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PEER-REVIEWED CONFERENCE REPORT

Venetoclax Combination Therapy in Acute Myeloid Leukaemia

AML patients who are ineligible for intensive chemotherapy may have a new therapy option with venetoclax in combination with low-dose cytarabine or with hypomethylating agents.

read more on PAGE 3

Treatment of Lymphoid Malignancies

Promising developments in chemotherapy-free treatment options include CAR T cell and BiTE immunotherapies.

read more on PAGE 7

Maintenance Therapy with Ixazomib Prolongs PFS

Results from the first randomised, double-blind, placebo-controlled trial of proteasome inhibitor ixazomib showed significantly prolonged PFS after autologous stem cell transplant in patients with newly diagnosed multiple myeloma.

read more on PAGE 10

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Editor Prof. Gert Ossenkoppele, VU University Medical Center, the Netherlands

Contents

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Letter from the Editor

Prof. Gert Ossenkoppele

Dear Reader,

To compose a selection of important papers presented at ASH is always difficult. Which to show and which to neglect? However, a selection is necessary because of the many thousands of abstracts that were presented and already survived a critical review by ASH reviewers. We tried to stick to papers that are really important for the daily clinical practice now or in the near future. Of special interest at this year's ASH were the papers on AML. For the first time in many years, several new drugs showed up and are really practice-changing already now or will be very soon. Targeted treatment is emerging as well as immunotherapy. CAR T cell therapy is very promising and abstracts in non-Hodgkin lymphoma are also summarized in this review.

Furthermore, you can read summaries in the field of hemostasis and thrombosis as well as nonmalignant hematology.

We hope that you will enjoy this selection of summarized abstracts and are convinced that they give a quick overview of many important abstracts.

Best regards,
Gert Ossenkoppele

Biography

Professor Gert Ossenkoppele was appointed in 2003 as professor of Hematology at the VU University Medical Center in Amsterdam. Gert Ossenkoppele has authored over 390 publications in peer-reviewed journals and is an invited speaker at many international scientific meetings. His research interests are mainly translational and include the (stem cell) biology of AML, leukemic stem cell target discovery, immunotherapy, and measurable residual disease (MRD) detection using flow cytometry to inform treatment of AML. He is the PI of various clinical trials in myeloid malignancies. He chairs the AML working party of HOVON (Dutch-Belgian Hematology Trial Group) and is appointed as vice-chair of the HOVON Executive Board. He is a lead participant of the AML Work package of the European LeukemiaNet (ELN) as well as a board member of the ELN foundation. He is recently appointed as chair of the EHA Educational Committee. He chairs the AML Scientific working group of EHA, and he is chair of the Global and EU steering committee of the AMLGlobalPortal an educational portal for hematologists (www.amlglobalportal.com).

Conflict of Interest Statement:
Prof. Ossenkoppele is consultant for Novartis and BMS.

Myeloid Malignancies

The management of myeloid malignancies has made significant steps forward as new therapeutic options emerge, offering new perspectives, especially in the area of relapsed and refractory malignancies.

Venetoclax plus low-dose cytarabine safe and effective for elderly AML patients ineligible for intensive chemotherapy

An open-label, phase 1/2 study by Wei et al. showed that venetoclax in combination with low-dose cytarabine resulted in complete responses in more than half of a heterogeneous group of elderly acute myeloid leukaemia (AML) patients, with a 71% response rate seen in treatment-naive patients. This study assessed the safety and efficacy of venetoclax –an oral agent targeting the anti-apoptotic protein BCL-2, which is overexpressed in AML and AML stem cells– in combination with low-dose cytarabine in patients with previously untreated AML who were ineligible for intensive chemotherapy due to comorbidities or age [1].

A total of 82 patients, of which 65% were male and 95% Caucasian, were enrolled between December 2014 and May 2017. Patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0-2 and adequate hepatic and renal function. In total, 60% of patients had intermediate and 32% poor cytogenetic risk, and 49% had secondary AML (of whom 60% had prior exposure to hypomethylating agents [HMA]). Transfusion dependence for red blood cells and platelets within 8 weeks prior to treatment was 65% and 28% of patients, respectively. Venetoclax was initiated at 50 or 100 mg daily and dose escalated over 4-5 days to reach the recommended phase 2 dose of 600 mg daily. In subsequent 28-day cycles, venetoclax was administered at 600 mg on all days. Low-dose cytarabine (20 mg/m^2 daily) was administered subcutaneously on days 1-10 of each cycle.

This study showed that 54% of patients achieved complete remission (CR) or complete remission with incomplete haematologic recovery (CRi). Median time to first response was 1.4 months (range 0.8-14.9), median time to best response was 2.8 months (range 0.8-22.4), and median duration of remission after CR/CRi was 8.1 months (95% CI 5.7-14.2). For patients with secondary and *de novo* AML, the rates of CR/CRi were 35% and 71%, respectively, and median duration of response was 8.1 and 11.6 months, respectively. For patients with selected genetic mutations, the rates of CR/CRi were 30% for TP53, 72% for IDH1/2, 44% for FLT3, and 89% for NPM1. Median overall survival (OS) in patients who achieved CR, CR/CRi, and other responses was not reached (95% CI, 16.9-NR), 18.4 months (95% CI, 14.0-NR), and 3.5 months (95% CI, 2.3-5.1), respectively. Minimal residual disease (MRD) response, which was defined as less than 10^{-3} leukaemic cells at any measurement in bone marrow aspirate, was achieved in 32% of patients with CR/CRi. Among patients that were red blood cells or platelet transfusion dependent at baseline, 49% and 65%, respectively, achieved transfusion independence while on venetoclax+low dose cytarabine therapy.

Regarding safety, the most common treatment-emergent adverse events (AEs) were nausea (70%), diarrhoea (49%), hypokalaemia (48%), and fatigue (43%). The most common grade ≥3 AEs across all patients were febrile neutropenia (43%), thrombocytopenia (38%), neutropenia (27%), and anaemia (27%). Two patients achieving the target dose of venetoclax were reported to have grade 3 tumour lysis syndrome (TLS). CYP3A inhibitors were safely co-administered (with appropriate venetoclax dose adjustments) in 47% of patients, with 40% receiving moderate agents and 7% strong agents for at least 7 days (these were predominantly azole antifungals).

Thus, venetoclax in combination with low-dose cytarabine led to rapid, deep, and durable responses in AML patients ineligible for intensive chemotherapy. Venetoclax plus low-dose cytarabine demonstrated an improved CR rate (26% vs 8%), CR/CRi rate (54% vs 11%), and median OS (10 months vs 5 months) compared with the historical rates of low-dose cytarabine alone. Furthermore, most patients achieved transfusion independence during venetoclax therapy.

Promising results venetoclax plus hypomethylating agents for AML patients ineligible for intensive chemotherapy

Venetoclax also yielded high (more than 70%) CR rates in previously untreated elderly AML patients who were ineligible for intensive chemotherapy, when combined with HMAs [2]. CR/CRi rates were similar whether venetoclax was paired with azacitidine or decitabine. Most patients had a response duration of 12 months or longer with the combination therapy. Moreover, baseline genetic mutations and cytogenetic risk did not affect response to the combination therapy.

This was demonstrated in a phase 1b, dose escalation/expansion study that evaluated venetoclax 400, 800, or 1200 mg daily with 20 mg/m of decitabine on days 1–5 or 75 mg/m of azacitidine on days 1-7, in 28-day cycles in older patients with untreated AML. The recommended phase 2 dose was identified as 400 mg. In total, 115 AML patients (median age 74 years; range 65-86) received 400 mg venetoclax daily in a 3-day ramp-up from 100-200-400 mg co-administered with azacitidine (n=84; median age 75 years) or decitabine (n=31; median age 72 years) on days 1–7 within each 28-day cycle. Patients treated with venetoclax plus azacitidine had a CR/CRi rate of 71%; those who were treated with venetoclax plus decitabine had CR/CRi of 74%. Median time to CR was 1.2 and 1.9, respectively (Table 1) [2].

Table 1 Various outcomes venetoclax plus azacitidine or decitabine [2]

Types of outcomes	Venetoclax plus azacitidine	Venetoclax plus decitabine
CR/CRi	71% (95% CI, 59-80%)	74% (95% CI, 55-88%)
Median time to CR	1.2 (range 0.7-5.5)	1.9 (range 0.9-4.6)
Median response duration after achieving CR/CRi	21.2 months (95% CI, 14.4-30.2)	15.0 months (95% CI, 5.0-22.5)
Median OS	16.9 months (95% CI, 11.3-NR)	16.2 months (95% CI, 9.1-27.8)
Transfusion dependence for red blood cells and/or platelets within 8 weeks prior to venetoclax treatment	64%	74%
MRD negative status (MRD negativity defined <10 leukaemic cells at any measurement in bone marrow aspirates) of patients with CR/CRi	48%	39%

CR, complete remission; CRi, complete remission with incomplete haematologic recovery; OS, overall survival; MRD, minimal residual disease.

The most common grade ≥3 AEs across all patients were febrile neutropenia (44%), anaemia (28%), pneumonia (25%), thrombocytopenia (22%), and neutropenia (18%). The ≤30-day mortality rate in patients receiving venetoclax plus azacitidine or decitabine was 2% and 7%, respectively.

The researchers concluded that venetoclax in combination with HMAs may provide a potent therapeutic option for AML patients who are not eligible for intensive chemotherapy. A phase 3 study evaluating venetoclax 400 mg combined with azacitidine in adults with untreated AML ineligible for intensive chemotherapy is currently being developed.

Ivosidenib or enasidenib plus standard induction and consolidation regimens promising in *de novo* AML with IDH1 or IDH2 mutations

Patients with newly diagnosed AML harbouring IDH1 or IDH2 mutations may benefit from treatment combinations of either ivosidenib (oral IDH1 inhibitor) or enasidenib (oral IDH2 inhibitor) with standard induction and consolidation regimens. The results of an open-label, phase 1 trial by Stein et al., showed that these combinations are safe and well-tolerated, and offer promising remission rates and 1-year survival rates of >75%. Ivosidenib plus chemotherapy was associated with the elimination of MRD evaluated by flow cytometry in 88% of treated patients and with IDH1 mutation-clearance in 41% of patients on or after day 28 of induction, while enasidenib plus chemotherapy was associated with elimination of MRD in 45% of patients and with IDH2 mutation clearance in 25% of patients on or after day 28 of induction.

Both agents were assessed in combination with standard induction therapy (either daunorubicin 60 mg/m^2 per day or idarubicin 12 mg/m^2 per day for 3 days, plus cytarabine 200 mg/m^2 per day for 7 days). Dosing was ivosidenib 500 mg once daily for patients with IDH1 mutations, and enasidenib 100 mg once daily for those with IDH2 mutations. A total of 134 patients were treated: 47 with ivosidenib (median age 63 years, range 24-76) and 87 with enasidenib (median age 63 years, range 27-77). After induction, patients with CR, CRi, or CR with incomplete recovery of platelets (CRp) could receive up to 4 cycles of consolidation therapy while they continued the IDH inhibitor. Patients who completed consolidation or who were ineligible for consolidation could continue with maintenance therapy with the assigned drug until the study was finished (up to 2 years after the last patient was enrolled).

All patients in each group received a least one full induction cycle; about 48% of patients in each arm received at least some consolidation treatment. Maintenance therapy was given to 18% of patients on ivosidenib and 19% on enasidenib. The results showed that the best overall response rates (CR+CRi+CRp) were 80% for those who received ivosidenib and 72% for those receiving enasidenib. Response rates were higher among patients with *de novo* AML when compared to patients with secondary AML. Median OS was not reached by either the patients on ivosidenib or enasidenib: the probability of surviving to 1 year after the start of induction was 79% and 75%, respectively. Treatment was discontinued in 55% of patients in the ivosidenib group, and in 84% of patients in the enasidenib group. The most important reasons for discontinuation included haematopoietic stem cell transplant (HSCT), AEs, progressive disease, and death (ivosidenib n=1 and enasidenib n=4). Specific AEs included IDH differentiation syndrome (ivosidenib n=2 and enasidenib n=1), leucocytosis, QT interval prolongation, and increased blood bilirubin. The 30-day and 60-day mortality rates were 5% and 8% in the ivosidenib arm and 5% and 9% in the enasidenib arm, respectively. These findings prompted a randomised, phase 3 trial to further evaluate the clinical benefit of adding either ivosidenib or enasidenib to induction, consolidation, and maintenance therapy for newly diagnosed AML patients with IDH mutations [3].

Survival benefit quizartinib vs salvage chemotherapy in relapsed/refractory FLT3-ITD AML patients

Quizartinib –an FLT3 inhibitor targeting driver mutations that are associated with high leukaemic burden and poor prognosis– has shown to reduce the risk of death by 24% compared with salvage chemotherapy in patients with an FLT3 internal tandem duplication mutation (ITD)-positive relapsed/refractory AML after frontline treatment with or without HSCT. This was the result of the global, phase 3, randomised controlled QuANTUM-R study [4]. Final efficacy and safety data of the QuANTUM-R study were presented.

A total of 367 adult patients with FLT3-ITD AML refractory to or relapsed after (duration of first remission ≤6 months) standard AML therapy, with or without HSCT, were randomised 2:1 to once daily quizartinib 60 mg, with a 30 mg lead-in (n=245) or to the investigators' choice of salvage chemotherapy selected prior to randomisation. Chemotherapy choices included low-dose cytarabine (n=29); the combination of mitoxantrone, etoposide, and cytarabine (n=40); or the combination of fludarabine, cytarabine, and GCSF with idarubicin (n=53). Primary and secondary endpoints of the study were OS and event-free survival (EFS), respectively. Baseline patient characteristics were well-balanced across the treatment arms. The median patient age in the quizartinib arm was 55 years (range 19-81 years) and 89% had and ECOG performance score of 0-1. In total, 33% of patients were refractory to prior therapy, 23% had relapsed after remission with HSCT, and 45% had relapsed after remission without HSCT. Median OS with quizartinib was 6.2 months (95% CI, 5.3-7.2) at a median follow-up of 23.5 months vs 4.7 months (95% CI, 4.0-5.5) with salvage chemotherapy (HR, 0.76; 95% CI, 0.58-0.98). Three pre-specified sensitivity analyses were done in which the OS benefit was maintained (Table 2).

Table 2 OS benefit quizartinib in different sensitivity analyses [4]

Sensitivity analysis	Characteristics of analysis	Median OS quizartinib vs salvage chemotherapy
1st sensitivity analysis	Censoring for the effect of transplant	5.7 vs 4.6 months (HR, 0.79; 95% CI, 0.59-1.05; P=0.519)
2nd sensitivity analysis,	Censoring for the use of other FLT3 inhibitors	6.6 vs 5.0 months (HR, 0.74; 95% CI, 0.55-0.99; **P=0.0203**)
3rd sensitivity analysis	Per-protocol set: patients who were randomised and treated without significant protocol deviations	6.2 vs 4.6 months (HR, 0.75; 95% CI, 0.57-1.00; **P=0.0246**)

The median OS benefit was also demonstrated across several patient subgroups, such as those with prior allogeneic HSCT (OS 5.3 vs 4.0 months with salvage chemotherapy), those without prior allogeneic HSCT (6.9 vs 5.2 months) and patients with intermediate AML risk score (6.2 vs 4.6 months) and unfavourable AML risk score (9.4 vs 5.8 months). The rates in subgroups defined by response to prior therapy were as follows: median OS was 6.5 vs 4.7 months in patients who relapsed with no HSCT, 7.9 vs 5.4 months in refractory patients, and 5.1 vs 4.0 months in patients who relapsed post-HSCT. The median EFS was 1.4 months (95% CI, 0.0-1.9) with quizartinib vs 0.9 months (95% CI, 0.4-1.3) with salvage chemotherapy (HR, 0.90; 95% CI, 0.70-1.16; 1-sided, stratified log-rank P=0.1071). Results showed that quizartinib was well-tolerated, grade 3 QT prolongation was uncommon, and no grade 4 were observed.

The most common grade ≥3 haematologic AEs for those on quizartinib included thrombocytopenia (35% vs 34% for salvage chemotherapy), anaemia (30% vs 29%, respectively), neutropenia (32% vs 25%), febrile neutropenia (31% vs 21%), and leukopenia (17% vs 16%). The most common grade ≥3 non-haematologic AEs with quizartinib were nausea (3% vs 1% for salvage chemotherapy), fatigue (8% vs 1%), pyrexia (3% vs 4%), musculoskeletal pain (4% in each arm), vomiting (3% vs 1%), hypokalaemia (12% vs 9%), and diarrhoea (2% vs 3%).

These findings confirm the survival benefit that was observed with single-agent quizartinib in comparison with salvage chemotherapy in patients with relapsed/refractory FLT3-ITD AML. The favourable safety profile provides evidence of meaningful clinical benefit in patients with few treatment options left. Researchers added that these findings, as seen across specific sensitivity and subgroup analyses, further demonstrate the consistency and robustness of the treatment effect seen in the QuANTUM-R study with quizartinib. Also, these new analyses further support the value of targeting the FLT3-ITD driver mutation with a highly selective and potent FLT3 inhibitor such as quizartinib. Currently, quizartinib is being assessed in the phase 3 QuANTUM-First study, which examines this agent in patients with newly-diagnosed FLT3-ITD-positive AML.

BiTE AMG 330 shows promise in relapsed/refractory AML

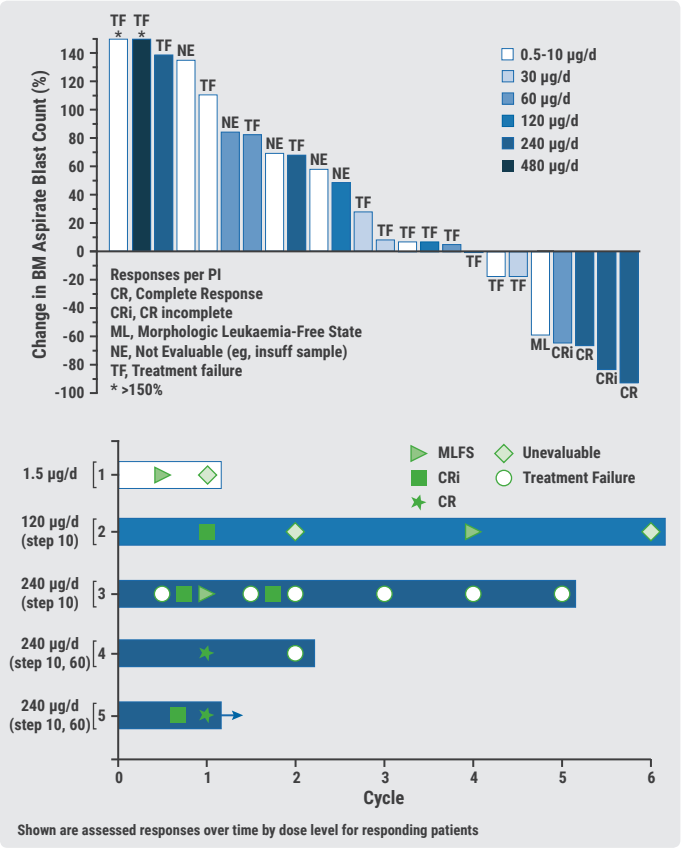
AMG 330 is a bispecific T cell engager (BiTE) that binds CD33 on AML blasts and CD3 on T cells, thus facilitating T cell destruction of CD33+ cells. Preliminary data from a phase 1, dose-escalation study evaluating AMG 330 as a continuous IV infusion in patients with relapsed/refractory AML with >5% blasts in their bone marrow showed encouraging evidence of tolerability and anti-leukaemic activity of AMG 330 in this population.

The objectives of this ongoing study were to evaluate the safety, pharmacokinetics, and pharmacodynamics of AMG 330 in relapsed/refractory AML and to define the maximum tolerated dose. The 40 patients included in this study had a mean age of 58.5 years and the median number of prior lines of therapy was 4 (range 1-15); 43% had a prior stem cell transplant. Patients received AMG 330 by continuous IV infusion for 2 to 4 weeks, depending on the cohort, followed by 1 to 4 weeks off therapy. Single cohorts were treated for the first 3 doses followed by cohorts of 3 to 6 patients each, up to a target of 480 µg/day. Duration of therapy was up to 6 cycles if no dose-limiting toxicity was encountered in the first cycle.

In total, 13% of patients (n=5) had a response: 2 achieved a CRs, 2 a CRi, and 1 achieved a morphologic leukaemia-free state (<5% blasts). All 5 patients had their best response within 1 cycle of starting treatment. Interestingly, most responses occurred at the higher doses with 2 CRs and one CRi at a target dose of 240 µg/day and one CRi at a target dose of 120 µg/day. Although the researchers emphasised that the patient population was small and the response rate low, an association was observed between achieving a response and a higher effector-to-target cell ratio. The same was true for a higher number of circulating CD4-positive and CD8-positive T cells at baseline (Figure 1).

A total of 35 patients discontinued treatment, of which 24 (68%) due to disease progression. The maximum tolerated dose was considered to be 480 µg/day, which was reached by 2 out of 6 patients. Cytokine release syndrome (CRS) occurred in 28%, of which 2 were grade 3 and 2 grade 4. There were 2 dose-limiting toxicities, persistent grade 2 CRS, and grade 4 ventricular fibrillation at the target dose of 480 µg/day. Treatment-related neurologic AEs were observed in 19 patients including 1 patient with a grade 2 seizure, 2 patients with grade 2 somnolence, and 1 with a grade 1 speech disturbance. The study is currently ongoing with the current cohort receiving a step-up dosing with a target dose of 360 µg/day [5].

Figure 1 AMG 330 responses in relapsed/refractory AML over time



Shown are assessed responses over time by dose level for responding patients

References

1. Wei A, et al. 2018 ASH Annual Meeting, abstract 284.
2. Pollyea DA, et al. 2018 ASH Annual Meeting, abstract 285.
3. Stein EM, et al. 2018 ASH Annual Meeting, abstract 560.
4. Cortes JE, et al. 2018 ASH Annual Meeting, abstract 563.
5. Ravandi F, et al. 2018 ASH Annual Meeting, abstract 25.

Lymphoid Malignancies

Among the recent developments in the treatment of lymphoid malignancies, CAR T cell therapy undoubtedly takes centre stage. BiTEs are also promising, for example in relapsed non-Hodgkin lymphoma. For CLL/SLL patients, chemotherapy-free treatment as first-line therapy shows encouraging results.

Real-world data CAR T cell therapy for relapsed/refractory diffuse large B cell lymphoma

Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy, approved by the FDA in November 2017 for the treatment of adults with relapsed/refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), transformed follicular lymphoma (tFL), and high-grade B cell lymphoma (HGBCL) who have failed at least 2 prior systemic lines of therapy. The pivotal ZUMA-1 trial examined 108 patients with relapsed/refractory DLBCL who were treated with axi-cel [1]. The best overall response rate (ORR) was 82%, and complete response (CR) rate was 58%. Ongoing remission was seen in 42% of patients at a median follow-up of 15.4 months (40% CR). Grade 3 or higher cytokine release syndrome (CRS) by Lee criteria and neurologic events occurred in 13% and 28% of patients, respectively. In a recent multicentre, retrospective study, Nastoupil et al. evaluated the real-world outcomes of patients (n=274) treated with standard of care axi-cel under the commercial FDA label [2].

Data was obtained from 17 academic centres in the USA. All patients who underwent leukapheresis as of 31 August 2018 (n=295), with the intention to manufacture commercial axi-cel, were included in this analysis. Of those 295 patients, 274 received conditioning chemotherapy and were infused with axi-cel. Median time from leukapheresis to start of conditioning chemotherapy was 21.5 days. Of the 21 remaining patients, 7 went on to receive axi-cel therapy on the ZUMA-9 expanded access trial (NCT03153462) due to non-conforming cell therapy product, 12 patients died because of lymphoma, 1 patient had non-measurable disease, and 1 patient experienced infection. Median age of the included patients was 60 years (33% was aged ≥65 years), and 65% of patients were male. Performance status was as follows: 81% ECOG 0-1, 15% ECOG 2, and 4% ECOG 3-4. In total, 68% of all patients had DLBCL, 26% had tFL, and 6% had PMBCL. Seventy-five percent of patients had received >3 prior therapies; 35% was primary refractory, 42% was refractory to second-line or later, and 33% relapsed post-autologous stem cell transplant (ASCT). Median follow-up was 3.9 months.

With regard to efficacy, the ORR in 238 patients evaluable at day 30 was 80% with 47% CR. Of the 248 patients evaluable at day 90, best ORR was 81% with 57% CR. Furthermore, 81% of those with a CR at day 30 maintained their response at day 90 and 37% of patients with a partial response (PR) at day 30 achieved a CR by day 90. In 78% of patients who had stable disease at day 30, disease progression was seen by day 90. Covariates which were not associated with ongoing CR at day 90 were age, disease histology, lymphoma subtype, double-/triple-hit, high risk International Prognostic Index (IPI), bridging therapy, tocilizumab/steroid use, and intensive care unit (ICU) admission. Covariates associated with ongoing CR at day 90 were female sex (72% vs 51% male patients, P=0.009), ECOG 0-1 (62% vs 35% ECOG ≥2, P=0.024), relapsed (79% vs primary refractory/refractory 47%/56%, P=0.011), non-bulky (62% vs bulky [≥10 cm] 42%, P=0.040), meeting eligibility for ZUMA-1 (65% vs not meeting criteria 47%, P=0.037). Median progression-free survival (PFS) was 6.18 months (95% CI, 4.57-NA); 6-month overall survival (OS) estimate was 72% (95% CI, 65-80%).

Real-world safety results included CRS (grading according to Lee criteria); this occurred in 92% of patients, with grade ≥3 CRS occurring in only 7%. Median time to CRS onset was 3 days. Neurological toxicity occurred in 69% of patients, with grade ≥3 neurological toxicity experienced by 33% of patients (median time to onset of neurological toxicity was 6 days). A total of 63% of patients received tocilizumab and 55% received corticosteroids. Grade 5 adverse events (AEs) were rare, occurring in 3% of patients. There were 2 treatment-related deaths (1%), and deaths due to non-relapse mortality added up to 7 in total (infection n=5; haemophagocytic lymphohistiocytosis n=1; cerebral oedema n=1). Median hospital stay was 14 days; 32% of patients required admission to the ICU. It should be noted that this study was limited by a short follow-up. However, 30-day responses in the real-world setting were comparable to the best responses observed in the pivotal ZUMA-1 clinical trial. Also, safety appeared comparable with the ZUMA-1 trial despite >40% of patients failing to meet ZUMA-1 eligibility criteria (Table 3).

Table 3 Key differences between ZUMA-1 study and evaluated real-world data [1]

	ZUMA-1	Nastoupil et al.
Infused patients, n	108	165
Patients meeting ZUMA-1 eligibility criteria	100%	51%
Age, median (range)	58 (23-76)	59 (21-82)
ECOG 0-1	100%	84%
Prior autologous transplant	23%	31%
DLBCL including HGBCL, not tFL or PMBCL	78%	61%
ORR/CR	82%/58% (best)	79%/50% (day 30)
Grade ≥3 toxicity	CRS 13%/neurological 31%	CRS 7%/neurological 31%

Initial disease progression after CD19 CAR T cell therapy predicts poor survival in lymphoma patients

Although CAR T cell therapy has significantly impacted outcomes for relapsed/refractory large B cell lymphomas, a large number of patients still experience progression. In these patients, progression after CD19-specific CAR T cell therapy is a predictor for poor survival, especially when this concerns initial disease progression. This was found by Chow et al., who identified 58 patients with DLBCL, HGBCL, tFL, and PMBCL who received CD19-specific CAR T cell therapy (median age 60 years; 65% male). Primary endpoint of the study was OS. Median duration between CAR T infusion to progression was 42 days (range 11-609).

Initial progressive disease, defined as patients who had evidence of disease progression on the initial response assessment, was experienced by 53% of patients. Median follow-up after progression was 4.2 months. Initial progressive disease increased the risk of death (HR 2.37, 95% CI, 1.19-4.75). Patients who had initial progressive disease had a median OS of 3.75 months. This was in contrast with patients with delayed progression (patients with a CR, PR, or stable disease on the initial response assessment, followed by progression or subsequent anti-lymphoma therapy) who showed a median OS of 13.4 months.

In total, 75% of patients received one or more subsequent therapies after progressive disease. This included a second CAR T infusion, targeted therapy, chemotherapy with or without rituximab, other form of immunotherapy, radiotherapy, intrathecal chemotherapy, or allogeneic haematopoietic stem cell transplant (alloHSCT). No difference was found in survival between second CAR T infusion compared with other next-line therapies. Further, patients who had bridging therapy had a numerically inferior OS vs patients who did not, but this was not statistically significant.

Although there is no clear guidance on how to treat patients who progress after CAR T cell therapy, it seems that patients who are treated with any form of therapy after they showed progression had longer survival. It should also be noted that patients who were treated after they showed evidence for progression potentially had better patient- and/or disease-specific characteristics (e.g. less aggressive disease or better ECOG performance status).

The researchers recommended that all patients should be human leukocyte antigens (HLA) typed, which enables the swift identification of a matched donor for an alloHSCT in case of progression. They also noted that physicians should be aware of suitable clinical trials for these patients so they can receive immediate next-line therapy after disease progression has been observed [3].

Mosunetuzumab demonstrates promising remission rates in relapsed/refractory non-Hodgkin lymphoma

Mosunetuzumab –a CD3 and CD20 bispecific (BiTE) antibody– has shown promising CR rates and a tolerable toxicity profile in patients with relapsed/refractory B cell indolent and aggressive non-Hodgkin lymphoma. In a phase 1/1b open-label study, 75 patients with relapsed/refractory FL or tFL and 38 patients with FL were divided into 2 arms [4]. In arm A, mosunetuzumab was administered at a fixed dose on day 1 of a 21-day cycle at doses ranging from 0.05 mg to 2.8 mg. In arm B, step-up dosing was used. This was done during the first cycle on days 1, 8, and 15, followed by a fixed dose on the first day of each 21-day cycle afterwards with doses starting at 0.4, 1.0, and 2.8 mg, which were escalated to 1.0, 2.0, and 20.0 mg at the end of the first cycle. Median age was 63 years and patients had a median number of 3 prior systemic regimens; 26% had received a prior stem cell transplant. In total, 67.9% of patients were refractory to prior therapy: all patients had received a prior anti-CD20 agent whereas 6.1% of patients had received prior CAR T cell therapy. The first response in the trial was observed in arm A at doses ≥1.2 mg. CR was seen across all histologic types. Median duration of CR had not yet been reached. Median follow-up for CR in patients with DLBCL and tFL was 298 days. For FL, the follow-up for CR was 330 days. The results showed an ORR of 69.2% across mosunetuzumab doses and CR of 38.5%. Patients with relapsed/refractory DLBCL or tFL had ORR of 34% and CR of 19.1% across dose levels.

Largely due to disease progression, 54.2% of patients discontinued initial treatment. Treatment-related AEs were experienced by 72.7% of patients in arm A with 21.2% being

grade ≥3. In arm B, 59.2% experienced treatment-related AEs, of which 27.6% were grade ≥3. In total, 19% of events resolved within 24 hours, and the median duration for an event was 4 days. Median time to onset for all AEs was 18 days, and researchers found no evidence of cumulative or chronic toxicity. The most common treatment-related AEs were cytokine release syndrome, neutropenia, fatigue, hypophosphatemia, anaemia, nausea, pyrexia, diarrhoea, and headache. The maximum tolerated dose of mosunetuzumab was not reached.

The researchers concluded that mosunetuzumab offers promising outcomes for patients with relapsed/refractory non-Hodgkin lymphoma. Research assessing how to optimise dosing and schedule for monotherapy with mosunetuzumab, is currently ongoing. Also, the potential of this agent in combination with chemotherapy, atezolizumab, and the investigational anti-CD79b antibody-drug conjugate polatuzumab vedotin, will be evaluated [4].

4x CHOP may be new standard of treatment in 18-60-year-old DLBCL patients

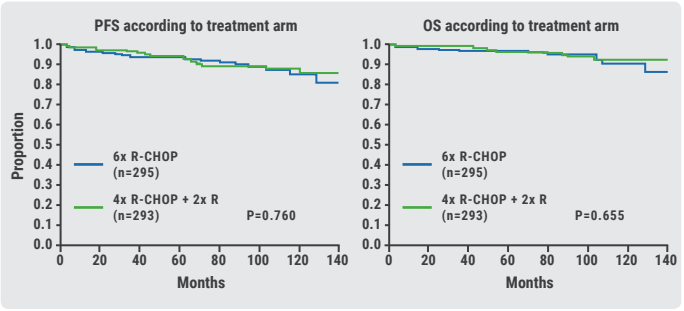
Standard treatment for young DLBCL patients traditionally consists of 6 cycles CHOP-like chemotherapy plus rituximab (R-CHOP). In the MInT trial, a subgroup with favourable prognosis was defined (aged 18-60 years, ≤1 risk factor on IPI, stage I-IV disease); they had a 3-year event-free survival (EFS) of 89%, PFS of 95%, and OS of 98% [5]. Based on these results, Poeschel et al. hypothesised that 4 cycles of CHOP plus 6 applications of rituximab would be non-inferior to the standard treatment of 6x R-CHOP in this population, and this was proven in the phase 3, randomised, multicentre FLYER trial.

The study enrolled 592 patients aged 18-60 years (median age 48) with stage I/II DLBCL. Patients were randomised to 6 (n=295) or 4 (n=293) cycles of CHOP every 21 days; and all patients received the standard 6 cycles of rituximab. Primary endpoint of the study was PFS; events were defined as progressive disease, relapse, or death. Patients were followed from 5 to 11 years.

Results for the primary endpoint of PFS, showed that 4 cycles of CHOP were non-inferior to 6 cycles of CHOP. 3-year PFS was 94% (95% CI, 91%-97%) and 96% (95% CI, 94%-99%; Figure 2), respectively.

The 3-year EFS rates were identical in both groups and corresponding 3-year OS rates were 99% and 98%. Equally important was that chemotherapy treatment with this shorter regimen consists of 84 days compared with 126 days with the 6-cycle regimen, which will allow for a better tolerability. Fewer haematologic AEs were reported with 4 cycles of CHOP compared with 6 cycles: any-grade leukocytopenia (171 vs 237 events) and anaemia (107 vs 172 events). Similarly, the occurrence of grade 3/4 events was also lower with 4 cycles of chemotherapy (leukocytopenia: 80 vs 110; anaemia: 2 vs 8), as well as less non-haematologic toxicities (835 vs 1,295 for any-grade event and 46 vs 70 for grade 3/4 events). Patients will be followed up for an additional 5 years to assess the effect of reducing the number of cycles of chemotherapy on long-term side effects. The researchers emphasised that reducing chemotherapy from 6 to 4 cycles of CHOP should be considered only for patients aged 18-60 years, which is the age range of the study population, and should still be evaluated for elderly patients >60 years [6].

Figure 2 Progression-free survival and overall survival outcomes of the FLYER study [6]



Ibrutinib-obinutuzumab combination therapy is a viable chemotherapy-free first-line option in CLL/SLL

Ibrutinib is a first-in-class, once daily inhibitor of Bruton's tyrosine kinase, approved in the USA and EU for patients with chronic lymphocytic leukaemia (CLL). The potential for improved efficacy with addition of obinutuzumab to single-agent ibrutinib vs chlorambucil + obinutuzumab was assessed in the international, open-label, randomised phase 3 study iLLUMINATE in first-line CLL/small lymphocytic lymphoma (SLL) [7].

Primary endpoint of this study was PFS, and secondary endpoints included PFS in high-risk populations (e.g. patients with del17p, TP53 mutation, del11q, and/or unmutated immunoglobulin heavy-chain variable region gene [IGHV]), rate of undetectable minimal residual disease (MRD), ORR, OS, and safety. The study included 229 treatment-naïve CLL or SLL patients aged ≥65 years or patients aged <65 years who had comorbidities. Median age was 71 years, and 65% had high-risk genomic features. Patients were randomised 1:1 to ibrutinib + obinutuzumab for 6 cycles (n=113) or chlorambucil + obinutuzumab for 6 cycles (n=116). Median follow-up was 31.3 months. Patients who had disease progression on chlorambucil + obinutuzumab could cross over to next-line therapy with ibrutinib monotherapy.

Ibrutinib + obinutuzumab significantly prolonged PFS vs chlorambucil + obinutuzumab (median not reached vs 19.0 months; HR 0.231; 95% CI, 0.145-0.367; P<0.0001). A 77% reduction in risk for progression or death was observed. At 30 months, the PFS rates for ibrutinib + obinutuzumab and chlorambucil + obinutuzumab were 79% and 31%, respectively, and these PFS benefits for ibrutinib + obinutuzumab were consistent across all subgroups. In the high-risk group, PFS with ibrutinib + obinutuzumab was also superior (median not reached vs 14.7 months with chlorambucil + obinutuzumab (HR 0.154; 95% CI, 0.087-0.270; P<0.0001). The reduction in risk for progression or death was 85%. ORR rates were 88% and 73% for the ibrutinib + obinutuzumab arm and chlorambucil + obinutuzumab arm, respectively, and CR rates were also higher with ibrutinib + obinutuzumab (19% vs 8%, respectively). In the ibrutinib + obinutuzumab arm, MRD was undetectable in blood and bone marrow in 35% of patients, compared with 25% of patients on chlorambucil + obinutuzumab. OS rates at 30 months were 86% and 85% in the ibrutinib + obinutuzumab and chlorambucil + obinutuzumab arms, respectively, and 40% of patients in the latter arm were at that timepoint receiving single-agent ibrutinib as second-line therapy. The most common (≥3%) serious AEs seen with ibrutinib + obinutuzumab were pneumonia (5%), atrial fibrillation (4%), febrile neutropenia (4%), and pyrexia (4%). For the chlorambucil + obinutuzumab arm, the most common serious AEs were infusion-related reactions (7%), febrile neutropenia (6%), pneumonia (4%), tumour lysis syndrome (4%), and pyrexia (3%). Due to obinutuzumab infusion-related reactions, 7 patients (6%) discontinued obinutuzumab treatment in the chlorambucil + obinutuzumab arm; while in the ibrutinib + obinutuzumab arm not a single patient discontinued for this reason. Full therapy discontinuation occurred in 11 patients (9%) in the chlorambucil + obinutuzumab arm and 18 patients (16%) in the ibrutinib + obinutuzumab arm. Finally, 70% of patients in the ibrutinib + obinutuzumab arm continued to take ibrutinib monotherapy across a follow-up period spanning almost 3 years. These findings show that combination therapy of obinutuzumab with ibrutinib offers an effective chemotherapy-free treatment option for first-line CLL/SLL, including high-risk populations.

References

1. Neelapu SS, et al. N Engl J Med 2017; 377:2531-2544.
2. Nastoupil LJ, et al. 2018 ASH Annual Meeting, abstract 91.
3. Chow VA, et al. 2018 ASH Annual Meeting, abstract 94.
4. Budde LE, et al. 2018 ASH Annual Meeting, abstract 399.
5. Pfreundschuh M, et al. Lancet Oncol 2006;7:379-391.
6. Poeschel V, et al. 2018 ASH Annual Meeting, abstract 781.
7. Moreno C, et al. 2018 ASH Annual Meeting, abstract 691.

Multiple Myeloma

New developments in the treatment of multiple myeloma such as novel combinations and new agents offer significant advances in managing this complex and (still) incurable disease. Trial results presented at the 2018 ASH annual meeting showed, for example, how ixazomib maintenance therapy and the addition of daratumumab to existing regimens appear to improve patient outcomes.

Maintenance therapy with ixazomib significantly prolongs PFS after ASCT in NDMM patients

Results of the phase 3 TOURMALINE-MM3 trial showed that maintenance therapy with ixazomib improves progression-free survival (PFS) in patients with newly diagnosed multiple myeloma (NDMM) who achieved a partial response to induction treatment with a proteasome inhibitor (PI) and/or an immunomodulatory drug (IMiD) containing regimen after autologous stem cell transplant (ASCT) [1,2]. The study, which is the first randomised, double-blind, placebo-controlled trial of a PI for maintenance treatment after ASCT, evaluated ixazomib vs placebo. Eligible patients were aged >18 years, had a confirmed diagnosis of multiple myeloma (MM) with documented local cytogenetics/fluorescence in situ hybridisation before ASCT, International Staging System (ISS) disease stage at the time of diagnosis, a documented response to ASCT, and ECOG performance status of 0 or 2. Key characteristics of patients are outlined in Table 4. The most common induction regimens used were bortezomib, cyclophosphamide, and dexamethasone (46%), followed by bortezomib, thalidomide, and dexamethasone (19%) and cyclophosphamide, thalidomide, and dexamethasone (5%). Thalidomide was used in 87% of patients who received an IMiD. A total of 656 patients were randomised 3:2 to receive

either ixazomib (n=395) or placebo (n=261) on days 1, 8, and 15 of 28-day cycles (up to 26 cycles). After the first 4 cycles of treatment, the dose of ixazomib or placebo was increased from 3 mg to 4 mg (ixazomib n=317; placebo n=222). Primary endpoint of the study was PFS (assessed by an independent review committee), and the key secondary endpoint was overall survival (OS).

Table 4 Key patient characteristics [2]

	Ixazomib arm (n=395)	Placebo arm (n=261)
Median age (years)	58 (52-63)	60 (54-64)
MRD status at entry		
• Negative	117/357 (33%)	75/228 (33%)
• Positive	225/357 (63%)	139/228 (61%)
• Not evaluable	15/357 (4%)	14/228 (6%)
Cytogenetic features		
• High risk	61 (15%)	54 (21%)
• Standard risk	252 (64%)	152 (58%)
• Unclassifiable	82 (21%)	55 (21%)
Induction regimen		
• PI without IMiD agent	234 (59%)	155 (59%)
• IMiD without PI	43 (11%)	28 (11%)
• IMiD + PI	118 (30%)	78 (30%)

The results showed a median PFS of 26.5 months with ixazomib vs 21.3 months with placebo (HR, 0.72; 95% CI, 0.582-0.890; P=0.002). The PFS benefit was observed across different patient subgroups (including patients aged 60-75 years, those with high-risk and standard-risk cytogenetics, and those with ISS stage III disease). Median PFS for patients with MRD-negative disease at study entry was 38.6 months with ixazomib vs 32.5 months with placebo (P=0.034). For those with MRD-positive disease, median PFS was 23.1 months with ixazomib and 18.5 months with placebo (P=0.010). Among those who had MRD-positive disease, 12% and 7% converted to MRD-negative disease in the ixazomib and placebo arms, respectively. At a median follow-up of 31 months, 14% deaths have been reported, median OS has not been reached in either arm, and investigators are continuing follow-up. In the ixazomib arm, 46% of patients had improved response at study entry (assessed by independent review committee) vs 32% in the placebo arm. Patients on ixazomib with a very good partial response (PR) at time of study entry, improved to a complete response (CR) after treatment at 43% vs 32% with placebo, respectively. Patients in PR at time of study entry also improved to a CR or very good PR with ixazomib (53%) vs placebo (34%). An overview of key safety data is outlined in Table 5 [2].

A total of 79% of patients on ixazomib vs 86% of patients in the placebo arm who did not discontinue treatment due to disease progression completed the full 24 months of treatment. There was one death in the ixazomib arm (0 in the placebo arm). The patient-reported quality of life was similar in both arms over time. Researchers concluded that based on these findings, ixazomib offers a new treatment option for maintenance after transplantation. Additional studies of ixazomib combinations and time to progression are currently being carried out to gain more insights into its effects.

Table 5 Key safety data [2]

	Ixazomib arm (n=394)	Placebo arm (n=259)
All-grade treatment-related AEs	307 (78%)	149 (58%)
All grade ≥3 treatment-related AEs	73 (19%)	13 (5%)
Most common AEs:		
• Nausea	154 (39%) / grade 3: 1 (<1%)	40 (15%)
• Diarrhoea	137 (35%) / grade 3: 10 (3%)	61 (24%) / grade 3: 2 (1%)
• Vomiting	106 (27%) / grade 3: 6 (2%)	28 (11%)
• Arthralgia	86 (22%) / grade 3: 3 (1%)	30 (12%) / grade 3: 1 (<1%)
AEs leading to discontinuation	28 (7%)	12 (5%)
AEs leading to dose reduction	73 (19%)	13 (5%)
New primary malignancies	12 (3%)	8 (3%)

Addition of daratumumab to VMP significantly improves PFS in NDMM ineligible for ASCT

Adding daratumumab –a human IgGκ anti-CD38 monoclonal antibody with a direct on-tumour and immunomodulatory mechanism of action– to bortezomib, melphalan, and prednisone (D-VMP) showed improvement in PFS and response rates in NDMM patients, including older patients who are less likely to respond to treatment. Results from the prespecified, interim analysis of ALCYONE (a phase 3 study of D-VMP vs VMP in transplant ineligible NDMM patients) showed significant PFS benefit and a higher rate of MRD negativity without increased overall toxicity for D-VMP vs VMP after a median follow-up of 16.5 months [3].

Mateos et al. presented the updated efficacy and safety findings from ALCYONE after 1 year of additional follow-up. The primary endpoint was PFS. A total of 706 patients were randomised to either D-VMP (n=350) or VMP (n=356). Median age was 71 years and 29.9% was aged ≥75 years. Of the 616 patients eligible for cytogenetic risk assessment via fluorescence in-situ hybridisation/karyotyping, 84.1% had standard-risk and 15.9% had high-risk (del17p, t[14;16], and/or t[4;14] positive) disease. It was found that, at a median follow-up of 27.8 months, adding daratumumab to VMP reduced the risk of disease progression or death by 57% vs VMP alone (HR 0.43; 95% CI 0.35-0.54, P<0.0001). The 24-month PFS rate for D-VMP was 63% vs 36% for VMP alone. Median PFS for D-VMP was not reached, whereas the control arm of VMP alone had a median PFS of 19.1 months.

A significantly higher overall response rate (ORR; 91% vs 74%) was seen in D-VMP vs VMP alone. Treatment with D-VMP achieved deeper responses, which significantly improved the rate of very good partial response or better (73% vs 50%) and more than doubling the rate of stringent complete response (sCR; 22% vs 8%) when compared with VMP alone. A higher rate of sustained MRD negativity was reached with D-VMP compared with VMP alone (10% vs 2%). The most common grade 3/4 treatment-emergent AEs during cycle 10 and onwards for D-VMP were anaemia (4%), neutropenia (2%), and bronchitis (1%). Grade 3/4 infections occurred in 23.1% of patients in the D-VMP arm vs 14.7% in the VMP arm. These infections led to treatment discontinuation in 0.9% and 1.4% of patients, respectively. No new safety signals came to light. The researchers concluded that combining daratumumab with VMP in NDMM patients who are ineligible for ASCT continued to show a significant PFS benefit, including for patients aged ≥75 years. These results support the use of D-VMP in the first line of treatment in transplant ineligible NDMM [4].

Real-world treatment patterns in relapsed/refractory multiple myeloma

There are limited real-world data to describe utilisation, treatment patterns and clinical outcomes of the different available treatments for relapsed/refractory multiple myeloma (RRMM) [5]. Willson et al. assessed treatment patterns and outcomes of patients with RRMM receiving ≥2 lines of therapy in community oncology practices in the USA. This was done through chart reviews of ≥18-year-old patients with MM diagnosed between 1 January 2011 and 31 May 2017, from a large electronic medical record database (the International Oncology Network [ION] practices and the ION EMR data warehouse). Patient data was examined from the date of initiation of first-line therapy (1LT) for MM until death, loss to follow-up, or study end date. Out of 1,005 charts reviewed, 456 patients had received ≥2 lines of therapy and were included in the chart review study. Median age at diagnosis was 70.4 years. The percentage of female patients was 39.5%; 60.5% was male. Bone involvement at diagnosis occurred in 66.0% of patients. ISS within 1 month of diagnosis was I in 28.7%, II in 27.9%, and III in 43.4%. Third-line therapy was received by 40.1% of patients, 16.4% received 4LT, and 6.4% received 5LT. 1LT was dominated by bortezomib and lenalidomide, as well as the combination of the two, with 93.3% of patients using these agents as 1LT and 69.8% of patients using them as 2LT. In 3LT and beyond, newly approved drugs (approved since 2013) were used compared with 1LT and 2LT, and this use increased over time (Table 6).

Table 6 Usage of newer treatments by LT [5]

Treatment, %	1LT	2LT	3LT	4LT	5LT
Carfilzomib	2.2	17.8	31.7	28.0	31.0
Pomalidomide	0.9	12.1	26.2	33.3	37.9
Daratumumab	0	1.8	6.6	13.3	17.2
Elotuzumab	0	1.5	2.7	4.0	3.4
Ixazomib	0	1.5	3.8	8.0	6.9
Panobinostat	0	0.4	0	4.0	3.4

Percentage of patients using newer treatments in any LT, by year

	Index Year						
Treatment, %	2011 (n=131)	2012 (n=111)	2013 (n=88)	2014 (n=75)	2015 (n=39)	2016 (n=10)	2016 (n=2)
Carfilzomib	35.1	36.0	35.2	38.7	48.7	20.0	50.0
Pomalidomide	22.9	27.9	27.3	33.3	38.5	30.0	50.0
Daratumumab	2.3	3.6	5.7	14.7	25.6	20.0	0
Elotuzumab	1.5	2.7	1.1	5.3	12.8	0	0
Ixazomib	2.3	1.8	4.5	9.3	7.7	20.0	0
Panobinostat	2.3	0.9	1.1	1.3	2.6	0	0

However, patients receiving either bortezomib, lenalidomide, or both in combination as 1LT or 2LT often received the agents as re-treatment in lines 2-6 (46.2%-55.6%). Median time on treatment decreased from 7.5 months in 1LT to ≤2.3 months in 4LT and 5LT, and median treatment-free intervals decreased from 1.6 months between 1LT and 2LT to 0.5 months between 4LT and 5LT.

The most common reason for discontinuation was disease progression and drug toxicity/intolerability. The most commonly reported AEs for all lines of therapy were fatigue (71.6%-78.3%), bone pain (38.5%-69.1%), and anaemia (53.8%-69.3%). Overall, median PFS ranged from 12.0 months in 1LT to 3.5 months in 5LT, and median OS ranged from 48.2 months in 1LT to 5.8 months in 5LT. A trend was observed in increased PFS and OS with newer vs older drugs across treatment lines. The magnitude of the 'new' treatment benefit on PFS was most pronounced in 1LT.

These findings led to the conclusion that 40% of patients received therapy beyond 2 lines, which demonstrates a great unmet need in the treatment of RRMM. While bortezomib and lenalidomide were dominant in first and second lines, substantial fragmentation was seen in ≥3LT, which highlights the lack of defined treatment pathways for these patients. Bortezomib and lenalidomide were often used as retreatment after 1LT, with around half of previously-treated patients receiving these in combination or as a single agent in later lines. As could be expected, treatments in 3LT and beyond offer shorter benefit as disease progresses; median

time on treatment and median PFS decreased as treatment line increased. Median PFS and OS with newer agents in ≥3LT ranged from 2.9 months to 4.9 months, and 6.3 months to 15.4 months, respectively, which is slightly lower than that observed in recent clinical trials of novel agents such as daratumumab and pomalidomide. While there remains a need to replicate these results within a larger dataset where statistical comparisons could be made and confounding factors controlled for, the trends observed in this study suggest improved PFS and OS outcomes may be associated with newly approved treatments [5].

References

1. Dimopoulos MA, et al. 2018 ASH Annual Meeting, abstract 301.
2. Dimopoulos MA, et al. Lancet 2019;393(10168):253-264.
3. Mateos MV, et al. N Engl J Med 2018;378(6):518-528.
4. Dimopoulos MA, et al. 2018 ASH Annual Meeting, abstract 156.
5. Willson J, et al. 2018 ASH Annual Meeting, abstract 3290.

Non-Oncological Haematology

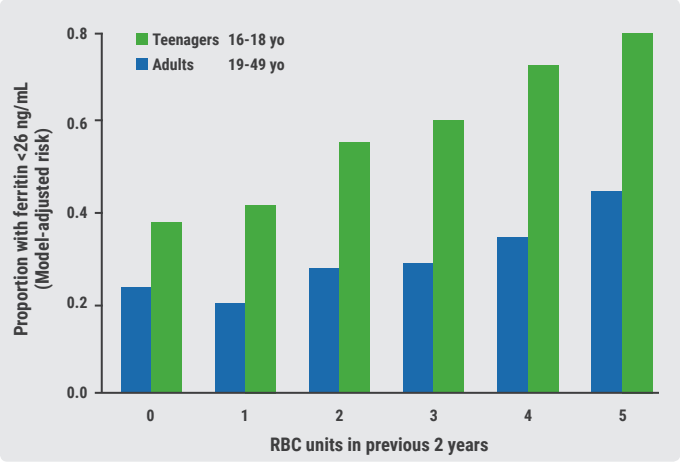
A variety of topics on non-oncological haematology was presented at the ASH Annual Meeting, of which a selection is presented in this chapter, including a presentation on the effects of regular blood donation and the latest insights into haemophilia prophylaxis.

Blood donation and iron deficiency

Blood donation can be considered an acute haemorrhage, according to Dr Alan Mast (BloodCenter of Wisconsin) [1]. Female donors lose about 12% of their blood per donation, whereas male donors lose about 8%. In the USA, donors can donate blood every 56 days, as long as their haemoglobin remains ≥12.5 g/dL in females and ≥13.0 g/dL in males. Although each donation removes 200-250 mg of iron from the donor, donors are not tested for iron deficiency. Some donors repeatedly pass the haemoglobin screening test and donate blood every 56 days for several years. This raises the question whether these so-called 'superdonors' might be genetically different. Studies of these superdonors have identified potential genetic variants such as TMPRSS6 A736V. Interestingly, the prevalence of different TMPRSS6 genotypes was the same for first-time donors.

In a repeated measures regression model, no effect of TMPRSS6 genotype was observed on superdonor haemoglobin or ferritin. Genome-wide association studies (GWAS) of 2,288 superdonors did not identify any genome-wide significant association compared with first-time donors. Regarding the link between genetics and blood donor haemoglobin, Dr Mast argued that donation intensity should not be defined by individual genetics, as biochemical features are more important: ferritin and reticulocyte haemoglobin content. He added that the use of iron supplements is more important than underlying genetics. He also briefly discussed blood donation by teenagers, which is a common practice in the USA. Dr Mast questioned whether blood donation runs in high schools are sensible, as teenagers have an increased iron need for physical growth and are more susceptible to donation-induced iron deficiency than adults (Figure 3). Recent onset of menses in girls and the poor dietary habits of many teenagers would also negatively influence their iron status. Moreover, young adults undergo active neurological development for which iron is essential.

Figure 3 Differences in impact of donation between teenagers and adults [1]



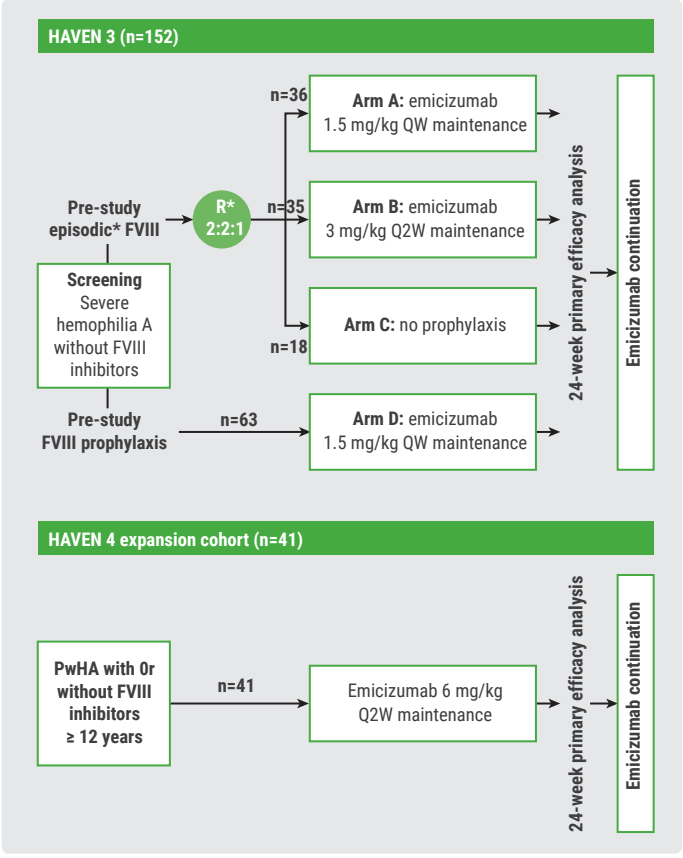
Dr Mast further discussed mitigation of iron deficiency in blood donors. This cannot be overcome by promotion of an iron rich diet. What does work are iron supplements (16 mg for 60 days following donation) and increasing the donation interval to at least 6 months. Evaluating ferritin levels and recommended action like delaying the donation motivates

donors to act on their own to mitigate iron deficiency, Dr Mast said. He concluded by stating that blood donors are a viable population for studies of iron deficiency and anaemia, and that this has helped gained insights into the role of genetics in relation to the impact of donating.

Emicizumab highly favoured over prior factor treatments

Emicizumab is a bispecific, humanised, monoclonal antibody that binds the activated form of factor IX (FIX) and factor X (FX) which facilitates activation of FX and restores effective haemostasis in patients with haemophilia A. Two phase 3 studies recently demonstrated the efficacy and safety of subcutaneous administered emicizumab weekly or every 2 weeks in patients with haemophilia A without inhibitors (HAVEN 3) and every 4 weeks in patients with haemophilia A with or without inhibitors (HAVEN 4; Figure 4) [2-4].

Figure 4 Study design of HAVEN 3 and HAVEN 4 [2-4]



The HAVEN 3 (n=152) and 4 (n=41) studies used questionnaires developed and validated to investigate patients' preferences and satisfaction with emicizumab compared with prior FVIII prophylaxis. In both studies, the Emicizumab Preference (EmiPref) questionnaire was offered at week 17 when patients had gained sufficient experience with emicizumab, potential bias due to anticipation associated with being in a study had subsided, and they could still reliably recall their experience with prior therapy. The survey included 3 questions: patients were initially asked if they preferred previous haemophilia treatment, new study treatment, or had no preference. Those expressing a preference were then asked to rank the top 3 reasons for their choice. Finally, patients could provide additional insights related to their experience with emicizumab. For HAVEN 3, the Satisfaction Questionnaire – Intraveneous Subcutaneous Haemophilia Injection (SQ-ISHI) was added to assess patients' satisfaction with emicizumab in comparison with FVIII prophylaxis. This 16-item questionnaire was to be completed at baseline and then either week 21 or 25 after initiation of emicizumab.

The EmiPref questionnaire was completed by 71% of patients from treatment arms A, B, or D in HAVEN 3. Results showed 94% preferred emicizumab to their previous treatment and only 2% favoured their previous treatment. The most frequent reasons selected for preference included a more convenient mode of administration ("frequency of treatments was lower" and "route of administration was easier") and reduced concern of bleeds ("worries about having bleeds were less"), reflecting the superior efficacy demonstrated in this study. In HAVEN 4, 100% of participants completed the EmiPref survey and 100% reported preferring emicizumab to their prior treatment. The most frequent reasons selected for preference were "the frequency of treatments was lower", followed by "the route of administration was easier", and "quality of life, in general, was better". When patients in HAVEN 3 and 4 were examined together, 99% of patients who received prior FVIII or bypassing agents (BPA) prophylaxis favoured emicizumab. Of the patients receiving prior episodic treatment, 92% preferred emicizumab.

The results of the SQ-ISHI, completed by 50 patients in arm D of HAVEN 3 at week 21, indicated that 90% of patients were "much more" or "a lot more" satisfied with their current emicizumab prophylaxis compared with their pre-study treatment. As almost all patients in HAVEN 3 and all patients in HAVEN 4 preferred emicizumab to their prior treatment, it was concluded that the results likely reflect the high efficacy and lower treatment burden with emicizumab. All participants in both studies have chosen to continue emicizumab beyond the primary analysis, which includes those patients who did not report to favour emicizumab. Such strong preference will be important for individuals with haemophilia A who are currently receiving either episodic or prophylactic treatment, as emicizumab may be associated with improved adherence and an increased willingness to consider prophylactic treatment.

Eltrombopag promising treatment option in ITP

Lucchini et al. explored the role of eltrombopag when administered for a defined period of time as second-line treatment in patients with newly diagnosed or persistent immune thrombocytopenia (ITP). In total, 55 adult patients (newly diagnosed or persistent ITP) were enrolled who did not respond/suffered relapse after standard first-line therapy. The study was divided into a period of treatment where patients received eltrombopag 50 mg/day, followed by a period of tapering and discontinuation (week 25-32), and a period of observation (week 33-52). Complete response was defined as platelet count ≥100x10^9/L; response was defined as platelet count ≥30x10^9/L and at least doubling of baseline count. Primary endpoint of the study was the proportion of patients who, being in remission at the end of the treatment period, were able to taper down and discontinue eltrombopag and maintained remission for all period of observation, without requiring any concomitant therapies. At the time of data cut-off, 38 patients were evaluable; at the end of 6 months of therapy 37% were in complete response and 32% in response; the overall response rate (ORR) was 69%. Twelve patients were non-responders; of those that responded (n=26), all started the period of tapering and discontinuation. Of the 18 patients who completed the period of tapering and discontinuation, 7 maintained the response (ORR 39%), with 28% achieving complete response and 11% response. At time of data cut-off, 42% had not yet completed the period of observation. At the end of the period of observation, 58% was evaluable: 3 maintained the response (ORR 20%), with 1 complete response and 2 response. Relapse occurred in 12 patients (period of tapering and discontinuation n=11; period of observation n=1). With regard to adverse events (AEs), 33% reported a total of 58 AEs; this was 16% for 11 grade ≥3 AEs. Four treatment-related AEs occurred, 1 of which was grade ≥3. There were two deaths during the study but these were not treatment-related. It was concluded that previously reported efficacy of eltrombopag was confirmed in primary ITP and that when eltrombopag is used at an earlier phase of the disease, it will be more effective. Also, 6 months of therapy seems a sufficient period to consider eltrombopag tapering and discontinuation [5]. Other promising data was derived from real-world evidence in which eltrombopag was compared to other second-line therapies. A total of 2,047 adults were included in the retrospective study. They were treated with different therapies and the rate of bleeding-related episodes (BREs) and thrombotic events (TE) was assessed. The results showed that platelet counts increased in all treatment cohorts when compared to baseline, and that the outcomes differed (Table 7) [6].

Table 7 Distribution of therapies [6]

Agent	n (%)	BREs	TEs
Eltrombopag	110 (4.4%)	25.5%	11.6%
Romiplostim	189 (7.5%)	36.5%	12.7%
Rituximab	1,488 (58.9%)	27.3%	13.9%
Splenectomy	260 (10.3%)	31.3%	15.7%

NB: 479 (18.9%) patients were treated with a mix of other second-line agents

These findings demonstrated that despite significant differences in mean platelet counts, the incidence of TEs was similar across all treatments. Patients who had been treated with eltrombopag had a numerically lower incidence of BREs [6].

Gene transfer safe and effective in haemophilia B

Stable therapeutic expression of FIX has been demonstrated in patients with severe haemophilia B over a period of 8 years following systemic administration of self-complementary adeno-associated virus (scAAV)2/8-LP1-hFIXco, and without late toxicities. These findings are the result of a follow-up to a previous study which showed that single IV administration of scAAV2/8-LP1-hFIXco resulted in a dose-dependent increase in plasma FIX gene levels [7].

The original cohort consisted of 10 patients with severe haemophilia B, of which 2 patients received 2 x 10^{11} vector genomes (vg)/kg (low-dose), 2 received 6 x 10^{11} vg/kg (middle-dose), and 6 patients received 2 x 10^{12} vg/kg (high-dose). Mean FIX levels were 1.9 IU/l in the low-dose cohort, 2.3 IU/l in the middle-dose cohort, and 5.1 IU/l in the high-dose cohort. Median follow-up was 6.7 years, during which transgenic FIX activity remained stable in all 10 patients. However, concerns over FIX expression declining over time remained [8]. Annual FIX gene concentrate usage dropped by 66% and annual bleed rate declined by 82% compared with pre-gene therapy levels.

In the original study, the only vector-associated AE was a rise in liver enzymes accompanied by a decline in FIX levels in two-thirds of patients who were treated with a dose of 2 x 10^{12} vg/kg. As the regimen contained empty capsids without a full-length viral genome, it was hypothesised they may cause an immune response against transduced hepatocytes. As a result, the regimen was changed for the follow-up study, by removing empty capsids by caesium chloride density centrifugation to reduce the risk for hepatoxicity.

In the current study, 2 patients with severe haemophilia B received a dose of 2 x 10^{12} vg/kg and 2 patients received a dose of 5 x 10^{12} vg/kg. Mean FIX gene activity with a dose of 2 x 10^{12} vg/kg was 2.6 IU/l, which appeared lower (but not significantly) than previously observed at this dose level.

Mean steady state FIX gene levels with 5 x 10^{12} vg/kg dose was 17 IU/l. Median follow-up for the new cohort was 2.1 years, and as the original cohort was followed-up as well, those 10 patients reached a follow-up of 8 years.

Of note, the new formulation of the gene therapy, which removed empty AAV capsids to reduce the capsid load, did not reduce the rate of hepatoxicity in patients with severe haemophilia B –3 of 4 patients had elevated serum alanine aminotransferase and were treated with corticosteroids– which may suggest that other factors play a key role here [9].

References

1. Mast AE. 2018 ASH Annual Meeting, abstract SCI-4.
2. Mahlangu J, et al. N Engl J Med 2018; 379:811-822.
3. Pipe et al. WFH 2018
4. Jimenez-Yuste V, et al. 2018 ASH Annual Meeting, abstract 1187.
5. Lucchini E, et al. 2018 ASH Annual Meeting, abstract 1135.
6. Said Q, et al. 2018 ASH Annual Meeting, abstract 2436.
7. Nathwani AC, et al. N Engl J Med 2011; 365:2357-2365.
8. Nathwani AC, et al. N Engl J Med 2014; 371:1994-2004.
9. Nathwani AC, et al. 2018 ASH Annual Meeting, abstract 491.

Thrombosis

Thrombosis management remains a cornerstone of treatment for a wide array of different patient populations with thrombophilia, including those with atrial fibrillation and increased risk of stroke, as well as cancer patients. Direct oral anticoagulants have become increasingly popular over the last few years with more and more data becoming available on various aspects of this particular class.

Bleeding rates similar with DOACs and LMWH in cancer-associated venous thromboembolism

Emerging data suggests that treating cancer-associated venous thromboembolism (VTE) with direct oral anticoagulants (DOACs) results in lower recurrence rates compared with low molecular weight heparins (LMWHs) at 6 months but may increase bleeding risk. The objective of a study by Park et al. was to determine the occurrence of major bleeding and recurrent VTE events on treatment using DOACs or LMWHs in a cohort study [1].

The study included a prospective observational cohort from the cancer-associated thrombosis (CAT) clinic, a centralised service for care of cancer patients with suspected deep venous thrombosis (DVT) and/or pulmonary embolism (PE) at the Tausig Cancer Institute of the Cleveland Clinic. Included were patients referred to the clinic from August 2014 through January 2018. Standards of treatment at the CAT clinic shifted in late 2017 from the use of LMWH (enoxaparin) to a DOAC (rivaroxaban) for cancer-associated VTE. Current exclusion criteria for rivaroxaban include recent active bleeding, GFR <30 mL/min, severe hepatic impairment, thrombocytopenia (platelet count <50,000), and/or expected malabsorption at the level of stomach or small bowel. Treatment with LMWHs is preferred for cancer patients considered at higher risk of bleeding, which includes patients with luminal gastrointestinal (GI) cancers with an intact primary, cancers at risk of bleeding from genitourinary (GU) tract, bladder or nephrostomy tubes, or patients with active mucosal abnormalities such as duodenal ulcers, gastritis/oesophagitis, or colitis. The study population included 258 patients with acute VTE. Of these, 93% had DVT, 14% had PE, 6.2% had both, and 1.2% had visceral vein thromboses. A total of 53% of patients was male; median age was 65 years. The most common cancer types were haematologic malignancies (19.5%), primary brain tumours (11.2%), lung cancer (8.5%), breast cancer (7.0%), and pancreatic cancers (6.6%). Enoxaparin monotherapy was prescribed in 72.1% of patients. Other treatments included rivaroxaban (17.3%), apixaban (0.8%), warfarin (2.8%), dalteparin (0.4%), and no anticoagulation (3.2%).

Major bleeding occurred in 5% of patients treated with anticoagulation within 6 months of the initial event, including 5.0% of patients (9/179) on enoxaparin and 4.7% of patients (2/43) on rivaroxaban (no significant differences). Clinically relevant non-major (CRNM) bleeding was observed in 16.2% of patients on enoxaparin and in 11.6% of patients on rivaroxaban. Common cancer types for patients with major bleeding events included primary brain tumours (n=4), GU cancers (n=2), and GI cancers (n=2). The 1-year incident rate of recurrent VTE was 11% for patients treated with enoxaparin and 9% for patients treated with DOACs; the 2-year rate was 13% and 11%, respectively. Overall, no significant difference was observed in the VTE recurrence rate at 1 or 2 years, as calculated by the competing risk model between patients on enoxaparin compared with rivaroxaban (P=0.19).

No differences in clinical outcomes between DOAC and warfarin users with major haemorrhage

The use of DOACs, introduced in 2010, has become increasingly common among patients with atrial fibrillation (AF) for prophylaxis and patients with venous thromboembolic disease for treatment. Haemorrhage is known to be the most frequent complication of oral anticoagulation. Bialkowksi et al. hypothesised that all-cause mortality among patients under oral anticoagulation presenting with major haemorrhage differs based on the anticoagulant medication class (DOAC vs warfarin) [2]. They screened patients presenting at 12 US hospitals from 2013 to 2016 using the Recipient Epidemiology and Donor Evaluation Study (REDS)-III Recipient Database. Exclusion criteria included no use of medication of interest, multiple hospitalisations, absence of major haemorrhage, and age <18. This approach led to 650 DOAC users and 3,081 warfarin users eligible for analysis. It emerged that the inpatient all-cause mortality among DOAC users was lower when the entire cohort was considered (HR 0.60, 95% CI 0.45-0.80, P=0.0005). Implementation of propensity score matching to account for confounding factors abrogated this difference (HR 0.84, 95% CI 0.58-1.22, P=0.36). Time to hospital discharge was shorter for DOAC users (HR 1.17, 95% CI 1.05-1.30, P=0.0034) and transfusion patterns were similar by medication, apart from plasma transfusion which occurred in 42% of warfarin encounters and 11% of DOAC encounters (Table 8). Vitamin K was administered in 63% of warfarin encounters, and it needs to be noted that specific DOAC reversal agents were largely unavailable during the analysis period (used in 1%).

Table 8 Matched analysis of transfusion and medication use [2]

	Warfarin (n=633)	DOAC (n=633)
Plasma	267 (42%)	69 (11%)
Red Blood Cells	330 (52%)	326 (52%)
Platelets	79 (12%)	66 (10%)
Cryoprecipitate	6 (1%)	3 (<1%)
rFVIIa	4 (1%)	13 (2%)
Vitamin K	396 (63%)	84 (13%)
3 or 4 Factor PCCs	86 (14%)	91 (14%)

Idarucizumab used in 5 (<1%) of DOAC bleeds

No statistically significant differences in inpatient all-cause mortality in the stratified analysis could be observed: HR 0.69 (95% CI 0.31-1.55) for traumatic head injuries; HR 1.10 (95% CI 0.62-1.95) for non-traumatic head injuries; HR 0.62 (95% CI 0.20-1.94) for traumatic, non-head injuries; and HR 0.69 (95% CI 0.29-1.63) for non-traumatic, non-head injuries [2].

No difference in intracranial haemorrhage or other bleeding event risk for patients with malignant intracranial tumours on DOAC or LMWH

Appropriate anticoagulation management in cancer patients is complicated by the high propensity for recurrent VTE and is influenced by history of bleeding, altered anatomy, impaired organ function, nutritional issues, and the presence of intracranial tumours/metastases. Intracranial tumours especially are challenging in treating cancer patients with VTE because of the concern for intracranial haemorrhage (ICH). Although a retrospective cohort study in 2015 showed no difference in ICH in patients with intracranial tumours treated with LMWH compared with matched controls not on anticoagulation, the risk of ICH in patients with intracranial tumours treated with DOACs remains unknown. A recent study compared the ICH rate in patients with intracranial tumours treated either with a DOAC or LMWH [3].

Researchers performed a retrospective analysis of patients at their centre with a diagnosis of malignancy with intracranial tumour(s) documented by imaging between 1 May 2011 and 31 December 2016. All patients were on therapeutic anticoagulation using either a DOAC or LMWH. The rate of ICH in patients with intracranial tumours on treatment with DOACs was compared with the rate in those on treatment with LMWH. Additionally, the rate of non-intracranial bleeding and recurrent VTE in both groups was compared. A total of 135 patients (LMWH n=90; DOACs n=45) were available for analysis. There was a significant difference between treatment group and type of cancer: a higher proportion of primary central nervous system malignancy (vs metastatic disease) occurred in the LMWH group, and a higher proportion of patients in the LMWH group had only 1 brain tumour (Table 9).

Table 9 Key patients characteristics [3]

Characteristic	LMWH (n=90)	DOAC (n=45)	P-value
Age, mean (SD)	59.69 (13.5)	60.36 (13.8)	
Cancer type, % (n)			0.003†
• Metastic disease	42.2% (38)	71.1% (32)	
• Primary CNS tumours	57.8% (52)	28.9% (13)	
Number of brain tumours, % (n)			0.035†
• 1	55.6% (50)	35.6% (16)	
• 2-5	30.0% (27)	33.3% (15)	
• >5	14.4% (13)	31.1% (14)	
Comorbidities, % (n)			
• Current Smoker	46.7% (42)	8.9% (4)	<0.001†
• Hypertension	61.1% (55)	46.7% (21)	
• Prior ischemic stroke	2.2% (2)	11.1% (5)	
• Prior ICH	4.4% (4)	6.7% (3)	
Concomitant medications, % (n)			
• Anti-platelet	8.9% (8)	16.7% (7)	
• Bevacizumab	28.9% (26)	4.4% (2)	0.002†
• Dexamethasone	65.6% (59)	57.8% (26)	

A significant association was observed between treatment group and whether or not patients were treated with bevacizumab (P=0.002), with a higher rate of bevacizumab treatment in the LMWH group. There was no significant difference between treatment groups and the occurrence of ICH (10.0% for LMWH vs 8.9% for DOAC). Across treatment groups, the majority of ICH events were grade 1-2, but the LMWH group did have one grade 4 and one grade 5 ICH compared with no high-grade ICH in the DOAC group. In the LMWH group, nearly all (8/9) of the observed ICH events required anticoagulation to be discontinued. In the DOAC group, only one ICH event required anticoagulant discontinuation, whereas one other ICH event required decreased anticoagulation to prophylactic dosing. In the LMWH group, nearly all (8/9) of the observed ICH events occurred at a time when patients were not on systemic antineoplastic treatment. One ICH event in the LMWH group occurred while the patient was on therapy with a tyrosine kinase inhibitor. In the DOAC group, two ICH events occurred at a time when patients were not on systemic antineoplastic treatment, whereas the other two events occurred while the patients were on immunotherapy. There was no significant difference between recurrent clotting or other bleeding events (Table 9). Thus, results showed no difference in the risk of ICH or other bleeding events between patients on therapeutic anticoagulation with a DOAC or LMWH in patients with malignant intracranial tumours.

References

1. Park DY, et al. 2018 ASH Annual Meeting abstract 1237.
2. Bialkowski W, et al. 2018 ASH Annual Meeting abstract 2538.
3. Abraham RS, et al. 2018 ASH Annual Meeting abstract 2524.

Stem Cell Transplantation

The use of stem cell transplantation has evolved over the years, with increasingly better outcomes for a growing number of patients. Despite these advances, stem cell transplantation remains a complicated therapy option that requires a high level of expertise and knowledge.

Using a haploidentical family member as donor is key in haploidentical transplantation

Limited data exists on whether outcomes of haploidentical stem cell transplantation (haploSCT) are affected by the characteristics of the haploidentical donor, the stem cell source, or the conditioning. Bazarbachi et al. undertook a large retrospective study on the influence of these characteristics in haploSCT with post-transplant cyclophosphamide (ptCy) for lymphoma, identifying 474 adult patients (35% female, median age 41 years) [1].

Participants had either Hodgkin lymphoma (HL; n=240; 51%), peripheral T cell lymphoma (PTCL; n=88; 19%), diffuse large B cell lymphoma (DLBCL; n=77; 16%), mantle cell lymphoma (MCL; n=40; 8%), or follicular lymphoma (FL; n=29; 6%) and received a haploSCT with ptCy between 2010 and 2016 in a European Blood and Marrow Transplantation centre (Table 10).

Table 10 Patient and donor characteristics [1]

Patients characteristics	n (%)
Number of patients	474 (100%)
Age (years) at SCT median (range)	41 (18-72)
Female	164 (35%)
CMV serology positive	305 (65%)
Lymphoma subtype	
Diffuse large B cell	77 (16%)
Follicular	29 (6%)
Hodgkin	240 (51%)
Mantle cell	40 (8%)
Peripheral T cell	88 (19%)
Prior autoSCT	329 (69%)
Disease status at alloSCT	
CR	228 (48%)
PR	156 (33%)
Active disease	87 (19%)
PET status at alloSCT	
Negative	212 (46%)
Positive	211 (45%)
Not evaluated	42 (9%)

Donor and Transplant characteristics	n (%)
Age of the donor	42 (13-85)
ABO compatibility	
Isogroup	303 (64%)
Bidirectional incompatibility	16 (3%)
Major incompatibility	77 (16%)
Minor incompatibility	78 (17%)
CMV positive	310 (66%)
Female	215 (45.5%)
Relationship to recipient	
Daughter/son	118 (25%)
Mother/father	120 (26%)
Other family member	15 (3%)
Sister/brother	218 (46%)
HLA mismatch	
3/6	308 (72%)
4/6	106 (25%)
5/6	14 (3%)
Year of alloSCT	2014 (2010-2016)
Conditioning regimen	
Baltimore (Flu-Endoxan-TBI low dose)	234 (50%)
TBF (thiotepa/busulfan/ fludarabine)	64 (14%)
Other MAC	61 (13%)
Other RIC	114 (24%)
Stem cell source PBSC	255 (54%)

Median follow-up of alive patients was 32 months (range 3-93). In 95% of patients, engraftment by day 100 was successful. In multivariate Cox analysis, the use of peripheral blood stem cells (PBSC) positively affected engraftment (HR 1.53; P<0.001). Day 100 acute graft vs host disease (GVHD) grade II-IV and grade III-IV was diagnosed in 32% and 8% of patients, respectively, and was significantly affected by the use of PBSC as a stem cell source (HR 2.1; P<0.001 for grade II-IV and HR 4.5; P=0.001 for grade III-IV). The use of sibling haploidentical donors increased the risk of acute GVHD grade II-IV (HR 1.87; P=0.01) whereas a cytomegalovirus (CMV)-negative donor in a positive recipient increased the risk of acute GVHD grade III-IV (HR 5.3; P=0.04). The 2-year cumulative incidence of chronic GVHD and extensive chronic GVHD was 25% and 9%, respectively. On multivariate analysis, male patients had a higher risk of chronic GVHD and extensive chronic GVHD (HR 1.7; P=0.03; and HR 2.8; P=0.04, respectively), whereas a male donor had a protective effect (HR 0.6; P=0.02; and HR 0.3; P=0.008, respectively). The risk of chronic GVHD and extensive chronic GVHD was also higher for patients in PR (HR 1.7; P=0.03, and HR 2.4, respectively; P=0.04). The 2-year cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) were 29% and 19%, respectively. In multivariate analysis, both CIR and NRM were negatively affected by the lymphoma subtype and by disease status at transplantation, both being highest for DLBCL and for advanced disease. Older age was associated with a higher NRM but with a lower CIR. The type of conditioning regimen and CMV compatibility also influenced NRM, whereas ABO incompatibility influenced CIR. The 2-year progression free survival (PFS) and overall survival (OS) for HL were 57% and 72%, respectively; 54% and 62% for PTCL; 35% and 35% for DLBCL; 52% and 61% for MCL; and 56% and 56% for FL. In multivariate analysis, complete response (CR) at SCT significantly improved PFS and OS whereas a diagnosis of DLBCL as well as a CMV donor-positive/recipient-positive transplant negatively affected PFS and OS. The researchers emphasised that these findings offer critical information to help selecting the best donor in the setting of haploSCT for lymphoma.

Durability of non-myeloablative alloSCT for relapsed follicular lymphoma confirmed

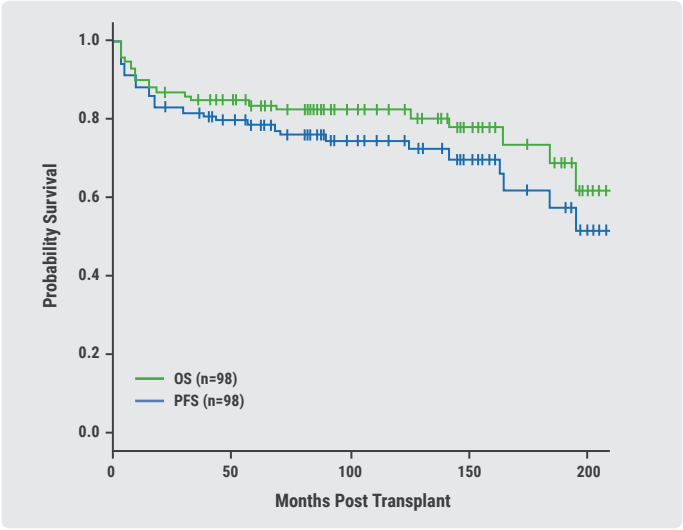
A previous trial reported on outcomes of non-myeloablative (NMA) allogeneic stem cell transplantation (alloSCT) concerning 47 patients with relapsed/chemosensitive FL who received a matched sibling donor (MSD) transplant after rituximab-containing regimen (FCR) conditioning [2]. In subsequent trials, eligibility was expanded to include transplants from matched unrelated donors (MUDs) using a ^{90}yttrium ibritumomab tiuxetan (90YIT)-based regimen or, more recently, BFR (bendamustine, fludarabine, rituximab) conditioning [3,4]. Khouri et al. examined long-term outcomes in 98 FL patients treated during these 3 consecutive trials between 1999-2017 [5].

Median age of the patients was 53 years and 24% of patients was aged >60 years; 29% of patients had a haematopoietic cell transplantation-specific comorbidity index (HCT-CI) of ≥3. The median prior number of treatments was 3 and 52% had rituximab-chemo induction at diagnosis. The BFR regimen (n=20) consisted of bendamustine 130 mg/m^2 IV daily on days -5 to -3 prior to transplantation; thus, substituting the cyclophosphamide in the FCR regimen (n=47). The dose and schedule of fludarabine (30 mg/m^2 IV daily x3) and rituximab (375 mg/m^2 IV on day -13 and 1000 mg/m^2 on days -6, +1, and +8) were similar in both regimens. 90YIT-regimens (n=31) consisted of a diagnostic dose of ^{111}In-ibritumomab administered on day -14, followed by a fixed dose of 0.4 mCi/kg 90YIT on day -7; FC or BF chemo was then administered at the same dose and schedule (days -5 to -3) as described above. In all regimens, tacrolimus and methotrexate were used for GVHD prophylaxis. In addition, thymoglobulin of 1 mg/kg was given on days -2, -1 in patients receiving a MUD transplant.

A total of 72% of patients relapsed within 2 years of their induction treatment and median duration of last remission prior to alloSCT was <1 year in 61% of patients. At transplant, 84% had chemosensitive disease (46% CR, 38% PR) and 16% had refractory disease. In total, 71% received a transplant from an MSD and 29% from a MUD; 15% of transplants had female-to-male donors, and 43% were ABO-mismatched. CMV was reactive in 80% of patients and/or donors. In almost all patients (94%), the stem cell source was mobilised peripheral blood. A significant difference was found in absolute neutrophil count recovery between the 3 conditioning regimens. Neutrophil counts recovered to >0.5 x 10^9/L at median of 0 days (range 0-16) for the BFR groups vs 10 days and 11 days for the FCR and 90YIT-regimen groups, respectively (P<0.0001). This difference was consistent for each transplant type. Median follow-up time for all patients was 98 months; OS and PFS at 98 months were 82% (95% CI, 73-89) and 74% (95% CI, 64-82), respectively (Figure 5) [5].

The cumulative incidence of grade II-IV and III-IV acute GVHD was 22% and 9%, respectively. The cumulative incidence of chronic GVHD was 38%. Treatment-related mortality at 1 year was 9%. It was found that disease status of >1 relapse, >2 prior chemotherapies, duration of last remission prior to alloSCT <1 year, ≥3 comorbidities, elevated LDH, acute II-IV GVHD, and chronic extensive GVHD were associated with inferior OS. Multivariable analysis showed that duration of last remission prior to alloSCT (<1year; HR 6.48; 1.28- 32.69; P=0.024) and

Figure 5 OS and PFS [5]



acute II-IV GVHD (HR 8.61; 2.99-24.83; P<0.001) were associated with inferior OS. There were no significant prognostic factors on multivariable analysis for PFS, or risk for acute GVHD or chronic GVHD noted for this cohort of patients.

The researchers concluded that NMA alloSCT can induce complete responses lasting over a decade in most patients with relapsed FL. The initial findings, which were published in 2008, were thus confirmed in a larger number of patients, including patients who received MUD transplants. BFR conditioning has been associated with significantly lesser myelosuppression and a faster neutrophil recovery than other regimens used, validating the initial observation in earlier reports.

Double autologous stem cell transplant improves survival in NDMM

As two recent randomised trials comparing a single autologous stem cell transplant (ASCT-1) with a double ASCT (ASCT-2) showed conflicting results, Cavo et al. performed a long-term follow-up analysis of patient-level data from 3 clinical trials of bortezomib-thalidomide-dexamethasone (VTD) or bortezomib-doxorubicin-dexamethasone (PAD) as induction therapy before ASCT, followed by post-ASCT bortezomib-based consolidation and/or maintenance treatment [6].

This retrospective analysis included 909 patients with a median age of 58 years. Patients had been randomised to VTD or PAD and assigned to either ASCT-1 (n=501) or ASCT-2 (n=408). Rates of Multiple Myeloma International Staging System (ISS) stage III were 20% in the VTD arm and 17% in the PAD arm, respectively. Median follow-up was 117 months. Results showed that patients receiving ASCT-2 vs ASCT-1 demonstrated longer PFS (median 47 vs 38 months; HR 0.76; 95% CI, 0.65-0.89; P=0.0008) and longer OS (estimated 10-year probability, 58% vs 47%; HR 0.69; 95% CI, 0.56-0.84; P=0.0002). The PFS benefit with ASCT-2 was sustained across pre-specified subgroups, including patients with standard-risk or high-risk cytogenetics. Patients with standard-risk cytogenetics had 10-year OS rates of 72% for ASCT-2 vs s 60% for ASCT-1 (HR 0.68; 95% CI 0.52-0.88; P=0.004). In high-risk cytogenetics patients, this was 51% for ASCT-2 vs 34% for ASCT-1 (HR 0.54; 95% CI, 0.36-0.83; P=0.004). Thus, the superiority of ASCT-2 over ASCT-1 with regard to extended PFS and OS was established. The subgroup of patients at high risk mostly benefited from ASCT-2, particularly those who had advanced ISS stage, adverse cytogenetics, and failed to achieve complete response.

Increasing lenalidomide dosage feasible option for relapsed MDS/AML patients post-alloSCT

In the second interim-analysis of the Azalena trial, outcomes suggest that an increase in the lenalidomide dosage to 5 mg/day is feasible, safe, and not associated with excess GVHD and toxicity. Current results suggest that the combination of azacitidine, lenalidomide, and donor lymphocyte infusions (DLI) has promising clinical activity [7]. It can induce durable responses in a substantial proportion of patients with myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), relapsing after alloSCT.

The prospective, multicentre, single-arm, phase 2 Azalena trial evaluated the combination of azacitidine, lenalidomide, and DLI in patients with MDS, AML, or chronic myelomonocytic leukaemia (CMML) who had relapsed after allo-SCT. Overall, 24 patients with molecular (54%) or haematological (46%) relapse of MDS (58%), AML (38%), or CMML (4%) after median of 260 days following alloSCT were treated with a median of 5.5 cycles of lenalidomide per patient (total number of cycles 121; 83 cycles 2.5 mg/day, 38 cycles 5 mg/day). Concomitantly, patients received a median of 7 courses azacitidine and 71% received at least one DLI (median: 2). Two safety interim analyses were performed. The first analysis concerning the first 10 patients did not reveal a dose-limiting toxicity (DLT); thus, enabling an increase in the daily lenalidomide dosage from 2.5 mg to 5 mg in the next cohort. The planned second interim safety analysis (data lock March 2018) was performed in the next 10 patients who were treated with a daily dose of 5 mg lenalidomide during 21 days of a 28-day cycle in combination with up to 8 cycles azacitidine (75 mg/m^2/day days 1-7, every 28 days) and 3 DLI with increasing T cell dosages (0.5×10^6 – 1.5×10^7 cells/kg).

Efficacy and safety results of all 24 patients included in this trial so far were discussed at the ASH Annual Meeting. The protocol demanded a dose reduction of lenalidomide to 2.5 mg/day for the remaining 30 patients in case of DLT defined as steroid refractory acute GVHD grade 3/4, chronic GVHD NHI score severe, or any unexpected haematologic and non-haematological toxicity grade ≥3 in more than 3 patients. In the absence of DLT in more than 3 patients, the study was continued with 5 mg/day. The increased lenalidomide dose did neither result in a higher frequency of dose reductions and treatment interruptions in this cohort, nor to a higher number of adverse events (AEs) per cycle (2.5 mg/day: 5.45 AEs vs 5 mg/day: 3.15 AEs). An overall response rate was observed of 68% (CR 58%, PR 10%). CR rate was by trend higher in patients with molecular than in those with haematological relapse (67% vs 43%) and all patients with CR remained in remission for a median of 183 days. In total, 17% of patients developed acute GVHD (overall grade II, II, III, IV) and 21% developed chronic GVHD (mild n=2; moderate n=2; severe n=1). While therapy-related CTC grade 3/4 neutropenia (90%), thrombocytopenia (71%), or anaemia (29%) occurred frequently, non-haematological AEs >grade 2 were rare and mainly consisted of gastrointestinal (GI) toxicity and infections.

References

1. Bazarbachi A, et al. 2018 ASH Annual Meeting, abstract 484.
2. Khouri IF, et al. Blood 2008;111:5530-5536.
3. Khouri IF, et al. Blood 2012;119:6373-6378.
4. Khouri IF, et al. Blood 2014;124:2306-2312.
5. Khouri IF, et al. 2018 ASH Annual Meeting, abstract 4651.
6. Cavo M, et al. 2018 ASH Annual Meeting, abstract 124.
7. Schroeder TM, et al. 2018 ASH Annual Meeting, abstract 703.