



# Congress Review

## Review of the European Hematology Association (EHA) Virtual Congress 2020

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FRANKFURT am Main, Germany, more commonly referred to as Frankfurt, is known for its futuristic skyline and houses the busiest German airport, which is also the fourth busiest in Europe. The city is the financial capital of mainland Europe, home to the European Central Bank (ECB) and the Frankfurt Stock Exchange. For these reasons, Frankfurt is no stranger to international attention and serves as an ideal venue to host a world-leading congress. However, as a result of the COVID-19 pandemic, the physical 25<sup>th</sup> European Hematology Association (EHA) Congress, scheduled June 11-14<sup>th</sup> 2020 in Frankfurt, was replaced by a virtual meeting (11<sup>th</sup>-22<sup>nd</sup> June). Although attendees did not land at Frankfurt am Main Airport, traffic control provided clearance to land at EHA25 Virtual, providing an exhilarating 10-day congress experience from the comfort and safety of our homes.

Twenty-five years of the EHA annual congress have meant 25 years of inspiring innovations and scientific results

contributing to EHA's annual congress evolving into the premier haematology congress in Europe. The Opening Ceremony was hosted by EHA President Prof John Gribben, Barts Cancer Institute, London, UK, who first commented on how COVID-19 has not only stopped the physical congress but also made EHA rethink the organisation of this and future congresses. "This crisis should not and will not stop us from sharing knowledge," he proclaimed before thanking the attendees for joining the innovative virtual edition of the 25<sup>th</sup> congress.

Following the Welcome Ceremony, Prof Gribben introduced the EHA 2020 winner of the José Carreras Award, established to honour leaders in clinical and translational haematology research. This is awarded every year to a recognised and active investigator who has made a significant contribution to the field of haematology. This year's winner, Prof Gilles Salles, University of Lyon, France, is a respected figure in the treatment of lymphomas. Prof Salles delivered a lecture on "Follicular

Lymphoma from Genetics to The Clinic,” providing an overview of how follicular lymphoma develops in patients and how to choose optimal treatment options. Further honoured for his contributions to haematology was Prof Radek Skoda, University Hospital Basel, Basel, Switzerland, recipient of the David Grimwade Award, who delivered a lecture on “Clonal Evolution of Myeloproliferative Neoplasms.”

Although held online, EHA still managed to provide a fantastic and effortless congress experience. The congress programme was split into on-demand and live sessions, including plenary presentations and symposia, and a regular theme-of-the-day programme. Themes included acute leukaemia, coagulation disorders, lymphoma, and red and white cell disorders. Coupled with overview presentations, Q&A panel discussions, and a modern virtual exhibit hall, the experience was like no other.

As always, EHA has brought its audience a plethora of significant breakthroughs in the field. We are proud to present reports on some of this cutting-edge research over the next few pages. Topics span from improved outcomes for patients with amyloidosis using daratumumab, a patient group urgently requiring novel therapies; to achieving blood cell transfusion independence in patients with lower-risk myelodysplastic syndromes. These stories and more are described in the following pages. Our topical article covering “Coagulopathy and Hyperinflammation in COVID-19,” based on the EHA three-part session on “COVID-19 and Hematology”, will no doubt be of particular interest.

Here you will also find summaries of some of the finest abstracts presented at EHA, written by the authors themselves, providing a first-hand account into the research. Erkeland et al. detail the effects of reactivation of *MIR139* on *MLL-AF9* acute myeloid leukaemia, with results indicating that both *miR139* expression, or inactivation of *miR139* targets, eliminate *MLL-AF9* acute myeloid leukaemia. Ionova et al. focus on the quality of life of patients with haematological malignancies and demonstrate that the Haematological Malignancies Patient-Reported Outcome (HM-PRO) measure, developed by the EHA Scientific Working Group, is a valuable tool in capturing the patient’s needs regardless of the state and stage of the disease.

It is tremendously exciting to gain a better understanding of the planning of a congress and the valuable work provided by the committees. Complementary to the congress coverage are informative interviews with the EHA Chair of the European Board for Accreditation in Hematology, EHA Chair Curriculum Committee, and the EHA Chair Guidelines Committee. The icing on the cake is our panel interview with two aspiring haematologists from the YoungEHA Committee, catering to the upcoming haematologists among you.

EHA25 Virtual presented a scientific programme of first-rate quality and immense variation, living up to its title as the premier haematology congress in Europe. It was inspiring to see how much the organisation has grown since being founded in 1992. We hope you take the time to indulge in the following pages and we look forward to seeing you at the 26<sup>th</sup> Congress of EHA in Vienna, Austria.



EHA 2020 REVIEWED →



## Improved Outcomes for Patients with Amyloidosis with Daratumumab

ESTIMATED to have an incidence of 3–12 cases per million population annually, there are currently no health authority-approved therapies for light-chain (AL) amyloidosis. However, a recent clinical trial has reported success in treating patients with AL amyloidosis with the subcutaneous cluster of differentiation (CD)38-directed antibody drug daratumumab, traditionally used to treat multiple myeloma, in combination with cyclophosphamide-bortezomib-dexamethasone (CyBorD). This was announced in a press release at EHA25 Virtual on 12<sup>th</sup> June 2020.

A rare multisystem disorder that can become fatal, AL amyloidosis presents in patients whose bone marrow produces abnormal pieces of antibodies that accumulate into clumps called amyloid. These clusters are deposited in tissues and vital organs, interfering with normal bodily function.

The Phase III ANDROMEDA study compared daratumumab plus CyBorD (D-CyBorD) with CyBorD alone in patients diagnosed with AL amyloidosis. Here, 388 participants were eligible for the study, as determined by measurable haematologic disease,  $\geq 1$  involved

organ, estimated glomerular filtration rate  $\geq 20$  mL/minute, and absence of symptomatic multiple myeloma.

The primary endpoint of haematologic complete response rate was 53% for D-CyBorD compared to 18% for CyBorD. Analysis of the 6-month response rate for patients treated with D-CyBorD for cardiac and renal responses were 42% and 54%, respectively, compared to 22% and 27%, respectively, for CyBorD.

Additionally, D-CyBorD was shown to have an acceptable safety profile, consistent with previous studies on daratumumab or CyBorD alone. Systemic administration-related reactions with D-CyBorD, mostly arising during the first infusion, occurred in 14 patients (7%), though all were Grade 1–2.

The deeper and more rapid haematologic responses observed with D-CyBorD, combined with improved clinical outcomes and an acceptable safety profile, highlight the promise of this treatment option for patients with AL amyloidosis, who are in urgent need of novel therapies.

*"The primary endpoint of haematologic complete response rate was 53% for D-CyBorD compared to 18% for CyBorD."*

## Omission of Radiotherapy Does Not Worsen Survival in Hodgkin Lymphoma

RADIOTHERAPY could be avoided in young patients with Hodgkin lymphoma (HL), as positron emission tomography (PET)-guided chemotherapy protocols provide equally good tumour control as combined therapy. While combined therapy has been the standard care for patients with early-stage unfavourable HL for several decades, a European study has shown no worsening of tumour control with omission of radiotherapy.

Patients with risk factors suggesting an unfavourable prognosis despite early-disease HL are usually treated with a four-cycle protocol of combined chemoradiotherapy. However, as median age at disease onset is 30 years, the use of radiotherapy poses long-term risk of developing secondary malignancies or cardiovascular disease.

The European prospective, randomised trial of 1,100 patients assessed the impact of omitting radiotherapy compared to combination chemoradiotherapy, led by PET assessment of treatment response. The study altered the usual chemotherapy regimen of combined therapy (four cycles of ABVD) to two cycles

of eBEACOPP and two cycles of ABVD ('2+2' therapy). There was no reduced tumour control without radiotherapy treatment in those patients responding well to chemotherapy. The study also identified that most patients respond well to chemotherapy and benefit from the radiotherapy-free treatment strategy.

Longer term outcomes were encouraging, with very high survival rates. Of the 1,100 patients enrolled, one death from HL and one death from treatment-related adverse events were reported. The mortality rate for the patients matched the control group; however, there was more severe haematological toxicity and infections with the new chemotherapy-alone regimen.

"The vast majority of early stage unfavourable HL patients can be treated with the brief and highly effective 2+2 chemotherapy alone," outlined Prof Peter Borchmann, German Hodgkin Study Group (GHSG), Cologne, Germany in his presentation of the study's findings at EHA25 Virtual. The long-term value of avoiding radiation exposure and the very high survival rates mean that this omission of radiotherapy is now considered the standard of care for the GHSG.



*"The vast majority of early stage unfavourable HL patients can be treated with the brief and highly effective 2+2 chemotherapy alone."*



## COVID-19 Treatment Prioritisation Required for Adult Haemoglobinopathy Patients

ADULT patients with the severe inherited blood disorders sickle cell disease (SCD) and thalassaemia could be at risk of experiencing severe outcomes from COVID-19. National data collected by the newly launched National Haemoglobinopathy Panel (NHP) were analysed by researchers at Queen Mary University of London, London, UK and outlined in a EHA25 Virtual press release dated 13<sup>th</sup> June 2020.

The survey of 199 patients with SCD and 26 patients with thalassaemia revealed that most confirmed and suspected cases of COVID-19, as classified by the World Health Organization (WHO) surveillance criteria, were mild. There was no associated increased risk in paediatric patients; however, adults with SCD appeared to be at increased risk of adverse outcomes of the virus. Cases included in the study were reported up to 5<sup>th</sup> June 2020.

The National Health Service (NHS) recently commissioned regional care networks across England to provide improved support and specialised services for haemoglobinopathy patients. These networks, overseen by the NHP, have accumulated clinical data collected throughout the spread of COVID-19 to quickly determine the associated level of risk for patients.

“For adults with SCD, isolation precautions should be lifted cautiously, and they should be prioritised for new therapies and vaccination when available,” explained Dr Paul Telfer, Queen Mary University of London, Barts Health NHS Trust, London, UK. Identifying and quantifying the risk profile of this subgroup of patients with SCD or thalassaemia may allow for more targeted approaches to their care, and more specific considerations for reducing their risk of exposure to the infection. This study demonstrated the value of obtaining real-time data to evaluate risks faced by different patient groups during the COVID-19 pandemic.

*“For adults with SCD, isolation precautions should be lifted cautiously, and they should be prioritised for new therapies and vaccination when available.”*

## Novel C3 Complement Inhibitor Treatment for Paroxysmal Nocturnal Haemoglobinuria

PEGCETACOPLAN, a new investigational drug for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), has shown to be more effective than eculizumab in the resolution of anaemia according to a new study presented in a press release at EHA25 Virtual on 12<sup>th</sup> June 2020.

PNH is a rare but severe disease, affecting the blood cells and making them more fragile and prone to premature death by parts of the innate immune system. Here, the complement system attacks the cells, resulting in fatigue and severe anaemia. Often the patient will pass red or black urine as a result of intravascular and extravascular haemolysis, require blood transfusions, and experience dyspnoea and severe life-threatening blood clots in critical organs including the liver.

Eculizumab, a complement component 5 (C5) inhibitor, is the current standard treatment for PNH and although beneficial, many patients remain anaemic, fatigued, and require transfusion. As a result, the PEGASUS study aimed to find a more effective treatment option. The trial consisted of a 4-week run-in period to assess baseline values, followed by a 16-week randomised controlled period divided into the pegcetacoplan and eculizumab arm. Primary endpoints were analysed at Week 16.

PEGASUS is the first randomised Phase III trial of a proximal C3 inhibitor and the results showed that pegcetacoplan is considerably more effective than eculizumab in improving haemoglobin and other key disease markers in patients with PNH. Results highlighted pegcetacoplan's superiority to eculizumab for change in haemoglobin levels from baseline at Week 16 and the haemoglobin increase was maintained in all patients. After Week 16, all patients continued pegcetacoplan monotherapy to Week 48.

The safety profile of pegcetacoplan was comparable to that of eculizumab and, coupled with its superior treatment effects, these results demonstrate the potential for pegcetacoplan to control haemolysis in patients with PNH, making it a prospective new therapy option for patients with PNH.





## Hopeful Treatment for Steroid-Refractory Acute Graft-Versus-Host Disease

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ALLOGENEIC stem-cell transplantation has the major limitation of patients developing acute graft-versus-host disease (GVHD), and some patients are refractory to steroid treatment. Results from the REACH2 Phase III trial, revealed in a press release at EHA25 Virtual on 11<sup>th</sup> June 2020, have shown that the drug ruxolitinib can improve the outcomes of refractory patients with the disease.

Ruxolitinib is a selective inhibitor of JAK1 and JAK2 and is a medication used to treat myeloproliferative neoplasms. In the multicentre, randomised, open-label REACH2 trial, the efficacy of oral ruxolitinib (10 mg twice daily) was compared against nine commonly used treatment options. A total of 309 patients participated; all were  $\geq 12$  years old and had undergone allogeneic stem-cell transplantation and subsequently developed glucocorticoid-refractory acute GVHD.

At Day 28, the primary endpoint of overall response (complete response or partial response) was higher in the ruxolitinib group than the control group, at 96 patients compared to 61, respectively

(odds ratio [OR]: 2.64; 95% confidence interval [CI]: 1.65–4.22;  $p < 0.001$ ).

At Day 56, the key secondary endpoint of durable overall response was again higher in the ruxolitinib group than the control group, at 61 patients compared to 34 (OR: 2.38; 95% CI: 1.43–3.94;  $p < 0.001$ ). Estimation of cumulative incidence of loss of response at 6 months was deemed to be 10% for the ruxolitinib group and 39% for the control group, a stark contrast.

Median overall survival in the ruxolitinib group was almost twice as long as the control group, at 11.1 months compared to 6.5 months, respectively. However, thrombocytopenia had an increased incidence in the ruxolitinib group, with 33% of the 152 patients presenting with this adverse event, compared to 18% in the control group.

Despite the increased presentation of toxic side effects, the observed significant improvement in efficacy outcomes proves ruxolitinib to be the first novel agent to demonstrate superiority to standard therapy in patients with steroid-refractory acute GVHD in a Phase III trial.

# Better Treatment Responses with Combination Therapy for Acute Myeloid Leukaemia

LIMITED treatment responses are often experienced with the standard commonly used lower-intensity therapies for acute myeloid leukaemia (AML). The combination regimen of azacitidine and venetoclax in patients with treatment-naïve AML has shown good efficacy in results from a Phase III trial presented at EHA25 Virtual, reported in a press release dated the 13<sup>th</sup> June 2020.

The median age of diagnosis for AML is 68-72 years, meaning that AML is primarily a disease of older adults. A median survival of 9-10 months and complete remission (CR)/CR with incomplete count recovery (CRi) rates <40% are commonly experienced with lower-intensity treatment regimens, for example azacitidine or decitabine alone. These limited responses can be attributed to medical comorbidities and high-risk disease-related biology in older adults.

VIALE-A is an ongoing, Phase III, randomised, double-blinded, multicentre trial investigating the efficacy of the combination of azacitidine and venetoclax in patients with treatment-naïve AML who were ineligible for intensive therapy.

Those included were either  $\geq 75$  years of age or were 18-74 years with at least one of the predefined comorbidities, for example, chronic stable angina. Study participants (N=431) were randomised 2:1 to receive either the combination of azacitidine and venetoclax or azacitidine and placebo, respectively. The combination regimen of azacitidine and venetoclax resulted in an improved overall survival (14.7 versus 9.6 months) and improved response rates CR/CRi (66% versus 28%) compared with azacitidine alone. Additionally, a quicker response was associated with the combination regimen (median time to CR/CRi was 1.3 versus 2.8 months) and these responses were more durable (lasting 17.5 versus 13.4 months). An increased incidence of transfusion independence was also seen with the combination regimen (58% versus 34%).

Overall, the combination of azacitidine and venetoclax for patients with treatment-naïve AML extended survival in comparison with azacitidine and placebo. The results from this trial could pave the way for a new standard of care for older patients with AML.



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# Red Blood Cell Transfusion Independence Using Imetelstat

TRANSFUSION therapy, used in the treatment of patients with lower-risk myelodysplastic syndromes (LR-MDS), is an essential part of haematology practice. The results of the IMerge study were recently presented in a press release at EHA25 Virtual on the 12<sup>th</sup> June 2020 and report long-term efficacy with imetelstat to achieve 8-week red blood cell transfusion independence (RBC-TI).

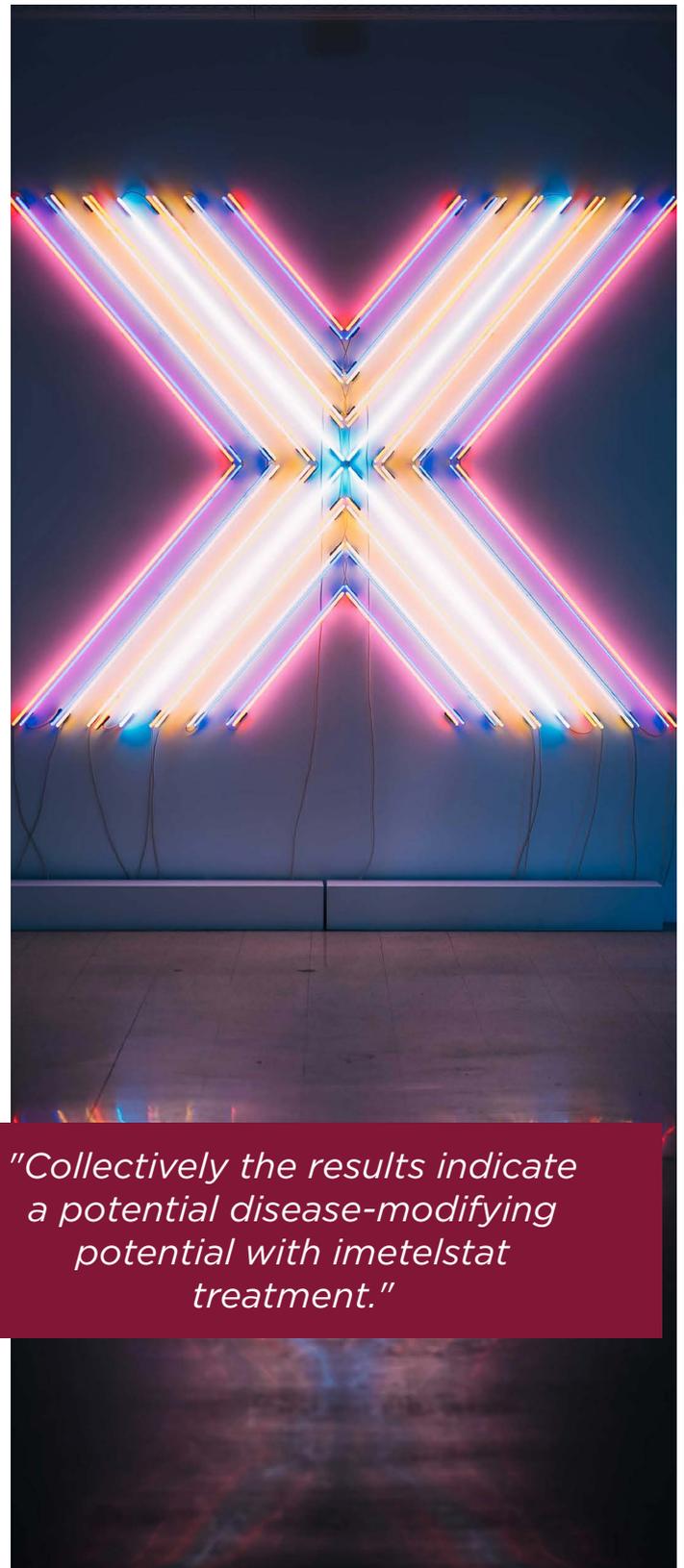
Currently, patients with transfusion-dependent LR-MDS have limited treatment options; however, studies have shown that higher telomerase activity, expression of human telomerase reverse transcriptase, and shorter telomeres are risk factors for shorter overall survival in LR-MDS patients. Imetelstat is a potent competitive telomerase inhibitor that targets cells with short telomere lengths and active telomerase.

IMerge is a Phase II/III clinical trial evaluating imetelstat as a treatment option for LR-MDS patients (non-*del*[5q] MDS) that are dependent on red blood cell transfusion and relapsed after or are refractory to treatment with erythropoiesis-stimulating agents. The primary endpoint of the IMerge Phase II trial was to achieve 8-week RBC-TI, defined as the proportion of patients not receiving any RBC transfusion during any consecutive 8 weeks since starting the trial.

Of the 38 patients recruited, results highlighted long-term efficacy and overall safety. IMerge Phase II data showed that 16 patients (42%) achieved 8-week RBC-TI, and 12 of these responders (75%) experienced a haemoglobin rise compared to pretreatment during the transfusion-free interval. Furthermore, 12 patients (32%) achieved a 24-week RBC-TI and 11 patients (29%) were transfusion-free for >1 year.

This trial reported a median RBC-TI duration of 88 weeks, the longest reported to date in non-*del*(5q) LR-MDS, and collectively the results indicate a potential disease-modifying potential

with imetelstat treatment. Ultimately, the most reported adverse events (reversible cytopenia) were not frequent and imetelstat showed promising treatment results that may help eliminate transfusion dependency for patients with LR-MDS, something that will be further evaluated in the currently recruiting, ongoing Phase III IMerge trial.



*"Collectively the results indicate a potential disease-modifying potential with imetelstat treatment."*



## Pembrolizumab Improves Progression-Free Survival in Transplant-Ineligible Hodgkin Lymphoma

LIMITED treatment options for transplant-ineligible patients with chemorefractory Hodgkin lymphoma have been broadened by evidence that pembrolizumab increases progression-free survival. A Phase III study has compared safety and efficacy of pembrolizumab to brentuximab vedotin, and found superior progression-free survival with pembrolizumab.

Transplant ineligibility in Hodgkin lymphoma may result from chemorefractory disease, age, or comorbidities. While the standard of care for relapsed, refractory Hodgkin lymphoma is salvage chemotherapy and autologous stem cell transplantation, for those ineligible for transplant there is no standard of care. The Italian Phase III study KEYNOTE-204 compared pembrolizumab (n=81), a PD-1 inhibitor, to brentuximab vedotin (n=88) in patients who had relapsed after, or were ineligible for, autologous stem cell transplant.

The study found a statistically significant increase in progression-free survival with pembrolizumab

treatment. Median progression-free survival for the patients treated with pembrolizumab monotherapy was 13.2 months versus 8.3 months for those treated with brentuximab vedotin (hazard ratio: 0.65; 95% confidence interval: 0.48–0.88;  $p=0.00271$ ). The benefits of pembrolizumab treatment extended to those patients in subgroups of primary refractory disease and those who had not received a previous autologous stem cell transplant.

The findings of this Phase III trial were presented at EHA25 Virtual. Dr Pier Luigi Zinzani, Institute of Haematology “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy outlined his view of the impact of the study on the treatment paradigm for Hodgkin lymphoma: “Pembrolizumab should be considered the preferred treatment option and new standard of care for the treatment of relapsed/refractory classical Hodgkin lymphoma in patients who have relapsed after autologous stem cell transplant or are ineligible for auto-SCT.”

*“A Phase III study has compared safety and efficacy of pembrolizumab to brentuximab vedotin, and found superior progression-free survival with pembrolizumab.”*

# Biologic Therapy for Hereditary Haemorrhagic Telangiectasia

HEREDITARY haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is the second most common blood disorder worldwide and has a prevalence of 1 in 5,000. Currently no U.S. Food and Drug Administration (FDA)-approved therapy exists; however, a new study has evaluated intravenous bevacizumab and considers it a potential standard treatment option for HHT patients. These findings were reported in a press release at EHA25 Virtual on 12<sup>th</sup> June 2020.

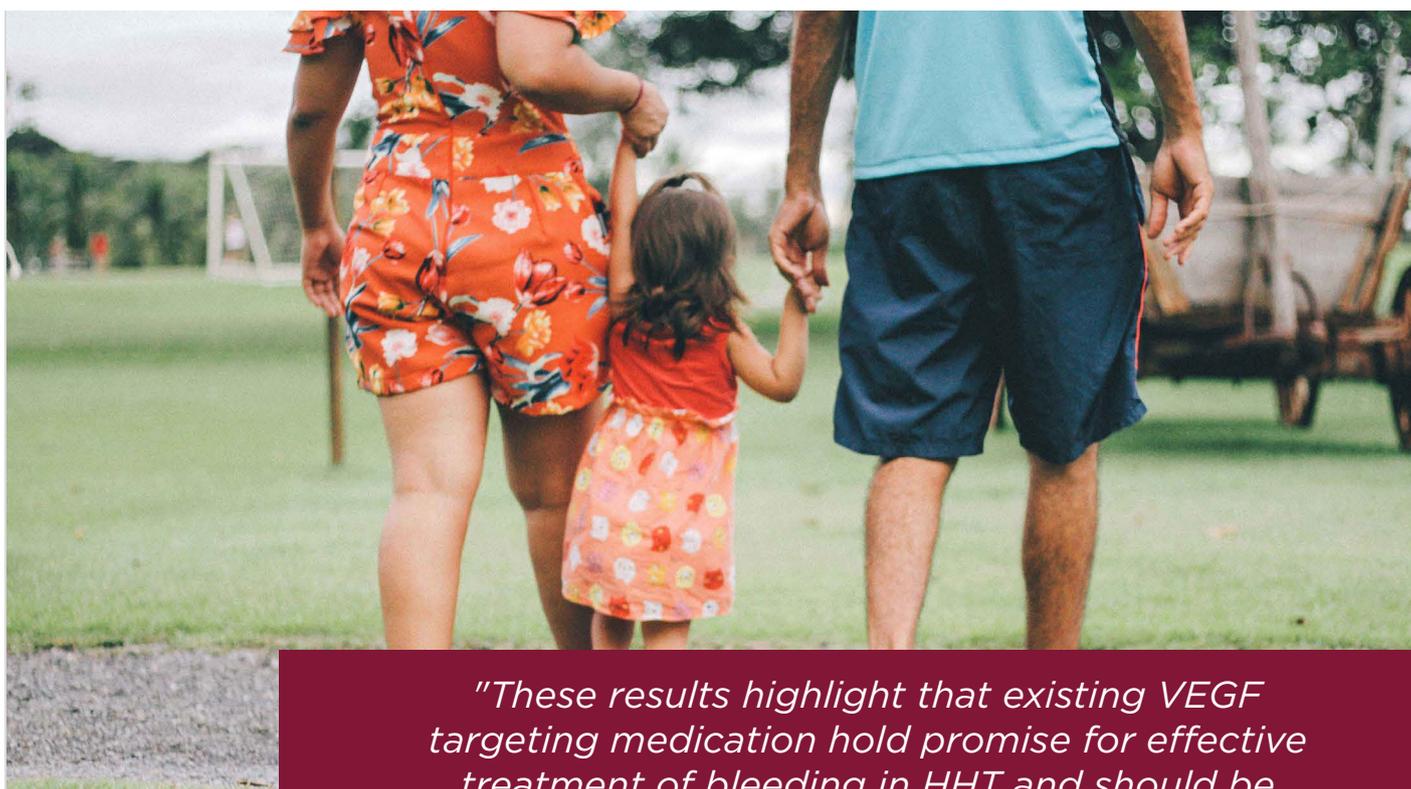
HHT patients are affected by chronic gastrointestinal bleeding and severe recurrent epistaxis that results in chronic and often severe iron deficiency anaemia. To maintain safe blood counts, patients generally depend on blood transfusions and iron infusions. Furthermore, HHT results in elevated levels of vascular endothelial growth factor (VEGF); therefore, existing VEGF-targeting medication may be effective in the treatment of HHT.

In the multicentre retrospective study InHIBIT-Bleed, Dr Hanny Al-Samkari and his team, Massachusetts General Hospital, Boston,

Massachusetts, USA, evaluated the efficacy of intravenous bevacizumab. Bevacizumab, a bioengineered VEGF-targeting antibody, was used in 238 patients with HHT to treat bleeding for a median duration of 1 year.

The study measured haemoglobin levels, epistaxis, and red cell transfusion and iron infusion requirement before and after bevacizumab initiation. The results showed that 67% of patients anaemic at baseline achieved freedom from anaemia, 92% achieved a clinically meaningful reduction in Epistaxis Severity Score (ESS), 80% were red blood cell transfusion-free after 6 months of treatment, and 61% were iron infusion-free after 6 months of treatment.

Treatment was safe and no fatal treatment emergent adverse events were recorded. These results highlight that existing VEGF-targeting medication hold promise for effective treatment of bleeding in HHT and should be evaluated in future studies. Collectively, the study proved that bevacizumab is a safe and effective biologic therapy option to treat bleeding in patients with HHT.



*"These results highlight that existing VEGF targeting medication hold promise for effective treatment of bleeding in HHT and should be evaluated in future studies."*



## Total Body Irradiation Benefits Conditioning for Stem Cell Transplantation

*"Allogenic haematopoietic stem cell transplant (HSCT) cures approximately 50-80% of paediatric ALL patients, making it one of the most powerful leukaemia therapies."*

SUCCESSFUL treatment for acute lymphoblastic leukaemia (ALL) in patients aged <18 years is achieved in >90% of cases using contemporary chemotherapy. However, for the remaining 10% there are lasting effects from the conditioning process of the alternate treatment regimen. In the ALL SCTped FORUM trial, the possibility of not including total body irradiation (TBI) in the conditioning was explored, but this trial was terminated early because of the significantly better results of the standard approach. Results from this study were presented at EHA25 Virtual and in a press release dated 12<sup>th</sup> June 2020.

For the 10% of patients with ALL who have resistant or recurring leukaemia, alternative treatment regimens are needed. Allogenic haematopoietic stem cell transplant (HSCT) cures approximately 50-80% of paediatric ALL patients, making it one of the most powerful leukaemia therapies. There are five main steps in the allogenic HSCT procedure: 1) identify a suitable donor; 2) reduce the patient's leukaemia to an undetectable level; 3) harvest haematopoietic stem cells from the donor; 4) condition the patient for transplantation; 5) transplant the stem cells.

Sterility, growth retardation, pulmonary issues, and secondary cancer are highly negative consequences of the conditioning step of allogenic HSCT, despite its efficacy to control the leukaemia. A global study, FORUM, was launched to investigate whether chemotherapy-based conditioning could substitute TBI. Patients (N=413) were aged 4-21 years, and only those in complete remission were eligible. Lower overall survival rates were experienced in the chemotherapy-based conditioning compared with the standard combination of TBI and chemotherapy, leading to the trial being terminated early.

Although FORUM was not a positive trial, much was learnt during the process, such as the feasibility and efficacy of national and international collaboration and that there were no differences between the two chemo-conditioning groups (busulfan- or treosulfan-based). Many questions remain, and the researchers are now performing prospective monitoring to facilitate better defined advantages and limitations of a collection of conditioning approaches.