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Dear colleagues,

2015 was the first year for ELN to get along without public funding. Thanks to the ELN Foundation, the ELN Foundation Circle, and support from new projects of ELN participants, it was nevertheless a productive and successful year. Since sustainability is a key issue to keep the ELN as source of interaction and cooperativity alive, we are proud that the new finance concept turned out to perform well.

In June at EHA, we had a very lively press conference focusing on the conclusion of a unique public private partnership: the European Treatment and Outcome Study (EUTOS) for CML project. Starting in 2007, this cooperation between Novartis Oncology Europe and the ELN aimed at fostering diagnosis, treatment, and outcome of chronic myeloid leukemia and resulted in a European patient registry of 7000 CML patients and improved quality of molecular monitoring across Europe.

Also in June at EHA, a new European project with the ELN as broadly positioned partner started: In the frame of the European Horizon 2020 program, the MDS-RIGHT project targets on how to provide the right care to the right patient with myelodysplastic syndrome at the right time. The ELN will be involved in dissemination, guideline and website development, and network setup.

This ELN newsletter again presents current activities within the ELN. The reports on recent ASH abstracts reflect the ongoing discussions in leukemia research and management. I am sure this Information Letter will catch your attention.

I wish you a successful 2016.

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

Dear colleagues,

we are pleased to present you the 12th Information Letter of the European LeukemiaNet - visually altered, but as informative as usual. In this year’s issue, we report on the results of PROMYSE, a registry for relapsed APL which was started in 2009, on new therapies and the role of TP53 alterations in chronic lymphocytic leukemia, and on interferon-based CML-regimens. The broad range of topics also involves a new prognostic score for chronic myeloid leukemia, the validation of the MDS international prognostic scoring system based on FISH analyses, and again the new EU-regulation on clinical trials.

We also introduce two new partner projects of the European LeukemiaNet: As part of the European Horizon 2020 program, the MDS-RIGHT project has started earlier last year and in AML, a novel international online resource – the AML global portal – has been launched.

One comment on our own behalf: Much to our regret, the European Leukemia Trial Registry (ELTR) has been shut down in 2015 due to lack of funding. Despite this, we try to keep the website as well as the e-newsletter and the Information Letter available for the announcement of new studies and we would like to encourage all ELN members to take advantage of these services.

Last but not least, we would like to thank the contributing authors for their support.

We hope you will enjoy reading.

With best regards,

Dr. Sina Hehn | Dr. Nicola Gökbuget
Information Center
During the last decades, acute promyelocytic leukemia (APL) has developed from a highly fatal to the most curable type of acute myeloid leukemia with a very low relapse rate. Arsenic is the most effective mono-substance in all stages of APL [1]. In the year 2008, a European registry of relapsed APL (PROMYSE) was established under the auspices of the European LeukemiaNet (ELN) to gain insights into the characteristics of relapsed APL and to assess the curative potential of salvage therapy with arsenic trioxide (ATO). Patients with all grades of genetically confirmed PML/RARA-positive molecular or clinical relapse of APL occurring from January 2003 onwards were eligible independent of the administered therapy.

Among 237 registered patients, 155 cases with relapse of APL after standard frontline therapy with all-trans retinoic acid (ATRA) and chemotherapy from eight European countries (France, Germany, Greece, Italy, Spain, Sweden, Switzerland, United Kingdom) had received salvage therapy with ATO for first hematological (n = 104, 67%), molecular (n = 40, 26%), or extramedullary (n = 11, 7%) mainly CNS relapse.

Treatment was performed according to the recommendations for relapsed APL available at the ELN website (www.leukemia-net.org) based on a consensus of the European APL Group of Experts [2]. After two courses of ATO±ATRA for induction and consolidation therapy, options for post-consolidation therapy were autologous and allogeneic stem cell transplantation, further ATO cycles, or various modifications of maintenance therapy of which the most appropriate treatment should be selected individually by the treating physician. The characteristics, therapy, and outcome of the 155 patients were described in detail in an original article published in Leukemia in May 2015 [3]. Most relevant results are summarized here.

**Induction and consolidation therapy with ATO±ATRA**

In the 104 patients with hematological relapse, complete hematological remission (CR) was seen in 91%, resistance in 2%, and induction death in 7%. No induction death occurred in patients with molecular or extramedullary relapse. There was no significant difference in the molecular remission rates in patients with hematological and molecular relapse after induction (53% vs. 54%; p = 1.0) and consolidation therapy (74% and 62%; p = 0.3). All patients with extramedullary relapse entered CR. ATO was less well tolerated in patients with hematological compared to molecular relapse (APL differentiation syndrome p < 0.001, leukocytosis p < 0.001, infections/fever of unknown origin p = 0.002).

**Results of post-consolidation therapy with or without transplantation**

After ATO±ATRA induction and consolidation treatment, 60 patients underwent autologous, 33 allogeneic transplantation, or received other treatments (n = 55). The characteristics of the patients assigned to the respective options of post-consolidation therapy were heterogeneous as in 52% of the allogeneic transplanted group the RT-PCR for PML/RARA was positive before transplantation compared to only 2% in the autologous group (p < 0.001). Not-transplanted patients were significantly older (p < 0.001) precluding a direct comparison of the approaches. Patients who were not transplanted (n = 55) received heterogeneous treatment including continuation of ATO cycles in 21 cases.

With a median follow up of 3.2 years, 3 year overall survival (OS) and cumulative incidence of relapse (CIR) in the whole population were 70% and 42%, respectively (Fig. 1). There was no difference in OS (p = 0.85) and CIR (p = 0.39) between the patients in hematological and molecular relapse.

![Figure 1: OS (A) and CIR (B) of all pts treated with ATO in first relapse of APL](image-url)
lapse (Fig. 2). The outcome after autologous or allogeneic transplantation or other treatments is shown in Figure 3. Three year OS was 80% in the combined transplantation group (autologous or allogeneic) compared to 59% of non-transplanted patients (p = 0.03).

Prognostic factors of outcome
Multivariable analysis demonstrated the favorable prognostic impact of first remission duration ≥ 1.5 years, achievement of molecular remission after ATO salvage, and allogeneic or autologous transplantation on OS of patients alive after induction (p = 0.03, p = 0.01, p = 0.01) and on leukemia free survival (LFS) (p = 0.006, p < 0.0001, p = 0.003), respectively.

Conclusions
The PROMYSE registry includes the largest cohort of APL patients in first relapse of APL treated with ATO after frontline therapy with ATRA and chemotherapy. At least 50% of these patients can probably be cured by ATO-based salvage suggesting a survival improvement after first relapse of approximately 20% by comparison to previous results obtained with ATRA and chemotherapy salvage [4]. By multivariable analysis, short remission duration, persistent PCR positivity, and the absence of transplantation were associated with poor prognosis of OS and LFS.

Unexpectedly and contrary to previous reports, there was no survival advantage beyond one year in patients with molecular compared to those with hematological relapse. The more favorable clinical and laboratory parameters of patients in molecular relapse may explain the lower-risk of early complications. Despite the lower leukemic burden in patients with molecular relapse, the rates of molecular remission after induction were similar. In patients with extramedullary relapse, it appears that ATO which penetrates the CNS may contribute to improved prognosis (OS of 90%).

Regarding post-consolidation therapy, the results indicate a potential survival benefit for transplantation (al-
logeneic or autologous) compared to no transplantation in 2nd CR. Despite limited comparability of the three patient groups, the present results still support performing transplantation after first relapse whenever possible. Interestingly, in not-transplanted patients, prolonged second remissions could be observed with continuation of ATO therapy suggesting further investigations of this transplantation-free approach.

The retrospective nature of data collection and the heterogeneous post-consolidation therapy are limitations of this analysis. However, virtually all patients had received state-of-the-art frontline therapy and all participating countries followed the European treatment recommendations for relapsed APL [2]. By uniform CRFs, too large differences in the management and documentation of patients were avoided. Under such conditions, registry data, as generated by this common European initiative, may provide valuable information on the outcome of patients with rare diseases like relapsed APL.

References

TP53 defect: The irrepressible fortress in chronic lymphocytic leukemia?

Joost S. Vermaat¹, G. Doreen te Raa¹ and Arnon P. Kater¹,² on behalf of the European Research Initiative on CLL

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Thus far, cytogenetic aberrations of the pivotal regulators of the DNA damage response (DDR) pathway, i.e. TP53 and ATM, have been shown to provide the most powerful predictive information on clinical outcome and on responsiveness to both chemotherapy as well as novel targeted treatment options. In fact, at present, the only markers influencing treatment decisions are TP53 mutations and/or deletions as well as ATM deletions (11q deletions) and to some extent TP53 mutations (17p deletions). The fact that CLL patients with TP53 defects are susceptible to becoming resistant to drugs that do not directly depend on functional p53 is believed to be caused by increased genomic instability of TP53 mutated cells thereby easily inducing novel genetic aberrations such as mutations in BTK or gain-of-function mutations in PLCG1.

The principal study that introduced the detection of TP53 defects into clinical practice using fluorescent in situ hybridization (FISH) was by Döhner et al. (2000) [2]. Patients with a 17p deletion (TP53 deletion) showed the worst prognosis followed by 11q deletion (ATM deletion), trisomy 12, and those with normal diploid karyotype while patients with 13q deletion as the sole chromosomal abnormality displayed a good prognosis. In CLL, the majority of TP53 defects consist of biallelic TP53 defects, i.e. a TP53 deletion (17p deletion) in one allele in conjunction with a TP53 mutation in the other allele. Therefore, for several years, only FISH analysis was determined and sequencing of the TP53 gene was not performed routinely. However, later studies showed that a proportion of patients carry a TP53 mutation in the absence of a 17p deletion. TP53 mutations without 17p deletion represents ~30% of TP53 defects while sole 17p deletions in the absence of TP53 mutation are less frequent (~10% of all TP53 defects). Recent evidence showed that both sole 17p deletions and sole TP53 mutations are independent prognostic factors and significantly reduced time to first treatment, progression free survival (PFS), and also overall survival (OS). Mutation analysis of TP53 is therefore advocated into current diagnostic work up in addition to FISH analysis in daily clinical practice.

In recent years, the CLL genome has been thoroughly characterized by next-generation sequencing (NGS). First studies using this approach unraveled an expanding list of somatic mutations targeting multiple genes among which TP53, SF3B1, NOTCH1, MYD88, and ATM were the most frequent [3]. Based on the most recently published integrative mutational and cytogenetic model for classifying risk of death in newly diagnosed CLL patients including novel mutations, TP53 defects had the most powerful adverse impact on OS [4]. Ultra-deep NGS which allowed the detection of very small subclones (down to 0.3%) revealed that 59% (50/85) of the detected TP53 mutated clones were already present in very small subclones (<20%) prior to treatment. Remarkably, even patients harboring small TP53 subclones had the same unfavorable prognosis as patients with larger TP53 clones and inferior to cases with wild-type TP53 [4,5]. This retrospective analysis indicates that even small TP53-mutated subclones detected at diagnosis are of clinical relevance and that these subclones are already present before the start of therapy and expand under the selective pressure of ineffective therapy.

Currently, the only curative treatment option for TP53-defective CLL is still allogeneic hematopoietic stem cell transplantation. Other treatment strategies such as rationale combinations of agents with different (TP53 independent) targets including kinase inhibitors and inhibitors of antiapoptotic molecules such as venetoclax but also immunomodulatory agents are currently being tested.

References

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the Western world mainly affecting elderly persons (median age: 72 years). Over the last years, important progress has been made in the treatment of patients with CLL resulting in improved survival. Chemo-immunotherapy (CIT) (i.e., fludarabine, cyclophosphamide, and rituximab) is considered the gold-standard for treating CLL but its benefit is restricted to younger (< 70 years-old) and fit patients with no comorbidity and not displaying del(17p)/TP53 mutation. This scenario is rapidly changing as a result of small molecules targeting components of the BCR signaling pathways, antagonists of the protein BCL2, and CAR-T cells which circumvent limitations of standard therapy. Here, a brief review on how two of these agents (namely idelalisib and ibrutinib) approved in 2015 are changing treatment algorithms for CLL.

**PI3K inhibitor idelalisib**

Idelalisib has demonstrated clinical activity in patients with CLL with relapsed or refractory disease. Idelalisib was studied as a single agent in a phase I study in patients with relapsed or refractory hematologic malignancies. The CLL cohort was comprised of 37 heavily pretreated patients of which 63% had a del(17p), del(11q), or both. Ninety-two percent of patients achieved durable lymph node responses (> 50% reduction) of which 33% were considered partial responses. A phase II randomized clinical trial compared rituximab with idelalisib or placebo in 220 previously treated patients who progressed within 24 months from their last therapy and not candidates to CIT. Forty-two percent presented del(17p)/TP53 mutations, 83% IGHV unmutated CLL. The idelalisib + rituximab arm yielded a superior nodal response rate compared with single agent rituximab + placebo (93% vs. 4%), overall response rate (ORR) (81% vs. 13%), median progression-free survival (PFS) (not reached vs. 5.5 months), and overall survival (OS) (92% vs. 80% at 12 months). The addition of rituximab to idelalisib reduced the increase and duration of rebound lymphocytosis as compared with single agent idelalisib. The combination of rituximab + idelalisib overcame poor risk features of CLL (del(17p)/TP53 mutation, unmutated IGHV). The most common adverse events were pyrexia, fatigue, nausea, chills, and diarrhea. At least one serious adverse event occurred in 40% of patients in the idelalisib and rituximab group with the most common serious adverse events being pneumonia, pyrexia, and febrile neutropenia. Unique toxicities observed include colitis (grade 3 ≥ 5%), pneumonia (grade 3 ≥ 4%), and transaminitis (grade 3 ≥ 8%). Likewise, a phase III clinical trial for the combination of idelalisib and ofatumumab showed similar results. This work led to the approval of idelalisib in combination with rituximab for the treatment of relapsed-refractory CLL in patients for whom rituximab alone would be considered appropriate therapy due to comorbidity. This approval includes a “black box” informing about the possibility of fatal and serious toxicities including hepatic toxicity, severe diarrhea, colitis, pneumonitis, and intestinal perforation. In untreated patients, the combination of idelalisib + rituximab demonstrated an ORR of 97% (78% partial remission (PR), 19% complete remission (CR)) in 64 patients with CLL (age ≥ 65 years). Phase I data for the combination of idelalisib and rituximab and/or bendamustine showed an acceptable toxicity profile and an ORR of 81%, a 2-year PFS of 62%, and an OS of 85%. Final results of the combination of bendamustine-rituximab with or without idelalisib in patients with relapsed CLL will be soon available as those of several front-line CLL studies examining idelalisib either as a single agent or in combination (e.g., ofatumumab, rituximab, bendamustine + rituximab).

**BTK inhibitors ibrutinib**

Ibrutinib has been extensively studied in CLL and is currently approved for the treatment of patients with CLL who have received at least one prior therapy and those with a del(17p) independently of the line of therapy. Interestingly, ibrutinib penetrates the blood-brain-barrier and does not trigger autoimmune hemolytic anemia. Also ibrutinib is effective in patients progressing after allogeneic stem cell transplantation. In a pivotal phase I clinical study, 69% of patients with CLL achieved an objective response. Subsequently, 85 previously treated patients experiencing disease progression were included in a phase Ib/II study. Patients were treated with either 420 mg or 840 mg daily resulting in a 71% ORR, 75% PFS, and 83% OS at 26 months. An additional 10 to 15% of patients experienced a nodal response with lymphocytosis. Although there was no difference in the proportion of patients with lymphocyte redistribution based on IGHV mutational status, this phenomenon resolved more rapidly in patients with unmutated IGHV CLL. Poor prognostic features such as the presence of del(17p), del(11q), or unmutated IGHV did not adversely correlate with response rate (68% ORR in del(17p) cases) but did impact response duration particularly in patients with del(17p) (at 26 months PFS and OS were 57% and 70%, respectively). Of the 11 patients with disease progression, 10 of 11 had either del(17p) or del(11q) and 7 of 11 presented Richter’s transformation. The potential relationship between ibrutinib treatment
and Richter’s transformation is of concern and deserves investigation. Ibrutinib was well tolerated, the most common grade 1–2 adverse events being diarrhea, upper respiratory tract infection, fatigue, and cough. The most common grade ≥ 3 serious adverse events (≥ 4% of cases) were pneumonia, bacteremia, cellulitis, sinusitis, and atrial fibrillation. Immunoglobulin levels were not negatively affected by therapy. In fact, a recent study has shown a partial restoration of IgA levels in a proportion of patients treated with ibrutinib. As hemorrhages can be observed upon treatment with ibrutinib, this agent should be discontinued before minor (3 days pre and post procedure) and major (7 days pre and post procedure) surgical procedures and should be omitted or used with caution in patients receiving concomitant antiplatelet therapy or systemic anticoagulation.

Treatment results in 132 patients treated with ibrutinib (within different trials) and a median follow-up of three years have been recently reported. Previously untreated patients showed an ORR of 84%, with 23% attaining CR, 55% PR, and 6% PR with lymphocytosis (PR-L). For the relapsed/refractory (R/R) cohort, a 90% ORR was observed with 7% of patients achieving CR, 80% PR, and 3% PR-L. With a median time on study of 35.2 months, median PFS was not reached for all treatment naïve (TN) or R/R patients. In patients with TN CLL/small lymphocytic lymphoma (SLL) the estimated PFS rate was 96% at 30 months. In previously treated patients the estimated PFS at 30 months was 69%. PFS varied according to FISH cytogenetic abnormalities with del(17p) patients having a 30-month estimated PFS rate of 48% which was less than the 74% rate observed for del(11q) and the 87% rate observed when neither aberration is present. The toxicity profile was consistent with that observed in other studies. With 3-year follow-up, median OS was not reached. For patients with TN CLL, the estimated 30-month OS rate was 97%. In patients with previously treated CLL, the 30-month OS was 79%. Similar to PFS in patients with heavily pretreated disease, OS with ibrutinib varied according to FISH cytogenetic abnormalities with del(17p) patients having a 30-month estimated OS rate of 65% which is shorter than the 85% rate observed for del(11q) and the 90% rate observed when neither aberration is present. The poorer outcome of patients harboring del(17p) indicates that the negative impact of this aberration on treatment results is not entirely overcome by ibrutinib. Combination studies of ibrutinib with rituximab (ORR 95%, PFS at 18 months 78%) and bendamustine with rituximab (ORR 93%, PFS at 12 months 86%) have been conducted in patients with relapsed CLL aiming at increasing responses. Importantly, there is a proportion of patients (around 30%) who discontinue treatment because of toxicity or disease progression. Two independent reports have shown that patients progressing early upon ibrutinib treatment may have a very poor outcome in spite of salvage therapy, a fact that may be due to the emergence of mutations conveying resistance to treatment or the high risk of patients. Mechanisms of resistance to ibrutinib should be an important area of research. Using whole exome sequencing, it has been found that a cysteine to serine (C481S) point mutation affecting ibrutinib-BTK binding and two additional gain of function mutations in PLCγ2 (R665W, L845F) as causes of the resistance to ibrutinib. It remains to be seen whether the addition of a monoclonal antibody or cytotoxic chemotherapy to ibrutinib or a PI3K inhibitor will further improve the durability of responses.

Recommended References
As imatinib (IM) and interferon (IFN) were initially the two most active forms of non-transplant therapy available for patients with chronic myeloid leukemia (CML), this combination has been investigated in vitro and in vivo. Following the demonstration of additive or synergistic antiproliferative effects of the combination, clinical studies were initiated using the standard form of IFN and more frequently the pegylated (Peg) forms of IFNα 2a or 2b. The first phase I/II trials from the Italian, British, and Nordic study group established the feasibility, safety, and appropriate doses to be proposed to the patients. The French and the German group reported preliminary results of two large phase III randomized trials. The French CML group designed a prospective trial comparing imatinib 400 mg/d (n = 223) with 3 experimental arms: IM 600 mg/d (n = 171), IM 400 g/d combined to s/c cytarabine (20 mg/m²/d, d15 – 28 of 28-day cycles) (n = 221), and IM 400 mg/d combined to s/c PegIFN2α (90 µg/wk) (n = 172). This trial demonstrated that the addition of PegIFN significantly increased the rate of molecular responses with very little progression. The German phase III trial (German study IV) initially included 1014 patients. The patients were randomly assigned to IM 800 mg/d (n = 338), IM 400 mg/d (n = 325), or IM 400 mg/d plus interferon α (n = 351). Regular non-pegylated form IFNα was added six weeks after the start of IM (dose 1.5 to 3 MIU 3 times per week). A significantly higher rate of major molecular remission (MMR) at 12 months occurred with tolerability-adapted IM 800 mg than with IM 400 mg or IM 400 mg plus IFN. In a subsequent analysis published in 2014 on 1551 randomized patients, deep molecular response (i.e. MR4.5) was identified as a new molecular predictor of long term outcome. Of interest, patients with optimized high-dose IM achieved MR4.5 more quickly than did patients with any other treatment except IM plus IFN (p = 0.016). Limited experience with second generation tyrosine kinase inhibitors (TKIs) in combination with IFN has been reported. The French CML group has completed the Nilopeg trial evaluation with a recent ASH 2015 up-

Table 1: Summary of the current status of a number of ongoing trials worldwide.

<table>
<thead>
<tr>
<th>Study group / country / trial / phase</th>
<th>IFNα form and dose</th>
<th>TKI</th>
<th>Patients</th>
<th>Cytogenetic and / or molecular response</th>
<th>Progression according to study definition</th>
<th>Survival</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>French SPIRIT Trial, Phase III</td>
<td>PegIFNα 2a 90 – 45 µg/week</td>
<td>IM 400 mg QD</td>
<td>Early CP-CML n = 223 IM, n = 229 IM + IFN</td>
<td>At 36 months IM + PegIFN= 28 % IM 17 % (p&lt;0.01)</td>
<td>93 % at 3 years 94 % at 5 years</td>
<td>N Engl J Med 2010, Cancer 2013</td>
<td></td>
</tr>
<tr>
<td>German Study IV, Phase III</td>
<td>IFNα 2a 1.5 – 3 MIU/week</td>
<td>IM 400 to 800 mg QD</td>
<td>Early CP-CML n = 325 IM 400, n = 351 IM + IFN n = 338 IM 800</td>
<td>MMR at 12 months IM 800 = 59 % IM + IFN = 46 % IM 400 = 44 %</td>
<td>87 % at 5 years overall 90 % at 5 years overall</td>
<td>J Clin Oncol 2011-2014</td>
<td></td>
</tr>
<tr>
<td>FILMC, France, Phase II</td>
<td>PegIFNα 2a 90 µg/week</td>
<td>Nilotinib 300 mg BID</td>
<td>Early CP-CML n = 42</td>
<td>MR4 at 2 years = 34 % MR4.5 at 4 years = 44 %</td>
<td>1 progression at 6 months 1 death of progression</td>
<td>Lancet Haematol 2015, ASH 2015, Abs #1578</td>
<td></td>
</tr>
<tr>
<td>FILMC, France, Phase II</td>
<td>PegIFNα 2b 30 µg/week</td>
<td>Dasatinib 100 mg QD</td>
<td>Early CP-CML n = 81</td>
<td>MR4 at 1 year = 30 %</td>
<td>NR Too early</td>
<td>NR Too early</td>
<td>ASH 2015, Abs #134</td>
</tr>
<tr>
<td>Nordic Group, Phase II</td>
<td>PegIFNα 2b 15 – 25 µg/week</td>
<td>Dasatinib 100 QD</td>
<td>Early CP-CML n = 40</td>
<td>MR4 at 1 year = 18 %</td>
<td>NR Too early</td>
<td>NR Too early</td>
<td>ASH 2015, Abs #477</td>
</tr>
<tr>
<td>Australian study group, PINaCLe study, Phase III</td>
<td>PegIFNα 2b 30 – 50 µg/week</td>
<td>Nilotinib 300 mg BID</td>
<td>Early CP-CML n = 100</td>
<td>Ongoing, recruiting</td>
<td>NR</td>
<td>NR</td>
<td>NCT02001818</td>
</tr>
<tr>
<td>FILMC, PETALS study, Phase III</td>
<td>PegIFNα 2a 30 – 45 µg/week</td>
<td>Nilotinib 300 mg BID vs. Nilo + PegIFN</td>
<td>Early CP-CML n = 200</td>
<td>Ongoing, recruiting</td>
<td>NR</td>
<td>NR</td>
<td>NCT02201459</td>
</tr>
<tr>
<td>German Group, TIGER study, Phase III</td>
<td>PegIFNα 2b 30 µg/week</td>
<td>Nilotinib 300 mg BID vs. Nilo + PegIFN</td>
<td>Early CP-CML n = 652</td>
<td>Ongoing, recruiting</td>
<td>NR</td>
<td>NR</td>
<td>NCT01657604</td>
</tr>
</tbody>
</table>
In this single arm trial, the nilotinib 300 mg BID was combined with pegylated interferon α 2a (90 µg/week) in 42 newly diagnosed CML patients. The rate of MR4.5 at 2 and 4 years were 34 and 44%, respectively; tolerability was acceptable with 64% of the patients who continued IFN for 12 months. In a subsequent French trial, chronic phase (CP) CML patients started dasatinib 100 mg/day. At 3 months, they were assigned to receive PegIFNα 2b associated to dasatinib when platelets > 100 x 10^9/L, neutrophils > 1.5 x 10^9/L and lymphocytes < 4.0 x 10^9/L were achieved. The MR4.5 rate at 12 months is 30%. The Nordic trial is similar except for the dose of PegIFN (15 – 25µg); the MR4.5 response at 12 months is 18%.

References
Prognosis of long-term survival in patients with chronic myeloid leukemia

Markus Pfirrmann on behalf of the investigators involved in the European Treatment and Outcome Study (EUTOS) registry project
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For patients with Philadelphia chromosome (Ph)-positive chronic phase (CP) chronic myeloid leukemia (CML), the introduction of imatinib led to 8-year overall survival (OS) probabilities above 80% [1–3]. Together with the fact that half of the patients are more than 55 years of age at diagnosis [4] with many suffering from concomitant diseases, treatment success with imatinib increased the proportion of patients dying of causes unrelated to CML [2]. However, hematologists would like to know to what extent a tyrosine kinase inhibitor (TKI) like imatinib is able to prevent dying because of CML.

In the in-study registry of the European Treatment and Outcome Study (EUTOS), data on 2,290 adult patients with Ph-positive CP CML were collected. Between 2002 and 2006, these patients were enrolled in six prospective, controlled clinical trials. Further inclusion criteria were transcript type b2a2 and/or b3a2 and any form of imatinib treatment started within six months from diagnosis [5]. A median observation time of 6.3 years enabled the investigation of the probabilities of dying from CML while considering “death unrelated to CML” as a competing risk [5]. Only after prior disease progression, an event was rated as “death because of CML”. Progression corresponded to the observation of accelerated phase or blast crisis both defined in accordance with the recommendations of the European LeukemiaNet (ELN) [6].

At 8 years, the OS probability of the 2,290 patients was 89% [95% confidence interval (CI): 87 – 90%] and progression-free survival 87% [95% CI: 85 – 89%] (Fig. 1). For 99 patients with allogeneic hematopoietic stem cell transplantation (HSCT) in first CP, survival time was censored at the day of transplantation. With early transplant-related mortality, survival probabilities would not have been representative for patients continuing TKI treatment while still in first CP. Of the 2,191 patients without HSCT in first CP, 208 patients died; in 92 cases (44%), cause of death was CML. The 8-year cumulative incidence probability (CIP) of dying of CML was 4% [CI: 4 – 5%] and of non-CML-related death 7% [CI: 5 – 8%] [5].

Using the regression model of Fine and Gray [7], the influence of the nine candidate prognostic factors age, sex, spleen size below costal margin, hemoglobin, white blood cell count, blasts, basophils, eosinophils (all in peripheral blood), and platelet count on the probabilities of dying of CML was investigated in 2,205 patients with complete data on all variables. Higher age (p = 0.009), a bigger spleen size below costal margin (p < 0.001), a higher percentage of peripheral blasts (p = 0.005), and low platelet counts (p = 0.022) increased the probability of dying of CML. Weighted by their estimated regression coefficients, the four significant prognostic factors were combined in the new EUTOS long-term survival (ELTS) score [5]:

**ELTS score**

\[ 0.0025 \times \text{(age in completed years/10)}^3 + 0.0615 \times \text{spleen size in cm below costal margin} + 0.1052 \times \text{percentage of blasts in peripheral blood} + 0.4104 \times \text{(platelet count in 10^9/L/1000)}^{0.55} \]

All factors are entered as integers. After polynomial transformation, age and platelet count are rounded to three and the resulting ELTS score to four decimal places. To find cutoffs for risk group definition, a combination of bootstrap resampling, the minimal P value approach, and kernel density estimation was applied. Two cutoffs were identified and led to a low-risk group with ELTS score ≤ 1.5680, an intermediate-risk group (1.5680 < ELTS score ≤ 2.2185), and a high-risk group (ELTS score > 2.2185) [5]. To calculate the score, the ELN provides a link:

www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html
With reference to the low-risk group, probabilities of dying of CML were significantly higher in the intermediate- (subdistribution hazard ratio (SHR): 2.996 [95% CI: 1.800-4.987], p = 0.014) and the high-risk group (SHR: 5.627 [95% CI: 3.271-9.681], p < 0.001), Figure 2. Also between the latter groups significant differences were observed (p < 0.001) [5].

Prior to the ELTS score, the Sokal [8], the Euro [9], and the EUTOS score [10] had been suggested. For a fair comparison with these established scores and for attempting validation of the ELTS score, independent data of the out-study registry were used. Above inclusion criteria were met by 1120 evaluable patients originally entered into seven prospective registries [5].

Table 1: Probabilities of dying of CML according to the risk groups of four different prognostic scores in 1120 out-study patients. For any prognostic score, subdistribution hazard ratios of the intermediate- or high-risk group were referred to the low-risk group. For the out-study section of the registry, 5-year probabilities were preferred as too few observations at 8 years did not allow a reliable probability estimation for all risk groups at this time.

CML: chronic myeloid leukemia; CI: confidence interval; EUTOS: European Treatment and Outcome Study.*


Figure 2: Cumulative incidence probabilities of dying due to chronic myeloid leukemia in 2205 patients from the in-study registry stratified for the risk groups according to the EUTOS long-term survival (ELTS) score. At 2, 5, and 8 years, horizontal crossbars indicate the upper and lower limit of the 95% confidence interval (CI) for the estimated probability.

Tab.: Number of patients still at risk (n) at different years of observation.*
Estimated with Cox regression, the HRs of the intermediate- and the high-risk group were the highest with the ELTS score (Tab. 2) [5].

The first EUTOS score [10] was not designed to distinguish intermediate- and low-risk patients. However, for the ELTS score, a significant discrimination of the probabilities of dying of CML between these two groups was confirmed in the out-study registry (Tab. 1). The SHR of high- to low-risk patients was more than twice as high as with the EUTOS score where intermediate- and low-risk were not separated [5]. Also, the first EUTOS score could not identify significantly different OS probabilities in the in-study registry (Tab. 2). All these facts support the view that for long-term outcome a homogeneous low-risk group consisting of about 90% of the patients as suggested by the first EUTOS score does not exist. Instead, intermediate-risk patients should be separated from a low-risk group which has particularly excellent prospects for survival [5].

Table 2: Overall survival probabilities according to the risk groups of four different prognostic scores in 2,205 in-study patients. For any prognostic score, hazard ratios of the intermediate- or high-risk group were referred to the low-risk group.

<table>
<thead>
<tr>
<th>Prognostic score</th>
<th>Number of cases n (%)</th>
<th>Number of deaths due to CML n (%)</th>
<th>8-year survival probability [95% CI]</th>
<th>Hazard ratio</th>
<th>Lower 95% confidence limit for hazard ratio</th>
<th>Upper 95% confidence limit for hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>908 (41%)</td>
<td>55 (6%)</td>
<td>93% [90–95%]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>798 (36%)</td>
<td>84 (11%)</td>
<td>86% [82–89%]</td>
<td>1.744</td>
<td>1.245</td>
<td>2.462</td>
<td>0.001</td>
</tr>
<tr>
<td>High risk</td>
<td>499 (23%)</td>
<td>54 (11%)</td>
<td>88% [85–91%]</td>
<td>1.918</td>
<td>1.316</td>
<td>2.797</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Euro score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>909 (41%)</td>
<td>57 (6%)</td>
<td>92% [90–94%]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1074 (49%)</td>
<td>107 (10%)</td>
<td>88% [85–90%]</td>
<td>1.588</td>
<td>1.156</td>
<td>2.203</td>
<td>0.005</td>
</tr>
<tr>
<td>High risk</td>
<td>222 (10%)</td>
<td>29 (13%)</td>
<td>85% [79–89%]</td>
<td>2.283</td>
<td>1.441</td>
<td>3.538</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EUTOS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1973 (89%)</td>
<td>170 (9%)</td>
<td>89% [87–91%]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>High risk</td>
<td>232 (11%)</td>
<td>23 (10%)</td>
<td>89% [84–92%]</td>
<td>1.245</td>
<td>0.785</td>
<td>1.883</td>
<td>0.32</td>
</tr>
<tr>
<td>EUTOS long-term survival score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>1349 (61%)</td>
<td>70 (5%)</td>
<td>93% [91–95%]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>596 (27%)</td>
<td>83 (14%)</td>
<td>84% [80–87%]</td>
<td>2.781</td>
<td>2.024</td>
<td>3.830</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High risk</td>
<td>260 (12%)</td>
<td>40 (15%)</td>
<td>81% [74–86%]</td>
<td>3.282</td>
<td>2.207</td>
<td>4.814</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*CML: chronic myeloid leukemia; CI: confidence interval; EUTOS: European Treatment and Outcome Study.*

Successful validation and the significant differences also for OS both indicate that no relevant bias was introduced by our definition of CML-related deaths. For the low-risk patients (61%), the ELTS score showed a very favorable long-term outcome when starting treatment with imatinib. This outcome is difficult to improve. It is clinically highly relevant as imatinib is the primary choice in many countries. Its use will be further boosted by its availability as a generic drug. Significantly worse results for (overall) survival in the high-risk patients (12%) call for an upfront comparison between different TKIs, possibly including intermediate-risk patients [5].

The new ELTS score supports the prospective assessment of long-term antileukemic efficacy of first-line imatinib therapy. The score backs risk-stratified planning, analysis and outcome interpretation of clinical trials, and the application of risk-adapted treatment [5].

**References**


**Acknowledgement**

The European Treatment and Outcome Study (EUTOS) is a common project of the European LeukemiaNet and Novartis Oncology Europe. Novartis Oncology Europe provided financial support for the EUTOS project.
For patients with myelodysplastic syndromes (MDS) the International Prognostic Scoring System (IPSS) [1] and the revised version (IPSS-R) [2] are used to evaluate prognosis and to recommend therapeutic options based on the individual risk classification. For IPSS and IPSS-R assessment, the knowledge of peripheral blood (PB) counts, the percentage of bone marrow (BM) blasts, and the cytogenetic risk based on chromosome banding analyses (CBA) of BM metaphases is mandatory. At the time of initial MDS diagnosis, 5–20% of MDS patients present with dry marrow without liquid BM blood available for cytogenetic analysis [3–5]. Thus, the calculation of prognosis according to IPSS/-R is not possible for these patients. In MDS patients, CD34+ myeloid progenitor cells circulating in the PB [6] can be enriched by immunomagnetic cell sorting and used for fluorescence in situ hybridization (FISH). In former studies, we could show that FISH analyses of circulating CD34+ cells from PB with extended probe panels correlate significantly with CBA results and provide valid molecular-cytogenetic information from PB [7, 8]. For this study [9], FISH results from CD34+ PB cells of 328 MDS patients of our prospective multicenter German diagnostic study (https://clinicaltrials.gov/ct2/show/NCT01355913) [7, 8] from 18 German centers of hematology were compared to the results of CBA of 2902 previously published, untreated primary MDS patients [10] of the German-Austrian, Spanish Hematological Cytogenetic Working Group, IMRAW, and IWCG databases. The FISH probe panel used can detect at least 70% of chromosomal anomalies typical for MDS [10, 11] (1p36/1q25 CSF1R/D5, EGR1/D5, D7/CEP7, CEP 8, MLL, TEL/AML1, RB1, IGH/BCL2, TP53, D20, CEP X/Y, TET2). The CBA control group of 2902 patients received best supportive care (BSC) or non-disease altering therapies only [10]. The CD34+ PB FISH group received BSC or different specific treatment modalities. Median observation time was 26.7 months (range 0–53.1) for the FISH group and 50 months for the CBA group (range 0.1–326) [9, 10]. Treated and untreated patients of the CD34+ PB FISH group did not differ significantly concerning overall (OS, 29.8 vs. 46.5 months, p = 0.378) and AML-free survival (AFS, both not reached, p = 0.102). There were also no significant differences between the CBA group and the CD34+ PB FISH group for OS and AFS. The curves for median OS and AFS for IPSS and IPSS-R cytogenetic subgroups separated significantly by CD34+ PB FISH (p < 0.01). Compared to the CBA results, OS and AFS did not differ significantly. Replacing CBA with molecular-cytogenetic data from CD34+ PB FISH for the complete IPSS allowed separation of prognostic risk groups with significant differences. *This research was originally published in Haematologica. Braulke F, Platzbecker U, Müller-Thomas C, et al. Validation of cytogenetic risk groups according to International Prognostic Scoring Systems by peripheral blood CD34+FISH: Results from a German diagnostic study in comparison with an international control group. Haematologica. 2015;100(2):205–213.
differences in OS and AFS (Fig. 3). There were no significant differences between CD34+ PB FISH and chromosome banding results. Results from the multivariate analyses for both IPSS/-R cytogenetic risk groups and IPSS prognostic subgroups showed that neither the diagnostic tool (banding vs. CD34+ PB FISH) nor the treatment (BSC vs. any other) could significantly change the predictive power of the scoring systems. Our data show that the attribution to a certain cytogenetic risk group is also possible by CD34+ PB FISH analysis [9].

FISH should not replace CBA in general. But our results show that a valid cytogenetic profiling according to international prognostic scoring systems is possible using FISH analyses of CD34+ PB cells with extended probe panels.

References

MDS-RIGHT: Providing the right care to the right patient with Myelodysplastic Syndrome at the right time

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Objectives and work plan
MDS-RIGHT addresses six important objectives each represented by a dedicated work package (WP). The EU-MDS registry will be used to evaluate and compare the efficacy of existing healthcare interventions in lower-risk MDS patients across 16 European countries and Israel using established (e.g. survival and progression to high-risk myeloid cancers) and newly defined (blood transfusion dependency, bone marrow failure, and Health-Related Quality of Life (HRQoL)) treatment outcome sets. Combined with health technology assessments (HTA) this will enable WP1 (WP-leader: Prof. A. Manca) to provide robust evidence to underpin the sustainable use of healthcare resources.

WP2 (WP-leader: Prof. J. Jansen) addresses the second objective: to enhance compliance with diagnostic procedures by introducing and validating novel molecular and flow cytometric (FCM) diagnostic and prognostic markers. Various diagnostic tools in bone marrow and blood will be compared using the EU-MDS registry and the LifeLines cohort. Introduction of new minimally invasive diagnostic methods will provide insight in the burden of under diagnosis and resulting under treatment of MDS among elderly with unexplained anemia. This will increase the number of correctly and timely diagnosed patients. The focus of WP3 (WP-leader: Prof. R. Stauder) is to maximize HRQoL by raising awareness of the relevance of obtaining the right diagnosis in elderly. By restricting MDS-specific interventions to patients with the right (MDS) diagnosis who are likely to benefit from these interventions, HRQoL of the individual patient will improve. WP4 (WP-leader: Prof. L. Malcovati) will provide better treatment-outcome prediction models, enriched with (epi)genetics and new FCM techniques. This will provide evidence to guide stratified and personalized treatment decisions based on both clinical and economic considerations.

Outcomes of these four work packages will serve as a basis for newly developed and improved evidence-based diagnostic and therapeutic MDS guidelines (WP5: Prof. E. Hellström) and to establish a European MDS competence network for dissemination and communication to various stakeholders (health care providers, health insurers, medical associations, and governmental bodies) and end-users (physicians and patient organizations) (WP6: Prof. P. Fenaux). Amongst others, the European MDS competence network encompasses a network website which will be used to actively share interactive guidelines and MDS-resources and which will serve as a platform for discussion.

Early 2015, the European Commission recognized the relevance of MDS and the MDS-RIGHT Consortium to the rapidly growing elderly population in Europe by granting 6 million euro from the Horizon2020 program. MDS-RIGHT is one of the few projects successfully submitted to the PHC-17-2014 call titled Comparing the effectiveness of existing healthcare interventions in the elderly. The overall goal of MDS-RIGHT is to contribute to healthier aging by defining and implementing more effective and safer interventions for patients with lower-risk MDS and to create more awareness for ‘Anemia of the Elderly’. To achieve this, valuable data from the EU-MDS registry and the LifeLines cohort and expertise in the field of clinical and experimental hematology, health related quality of life, health economics, statistics, bioinformatics, and dissemination represented by 15 top leading partners from 8 countries have been brought together in the MDS-RIGHT Consortium (Fig. 1) coordinated by the Radboud University Medical Center, Nijmegen, the Netherlands. The project has been granted for the duration of five years (until May 2020) and consists of 7 work packages each of which has presented their work plan during the official kick-off meeting in Vienna on June 11th.

The EU-MDS registry forms the backbone of the project providing data on existing healthcare interventions from lower-risk MDS patients across 16 European countries and Israel. The LifeLines cohort, a 3-generation general population-based cohort from the northern part of the Netherlands, and its associated biobank will serve as reference population of elderly patients with anemia without clear cause.
Status
Currently, the project has completed its start-up phase. Within the work packages, activities for the first 18 months are being performed. One of the first steps within WP1 will be to define the missing HTA data in the EUMDS database since the database is not rich in HTA data. In WP2, steps are taken to validate molecular methods in patients with established diagnosis of MDS and to define a minimum data set necessary for molecular evaluations. WP3 has started a systematic search for the identification and definition of new core outcome sets. Moreover, the newly developed MDS specific QUALMS questionnaire will be translated in various European languages and validated in a selected number of large countries to address disease specific HRQoL issues in the elderly with anemia. Activities in WP4 (outcome prediction) have started by selecting LifeLines subjects for the MDS-RIGHT project. This selection will be followed by a definition of relevant outcome data and finalization of a robust statistical plan as described in the application for LifeLines. An important step in WP5 and 6 is taken by sending out an inventory to stakeholders in MDS to create a catalogue of stakeholder groups and information available on MDS. This face-to-face meeting dedicated to guideline development and dissemination has been organized in Paris in October 2015. Main topics discussed were modern ways to develop and disseminate guidelines in MDS including the development of an interactive website to be used by different stakeholders and end-users involved in MDS.

Figure 1: MDS-RIGHT Consortium.
The new clinical trial EU-Regulation (EU-Reg) was established to form a harmonized approach on application and conduct of clinical trials (CTs) within the EU. The EU-Reg depends on the functionality of the EU-Portal (EU-P) and EU-Database (EU-DB) as a single entry point for submission and information relating to CTs. In line with this, the EU-Reg will become active 6 months after the publication in the Official Journal of the EU but not before May 28th 2016. This means that the currently legal Directive 2001/20/EC applies for all clinical trial applications submitted before the effective date of the EU-Reg (no earlier than May 28th 2016). Also sponsors can decide to submit clinical trial applications regulated by the current Directive within one year after the effective date of the EU-Reg. For ongoing CTs, the commencement of the EU-Reg can become relevant after another 3 years. This long period of transition is necessary to adapt national regulations and for study centers to adapt their existing organizational systems in the conduct of CTs. 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.

In general, the EU-Reg describes the following main characteristic modifications:

- a harmonized application approach via a single entry point (EU-P)
- a defined single set of application documents
- a harmonized assessment procedure
- defined deadlines (including the involvement of ethics committees (ECs) as construed by the law of the member states (MS))
- legal certainty to authorization by tacit principles
- transparency of data whereas all information in the database should be publicly accessible unless they conflict with the protection of confidentiality or personal data and a summary of results should be submitted one year after the end of the CT

Also, simplified rules for safety reporting by using a CT Eudravigilance database were implemented:

- a CT protocol may define that not all AEs and SAEs are recorded and reported
- for more than one investigational medicinal product used in CTs, one single safety report can be provided
- SUSAR reporting via the Eudravigilance database
- possibility of a common annual safety report for all MS

**Figure 1:** Timelines on the new application process defined in the EU-Reg.
The application of a CT via the EU-P includes three main steps including validation of the application dossier within 10 days where the sponsor can propose one of the MS concerned (MSC) as the reporting MS (RMS), the main contact for communication and other decisions, as well as two assessment reports part I and II within 45 days (see also Fig. 2). The EU-Reg comprises strict timelines which are further outlined in Figure 1. Thus, the sponsor needs to provide required additional information within 10 or 12 days for the application or assessment reports, respectively. Each MSC must notify the sponsor through the EU-P about the authorization of the CT by one single decision within 5 days from the reporting date (or the last day of the assessment) whereas the sponsor needs to notify the MSC about the start, the first visit of the first subject, and the end of the recruitment within 15 days at the latest. A possibility to prolong a conclusion of part II is given in article 11 constituting that the sponsor can apply for an authorization limited to aspects covered by part II of the assessment report within 2 years. In case no subject has been included in the CT in a MSC within 2 years from the notification date and no further extension has been approved, the authorization expires in that MSC. Also, a MS may still demand additional approval for national regulations (e.g. approval of the federal office for radiation protection). Especially here, the current processes might be challenging and involvement and communication between authorities and ECs must be newly organized to apply with the strict timelines.

By creating a harmonized 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 especially in investigator initiated trials (IITs), study centers need to adapt standard operating procedures, quality control, and training. As on the long term, the administrative effort is hoped to be less, it still remains questionable how the different nations will act on the requirements, how the current processes that have been already established can persist, and notably if the organizational burden for IITs is still acceptable.

Figure 2: Contents of the Assessment Reports.
Experts unite to form a new global acute myeloid leukemia network

Gert Ossenkoppele
Department of Hematology, VU University Medical Center, Cancer Center Amsterdam, The Netherlands

Experts at the forefront of research into acute myeloid leukemia (AML) have launched a new global information network, the AML Global Portal (www.amlglobalportal.com), which is dedicated to providing a trusted online resource for all healthcare professionals (HCP) treating AML around the world through sharing of expertise and discussion on current and future practices (Fig. 1). It is a new initiative under the umbrella of the AML work package (WP) of the European LeukemiaNet (ELN).

“AML is a niche disease and often does not receive the same amount of attention as other hematological malignancies,” said Gert Ossenkoppele, MD, professor in translational hematology at the VU University Medical Center in Amsterdam, who is chair of the AML Global Portal steering committee.

“There is a clear need for more effective medical education about the diagnosis and management of AML and developing effective treatment strategies including the dissemination and discussion of clinical trial results,” added Professor Ossenkoppele who also chairs the AML working party of HOVON (Haemato Oncology Foundation for Adults in the Netherlands) and is Lead Participant of the WP5 – AML of ELN.

The AML Global Portal aims to address the unmet educational and information needs among all the HCPs working to improve the treatment and outcome for patients with AML. It is hoped that a truly global community will be created fostering greater communication between researchers and clinical practitioners.

Professor Gert Ossenkoppele is joined on the steering committee by some of the worldwide experts in AML and hematology-oncology research (Fig. 2).

“The AML Global Portal aims to be a place for all of us working towards a cure for AML to share our knowledge, learn about the latest research findings, and provide clear updates and information on how to diagnose and manage this disease for the better of all our patients.”

Join your AML colleagues to:
- read the latest research news in AML and about novel treatments
- hear what the experts have to say about AML clinical trials
- learn about the latest advances in the disease and its management
- use online tools to help make an accurate diagnosis
- participate in case discussions
- share your knowledge with the AML community

The AML Global Portal secretariat, PHASE II (www.phase-ii.com), is a communications agency serving life science companies worldwide. All content is determined by an independent Steering Committee. The website is supported by educational grants from industry partners that currently include Celgene and Seattle Genetics. Sponsors do not have any influence over the content.

Twitter https://twitter.com/AGP_hematology (@AGP_hematology)
Facebook https://www.facebook.com/amlgp
LinkedIn https://www.linkedin.com/company/aml-global-portal

Figure 1: The AML Global Portal.

Figure 2: The AML Global Portal steering committee.
From above left to right down: Prof. Gert Ossenkoppele (NL), Prof. Clara Bloomfield (USA) as Co-Chair, Prof. Sergio Amadori (Italy), Prof. Charles Craddock (UK), Prof. Hartmut Döhner (Germany), Prof. Hervé Dombret (France), Prof. David Grimwade (UK), Prof. Gunnar Jullusson (Sweden), Dr. Ross Levine (USA), Prof. Uwe Platzbecker (Germany), Dr. Gad Roboz (USA), Prof. Jacob Rowe (Israel), Dr. Andre Schuh (Canada), Prof. Jorge Sierra (Spain), Dr. Martin Tallman (USA), Prof. Norbert Vey (France), Dr. Roland Walter (USA), Dr. Andrew Wei (Australia).
ASHT abstract summaries

The 57th ASH Annual Meeting and Exposition took place from December 5 – 8 2015 with more than 3000 abstracts having been accepted for oral and poster presentations. As in previous years, ELN experts were invited to select and summarize their favorite abstracts to give an overview on the latest clinical advances. We are pleased to present you the expert’s digest for chronic lymphocytic leukemia, chronic myeloid leukemia, and myelodysplastic syndromes.

Chronic lymphocytic leukemia (CLL)
Aliki Xochelli1,2, Marek Mráz3, Lydia Scarfo4
1 Institute of Applied Biosciences, CERTH, Thessaloniki, Greece
2 Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
3 University Hospital Brno and CEITEC MU, Brno, Czech Republic
4 Department of Oncohematology, IRCCS San Raffaele Hospital, Università Vita-Salute San Raffaele, Milan, Italy

Our growing knowledge on CLL biology has offered new treatment options for CLL patients (pts). We herein present a short summary of the most relevant abstracts presented at this year’s ASH.

The introduction of signaling inhibitors (SIs) in CLL management has been instrumental for the improvement of the overall survival and quality of life of CLL pts especially those with an aggressive biological background and relapsed/refractory (R/R) disease. Tedeschi et al. (#495) presented the results of a randomized, open-label phase III trial reporting that the SI ibrutinib (Ibr) is safe when used as 1st line treatment for CLL/small lymphocytic lymphoma pts of advanced age with an overall superiority concerning disease progression and response to therapy compared to chlorambucil (Clb): ORR (overall response rate) was 86% with Ibr vs. 35.3% with Clb. To note, a significant overall survival (OS) advantage was reported in the Ibr arm vs. Clb with a hazard ratio of 0.16.

Lampson et al. (#497) presented the results of a single-arm phase II study using the SI idelalisib (Idel) plus ofatumumab as 1st line therapy in CLL pts highlighting that it may result in higher rates of ≥ grade (G) 3 toxicities (76%) especially transaminitis, pneumonitis, and enterocolitis compared to those previously reported for R/R patients. They also provided evidence that these adverse events (AEs) may be immune-mediated and suggested that they can be avoided through better selection of pts.

Turning to Ibr-related AEs and bleeding in particular, Kazianka et al. (#718) demonstrated a significant impairment of platelet aggregation during Ibr treatment with a quick recovery after treatment discontinuation. They proposed that quantitative assessment of ristocetin-induced platelet function could serve as bleeding tendency and coagulation monitoring tool but also as guidance through invasive procedures.

Mato et al. (#719) performed a multicenter, retrospective analysis on pts who discontinued treatment with Ibr or Ide reporting that in most cases discontinuation was due to distinct toxicity events (58% Ibr, 60% Ide) followed by disease progression (24% Ibr, 30% Ide). They also argued that treatment discontinuation due to toxicity does not exclude therapy with alternative SIs by documenting an ORR to salvage therapy with alternative inhibitors superior to non-inhibitor therapies (50% for Ide following Ibr, 77% for Ibr following Ide vs. 40% for non-SIs therapy).

Updated results about venetoclax (VEN), an orally available BCL-2 inhibitor, and its use as single agent or in combination with anti-CD20 monoclonal antibodies were also presented at this year’s ASH meeting.

Fisher et al. (#496) reported the results of the safety run-in phase of CLL14, a phase III study comparing VEN (i.e. ABT-199) + obinutuzumab with Clb + obinutuzumab in previously untreated elderly CLL pts with comorbidities. 12 pts received the combination of VEN+obinutuzumab and one was withdrawn before receiving VEN due to G4 obinutuzumab-related infusion-related reaction (IRR). The most relevant G3-4 toxicities included IRR (15.4%), neutropenia (23.1%), and infections (15.4%). The combination appeared tolerable and the randomized phase was opened in August 2015.

Shuo Ma et al. (#830) reported the results of a phase Ia study based on the combination of VEN with rituximab in R/R CLL pts. This combination obtained deep responses also in pts with unfavorable prognostic factors with an ORR of 86%, complete remission (CR)/CR with incomplete recovery of 41% and MRD (minimal residual disease) negativity in up to 53%. Responses seem durable with a 24 months progression-free survival of 84% and a 12 months OS of 94%. The safety profile was similar to that previously reported for VEN single-agent. One fatal treatment-emergent AE (tumor lysis syndrome, TLS) led to protocol amendment without any other occurring after the introduction of TLS prophylaxis.

Jones et al. (#715) presented the first results about efficacy and tolerability of VEN monotherapy in CLL pts R/R to Ibr or Ide (phase II study). The ORR at 8 weeks in 15 pts previously treated with Ibr was 53% (all partial remissions (PRs)) with 40% of pts experiencing SD (stable disease) and 1 pt is evaluable. In the Ide-treated arm, 2/4 achieved a PR, 1 had SD, and 1 experienced early progressive disease.

During the meeting, there were two reports of novel BTK inhibitors in CLL and also the use of anti-PD-1 blockade in the treatment of R/R CLL/Richter’s syndrome (RS).

Byrd et al. (#831) presented the results of acalabrutinib (ACP-196), a second-generation BTK inhibitor designed to improve on the safety and efficacy. In this uncontrolled, phase I–II, multicenter study, acalabrutinib was orally administered in 61 pts who had R/R CLL. The most common AEs observed were headache (43%), diarrhea (39%), and increased weight (26%). Only 11 G3–4 AEs were observed.
Discontinuation of tyrosine kinase inhibitors (TKIs) may be associated with a TKI withdrawal syndrome dominated by musculoskeletal pain. In a cohort of 428 French patients (abstract #137), 23% of patients who stopped imatinib (n = 100) or nilotinib (n = 2) experienced a withdrawal syndrome with osteoarticular pain. Predisposing factors were the duration of TKI treatment and a history of arthritis. Treatment was symptomatic with antiinflammatory drugs and second-generation BCR inhibitors are currently under clinical development and hopefully will soon be added to the therapeutic armamentarium for CLL patients.

At a median follow-up of 14.3 months, the ORR was 95%; 5% of pts had SD. Among pts with 17p13.1 deletion (31%), the ORR was 100% and no cases of RS occurred.

Tam et al. (#832) presented the data on another novel selective BTK inhibitor, BGB-3111. This open label phase I study enrolled 25 pts with relapsed or refractory B-lymphoid malignancies (CLL n = 8). 22/25 pts remained on study treatment at a median of 204 days and 3 pts discontinued BGB-3111 due to disease progression. There were no drug-related severe AEs (SAEs), AEs leading to drug discontinuation, or AE-related deaths. Of 21 ≥ G3 AEs, 3 were assessed by investigators as potentially drug-related - all were self-limiting neutropenia. No G3/4 bleeding events were recorded.

**Chronic myeloid leukemia (CML)**

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A total of 138 abstracts (36 as oral, 102 as poster presentations) reported on progress with CML. There was no breakthrough this year, but many small advances and progress reports particularly in the fields of treatment discontinuation and personalization of treatment.

**Treatment discontinuation:** Abstract #345 updated the STIM 1 study. After a median follow-up of 65 months after stopping treatment, stable relapse-free survival continues at 39% with no molecular relapse recorded after 2 years. Five patients died from CML-unrelated causes, 16 patients were in sustained complete molecular remission, 23 patients are intermittently **BCR-ABL1** positive without molecular relapse.

Discontinuation of tyrosine kinase inhibitors (TKIs) may be associated with a TKI withdrawal syndrome dominated by musculoskeletal pain. In a cohort of 428 French patients (abstract #137), 23% of patients who stopped imatinib (n = 100) or nilotinib (n = 2) experienced a withdrawal syndrome with osteoarticular pain. Predisposing factors were the duration of TKI treatment and a history of arthritis. Treatment was symptomatic with antiinflammatory drugs including steroids or local measures.

The mechanism(s) why some patients in deep molecular remission after TKI discontinuation remain relapse free and others do not, were addressed by two abstracts: Abstract #343 reports that patients after successful discontinuation display a higher number and frequency of adaptive-like NK-cells (CD56DIM) capable of secreting cytokines like TNFa/IFNγ than relapsing patients. Abstract #599 proposes that the T-cell inhibitory immune check-point receptor CTLA-4 impedes a T-cell dependent control of CML stem cell survival. The authors suggest that CTLA-4 blocking antibodies such as ipilimumab might prevent molecular relapse.

Another area of special interest in CML management is the **personalization of treatment**. This approach uses disease features at diagnosis such as transcript type or indicative gene expression profiles, drug levels after the start of TKI treatment, or improved risk prediction for dying of CML by a new score.

Ding et al. (#834) conducted a phase 2 trial to test the safety and clinical efficacy of the anti-PD-1 antibody pembrolizumab in pts with R/R CLL or RS. Authors reported results from the interim analysis of CLL arm including 5 RS and 2 CLL. 4/5 RS pts had responded to therapy. The remaining had SD and continued on therapy. This early efficacy observed in heavily pretreated RS pts indicate a promising novel approach in RS.

In summary, the oral presentations on CLL at ASH 2015 updated us about long-term follow up of pts treated with SIs and treatment-related toxicities management. BCL-2 and second-generation BCR inhibitors are currently under clinical development and hopefully will soon be added to the therapeutic armamentarium for CLL patients.
dependent antitumor activity in a phase I study. ABL 001 is well tolerated. The phase I study is ongoing in dose escalation. The 2 G-TKI radotinib demonstrated in a randomized study significantly higher and faster rates of complete cytogenetic remission and MMR by 12 months than imatinib 400 mg. The 3-arm study of 241 patients compared radotinib 300 mg bid, radotinib 400 mg bid, and imatinib 400 mg qd (an inferior comparator according to abstracts #133 and #2787). The adverse effect profile of radotinib is different from that of imatinib (less fluid retention, more skin rash and pruritus).

Myelodysplastic syndromes (MDS)
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Genetics: After we learnt that most MDS patients harbor somatic mutations, we are studying gene functions, interactions, and clinical correlation. Chun-Wei Lee (#4) showed that an SRSF2 splicing mutation can serve as a therapeutic target. A heterogenous mouse for Srsf2 P95H, a common MDS splicing mutation, was generated with two types: Srsf2 P95H/+ and Srsf2 P95H/-. They then generated a murine leukemia using MLL-AF9 overexpression, on either Srsf2+/+ or Srsf2 P95H/+ background. These mice were treated with the splicesome modulator E7107. Mice with Srsf2+/+ background did not respond while mice with Srsf2 P95H/+ background responded favorably to E7107. This clarifies MDS/acute myeloid leukemia (AML) pathophysiology and provides new therapeutic option. Rejeski (#141) showed in cell lines that SRSF2 mutants bind RNA more strongly than the wild type.

Mupo (#140) generated a mouse model with SF3B1 K700E mutation. The mouse shows mild MDS suggesting that additional molecular events are required for disease progression. Yin (#142) used a mouse model carrying the U2AF1 S34F mutation and leading to abnormal splicing. Overexpression of U2AF1 S34F mutation in human bone marrow (BM) CD34+ progenitors resulted in impaired erythropoiesis and skewed myeloid differentiation towards granulocytes.

TRAF6 is a downstream Toll-like receptors effector with ubiquitin E3 ligase activity overexpressed in MDS progenitors. Mice over-expressing TRAF6 in progenitors developed aggressive MDS. The study (#143) described a novel MDS molecular mechanism – sustained TRAF6-mediated signaling.

Eksioglu (#144) studied inflammation and aging, "inflammaging", inducing metabolic alterations fostering MDS development. BM myeloid derived suppressor cells activated by the DAMP protein S100A9 promote MDS. S100A9 and ROS-induced inflamming was found to be associated with insulin resistance and hyperglycemia in the BM microenvironment that triggers activation of adaptive oncogenic pathways and genomic instability in progenitors. S100A9 transgenic mice displaced age-depen-

Epidemiology of CML in Europe: In abstract #2780 the treatment and outcome analysis of 2904 patients from 20 countries from the population based section of the EUTOS-registry is reported. Median age is 55 years. The registry provides the first unselected sample of Philadelphia- and/or BCR/ABL1-positive adult CML patients across Europe. 12, 24, and 30 months probabilities of progression free and overall survival in the registry are comparable to those in clinical trials indicating that the success reported from commercial and academic studies is transferred to the general population.
and platelet transfusions were reduced but increased blast % led to study termination. 71 patients continued long term follow-up (FU) with a median FU of 27.5 m, death in 53.3 % (romiplostim group) vs. 53.0 % (placebo) and AML in 11.3 % vs. 11.0 %.

Oliva (#91) treated thrombocytopenic LR MDS patients (30 Gi/L) with eltrombopag, an oral thrombopoietin receptor agonist. 23/46 (50 %) responded vs. 2/24 (8 %) on placebo. Response was associated with improved quality of life, mild adverse events, and no MDS progression (11 % vs. 8 %).

Short (#94) treated 83 LR MDS patients with low dose HMA, Aza (75 mg/m² x 3d) or decitabine (20 mg/m² x 3d), with 61 % response and 39 % complete remission (CR). Tolerance was good and AML evolution low (5 %).

Sekeres (#908) treated 277 high-risk MDS patients with Aza or Aza+LEN or Aza+vorinostat (HDAC inhibitor). The overall response rate and OS were similar to all 3 groups with a trend of longer response for the combination. Nevada (#910) treated 45 patients with Aza+rigosterib, a RAS-mimetic. The protocol was tolerated with 8 marrow CR.

Arber reviewed the changes in the 5th WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. a) Nomenclature: MDS with single lineage dysplasia (MDS-SLD) instead of RCUD and MDS-EB1/EB2 instead of RAEB1/RAEB2. b) Genetics: SF3B1 mutation can diagnose RS in < 15 % of sideroblasts. c) Del(5q): MDS del(5q) can include one additional cytogenetic defect (not -7). d) MDS Unclassified (MDS-U): 1 % peripheral blood blasts measured twice will classify a single-lineage dysplasia as MDS-U. e) Erythroleukemia (erythroid-myeloid type): Increased non-erythroid blast % defines MDS with EB not AML. f) Familial myeloid neoplasms: A chapter covering disorders (specific familial/constitutional gene mutations with a risk of hematologic abnormalities) will be added.
Meetings

3. – 6.4.2016
42nd Annual Meeting of the European Society for Blood and Marrow Transplantation
València, Spain

5th International Conference on Myelodysplastic Syndromes
Estoril, Portugal

11. – 14.5.2016
20th Training Course on Haemopoietic Stem Cell Transplantation
Budapest, Hungary

ASCO Annual Meeting 2016
Chicago, USA

21st Congress of EHA
Copenhagen, Denmark

15. – 18.9.2016
18th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy
Houston, USA

Jahrestagung der DGHO, ÖGHO, SGMO und SGH
Leipzig, Germany

27. – 29.10.2016
7th International Conference on Myeloproliferative Neoplasms
Estoril, Portugal

58th ASH Annual Meeting & Exposition
San Diego, USA

19. – 22.2.2017
16th International Symposium ACUTE LEUKEMIAS
Munich, Germany
