# Miscellaneous news from ASH 2019

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In addition to the plethora of abstracts in the larger haematological subdomains discussed in this special issue of the BJH, ASH 2019 also featured many interesting presentations that do not fall within one of these categories. In this article we would like to address some of this 'miscellaneous news' from ASH 2019. In the field of venous thromboembolism (VTE), bodyweight-adjusted rivaroxaban could provide a new alternative treatment option for paediatric patients. Also with respect to VTE, the Ottawa score failed to demonstrate its predictive value for VTE recurrence in cancer patients. In addition, interesting new data were presented on the prevention of graft-versus-host-disease (GVHD) after an allogeneic transplantation. At this year's meeting, there was also a session dedicated to disorders in the number or function of platelets in which much attention went to novel drug targets and novel drug combinations for the treatment of immune thrombocytopenia. Finally, some interesting presentations on sickle cell disease, myelofibrosis-associated anaemia and cold agglutinin disease (CAD) will be discussed in this overview.
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## ANTITHROMBOTIC THERAPY

### RIVAROXABAN FOR THE TREATMENT OF PAEDIATRIC VENOUS THROMBOEMBOLISM

To date, only dalteparin is licensed for the use in paediatric patients with venous thromboembolism (VTE). The Einstein-Jr phase III study aims at providing evidence for the use of rivaroxaban in children with VTE. *Prof. Young et al.* presented the results of the dose-exposure-response relationship during ASH 2019. In total, 365 children were allocated to receive rivaroxaban in the following age groups: birth - < 0.5 years (N=13); 0.5 - <2 years (N=21); 2 - <6 years (N=44); 6 - <12 years (N=65); and 12 - <18 years (N=173). Of these patients, 94.3% were evaluable for pharmacokinetic analyses. Rivaroxaban was administered in the traditional tablet form or as newly developed granules for oral suspension. The dosing was body-weight adjusted and was given once (patients ≥ 30 kg), twice (12 - < 30 kg) or thrice daily (< 12 kg). Symptomatic recurrent VTE occurred in 2 children and repeat imaging outcomes in the asymptomatic patients were classified as normalised (39.2%), improved (39.6%), no relevant change (5.1%) and deteriorated (0.3%) while the result was uncertain in 15.2% of the patients. With respect to the dose-exposure relationship, the vast majority of the individual values were within the 5$^{th}$-95$^{th}$ percentile for AUC(0-24)$_{ss}$, $C_{max,ss}$ and $C_{trough,ss}$. No clustering was observed for any of the pharmacokinetic parameters with regards to efficacy, bleeding or adverse event outcomes. The results were similar for the tablet and suspension formulation. As such, these data support bodyweight-adjusted rivaroxaban as an alternative treatment option for VTE in children.[1]

### NO PREDICTIVE VALUE OF THE OTTAWA SCORE IN CANCER PATIENTS WITH VENOUS THROMBOEMBOLISM

In order to predict the risk of recurrent venous thromboembolic events (VTE) in cancer patients on anticoagulant therapy, the Ottawa score was developed.[2] In the PREDICARE study, the performance of the Ottawa risk score in patients with cancer-associated thromboembolism treated with the low-molecular weight heparin tinzaparin was studied. In total, 409 patients from 75 centres in France were included

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between May 2015 and April 2016. Median age of the patients was 67.6 years with a mean body mass index of 25.3. Most patients (67.0%) had a stage IV tumour and 81.7% of the patients received systemic antitumour treatment. According to the Ottawa score, 58.2% of the patients were classified as having a high clinical probability of recurrence (score ≥ 1). In total, 28 patients had a recurrent VTE during the six-month treatment period. The recurrence rate was estimated to be 9.1% (95%CI: 6.1-13.6) for patients at high risk according to the Ottawa score, as compared to 5.0% (95%CI: 2.3-10.8) for the other patients. During the treatment period, 15 patients had a major bleeding and two patients experienced a heparin induced thrombocytopenia. A total of 144 patients had died, mainly because of the underlying cancer (N=130). The PREDICARE study is thus the first prospective study that was specifically designed to validate the Ottawa score but failed to confirm its predictive value. No other clinical predictors of recurrent VTE were identified so further research remains needed.[3]

## GRAFT-VERSUS-HOST-DISEASE (GVHD) AFTER ALLOGENEIC TRANSPLANTATION

### A NOVEL LABORATORY BIOMARKER FOR THE RESPONSE TO TREATMENT OF ACUTE GVHD

Recent studies from the Mount Sinai Acute GVHD International Consortium (MAGIC) validated an algorithm probability (MAP) that combines serum concentrations of two biomarkers of GVHD (REG3α and ST2) to generate an estimated probability of six-month non-relapse mortality for individual patients.[4,5] Serum samples and clinical staging from 368 HSCT patients who received systemic treatment for acute GVHD between January, 2016 and February, 2018 were collected. A change in MAP between the start of treatment and 28 days later indicated that patients crossing the threshold of 0.290 had a significantly worse survival compared to those who remained below this threshold (p< 0.001). Patients with an initial high MAP who remained above the threshold also had a large increase in mortality (p= 0.007). Interestingly, the MAP was significantly more accurate in predicting non-relapse mortality than the gold standard of the clinical response (p< 0.0001). Moreover, MAP provides prognostic information over and above the change in clinical symptoms, further stratifying both responders and non-responders at four weeks of treatment.[6]

### PREVENTION OF SEVERE GRAFT-VERSUS-HOST-DISEASE AFTER HSCT: THE HOVON-96 TRIAL

In the prospective randomised HOVON-96 trial, conventional immunosuppression (CIS) was compared to time-restricted immunosuppression and post-transplant cyclophosphamide (Pt-Cy) in patients qualifying for an allogeneic peripheral blood stem cell transplantation.[7,8] In arm A of the trial, patients received CIS (cyclosporine A [CyA] twice daily until day +120 followed by tapering until day +180 and mycophenolic acid 16 mg/kg twice daily with a maximum dose of 2160 mg a day until day 84 post-transplant) whereas in the time-restricted regimen (arm B) mycophenolic acid was discontinued at day 28 post-transplant and CyA was continued until day +84, followed by tapering. In arm C of the trial, patients received Pt-Cy (50 mg/kg of Cy on day +3 and +4 combined with cyclosporine A from day +5 until day +70).

In the first part of the study, a total of 389 patients were randomised (1:1) between arms A and B, of whom 95% (184 in arm A *versus* 185 in arm B) proceeded to transplant. The median follow-up of the study was 61 months and patient as well as graft characteristics were well balanced between both arms. In both treatment arms, 24% of the patients developed non-severe GVHD within 180 days post-alloHSCT (OR[95%CI]: 1.01[0.61-1.67], p= 0.98). As such, the time-restricted immunosuppressive regimen did not increase the proportion of patients with non-severe GVHD. In addition, no difference in the cumulative percentage of acute GVHD of grade II-IV (p= 0.72) or grade III-IV (p= 0.20) was detected between both treatment arms and a similar incidence of chronic GVHD was reported (p=0.69). Also with respect to GVHD-free, relapse-free survival, no difference was detected (p=0.83). The overall survival (OS) at three years was 59% in the standard arm *versus* 57% in the time-restricted arm (p=0.74). Finally, the incidence and nature of adverse events were comparable between both arms.[7]

In the second part of the study, a total of 160 patients were randomly assigned (1:2) to arm A and C. A total of 94% of the patients proceeded to transplant. Application of a high-dose Pt-Cy combined with a short course of CyA resulted in a significant reduction in the incidence of grade II-IV acute (48% *vs.* 32%, SHR[95%CI]: 0.52[0.31-0.87], p= 0.014) or chronic (50% *vs.* 19%, SHR[95%CI]: 0.38[0.21-0.67], p= 0.001) GVHD compared to CIS. No difference was seen between CIS and Pt-Cy with respect to the cumulative incidence of progression/relapse (p= 0.36), PFS (p= 0.67) or OS (p= 0.63). The three-year estimates for PFS were 60% and 58% for CIS- and Pt-Cy respectively, with corresponding 3-year OS rates of 69% and 63%. The one-year estimate of GVHD free/relapse-free survival was 22% with CIS, which was significantly lower than the 45% seen with Pt-Cy (p=0.001), reflecting the long-term benefit and positive impact on the quality of life of patients after an alloHSCT (*Figure 1*).[8]

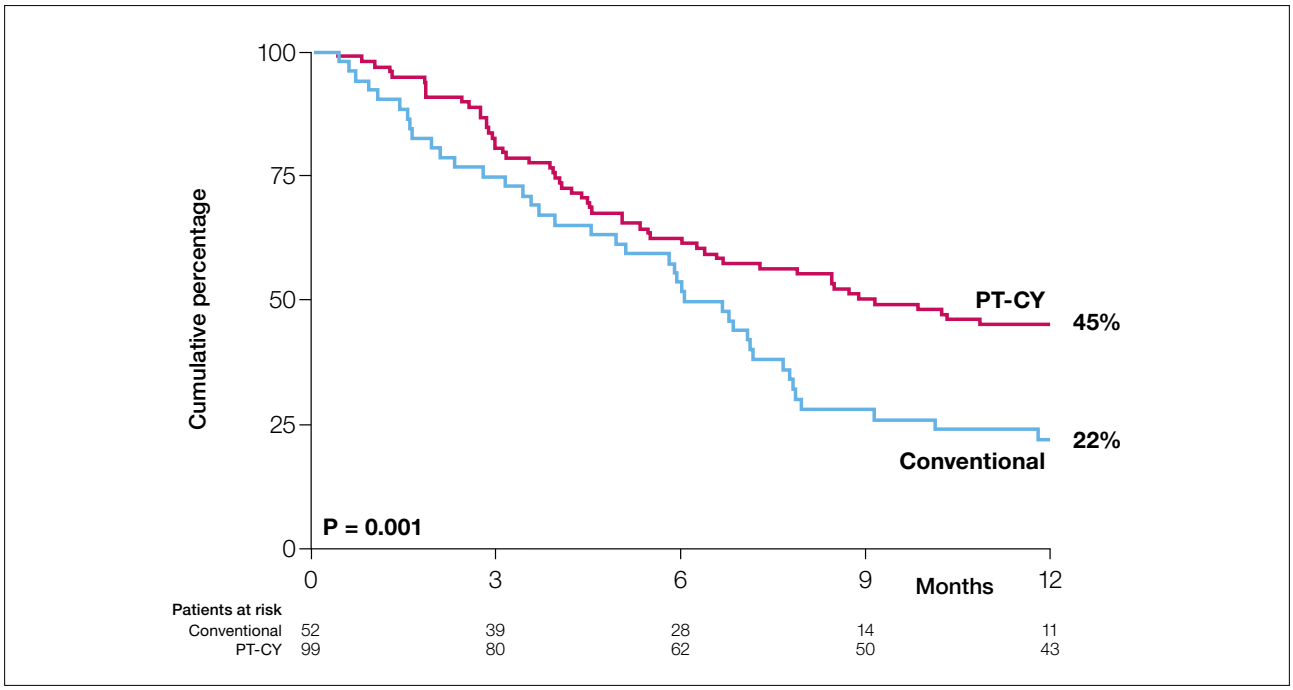


**FIGURE 1.** Graft-versus-host disease-free, relapse-free survival in the HOVON-96 trial.[8]

## ADVANCES IN IMMUNE THROMBOCYTOPENIA THERAPY

Rituximab is frequently used for refractory or relapsed immune thrombotic thrombocytopenic purpura (iTTP). In addition to this, it is increasingly being used to treat first episodes of iTTP. Unfortunately, there are no large randomised trials on which to base the use of rituximab. *Mazepa, et al.* therefore used The United States Thrombotic Microangiopathy (USTMA) iTTP registry, the world's largest database of patients with this rare disease, to assess whether the addition of rituximab improves the 5-year relapse-free survival (RFS) in both *de novo* and relapsing iTTP. In the *de novo* setting, the one- (p= 0.0002) and three-year (p= 0.004) RFS was significantly higher in patients treated with the combination of corticosteroids and rituximab as compared to those treated with corticosteroids alone. However, this was no longer the case after 5 years (p=0.39). As such, this indicated that the addition of rituximab can delay, but not prevent, relapses. In the setting of iTTP relapses, a significant interaction (p= 0.0007) between treatment and race was found. In Caucasian patients, the RFS significantly improved upon the addition of rituximab ($p < 0.0001$), while African Americans did not have any benefit from the addition of rituximab (p=0.43).[9]

In another trial, researchers investigated whether the oral thrombopoietin receptor agonist eltrombopag may be a good alternative for intravenous immune globin (IVIG) to raise the platelet count before surgery in patients with ITP. Eltrombopag was non-inferior to IVIG in both the intention-to-treat population (p= 0.005) and in the per-protocol analysis (p= 0.009) but could only show superiority to IVIG in the intention-to-treat analysis (p=0.047) but not in the per-protocol analysis (p=0.074). As one patient developed a pulmonary embolism after minor surgery and two patients had a post-splenectomy thrombocytosis, post-operative thromboprophylaxis should be considered with eltrombopag.[10]

## NEONATAL FC RECEPTOR AND THE COMPLEMENT PATHWAY AS NOVEL DRUG TARGETS?

At ASH 2019, *Robak et al.* presented the final results from a phase II, multiple-dose study of the anti-human neonatal Fc receptor (FcRn) antibody rozanolixizumab in patients with primary immune thrombocytopenia. Enrolled patients received a single dose (15 or 20 mg/kg) or multiple (5x4 mg/kg, 3x7 mg/kg, 2x 10 mg/kg weekly) doses of rozanolixizumab. Both the single and multiple doses of subcutaneous rozanolixizumab were well tolerated with mild-to-moderate headaches occurring at the higher doses. A decrease in IgG levels and an improvement in platelet count was observed in all cohorts but patients in the single dose infusions achieved these efficacy endpoints sooner (by day 8), more frequently and at numerically greater levels, compared to patients in the multiple doses cohorts. These data thus support further phase III development of rozanolixizumab in patients with primary ITP.[11]

In addition, *Broome et al*. presented the first clinical evidence that the complement pathway plays a role in thrombocytopenia in a subset of patients with ITP. Chronic ITP patients without adequate response to two or more prior therapies therefore received the inhibitor of the classical complement pathway sutimlimab on day zero and seven and then biweekly for up to 21 weeks (Part A), followed by a scheduled washout to evaluate relapse and re-treatment response (Part B) for an additional year. In a preliminary analysis of interim data, sutimlimab resulted in a rapid (< 24 hours), sustained increase in platelet count. In addition, washout kinetics demonstrated that the thrombocytopenia reoccurred when sutimlimab treatment was discontinued and that thrombocytopenia resolution occurred upon re-treatment. Further evaluation of complement pathway inhibition in ITP treatment is thus necessary.[12]

### NOVEL COMBINATIONS IN THE FIRST-LINE TREATMENT

All-trans retinoic acid (ATRA) can correct impaired platelet production by regulating the complement-IL-1β loop and TNFAIP3/NF-κB/SMAD7 signalling pathway in ITP. In a randomised, phase II, open-label trial it was therefore assessed whether the combination of ATRA and high-dose dexamethasone acts synergistically in the first-line treatment of adult ITP patients. At the six-months follow-up, there was no significant difference in the initial response but more patients in the ATRA group had sustained platelet counts (61% *vs*. 37%, p= 0.009). In total, 60% of the patients in the ATRA plus high-dose dexamethasone group achieved a complete response, as compared to 40.6% of the patients treated with high-dose dexamethasone only. The overall duration of response was greater in the combination group and fewer patients relapsed during follow-up (p< 0.001). Treatment was well-tolerated, and no grade 4 adverse events or treatment-related deaths were reported. ATRA plus high-dose dexamethasone can thus provide a sustained prolonged response in adults and can be a new treatment option for ITP patients.[13]

Similarly, also the combination of oseltamivir in combination with high-dose dexamethasone was assessed for its benefit in the first-line treatment of ITP. Although there was a higher incidence of initial response in the combination arm (p= 0.045), statistical significance was not reached for the sustained response rate at six months (p= 0.167). Relapse-free survival in the dexamethasone plus oseltamivir arm was significantly improved compared with the dexamethasone monotherapy arm during the follow-up period (HR[95%CI]: 1.96[1.02-3.80], Log Rank p= 0.043), as estimated by the Kaplan-Meier analysis. Most of the observed adverse events were of grade one or two and usually resolved spontaneously after medication was completed.[14]

## MISCELLANEOUS DISEASES

### ORAL ARGININE AS AN ADJUVANT IN SICKLE CELL DISEASE

In the Unites States, a phase II study previously demonstrated that arginine supplementation has opioid-sparing effects and significantly decreases the pain score in children hospitalised with sickle cell anaemia vaso-occlusive pain episodes (SCA-VOE).[15] To assess the potential benefit of arginine in Sub-Saharan African countries, a blinded, placebo-controlled, phase II trial was set up at two hospitals in Nigeria. Patients were randomised to receive oral L-arginine at 100 mg/kg/dose every 8 hours until hospital discharge for up to five days with a maximum of 15 doses (N= 35) or matching placebo (N= 33). All patients were between 5 and 17 years old and had a numerical pain scale score of ≥7 on a scale from 0 to 10. Upon arginine supplementation, plasma arginine levels significantly increased, which in turn reduced the mean total opioid dose (3.8 *vs*. 5.1 mg/kg, p= 0.11) and improved the pain scores of the patients (1.2±0.4 *vs*. 3.0±0.5; p<0.0001). In addition, oral arginine therapy increased the rate of pain reduction (p= 0.009), led to a shorter time-to-crisis resolution (p= 0.0216) and a reduced length of hospital stay (p= 0.015). No serious adverse events were detected in the arginine arm (as compared to four SAE in the placebo arm). Adverse events were similar in both groups, however there was a trend towards more vomiting in the arginine group as compared to the placebo group (20% *vs*. 3% respectively, p= 0.07). Oral arginine is thus a promising adjuvant therapy for SCA-VOE.[16]

### LUSPATERCEPT IN PATIENTS WITH MYELOFIBROSIS-ASSOCIATED ANAEMIA

In an ongoing phase II trial, the efficacy and safety of the erythroid maturation agent luspatercept in patients with myelofibrosis is evaluated. A total of 76 patients had been enrolled by the data cut-off in August 2019 and were divided over four cohorts. In cohort 1 (N= 222) patients did not receive a RBC transfusion within the last 12 weeks and were not receiving ruxolitinib, in cohort 2 (N= 21) patients were RBC transfusion dependent within the last 12 weeks but did not receive ruxolitinib and in cohort 3A (N= 14) and 3B (N= 19) patients received a stable dose of ruxolitinib and were transfusion independent and dependent, respectively. All patients received luspatercept 1.0 mg/kg with titration up to 1.75 mg/kg every 21 days for 168 days. At day 169, a disease response assessment was performed. In the extension phase of the treatment period, patients could

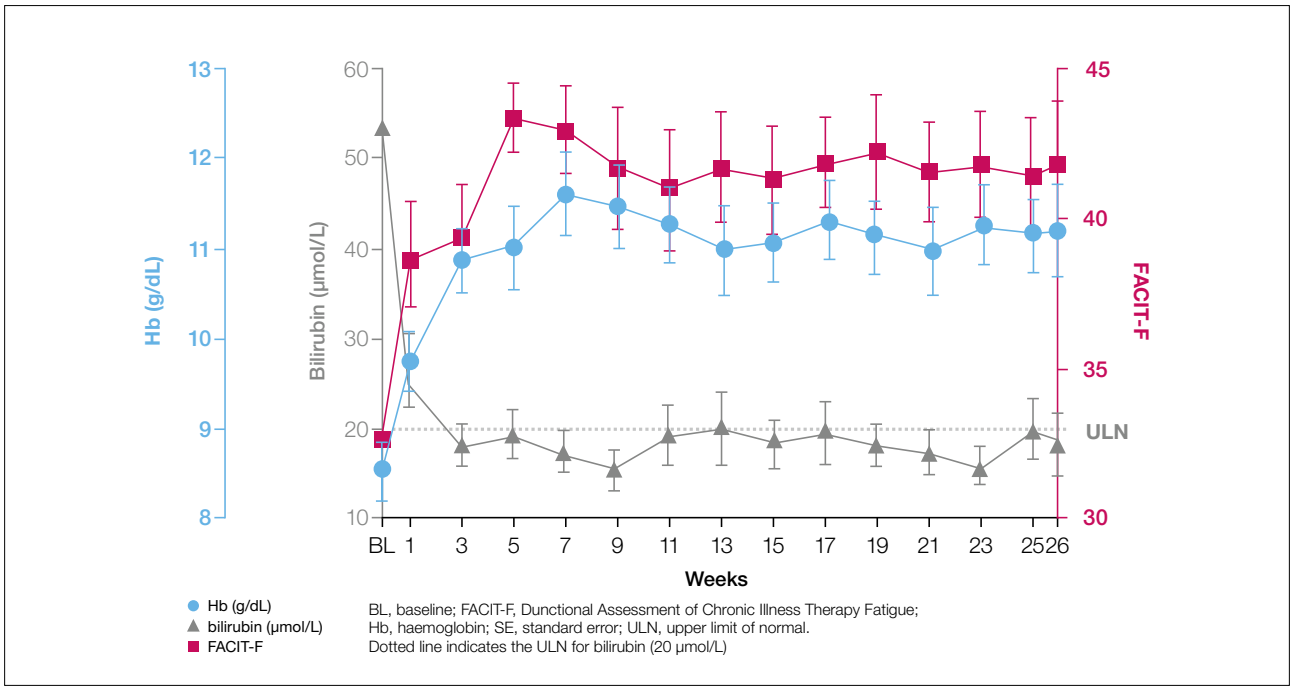


**FIGURE 2.** Mean (±SE) haemoglobin, bilirubin and FACIT-fatigue score following sutimlimab treatment.[18]

continue the study treatment upon clinical benefit of luspatercept or discontinued treatment if no clinical benefit was detected. Follow-up continued up to three years after administration of the last dose. In cohort 1 and 3A, 14% and 21% of the patients respectively achieved a haemoglobin increase of ≥ 1.5 g/dl from baseline over any consecutive 12-week time period without any RBC transfusion. In cohort 2 and 3B, 10% and 32% of the patients respectively, met the primary endpoint of being transfusion free for ≥ 12 consecutive weeks. The median duration of RBC transfusion independence was 32 and 39 weeks for cohorts 2 and 3B, respectively. Luspatercept could thus improve the anaemia in patients with and without RBC transfusions, with a more profound effect in patients treated with ruxolitinib. The majority of adverse events were grade 1 and 2 in severity, consistent with previous studies of luspatercept in myelodysplastic syndromes and β-thalassemia.[17]

## SUTIMLIMAB IN PATIENTS WITH COLD AGGLUTININ DISEASE: RESULTS FROM THE CARDINAL STUDY

Sutimlimab is a humanised monoclonal antibody against C1s that blocks the classical complement pathway, while leaving the alternative and lectin pathways intact. In the Cardinal study, the safety and efficacy of sutimlimab in adults with cold agglutinin disease (CAD) and a recent history of transfusion was assessed. Part A of the trial consisted out of a 26-week treatment period in which patients received sutimlimab intravenously on days 0 and 7, followed by weekly infusions. After the 26-week treatment period, there was a safety extension period with biweekly sutimlimab dosing (part B). The mean age of the patients was 73 years with a slight female dominance (62.5%). The mean number of transfusions in the six months prior to the study was 3.2. An analysis of part A of the study demonstrated a rapid and sustained increase in Hb (mean Hb increase > 1 g/dl from baseline by week one and > 2 g/dl by week three with Hb levels > 11 g/dl while patients remained on sutimlimab). The mean Hb increase was 2.6 g/dl. In addition, as haemolysis in CAD is predominantly extravascular, bilirubin is an accurate biomarker for the disease. The mean total bilirubin rapidly normalised within one to three weeks and was maintained below the upper limit of normal. The rapid inhibition of haemolysis correlated with the increase in Hb. Interestingly, the baseline FACIT-fatigue (FACIT-F) score of 32.5 indicates that the quality of life is significantly affected in these patients but improved by a mean of 7 points upon one-week treatment with sutimlimab and a mean of 11 points at the treatment assessment time point (*Figure 2*). The classical complement pathway activity was nearly completely inhibited by week one and the complement C4 rapidly normalised after sutimlimab administration. Targeting C1s in the classical complement pathway thus represents a novel therapeutic approach for the management of CAD and sutimlimab can potentially change treatment practices for patients with CAD.[18]

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