22nd Congress of EHA

European Hematology Association

22-25 JUNE • MADRID • SPAIN

PEER-REVIEWED CONFERENCE REPORT

Breakthrough: Chimeric Antigen Receptor T-Cell Therapy

CAR T-Cell therapy seems promising against non-Hodgkin lymphoma. Complete regression was observed in over one-thirds of cases, two studies found; FDA granted Breakthrough Therapy status in April 2017.

read more on PAGE 7

The Cause Discovered of Acute Lymphoblastic Leukaemia?

Exposure to certain infections triggers B-cell precursor acute lymphoblastic leukaemia in children. This was suggested by three mouse model studies and presented at the Presidential Symposium at EHA.

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Storing Capabilities for Platelets Improved

Another crucial investigation found a way to improve storage for platelet cells. Currently platelets are often kept at room temperature, they might soon be refrigerated instead.

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MEDICOM MEDICAL PUBLISHERS

Editor Dr. Eliezer Rachmilewitz (Prof. emeritus), Edith Wolfson Medical Center, Holon, Israel

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Letter from the Editor

Prof. Eliezer Rachmilewitz

Dear Reader,

The 22nd Congress of the European Hematology Association, one of the most important annual meetings of haematology, took place in Madrid between the 22nd and 25th of June, with more than 11,000 participants from all over the world. There were more than 250 sessions, workshops and over 1,600 posters. Clinicians and scientists presented new approaches for diagnosis and treatment, accesing recent results on clinical and translational research in haematological disorders.

A major part of the meeting was dedicated to a series of educational sessions, meet-the-expert, clinical debates, and haematology-in-focus sessions and a new official Journal of EHA - "HemaSphere" - was announced. An extended part of the program were satellite symposia by drug companies.

The highlights of the selected topics, which are presented below, are on acute and chronic myeloid malignancies, lymphoid malignancies (acute and chronic lymphotic leukaemia's, Hodgkin and Non-Hodgkin lymphoma and multiple myeloma). Other topics are updates in stem cell transplantation and in benign haematology (sickle cell anaemia, thalassaemia) as well as in paediatric haematology and thrombosis, and homeostasis.

The rest of the data can be obtained through the EHA learning centre: learningcenter.ehaweb.org.

The large number of younger participants was a very encouraging indication to validate success of the organisers to prepare a stimulating scientific and educational program.

Best Regards,
Eliezer Rachmilewitz

Biography

Prof. Rachmilewitz was the Head of the Haematology departments in Hadassah and in Wolfson Hospitals for 35 years. He is an adjunct professor of Medicine in New York Cornell University Presbyterian Hospital.

He is interested in the pathophysiology of thalassaemia. Original findings include non-transferrin-bound iron - generating increased oxidative stress, low hepcidin levels accounting for increased iron absorption and hypercoagulable state, particularly in asymptomatic ischaemic brain lesions. Iron overload resulting in oxidative stress in congenital and acquired haemolytic anaemias (myelodysplastic syndrome) and the risks for transformation to leukaemia is another area of his interest.

He published more than 300 papers including progress reports on thalassaemia in the New England Journal of Medicine, and "How I Treat Thalassemia" in Blood and is an associate Editor of Annals of Hematology.

He is one of the most prominent physicians in Israel and one of the 3 physicians of the Prime Minister. He was a host of a television program on Health issues for 15 years. He was a co-chairman of 3 international meetings on Controversies in Hematology.

Myeloid Malignancies

Myeloid malignant diseases have both chronic (including myelodysplastic syndromes, myeloproliferative neoplasms and chronic myeloid leukaemia) and acute (including acute myeloid leukaemia) stages. With the rise of next-generation sequencing and new (combinations of) drugs, the prognosis of many patients with myeloid malignancies has improved in recent years.

NGS Panel sequencing to molecularly define myeloid malignancies

The 2016 revision of the WHO classification for myeloid malignancies requires information on numerous genes for diagnosis, prognosis and therapeutic decisions [1]. This challenges conventional laboratory approaches and suggests next-generation panel sequencing. Researchers from the Munich Leukaemia Laboratory in Germany demonstrated the feasibility in routine diagnostics for a broad spectrum of myeloid malignancies [2]. Apart from relevant patterns and mutation interactions, they identified genetic aberrations supporting diagnosis for samples with borderline morphology or poor quality, and patient-specific clonality useful for follow-up.

At first, the 1,143 patients were morphologically categorised as acute myeloid leukaemia (AML) (n=261), myelodysplastic syndromes (MDS) (n=176), myeloproliferative neoplasms (MPN) (n=19), chronic myelomonocytic leukaemia (CMML) (n=51) or AML/MDS (n=21) and MDS/MPN overlap (n=28). Patients, who did not fulfil all characteristic criteria or had insufficient sample quality, were classified as "possible" AML (n=28), MDS (n=211), MPN (n=5), CMML (n=14) and as reactive (n=193) or unclear (n=136). Analysing 39 genes, they found ≥1 molecular change in 90% of patients with a definite morphologic diagnosis (median: 2 genes; max: 7).

In de novo AML, 93% of the patients showed ≥1 molecular hit, of which 92% had aberrations that define WHO categories or have prognostic or predictive value. NPM1 showed to be the most frequently mutated gene (30%), followed by RUNX1 as the second most (20%). In 72% of the patients they found more than one mutation, which in some cases contained information of adverse impact. For example: of 68 NPM1 positive patients, 17 had DNMT3A mutations and 20 FLT3-ITD. In the "possible AML" (including MDS overlap) cohort 94% patients had ≥1 hit. In this group most frequently mutated were ASXL1 (33%), TET2 (32%) and SRSF2 (29%), and 16% had all 3 mutations. This combination showed to be also the most frequent three-way interaction in CMML (23%).

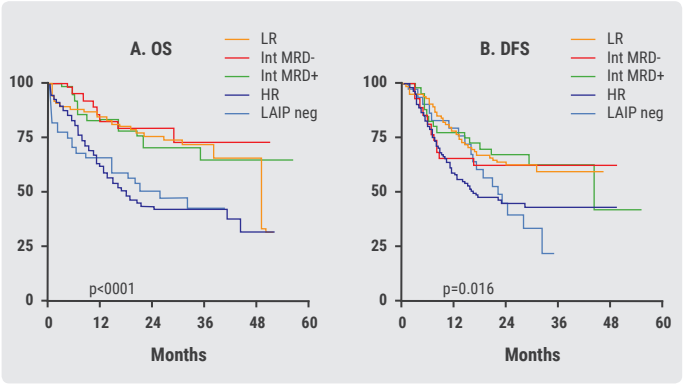
In MDS, mutations were seen in 79% cases, of which 108 had ≥1 prognostic change [2,3]. The prognostically favourable SF3B1 mutation was found in 31/157 (20%) and significantly enriched among cases with ring sideroblasts ($p<0.001$). Overall, TET2 showed the highest mutation rate (25%) and was also the most commonly mutated gene in cases with "possible" MDS (19%), reactive morphologic changes (8%) or even unclear morphology (17%). Of these 3 subsets, 5 patients had only the TET2 mutation with <10% burden, which is also seen in clonal haematopoiesis of indeterminate potential. However, panel sequencing in these 3 subsets revealed at least one molecular marker for clonal disease in 47%, 36% or 17% of cases, respectively (excluding sole ASXL1, DNMT3A, TET2 mutations with <10% burden).

Minimal residual disease-directed therapy in acute myeloid leukaemia

Risk-adapted therapy in patients with AML, driven by minimal residual disease (MRD) is feasible, according to the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA). The Italian researchers conducted a phase 2 trial of intensive chemotherapy in which risk-assignment and post-remission therapy of young patients with AML were based on pre-treatment cytogenetic/genetic data and post-consolidation levels of minimal residual disease MRD [4]. Low-risk patients were to receive an autologous stem cell transplantation (auto-SCT) as post-consolidation therapy, high-risk patients an allogenic SCT (ASCT), and intermediate-risk patients an auto-SCT or ASCT depending on MRD-levels after consolidation therapy.

After the induction therapy, which consisted of daunorubicin (50 mg/m^2 daily on days 1,3 and 5), etoposide (50 mg/m^2 daily on days 1 to 5) and cytarabine (100 mg/m^2 as a daily continuous infusion, days 1 to 10), all patients in complete remission (CR) or complete remission with incomplete haematologic recovery (CRi) after 1 or 2 induction cycles, received 1 consolidation course consisting of daunorubicin

Figure 1. OS and DFS per risk-group AML patients



OS=overall survival; DFS=disease-free survival;
MRD= minimal residual disease;
LR = low risk; HR = high risk;
LAIP = leukemia-associated aberrant immunophenotype

(50 mg/m^2 daily on days 4, 5 and 6) and cytarabine (500 mg/m^2 every 12 hours on days 1 to 6). Of the 515 patients, 341 completed the consolidation phase and were risk allocated: 114 (33%) to the low-risk category, 122 (36%) to the high-risk and 78 (23%) to the intermediate category.

In the intermediate-risk category 27 patients (8%) were MRD negative, so they were to receive an auto-SCT. Overall, 109 (33%) of the 341 patients received an auto-SCT, 123 (36%) received an ASCT. After 24 months, overall survival (OS) and disease-free survival (DFS) in general were 55.9% and 54.9%, respectively, with a cumulative relapse incidence of 32.9%. The 24 months-OS and 24 months-DFS in the low-risk category was 74.8% and 63.8%, respectively; in the high-risk category 42.5% and 44.8%, respectively; in the intermediate-risk category MRD negative 78.6% and 61.4%, respectively; in the intermediate-risk category MRD positive 69.8% and 66.6%, respectively (Figure 1). Based on these results the research group concludes that in the intermediate-risk category, ASCT can be avoided if MRD is not detectable. In patients who are MRD positive, an ASCT can prolong OS and DFS which equals those of the low-risk category who received an auto-SCT.

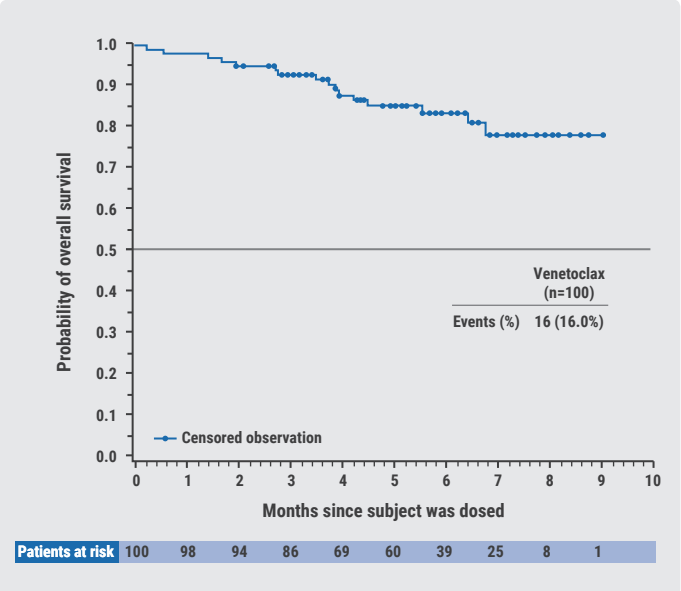
Venetoclax in elderly with acute myeloid leukaemia

Elderly (≥65 years) patients with AML have a poor prognosis, and treatment options are limited. Treatment with low-dose cytarabine (LDAC) in these patients results in CR/CRi rates of 11–19% and a median survival of only 5 to 6 months. The selective BCL-2 inhibitor venetoclax has shown single-agent activity in heavily pretreated patients with relapsed/refractory AML [5].

Preliminary phase 2 data showed the combination of venetoclax – an BCL-2 inhibitor originally used in CLL patients with 17p mutations - (600 mg QD) and LDAC is tolerable and exhibits significant and durable activity in older AML patients ineligible to receive intensive induction chemotherapy [6]. Now, the updated safety and efficacy data are reported [7]. Venetoclax (600 mg) and LDAC showed an acceptable safety profile and durable efficacy in this population. The objective response rate (RR) was 61% (37/61) and highly correlated with OS, with longer survival in responders than non-responders. To compare the different treatment regimens head-to-head, a phase 3 trial has been initiated.

In another phase 1b trial venetoclax demonstrated activity when combined with hypomethylating agents such as decitabine (DEC) or azacitidine (AZA), with an overall RR of 60% [8]. A group of American investigators reported the preliminary results from the expansion stage of a phase 1b trial comparing 2 doses (continuous 400 mg and interrupted 80 mg) of venetoclax plus DEC or AZA [8]. Overall, the safety profile was favourable when combining venetoclax at either dose with DEC or AZA. Promising activity with high overall RRs was observed at the lower 400 mg VEN dose in both HMA arms. The overall RR was 68%, with rates of 76% (venetoclax 400 mg plus DEC), 71% (venetoclax 800 mg plus DEC), 68% (venetoclax 400 mg plus AZA), and 60% (venetoclax 800 mg plus AZA). The Kaplan-Meier survival curve for all patients is shown in Figure 2.

Figure 2. OS of venetoclax in combination with decitabine or azacitidine in treatment-naïve, elderly patients (≥65 years) with acute myeloid leukaemia



DESTINY study: initial reduction of therapy before complete withdrawal in chronic myeloid leukaemia

All studies about treatment discontinuation in chronic myeloid leukaemia (CML) so far have only examined patients in stable molecular response (MR)4 at entry; patients in stable major molecular response (MMR) but not MR4 (<0.1 but >0.01%), neither have the effects of treatment de-escalation as a prelude to complete cessation. The present British DESTINY trial studies stepwise tyrosine kinase inhibitor withdrawal in patients in well stable MR4 as with MMR but not MR4.

In total 174 patients were included in the trail, of which 148 were receiving imatinib, 16 nilotinib and 10 dasatinib, for a median duration of 6.8 years. Before stopping completely, tyrosine kinase inhibitor treatment was reduced to half the standard dose (imatinib 200 mg daily, dasatinib 50 mg daily or nilotinib 200 mg twice daily) for the first 12 months. At ASH 2016 the researchers already reported that after 1 year of half-dose therapy molecular recurrence was lower in patients with stable MR4 at entry (3 of 125 patients; 2.4%) than in those in MMR but not MR4 (9 of 49 patients; 18.4%) (P<0.001) [9]. At EHA 2017 they showed that during the subsequent 12 months of complete treatment cessation in 117 stable MR4 patients, only 26 further recurrences and 4 withdrawals occurred [10]. This comes down to a 24 months relapse free survival (RFS) of 77% (90% Confidence interval (CI): 71-83%). This result is better than any comparable study to date (Figure 3), according to the researchers, and implies that the initial 12 months of dose reduction may be responsible, perhaps via improved compliance in the few months prior to stopping or through an as yet undefined mechanism. The RFS at 24 months among the 36 patients in the MMR but not MR4 group was 39% (90% CI: 29-52%); P<0.001), with 20 recurrences and 4 withdrawals during cessation.

10-year results of imatinib as first-line treatment of chronic myeloid leukaemia

According to the investigators of the STI571 (IRIS) study, one-quarter to one-third of CML patients on imatinib will become resistant or intolerant to therapy [11]. The International Randomised Study on interferon and IRIS study has evaluated imatinib and interferon-α combination therapy, to improve the durability of responses to imatinib [12]. The CML-study 4 was designed to confirm the results of the IRIS study and to explore whether treatment with imatinib at 400 mg/day could be optimised. In the German study 1,151 CML patients were randomised to imatinib 400 mg (n=400), imatinib + interferon-α (n=430), imatinib 800 mg (n=420), imatinib + cytarabine (n=158) and imatinib after interferon-α failure (n=128). Moreover, after a pilot-phase recruitment to the latter two arms was stopped [13].

First results showed that more patients receiving tolerability adapted imatinib 800 mg reached MMR than the other study arms (P=0.003). The investigators suggested that the superior remission rates were the result of the initially high dose and maintenance around 600 mg/day. Longer follow-up showed that patients on imatinib 800 mg achieved MR4.5 faster than patients on the other arms, except the patients who received imatinib plus interferon-α [13]. However, the results after 10 years of follow-up, presented at EHA 2017, revealed that this faster response does not necessarily translate into better survival [14].

Figure 3. Relapse free survival DESTINY trials and EUROSKI trial

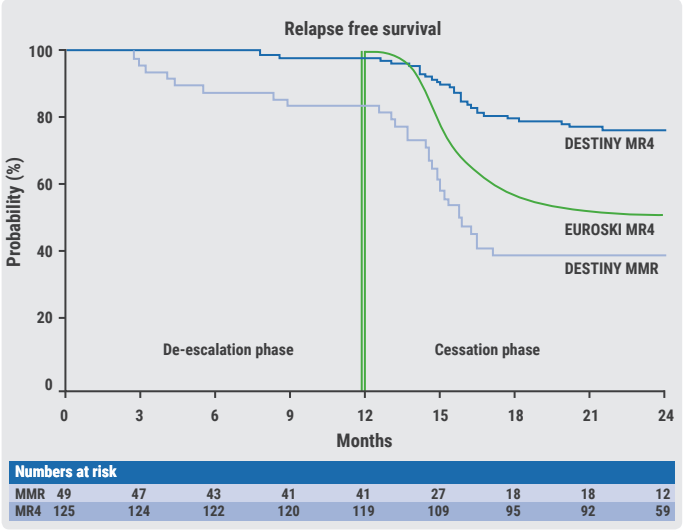
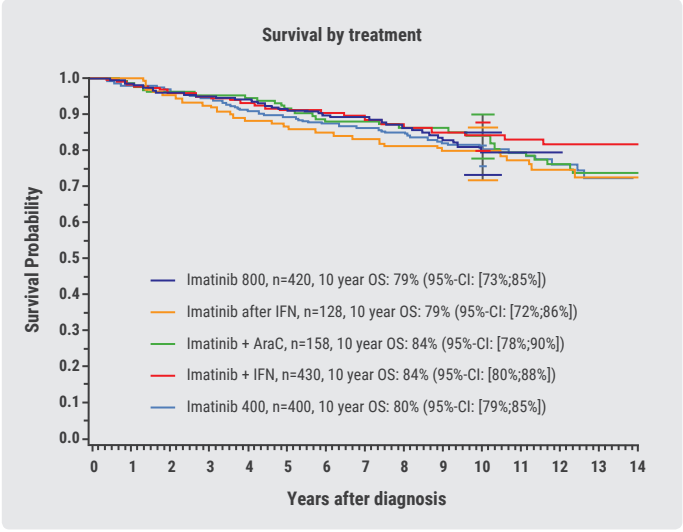


Figure 4. Results of the CML-study 4 by treatment group



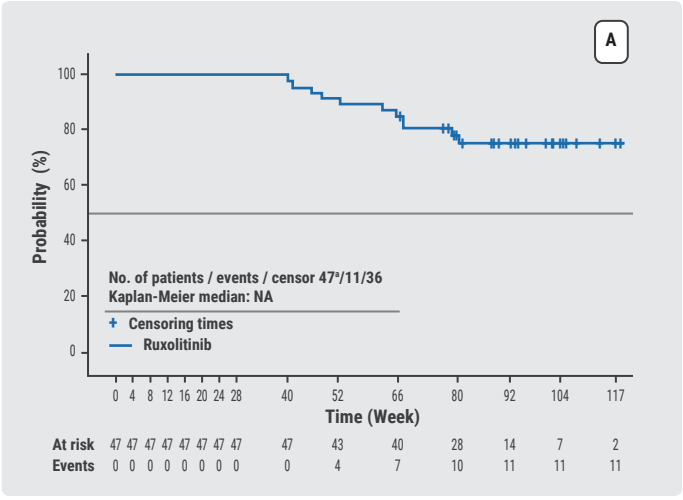
After a median observation time of 9.5 years, 10-year OS of all patients was 82%, 10-year progression free survival 80% and, 10-year relative survival 92%. The differences between the 5 arms were not significant (Figure 4). The faster response of the patients who received imatinib 800 mg did not translate into a better survival. Furthermore, multivariate analysis showed that outcome of CML is currently more determined by comorbidities, disease biology and demographics than by treatment optimisation [14].

New option for poorly controlled polycythaemia vera without splenomegaly

Ruxolitinib should be considered as a standard of care for second-line treatment for patients with polycythaemia vera (PV) without splenomegaly, stated the investigators of the RESPONSE-2 study after 80 weeks of follow-up.

Treatment of patients with PV is aimed at maintaining haematocrit (HCT) <45%. The RESPONSE-2 study compared the efficacy and safety of ruxolitinib (RUX; twice daily 10 mg) with 'best available therapy' (BAT) in adult hydroxyurea-resistant or intolerant PV patients without splenomegaly with whom phlebotomy is required to control HCT. At week 28, the time of primary analysis, HCT control was seen in 46 out of 74 patients in the RUX arm and 14 out of 75 patients in the BAT arm. In this pre-planned analysis, the efficacy and safety of RUX versus BAT was evaluated after 80 weeks of follow-up. In addition, BAT patients could switch to RUX from week 28. When the last patient reached the 80-week follow-up 69 patients in the RXU arm were still treated, while 58 patients in the BAT arm had switched to RUX. After 80 weeks, sustained HCT control was seen in 35 (47%) patients in the RUX arm versus 2 (3%) patients in the BAT arm. A haematologically CR, meaning HCT<45%, WBC ≤10 x 10^9/L, platelets ≤400 x 10^9/L) was observed in 18 (24%) patients in the RUX arm versus 2 (3%) patients in the BAT arm. No deaths were reported in the RUX arm, while in the BAT arm were 3 deaths [15].

Figure 5. RESPONSE-2: Kaplan-Meier Estimate of Maintaining Primary Response With Ruxolitinib (A); Phlebotomy Usage by Week 80 (B)



[a]During week 80 data review, 1 more ruxolitinib-treated patient was found to be responding at week 28 (compared to original analysis done with week 28 data cut): updating the number of primary responders to 47

Phlebotomy usage by week 80 (B)		
Phlebotomy frequency	**Ruxolitinib n=74, n(%)**	**BAT, n=75, n(%)**
0	54 (72.9)	27 (36.0)
1-2	15 (20.3)	29 (38.7)
3-4	5 (6.8)	16 (21.3)
>4	0 (0)	3 (4.0)
Total number of phlebotomies	36	106

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Lymphoid Malignancies

Lymphoid malignant diseases include lymphoma, lymphocytic leukaemia, and myeloma. They all derive from the lymphoid cell line, which produces B, T, NK and plasma cells. New promising techniques, such as chimeric antigen receptor T-cell therapy, are expected to change treatment and prognoses drastically. Especially for those with relapsed or refractory disease.

Treatment reduction Hodgkin lymphoma after negative interim PET

Patients with advanced-stage Hodgkin lymphoma (HL) and a negative interim PET may receive less intensive treatment. Data of the HD18 study from the German Hodgkin Study Group (GHSG) were presented at the Presidential Symposium [1].

According to the GHSG all newly diagnosed patients with advanced HL receive the intensive eBEACOPP regimen (with dose escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), regardless of their individual risk profile. However, some patients probably do not need this intensive treatment to cure from the disease. Previous research suggests that an early metabolic response assessment using FDG-PET (after 2 cycles) can predict the individual outcome better than baseline risk factors as defined in the International Prognostic Score [2].

Of the 2,101 patients who participated in the HL18 study, 1,005 patients had a negative PET after 2 eBEACOPP cycles. They were randomised to 8/6 cycles of eBEACOPP (n=504) or 4 cycles of eBEACOPP (n=501). After a median follow-up of 55 months, the estimated 5-years progression-free survival was 90.8% (95% CI: 87.9-93.7%) after 8/6 cycles of eBEACOPP and 92.2% (95% CI: 89.4-95.0%) after 4 cycles of eBEACOPP (difference + 1.4%; 95% CI: -2.7-5.4% excluding the non-inferiority margin of -6%). The estimated 5-year OS was 95.4% (95% CI: 93.4-97.4) after 6/8 cycles of eBEACOPP and 97.7% (95% CI: 96.2-99.3) after 4 cycles of EBEACOPP (log-rank P=0.004). None of the patients in the experimental group died of treatment-related toxicities.

CAR T-cell therapy in aggressive non-Hodgkin lymphoma

New promising data of two chimeric antigen receptor (CAR) modified T-cell therapies, both targeting CD19, for treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) were presented.

The planned interim analysis of a global phase 2 study of CAR T-cell therapy CTL019 in heavily pre-treated patients with diffuse large cell B-cell lymphoma (DLBCL), named JULIET, confirms the positive results of a previous single-centre study. The findings were presented in a Late Breaking Abstract by prof. Gilles Salles [3]. In the global study, 141 patients were treated in 27 centres on 4 continents. All participants had received two or more lines of chemotherapy and had disease progression or were ineligible for auto-SCT. Eventually, 85 patients received a single dose of CTL019 transduced cells (median 3.1×10^8 cells). Complete and partial remission rates were 37% and 8% respectively after 3 months. All patients with CR at 3 months were still in CR at the time of data cut-off. Three patients died from disease progression within 30 days after infusion. Cytokine release syndrome (CRS), which has been an issue in other CAR T-cell trials, occurred in 57% of patients treated (17% grade 3; 9% grade 4), but no CRS-related mortality occurred. Of all patients, 13% had grade 3/4 neurological adverse effects (AEs), which could be managed with supportive care [3]. Based on this data, the Food and Drug Administration granted in April 2017 a Breakthrough Therapy designation to CTL019.

The second trial showing impressive results, was the multicentre, phase 2 ZUMA-1 trial on axicabtagene ciloleucel in patients with diffuse DLBCL, primary mediastinal B-cell lymphoma (PMBCL) or transformed follicular lymphoma (TFL) [4]. In total 101 patients received a target dose of 2×10^6 anti-CD19 CAR T cells/kg after low-dose conditioning with cyclophosphamide and fludarabine. Overall RR in the combined DLBCL, PMBCL and TFL population, the primary endpoint for this analysis, was 82% (n=92; P<0.0001). After a median follow up of 8.7 months, 44% of the participants were still in response and 39% were in CR. The median duration of response was 8.2 months overall and not reached for patients who achieved a CR. With 80% of patients alive at 6 months, the median OS was not reached. The most common grade ≥3 AEs were neutropenia (66%), leukopenia (44%), anemia (43%), febrile neutropenia (31%), and encephalopathy (21%). Grade ≥3 CRS and neurologic events occurred in 13% and 28% of patients, respectively. All CRS and all neurologic events

resolved except one Grade 1 memory impairment. There were 3 (3%) grade 5 AEs reported. The use of tocilizumab and steroid, commonly given for management of these side effects, showed not to be associated with decreased clinical response [4].

Cerdulatinib relapsed or refractory CLL and NHL

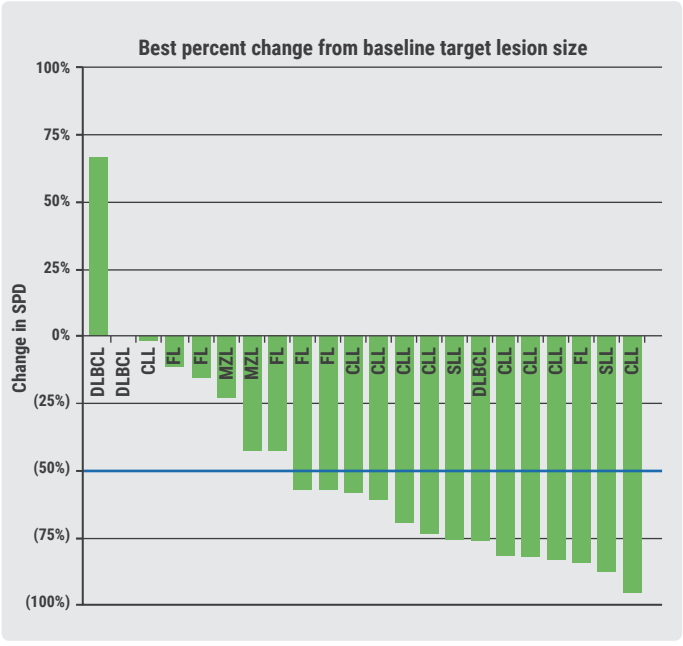
The dual SYK/JAK inhibitor cerdulatinib is effective and safe in treating heavily pre-treated patients with recurrent or refractory chronic lymphocytic leukaemia (CLL) and non-Hodgkin lymphoma (NHL). This was confirmed by an American phase 2 study [5].

Unlike ibrutinib, combined SYK and JAK inhibition by cerdulatinib induces apoptosis in primary CLL cells [6]. It also induces apoptosis in primary DLBCL and DLBCL cell lines with ibrutinib resistant B-Cell antigen Receptor (BCR) pathway mutations. Combined SYK/JAK inhibition could therefore be a potent treatment for B-cell malignancies.

The results of the phase 1 dose escalation study for the treatment of cerdulatinib in 43 patients with recurrent or refractory CLL and NHL were presented to the EHA last year [7]. In May 2016, an open-label phase 2 study was started and currently, 37 patients have been classified into 3 cohorts (17 with CLL or SLL, 15 with indolent NHL, and 5 with aggressive NHL). They were treated with bid 30 mg or 35 mg cerdulatinib (28-day cycles).

The safety profile was found to be similar to what was observed in the phase 1 study. However, 3 patients achieved higher blood levels at 35 mg bid than expected and also had serious side effects. Therefore, the starting dose was reduced to 30 mg bid. To date, this has led to a better safety profile. Partial responses occurred in all 3 cohorts, including 10 of 13 (77%) CLL or SLL patients and 3 of 6 (50%) follicular lymphoma patients. Of these 13 partial responses, 12 are still pending.

Figure 6. Sum of Products Dimensions (SPD) from baseline in relapsed or refractory B-cell malignancies [5]



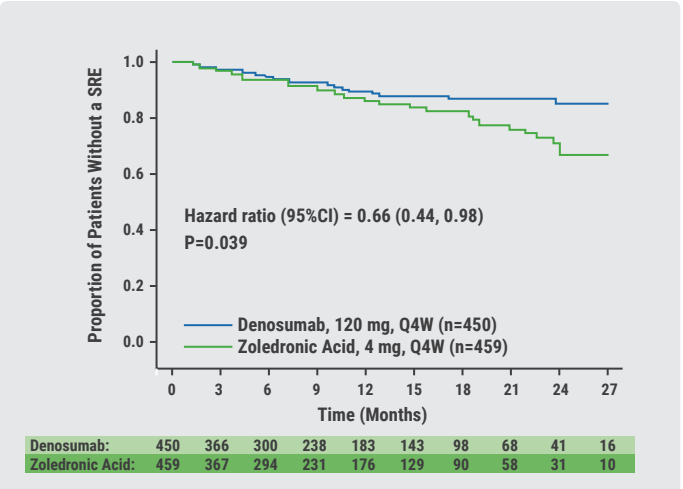
DLBCL: Diffuse large B-cell lymphoma
CLL: Chronic lymphocytic leukaemia
MZL: Marginal Zone Lymphoma
FL: follicular lymphoma
SLL: Small lymphocytic lymphoma

Denosumab for treatment bone disease in multiple myeloma

According to a group of international investigators, denosumab has the potential to be the new standard of care for multiple myeloma (MM) related bone disease. They presented their results of a head-to-head comparison of denosumab and zoledronic acid [8].

Up to 80% of patients with MM have detectable osteolytic bone disease. Myeloma bone disease is mediated by osteoclast activating factors such as RANKL, increasing the risk of skeletal-related events and impacting morbidity and mortality. The human monoclonal antibody denosumab targets RANKL, and can be administered subcutaneously regardless of renal function. In an international randomised phase 3 study, designed to evaluate the efficacy and safety of denosumab, 1,718 newly diagnosed myeloma patients were 1:1 randomised to denosumab (120 mg s.c. every 4 weeks) or zoledronic acid (4 mg IV (adjusted) Q4W) along with anti-myeloma therapy. The study met its primary endpoint, non-inferiority of denosumab compared with

Figure 7. Time to first skeletal-related event; 15-month landmark analysis [8]



zoledronic acid in terms of delaying time to the first on-study skeletal-related event: after a median follow up of 17.4 months 43.8% of patients who received denosumab had a first on-study skeletal-related event versus 44.6% of patients who received zoledronic acid. The investigators observed no significant difference in terms of the median time to the first skeletal-related event (22, 38 months with denosumab and 23.98 months with zoledronic acid). Furthermore, the rates of renal AEs were significantly lower in patients receiving denosumab. Overall rates of AEs, including hypocalcaemia and osteonecrosis of the jaw, were consistent with the known safety profile of denosumab [8].

Understanding chemo resistance in T-cell acute lymphoblastic leukaemia

Bone marrow sites seem to differentially imprint dormancy and chemo resistance to T-cell acute lymphoblastic leukaemia (T-ALL). The results of a study in mouse models were presented as Late Breaking Abstract [9]. In the course of the disease, T-ALL cells settle in various environments such as thymus, blood, bone marrow, pleura or lymph nodes. These environments differ in terms of cell content, extra-cellular matrix and secreted factors. The effects of these differences are not well understood. Therefore, French investigators compared the growth of leukaemic cells from human and mouse T-ALL in various bone marrow sites. Aim of the study was to uncover novel mechanisms of chemo resistance. They used grafts of human and mouse T-ALL in immune-deficient and normal mice, and explored the behaviour of leukaemic cells both ex-vivo as in vivo after they had engrafted different bone marrow sites of the mouse body (femurs, thorax and tail vertebrates). They also tested chemo resistance to the conventional drugs dexamethasone, vincristine, cytarabine.

Mouse and human T-ALL turned out to develop slowly in tail vertebrae bone marrow in comparison to thorax vertebrae and femur bone marrow. Furthermore, T-ALL from tail bone marrow displayed lower cell surface marker expression and decreased metabolism and cell cycle progression, demonstrating a dormancy phenotype. Functionally tail-derived T-ALL exhibited a deficient short-term ex vivo growth and a delayed in vivo propagation. Because T-ALL from tail and thorax share identical genomic abnormalities and functional disparities disappear in vivo and in prolonged in vitro assays, these features have to be non-cell autonomous. Tail-derived T-ALL showed to display higher intrinsic resistance to cell cycle dependent chemotherapeutics, such as vincristine and cytarabine, but not to dexamethasone. T-ALL recovered from gonadal adipose tissues or from co-cultures with adipocytes share metabolic, cell cycle and phenotypic or chemo resistance features with tail-derived T-ALL. In T-ALL derived from adipocyte–rich bone marrow, the investigators noticed a decreased response to cell cycle dependent chemotherapy, which may indicate that adipocyte-rich aged bone marrow or pathologies that enhance bone marrow adipocyte content help leukaemic cells escaping chemotherapy [9].

Safety results idelalisib chronic lymphocytic leukaemia del (17p)

Idelalisib, in combination with rituximab or ofatumumab, is registered in the EU as treatment of patients with previously treated CLL or primary treatment of CLL with either del(17p) or TP53 mutation not eligible for other treatments. However, previous single-arm phase 1 studies suggest an increased rate of increased transaminase in primary treatment compared with treatment of relapsing CLL [10,11].

Phase 2 data show the safety profile of idelalisib plus rituximab for the therapy of treatment-naïve patients with CLL and del(17p) is similar to that seen in studies in relapsed CLL patients [12].

In the phase 2 study, 102 untreated patients with CLL and confirmed del(17p) were treated with rituximab (375 mg/m² for weekly x8) and idelalisib (150 mg orally, bid until progression or intolerance). At the end of the study 77 patients were still in treatment. The response rate assessed by the investigators was 79%.

Of 102 patients, 101 (99%) had side effects. ≥ Grade 3 AEs occurred in 80.4% of the patients, the most common were ALT (27.5%), neutropenia (20.6%), infections (18.6%) and diarrhoea (14.7%). Laboratory ≥ Grade 3 increased ALT and/or AST was seen in 41.2% of the patients. The mean age of the patients was 66 years old with and without ≥ grade 3 ALT/AST, and the incidence of ≥3 ALT/AST was comparable to younger patients (43.9%, <65 years) and older (39,3%, ≥65 years). ≥ Grade 3 diarrhea or colitis was observed in 17.1% of the patients <65 years and in 14.8% of the patients ≥65 years. Serious AEs were observed in 46 (45.1%) patients, including pyrexia (10.8%), diarrhea or colitis (11.8%). ≥ Grade 3 infections occurred in 20 patients (19.6%) of whom 5 had cytomegalovirus (CMV) and 3 pneumocystis jiroveci pneumonia (PJP) infections. None of them were on prophylaxis. According to the investigators, although the occurrence of CMV and PJP infections is consistent with current labeling of idelalisib, patients possibly benefit from risk mitigation through PJP prophylaxis and CMV monitoring during treatment.

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Stem Cell Transplantation and Special Therapy

For many patients with blood malignancies, a haematopoietic stem cell transplantation (HSCT) remains the best therapeutic option. Consequently, numerous studies are being done to improve outcomes of these transplantations and to reduce (the burden of) acute and chronic graft versus host disease.

Optimisation of haematopoietic stem cell transplantations

With an incidence as high as 50%, acute graft versus host disease (aGVHD) is one of the main potentially fatal complications of HSCT. A potential treatment target for is the natural killer (NK) cell population, as these cells have the capacity to potentiate the graft versus leukaemia effect with a minimum risk for graft versus host reactions. A previous study showed that the abundance of circulating NK cells has been inversely correlated with the probability to develop aGVHD, while $CD69^{-/-}$ NK cells have shown to eliminate tumour cells more effectively than WT NK cells [1]. Hence, Spanish investigators examined whether $CD69^{-/-}$ NK cells possibly have a higher cytolytic capacity against activated allogenic T cells which could lead to successful prevention of aGVHD, using a fully allogenic aGvHD mouse model in which wild type (WT) or $CD69^{-/-}$ BALBc mice were lethally irradiated and reconstituted with C57/BL6 HSCs and naïve T cells [2].

$CD69^{-/-}$ mice seemed highly resistant to aGVHD and significantly more efficient at eliminating hyper-reactive allogenic T cells in vivo, in comparison with WT mouse. The mentioned phenotype was reproduced in WT mice treated with a CD69 neutralising monoclonal antibody during disease induction. Both in vivo and RNA-sequencing data indicated that $CD69^{-/-}$ NK cells are resistant to apoptosis. Also, preliminary data indicate that in patients host NK cells can persist shortly after conditioning and transplant. To avoid clonal expansion of hyper-reactive allogenic T cells and confer resistance to aGVHD, they could be targeted with anti-CD69. Finally, the investigators claim that their results, which were presented as Late Breaking Abstract, could easily pave the way for novel therapeutic strategies to optimise allogenic HSCT [2].

Ibrutinib as treatment chronic graft versus host disease

In an American phase 2 study ibrutinib has shown promising results as treatment option of chronic graft versus host disease (cGVHD) after failure of corticosteroid treatment [3]. There is currently no approved treatment for cGVHD after failure of steroid treatment. In preclinical models, ibrutinib reduced the severity of cGVHD by inhibition of Bruton's tyrosine kinase and interleukin-2-inducible T-cell kinase. That is why a multicentre open-label phase 2 study was conducted, to demonstrate the efficacy and safety of ibrutinib in patients with cGVHD [3].

Patients who underwent up to three previous lines of treatment for cGVHD and have erythema on at least 25% of the body surface or a NIH Oral Mucosal Score of 4 or more were included in the study. Participants were treated with ibrutinib 420 mg/day - this recommended phase 2 dose of 420 mg was previously determined in a phase 1b study [4] - until cGVHD progression or unacceptable toxicity. After a median follow up of 13.9 months, the overall RR was 67% (with a CR of 21%), with 71% of responders showing a durable response of ≥20 weeks. The mean steroid dose decreased in responders from 0.29 mg/kg/day at baseline to 0.12 mg/kg/day in week 49. Overall, 62% of patients achieved a steroid dose <0.15 mg/kg/day, while 5 responders side effects' could completely stopped using steroids.

Cyclophosphamide versus etoposide

According to a study from the Acute Leukaemia Working Party (ALWP) (EBMT) a conditioning regimen based on etoposide (Vep) combined with total body irradiation (TBI) is more effective than the combination cyclophosphamide plus TBI for adult patients with Philadelphia-negative acute lymphoblastic leukaemia (ALL) who are treated with allo-HSCT [5]. The investigators emphasise that prospective studies are necessary to confirm their results and potentially discriminate a subgroup of patients who are most likely to benefit from the use of etoposide.

In the retrospective analysis, 1,498 adult patients with Philadelphia-negative ALL treated with allo-HSCT from either HLA-identical sibling (n=696) or unrelated donor (n=802) in CR1 (n=1,186) or CR2 (n=312) were included. Compared to cyclophosphamide/TBI, the use of Vep/TBI showed to be associated with a significantly reduced relapse incidence (RI) 17% vs 30% at 5 years, P=0.007), increased rate of leukaemia-free survival (LFS) 60% vs 50%, P=0.04) as well as improved GVHD and graft relapse-free survival (GRFS 43% vs 33%, P=0.04). No significant effect could be observed in terms of the incidence of non-relapse mortality, acute or chronic GVHD. In a multivariate model the use of Vep/TBI was associated with reduced risk of relapse (hazard ratio (HR) =0.62, P=0.04) while the effect on other study end-points was no longer significant. Recipient age (HR=1.17 per every 10 years, P=<0.0001), year of allo-HSCT (HR=0.97 per every year, P=0.001) and disease stage (HR=2.14 for CR2, P<0.0001) appeared to have a significant influence on the risk of treatment failure, relapse mortality (RM) or non-relapse mortality (NRM) [5].

Haploidentical versus matched sibling donors

Another study from the ALWP showed some remarkable results: patients with intermediate risk AML who underwent HSCT from a matched sibling donor had better outcomes than those who had a HSCT from a haploidentical donors (HAPLO), while in high risk-AML relapse was lower in the HAPLO transplants and NRM, LFS and OS were comparable [6].

In patients lacking matched sibling (MSD) HSCT, the standard of care for patients with intermediate AML or high-risk AML, HSCT from haploidentical donors is an emerging option. However, it is uncertain if the results are similar. Therefore, the EBMT ALWP conducted a registry-based study to compare outcomes of these two types of HSCT. In total, 2,654 patients (HAPLO=185; MSD=2,469) for intermediate AML (HAPLO=122; MSD=1,888) or high risk-AML (HAPLO=63; MSD=581) in first CR undergoing transplantation were included. The median follow up was 30 (1-116) months. Graft failure was more frequently seen after HAPLO (3% vs 1%; P=0.002). For patients with intermediate AML the CI of aGVHD and cGVHD was 29% vs 20% (P<0.03) and 30% vs 36% (P<0.02) in HAPLO and MSD patients, respectively. At 2 years, NRM and relapse incidence (RI) were 26% vs 10% (P<0.01) and 17% vs 20% (P=0.52), while LFS and OS were 56% vs 70% (P<0.01) and 68% vs 79% (P<0.01) in HAPLO and MSD patients, and GRFS was 45% vs 53% (P<0.05), respectively. HAPLO showed to be associated with reduced LFS (HR 1.74; 95% CI: 1.30-2.33; P<0.01), OS (HR 1.80; 95% CI: 1.32-2.45; P<0.01) and GRFS (HR 1.32; 95% CI: 1.01-1.72; P<0.05) and higher NRM (HR 3.03; 95% CI: 1.98-4.62; P<0.01). Incremental age showed to be independently associated to lower LFS, OS, GRFS and higher NRM and cGVHD [6].

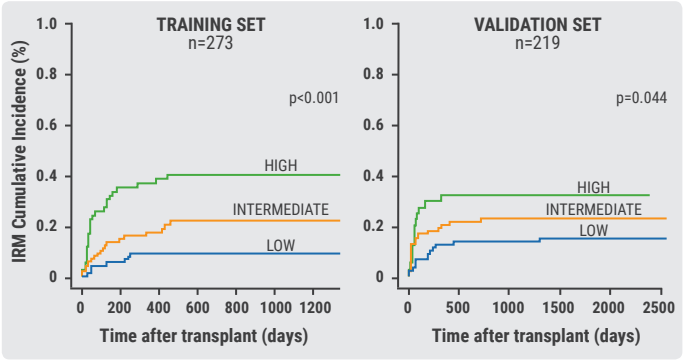
Prediction infection-related mortality

Italian investigators have developed a scoring system predicting infection-related mortality after allo-HSCT, based exclusively on pre-transplant data. In the study, data of 589 adult patients receiving allo-HSCT were analysed [7]. Using a training set of patients (n=273), the clinical and biochemical variables were challenged in a multivariate analysis and a 3-tiered weighted score was elaborated and tested in a retrospective validation set (n=219), and subsequently in a prospective validation set (n=97). Age of >60 years (P=0.003), CMV host/donor serostatus different from negative/negative (P<0.001) and pre-transplant levels of IgA <1.11 g/L (P=0.004) and IgM <0.305 g/L (P=0.028) proved to be the only independent predictors of increased infection-related mortality. Moreover, these associations seemed to be independent from disease type or status, donor type, intensity of conditioning, in vivo T cell or B cell depletion, or from previous colonisation by multidrug-resistant bacteria.

Based on their scores, patients were divided into 3 classes: low (<10.17 points), intermediate (10.17-11.11 points) or high-risk (>11.11 points). In both training and retrospective validation sets (n=492), the 2-years OS was different among the 3 groups; 59% (95% CI: 52-67), 50% (95% CI: 43-59) and 37% (95% CI: 29-48) for low, intermediate and high-risk groups, respectively (P=0.0001). In the prospective validation set, only 100-day OS was evaluated, being of 95% (95% CI: 88-100), 91% (95% CI: 82-100) and 80% (95% CI: 65-100), respectively (P=0.03). In total 129 infection-related deaths occurred, of which 94/129 (73%) were attributed to bacteria, 22/129 (17%) to viruses, 11/129 (8%) to fungi and 2/129 (2%) to parasites.

This new scoring system may contribute to a better identification of patients who have a higher risk of fatal infections prior to transplantation. Hence, the investigators

Figure 8. A and B cumulative incidence of infection-related mortality (IRM) after allo-HSCT [7]



emphasise post-transplant personalised intensive active surveillance strategies and immune-intervention approaches to improve the overall outcome of transplant. For external validation, a multicentric study is currently being set up [7].

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Benign Haematology

Benign disorders of blood, bone marrow or lymph include congenital anaemias and disorders of blood clotting, acquired disorders of blood cell production, and immune system disorders associated with degradation of blood cells. Improvement of management and treatment increase the quality of life and life expectancy of patients with blood diseases.

Luspatercept in adults with β-thalassaemia

Data from an ongoing phase 2, multicentre, open-label study followed by a long-term extension study showed long-term luspatercept treatment in patients with either transfusion-dependent (TD) or non-transfusion dependent (NTD) β-thalassaemia is generally safe and well tolerated [1]. Luspatercept (ACE-536), a fusion protein which a modified activin receptor type IIB, binds to select TGF-β superfamily ligands (such as GDF11). It reduces aberrant Smad2/3 signalling and promotes late-stage erythroid differentiation and increased haemoglobin. In a mouse model of thalassaemia luspatercept showed to correct the effects of ineffective erythropoiesis [2]. A phase 1 study in healthy volunteers learned the protein increased haemoglobin and was well tolerated [3].

In the base study and the extension study the majority of TD patients achieved ≥33% and even a ≥50% reduction in transfusion burden over a 12-week period compared to baseline (Table 1).
In NTD patients a significant amount of patients achieved ≥1.0 g/dL and ≥1.5 g/dL increase in mean haemoglobin over a 12-week period compared to baseline (Table 1). While treatment is ongoing, median duration of ≥33% reduction in transfusion burden was 6.3 months, and median duration of haemoglobin increase ≥1.0 g/dL over 12 weeks in responders was 13.5 months. According to data from the FACIT-Fatigue questionnaire, increases in mean haemoglobin over a 12-week period correlated with improvement of quality of life. Moreover, luspatercept was generally well tolerated, with most frequent related AEs (≥10%) were bone pain, myalgia, headache, musculoskeletal pain, arthralgia, and injection site pain. Only 6 patients had grade 3 AEs, namely bone pain (n=3), asthenia (n=2), and headache (n=1).

Table 1. Outcome measurement of luspatercept on blood transfusions and haemoglobin levels in adults with β-thalassaemia [1]

Outcome measure	TD patients in base study (n=31)	TD patients in extension study (n=24)
≥33% reduction transfusion burden	71% (22)	83% (20)
≥50% reduction transfusion burden	55% (17)	71% (17)
	NTD patients in base study (n=21)	NTD patients in extension study (n=27)
≥1.0 g/dL increases in mean haemoglobin	62% (13)	78% (21)
≥1.5 g/dL increases in mean haemoglobin	33% (7)	52% (14)

Re-creating HPFH to treat sickle cell disease and β-thalassaemia

American researchers have been able to create Hereditary Persistence Fetal Haemoglobin (HPFH) using CRISPR/CAS9, which may be used for the treatment of sickle cell disease and β-thalassaemia [4]. Extensive human genetic and epidemiological data show that the presence of HPFH significantly reduces the clinical manifestations of sickle cell disease and β-thalassaemia. HPFH is associated with various genetic variants on the β-globin locus that lead to transcription-reactivation of γ-globin genes, resulting in upregulation of the fetal haemoglobin.

CRISPR/Cas9 is a revolutionary technology that allows precise, targeted changes in genomic DNA. The researchers used the technology to restore specific genetic variants of HPFH in human primary haematopoietic stem cells and precursor cells, as well as in a number of other variants associated with elevated fetal haemoglobin. They managed to make genetic changes that upregulated fetal haemoglobin in samples from both healthy donors and patients. They also optimised the haematopoietic stem or progenitor cells modification conditions and demonstrated their safety.

Eculizumab in paroxysmal nocturnal haemoglobinuria

Real-world data from the International paroxysmal nocturnal haemoglobinuria (PNH) Registry has demonstrated that treatment with eculizumab is associated with improved outcomes in patients with PNH and high disease activity (HDA) [5]. Based on the results, the investigators conclude that patients with HDA, also patients with a history of major

adverse vascular events should be treated with eculizumab.

The progressive, life-threatening disease PNH is caused by somatic phosphatidylinositol glycan class A (PIGA) gene mutation in bone marrow stem cells. The International PNH Registry (NCT01374360) collects data about the natural history of PNH, including HDA, and long-term efficacy and safety of treatment with eculizumab. HDA is defined as lactate dehydrogenase ratio ≥1.5x upper limit of normal within 6 months of baseline and history of any of the following: fatigue, haemoglobinuria, abdominal pain, dyspnea, anaemia (haemoglobin <100 g/L), major adverse vascular events (including thromboembolisms), dysphagia, or erectile dysfunction. The 4,717 patients that were enrolled, were stratified into 4 groups: HDA/eculizumab-treated; HDA/eculizumab-untreated; no-HDA/eculizumab-treated; no-HDA/eculizumab-untreated. Data show that in patients with HDA status, treatment with eculizumab was associated with meaningful improvement in mean reduction from baseline in lactate dehydrogenase ratio (−5.0 [standard deviation 3.7] vs −0.4 [standard deviation 2.3]) and proportion of red blood cell transfusion-free patients (37.6% vs 15.8%). According to the data from the questionnaire FACIT-Fatigue, the HDA/eculizumab-treated group experienced greater mean score improvement than the HDA/eculizumab-untreated group (4.1 [standard deviation 10.3] vs 0.5 [standard deviation 6.8] points). More outcome parameters/ measurement are summarised in table 2.

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Table 2. Outcome measurements of the International PNH Registry [5]

Outcome measure*	HDA/Ecu-treated (n=786)	HDA/Never Ecu-treated (n=636)	No-HDA/Ecu-treated (n=111)	No-HDA/Never Ecu-treated (n=1138)
	n=767	n=636	n=108	n=1135
Years from baseline to last follow-up, median (min, max)	3.1 (0.0, 11.0)	1.5 (0.0, 10.0)	2.1 (0.1, 11.0)	1.5 (0.0, 9.5)
	n=583	n=356	n=67	n=582
Change from baseline in LDH ration, mean (SD)	-5.0 (3.7)	-0,4 (2.3)	-0.4 (2.0)	0.2 (0.9)
	n=210	n=107	n=25	n=248
Change from baseline in % GPI-deficient granulocytes, mean (SD)	3.5 (23.9)	-0.5 (20.2)	6.3 (21.8)	1.3 (17.6)
Change from baseline in number of patients requiring blood transfusions, n(%)	n=599	n=425	n=74	n=747
Yes to no	225 (37.6)	67 (15.8)	21 (28.4)	161 (21.6)
No change	332 (55.4)	317 (74.6)	47 (63.5)	549 (73.5)
No to yes	42 (7.0)	41 (9.6)	6 (8.1)	37 (5.0)
Change from baseline in number op patients vith MAVE, n(%)	n=699	n=460	n=94	n=766
Previous history of MAVE and occurrence of MAVE after baseline	17 (2.4)	3 (0.7)	3 (3.2)	4 (0.5)
Previous history of MAVE and no occurrence of MAVE after baseline	216 (30.9)	60 (13.0)	28 (29.8)	80 (10.4)
No previous history of MAVE and occurrence of MAVE after baseline	10 (1.4)	12 (2.6)	2 (2.1)	12 (1.6)
No previous history of MAVE and no occurrence of MAVE after baseline	456 (65.2)	385 (83.7)	61 (64.9)	670 (87.5)
Change from baseline in FACIT-Fatigue score, mean (SD)	4.1 (10.3)	0.5 (6.8)	-3.8 (14.5)	0.3 (7.7)

*All analyses of change from baseline to last follow-up were restricted to patients with at least 6 months of follow-up and who had data at both baseline and last follow-up time points.
Abbreviations: Ecu, eculizumab; FACIT, Fuctional Assessment of Chronic Illness; GPI, glycosylphosphatidylinositol; HDA, high disease activity; LDH, lactate dehydrogenase; MAVE, major adverse vascular event; SD, standard deviation

Paediatric Haematology

Many abstracts on paediatric haematology presented in the meeting reported the diversity and complexity of this field.

Exposure to infection with childhood BCP-ALL

Exposure to infections trigger PAX5 and ETV6-RUNX1 B-cell precursor ALL (BCP-ALL) of childhood, according to investigators after studying 3 mouse models. The promising results were presented at the Presidential Symposium. BCP-ALL in childhood is still an important cause of death in high-income countries. For years, the theory has been that infection is a potential trigger of BCP-ALL. Recently, in vitro and in vivo results have strengthened the causal role of exposure to infection in BCP-ALL [1,2]. However, it is unknown which molecular BCP-ALL subtype can be activated by exposure to infection and how the preleukaemic clone evolves into BCP-ALL. Therefore, researchers developed two independent genetically engineered mouse models, in addition to the PAX5+/- infection model [1]. They represent childhood BCR-ABL1p190 BCP-ALL and the most common subtype ETV6-RUNX1 BCP-ALL. PAX5+/- and Sca1-ETV6-RUNX1 mice only develop BCP-ALL after exposure to common pathogens, whereas BCR-ABL1p190 mice develop BCP-ALL independent following exposure to the common infection.

The Spanish and German researchers conclude that exposure to common pathogens actually can cause BCP-ALL in childhood based on PAX5 function loss or the common ETV6-RUNX1 rearrangement. However, the underlying molecular mechanism (Jak-Stat signalling in PAX5+/- mice and histone modification in ETV6-RUNX1 mice), which is activated by exposure to common infection, is determined by genetic predisposition. On the other hand, BCP-ALL which arises on the basis of a strong oncogene (such as BCR-ABL1p190) can occur independent of infection exposure [3].

Dasatinib in children and adolescents with chronic phase chronic myeloid leukaemia

A large prospective registration study proves that dasatinib is safe and effective in treating paediatric patients with a chronic phase of chronic myeloid leukaemia (CML-CP) [4]. Dasatinib has already showed to be effective in adults with newly diagnosed CML-CP, or patients who are resistant or

Table 3. Results of dasatinib in paediatric patients with chronic phase chronic myeloid leukaemia (CML-CP) [4]

	Treated pts with CML-CP (n=113)		
	IM-resistant/ intolerant CML-CP (n=29)	Newly diagnosed CML-CP (n=84)	
		Tablet (n=51)	PFOS (n=33)
Median average daily dose, mg/m^2 (range)	58 (35-72)	59 (37-78)	65 (38-99)
Median duration of treatment, months (range)	50 (2-90+)	52 (8-75+)	27 (<1-42+)
Patients on treatment, n(%)	14 (48)	61 (73)	
		37 (73)	24 (73)
Reasons fo discontinuation, n(%)			
Progressive disease	5 (17)	5 (10)	1 (3)
Study drug toxicity	0	0	1 (3)
Patients withdrawal[a]	3 (10)	2 (4)	1 (3)
Maximum clinical benefit	2 (7)	1 (2)	0
Noncompliance	1 (3)	0	0
Other	4 (14)	6 (12)	6 (18)
MCyR,[b] % (95% CI)			
By 3 months	55	57 (46, 68)	
		55 (40, 69)	61 (42,77)
By 12 and 24 months	90 (73, 98)	96 (90, 99)	
		98 (90, 100)	94 (80, 99)
Median time to MCyR,[b] % months (95% CI)	3.1 (2.8, 4.1)	3.0 (2.9, 4.3)	
		3.3 (2.9, 5.6)	3.0 (2.8, 5.0)
CCyR,[b] % (95% CI)			
By 6 months	66 (46, 82)	64 (53, 74)	
		61 (46, 74)	70 (51, 84)
By 12 months	76 (57, 90)	92 (84, 97)	
		94 (84, 99)	88 (72, 97)
By 24 months	83 (64, 94)	94 (87, 96)	
		96 (87, 100)	91 (78, 98)
Median time to CCyR,[b] % months (95% CI)	3.9 (2.8, 5.6)	5.6 (5.0, 6.0)	
		5.7 (3.7, 6.2)	5.6 (3.1, 6.0)
MMR, % (95% CI)			
By 12 months	41 (24, 61)	52 (41, 63)	
		57 (42, 71)	46 (28, 64)
By 24 months	55 (36, 74)	70 (59, 80)	
		75 (60, 86)	64 (45, 80)
Estimated 48 months PFS, % (95% CI)	78 (57, 89)	93 (83, 97)	
		92 (80, 97)	97 (79, 100)

[a]Refers to either study treatment discontinuation by Patients, or withdrawing consent from further follow-up.
[b]Responses based on ≥ 20 metaphases.
CI = confidence interval; MMR = major molecular response.

intolerant to imatinib [5,6]. In a phase 1 study, dosage and safety in paediatric patients have previously been confirmed [7]. However, a larger international prospective study is necessary to justify the use of dasatinib in newly diagnosed paediatric patients with CML-CP, as well as those resistant or intolerant to immunosuppression.

At the time of analysis, 48% of patients with imatinib-resistant or intolerant CML-CP and 73% of newly diagnosed CML-CP were still treated with dasatinib. A cumulative percentage of major cytogenetic response (MCyR)> 30% was achieved by imatinib-resistant or intolerant CML-CP patients after 3 months, and a cumulative percentage of complete cytogenetic response >55% was reached after 6 months for patients with newly diagnosed CML-CP. Estimated progression free survival at 48 months was 78% for the patients with imatinib-resistant or intolerant CML-CP and 93% for patients with newly diagnosed CML-CP (Table 3). AEs were consistent with reported AEs in dasatinib-treated adults, except that in this study no pleural or pericardial effusion, pulmonary edema, hypertension or pulmonary arterial hypertension was seen [4].

Low-dose cytarabine in children with Down syndrome and TMD

Low-dose chemotherapy with cytarabine does not seem to prevent the development of subsequent leukaemia in children with Down syndrome who are diagnosed with transient myeloproliferative disorder (TMD). That is the conclusion of the German AML-BFM TMD Prevention 2007 trial [8].
Within a few days after birth, about 10% of children with Down syndrome are diagnosed with TMD. This group of patients have approximately around 20% risk of early death and a 20% to 30% risk to develop myeloid leukaemia (ML-DS) before they turn 4 years old. The AML-BFM TMD Prevention 2007 trial, a multi-centre, non-randomised, historically controlled study, was established not only to analyse the outcome of TMD patients but also to evaluate whether low-dose cytarabine (1.5 mg/kg IV/subcutaneous daily) can prevent the progression to ML-DS.

In the cohort of 108 TMD patients 45 patients received low-dose cytarabine treatment, while 57 patients did not receive cytarabine. Overall, patients in the trial did not show a significantly better event-free survival (EFS) or OS compared with the historic control group (n=146). The cumulative incidence of death was lower, however not statistically significant, while the cumulative incidence of progression to ML-DS was also similar. Patients with TMD-related clinical symptoms (n=43) had a tendency for a better EFS, OS and cumulative incidence of death than the historical controls (n=45), but the differences were not significant. For the progression to ML-DS there was also no significant difference between the two groups. And finally, patients without any TMD-related symptoms (n=59) showed no significant differences regarding EFS, OS, and cumulative incidence of ML-DS compared to patients without symptoms in the historic control group (n=101). Outcome measures are summarised in table 4. Based on these results the German investigators cannot recommend a general preventive chemotherapeutic treatment of children who were diagnosed with TMD. They argue whether in order to reduce disease-related mortality, children with TMD-related symptoms should receive low-dose cytarabine.

Table 4. Outcome measures of the AML-BFM TMD Prevention 2007 trial [8]

Outcome measure	Trial cohort (n=108)	Historic controls (n=146)	p-value
EFS	72±4%	63±4%	P=0.15
OS	91±3%	85±3%	P=0.15
CI of death	8±3%	15±3%	P=0.09
CI of ML-DS	19±4%	22±4%	P=0.88
Patients with TMD-related clinical symptoms	**(n=43)**	**(n=45)**	
EFS	59±8%	44±8%	P=0.097
OS	80±6%	67±7%	P=0.10
CI of death	20±7%	33±7%	P=0.10
CI of ML-DS	21±7%	23±7%	P=0.91
Patients without TMD-related clinical symptoms	(n=59)	(n=101)	
EFS	81±5%	71±5%	P=0.27
OS	98%	93±3%	P=0.16
CI of ML-DS	19±6%	22±4%	P=0.95

EFS = event free survival
OS = overall survival
CI = cumulative incidence

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Thrombosis and Haemostasis

Major risk factors for thrombosis are age, exogenous factors such as surgery, hospitalisation, immobility, trauma, pregnancy, and endogenous factors such as cancer, obesity, and inherited and acquired disorders of hypercoagulation. Several abstracts focused on patient management and risk factors.

Improved storage platelets

At the Presidential Symposium investigators showed that activation of Ras homologous gene family, member A (RhoA) plays a crucial role in the lesions and phagocytosis that occur in the refrigerated storage of platelets. Reversible inhibition of RhoA in refrigerated platelets ensures platelets can be stored for longer periods of time [1].

The use of platelets in transfusion has increased drastically over the past three decades. However, a low temperature induces changes in glycosylation and clustering of platelet glycoprotein 1b and cytoskeletal rearrangements. As a result, platelets in current practice are stored at room temperature, which is associated with a relatively high risk of bacterial growth and thus infections in susceptible patients. Due to the cytoskeletal nature of platelet changes in refrigerated storage, the investigators hypothesised that the Rho family GTPase activity is pivotal in the cold platelet lesion. A targeted intervention is desirable. They found that both short and long-term refrigeration activates RhoA and Rac1, but not Cdc42. Inhibition of RhoA with the small molecule G04 proved to be sufficient to completely prevent lesions and phagocytosis after prolonged refrigeration. The effect of G04 was also reversible: upon removal of G04 after 7 days of storage, RhoA activity returned to normal levels.

Fostamatinib as treatment chronic immune thrombocytopenia

The oral spleen tyrosine kinase (syk) inhibitor fostamatinib, substantially improves platelet counts in certain patients with heavily pre-treated, severe chronic immune thrombocytopenia (cITP) of long disease duration. This is shown by the results of 2 parallel randomised placebo-controlled phase 3 trials [2]. Once approved, fostamatinib could be an important alternative as single agent and be a useful component of combination therapy for patients with difficult cITP, according to the investigators.

ITP is characterised by autoantibody-directed platelet destruction mediated by activated monocyte Fc receptors which signal via syk. A phase 2 trial of the oral already provided preliminary efficacy and safety data about the syk inhibitor fostamatinib [3].
In total, 150 patients with 3 platelet counts <30K/µL were included in the 2 studies, and 2:1 randomised to fostamatinib 100 mg or placebo bid. The objective RR was 29% (29/101) for patients in the fostamatinib group and 2% (1/49) for patients in the placebo group (P<0.0001). Most AEs on treatment with fostamatinib were mild or moderate, and all resolved over time. Most common were: diarrhoea (29% vs 15%), nausea (19 vs 8%), hypertension (20% vs 8%), ALT/AST increase (10% vs 0%). More outcome measures are shown in table 5.

Table 5. Results of in patients with heavily pre-treated, severe chronic immune thrombocytopenia (cITP) [2]

	Fostamatinib (n=101)	Controls (n=49)	P-value
Stable response	18% (18)	2% (1)	P=0.007
Intermediate response	11% (11)	0% (0)	P<0.0001
Objective response rate	29% (29)	2% (1)	P<0.0001
Platelet increase ≥20K/µL	54% (54)	29% (14)	P=0.005
≥ 1 Adverse Events	83% (83)	75% (37)	
Serious Adverse Events	13% (13)	21% (10)	

Cancer-related VTE and anticoagulants

A Canadian retrospective population-based study shows that in elderly cancer patients treated with anticoagulants due to venous thromboembolism (VTE), the risk of dying within a week after a major bleeding is 9 times higher than after a recurrent VTE [4].

According to a previous systematic review, the risk of mortality by repeated VTE or major bleeding is not increased for patients with cancer [5]. However, the Canadian investigators think the heterogeneity in study design, outcomes, and in particular the types of populations, limits the interpretation and applicability of the results. Therefore, they performed a retrospective population-based study. They collected data from patients 65 years and older with a diagnosis of cancer who developed a VTE within 6 months after the first cancer diagnosis. Between 2004 and 2014, 6,967 VTEs were found. Of all patients, 59.9% received a low molecular weight heparin, 15.3% low molecular weight heparin followed by warfarin, 22.1% warfarin and 2.7% rivaroxaban. At 180 days after the VTE, 235 (3%) had major bleedings and 1,184 (17%) had recurrent VTEs. Within 7 days after an event, 26 (11%) patients died after major bleeding and 6 (0.5%) after a VTE. The mortality rate for major bleeding versus VTE was 21.8% (95% CI: 9-53%). In exploratory analyses, the authors did not find differences between the various types of prescribed anticoagulants [4].

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