al. (#3251) have conducted a phase 2 study of sotatercept (ACE-011), an activin type IIA receptor fusion protein that acts on late erythropoiesis, in LR-MDS with ESA failure or high serum EPO. Response (Hi-E) was observed in 21/53 pts (40 %), while 19/44 pts with HTB responded with reduced TB. 8/9 pts with LTB increased their Hb. Santini et al. (#409) performed a phase 3 randomized controlled trial (RCT) with LEN vs. placebo in RBC-transfusion dependent pts with LR-MDS without del (5q) after failure to ESA. The population comprised 239 pts (LEN 160, placebo 79). The erythroid response rate among LEN-treated pts was 26.9 % vs. 2.5 %. Myelosuppression was the main adverse event (AE), with discontinuation of 32 % due to AE. Kuendgen et al. (#1918) administered LEN with valproic acid, a histone deacetylase (HDAC) inhibitor, and observed overall response rate (ORR) of 39 % (9/23).

Hypomethylating agents (HMA) have become the standard therapy in higher-risk MDS (HR-MDS). However, the response rate is only 50 % with response duration of 2 yr. Several groups are trying to address treatment of pts who have failed HMA therapy.

Garcia-Manero et al. (#163) conducted a multinational phase III RCT with rigosertib, a small molecule inhibitor of PI3-kinase and PLK pathways, vs. best supportive care (BSC), the ONTIME trial. 199 of 299 pts enrolled received rigosertib IV 1800 mg/24 h for 72 h every 2 weeks for the first 16 wk, then every 4 wk. The median overall survival (OS) of rigosertib-treated pts was only 8.2 m vs. 5.9 m for BSC. In a phase I/II trial, DiNardo et al. (#164) treated 88 HR-MDS pts with monthly cycles of AZA 75 mg/m/dx5d followed by LEN (optimal dose 25 mg/d). The ORR was 35 % (31/88) with 15 CR and CRi, and OS of 33 wk. The ORR in the pts receiving the optimal LEN dose was 55 % (22/40) with a longer OS (75 wk). 6/9 TP53 mutant pts and complex karyotypes achieved CR/Cri. Finelli et al. (#4648) compared AZA (75 mg/m/dx5d) + LEN (10 mg/d) combined (d1-21, 19 pts) vs. sequentially (21 pts), 13/22 (59 %) responded with 2 CR, 2 PR, 2 mCR, and 7 HI. The combined approach appeared superior. Hirai et al. (#3260) combined standard AZA regimen with low dose Ara-C (LDAC), given SC the same day. They treated 27 HR-MDS/AML pts with 1-2 cycles of AZA-LDAC followed by AZA maintenance, while 22 pts received AZA only. The ORR was 74 % (AZA-LDAC) vs. 27 % and OS of 19 m vs. 5.8 m! The safety profile was similar in both arms. Garcia-Manero et al. (#3277) tested the combination of AZA with the HDAC inhibitor vorinostat in untreated HR-MDS/AML pts with poor performance and comorbidities. The 60 d survival was superior (85 %) among the 52 pts treated with AZA-vorinostat vs. only 67 % (27 pts treated with AZA only), but the other outcomes were comparably poor. The safety profile was reasonable.

In conclusion, the current outcomes are not satisfactory yet, especially with HR-MDS, but progress is being made.
Ongoing studies in the ELTR
(European Leukemia Trial Registry)

Acute lymphoblastic leukemia

All subtypes
- GALL - Genotyping Analysis of Acute Lymphoblastic Leukemia
- GIMEMA LAL1308 - Combination Chemotherapy in Treating Young Adult Patients With ALL

de novo/non-treated
- ALL GRAALL 02/2005 - Treatment of Acute Lymphoblastic Leukemia (ALL) in Younger Adults
- ALL PALL S-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 Neltarabine or Rituximab in Newly Diagnosed ALL

B-precursor ALL

de novo/non-treated
- ALL GRAALL 02/2005-R - Mabthera + induction, consolidation and late intensification in Ph neg., CD20+ ALL
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
- TOWER - Phase 3 Trial of Blinatumomab vs Investigator’s Choice of Chemotherapy in Patients With Relapsed or Refractory 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
relapsed/refractory
- ALCANTARA - Phase 2 Trial of Blinatumomab vs. Investigator’s Choice of Chemotherapy in Patients With Relapsed or Refractory ALL
- B1931022 - Inotuzumab Ozogamicin Versus Investigator’s Choice Of Chemotherapy In Relapsed Or Refractory ALL
- CABL001X2101 - Phase I Studie zur Behandlung von CML oder PH+ALL mit ABL001

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 - Etrombopag 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
- MDS Clofarabine - Clofarabine, Cytarabine, and Idarubicin in Intermediate-Risk or High-Risk AML or High-Risk MDS

FAB M3 (APL)
de novo/non-treated
- P060504 - Timed-Sequential Induction in CBF-AML

relapsed/refractory
- PROMYSE - Acute PROMyelocytic Leukemia Study in Europe

Stem cell transplantation
- HCT vs CT - HCT Versus CT in Elderly AML
Chronic lymphatic leukemia

- TPLL2 - Combined Immunochemotherapy in Patients With T-Prolymphocytic Leukemia

Chronic myeloid leukemia

Accelerated phase
- CA180-373 - Phase I Study with Dasatinib plus Nivolumab in CML
- CABLO01X2101 - Phase I Study of oral ABL001 in patients with CML or Ph+ALL

Chronic Phase
- BFORE (AV001) - Phase 3 study of Bosutinib versus Imatinib in adult patients with de novo CP-CML
- CHOICES - Imatinib Versus Hydroxychloroquine and Imatinib in CML
- EUREKA - Registry in the ELN for CP-CML patients after two years of therapy with tyrosine kinase inhibitors
- OPTIM DASATINIB - Phase II study to optimize the residual plasma level of dasatinib in chronic phase CML
- SPIRIT 2 - Comparison of Imatinib Versus Dasatinib in Newly-diagnosed CP-CML

Complete molecular remission (MR4)
- DASFREE - Evaluating Dasatinib therapy discontinuation in patients with CP-CML with stable CMR
- EuroSKI - Stopping TKI in patients with CML in complete molecular remission (MR4)

Intolerant/resistant to one TKI
- CA180-373 - Phase I Study with Dasatinib plus Nivolumab in CML
- CABLO01X2101 - Phase I Study of oral ABL001 in patients with CML or Ph+ALL

Myelodysplastic Syndrome

All subtypes
- MDS Registry - German Registry for myelodysplastic syndromes
- OCEAN - Non-interventional trial on azacitidine in daily clinical practice in the Netherlands
- PIRON01 - Iron overload in MDS patients

Intermediate II and high risk
- AML-NILG 02/06 - Remission Induction Therapy and Risk-oriented Postremission Strategy for Adult AML
- ASPIRE - Ertrombopag 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
- 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

Low risk and intermedia I
- ARCADE - Darbepoetin Alfa in Anemic Low or Intermediate-1 Risk MDS
- A2A-MDS-003 - Azacitidine Plus BSC vs Placebo Plus BSC in Red Blood Cell Transfusion-dependent Anemia and Thrombocytopenia Due to Lower-risk 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
- SIMIDIS - Azacitidine and Beta Erythropoietin Treatment in Patients With MDS Red Cell Transfusion Dependent.
**Myeloproliferative neoplasm**

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

**Essential Thrombocythaemia**
- ARD12042 - Study With SAR302503 in Patients With Polycythemia Vera or Essential Thrombocythemia
- Gilead-US-354-0101 - Safety and Efficacy of Momelotinib in Subjects With Polycythemia Vera or Essential Thrombocythemia
- PEGASYS - Pegylated Interferon Alfa-2a Versus Hydroxyurea in PV and ET

**Myelofibrosis**
- CINC424A2104 (HARMONY) - Phase I trial on Ruxolitinib in combination with BKM120 in patients with PMF, PPV-MF and PET-MF
- CLDE225X2116 - Safety and Efficacy of LDE225 + INC424 in Patients With MF
- EXPAND - Dosefinding of Ruxolitinib with PMF, PPV-MF or PET-MF patients
- Gilead GS-US-352-0101 - Phase 2 Study evaluating Momelotinib vs. Ruxolitinib in subjects with in PMF, Post-PV-MF, Post-ET-MF
- JAKARTA - Phase III Study of SAR302503 in Intermediate-2 and High Risk Patients With Myelofibrosis
- JAKARTA2 - SAR302503 In MF Previously Treated With Ruxolitinib

**Polycythaemia vera**
- ARD12042 - Study With SAR302503 in Patients With Polycythemia Vera or Essential Thrombocythemia
- Gilead-US-354-0101 - Safety and Efficacy of Momelotinib in Subjects With Polycythemia Vera or Essential Thrombocythemia
- PEGASYS - Pegylated Interferon Alfa-2a Versus Hydroxyurea in PV and ET
- RESPONSE 2 (CINC424B2401) - Phase IIib Study Evaluating the Efficacy and Safety of Ruxolitinib vs BAT in PV Resistant or Intolerant to Hydroxyurea

**Supportive Care**
- BUM-S/GVH - 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

**22. - 25.02.2015**  
15th International Symposium on Acute Leukemias  
Munich, Germany

**29.04. - 02.05.2015**  
13th International Symposium on Myelodysplastic syndromes (MDS 2015)  
Washington, USA

**29.05. - 02.06.2015**  
ASCO Annual Meeting 2015  
Chicago, USA

**11. - 14.06.2015**  
20th Congress of EHA  
Vienna, Austria

**09. - 13.10.2015**  
Jahrestagung der DGHO, ÖGHO, SGMO und SGH  
Basel, Switzerland

**05. - 08.12.2015**  
57th ASH Annual Meeting and Exposition  
Orlando, USA