Congress Review

Review of the European Hematology Association (EHA) 2021 Virtual Congress

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THE GLOBAL community of clinicians and researchers shared in the latest advances in haematology care online at the 26th European Hematology Association (EHA) 2021 Virtual Congress. Despite the ongoing impact of the COVID-19 pandemic, affecting the ability for this large network of engaged healthcare practitioners to meet together to advance their individual and collective understanding of haematological care, the virtual congress provided a fantastic opportunity for the usual shared education and discussion to continue undaunted.

In his opening ceremony address, John Gribben, President of EHA, outlined the value and intention of the congress: "the congress and all its components are interwoven with the latest research and clinical practice updates, as well as various opportunities to connect with your colleagues from all around the world." In addressing the response to the challenges of the past year, Gribben highlighted a proverb: 'If you want to go quickly, go alone. If you want to go far, go together.' This ethos of shared journeying was evident throughout the congress, as sessions were shared amongst experts from around the globe; contributed to by EHA and partner associations; and carried by the many voices of expert clinicians, early-career researchers, laboratory and scientific researchers, and patient advocates.

The 9-day congress included 4 core, cross-discipline days followed by 5 thematic days, sharing plenary sessions, symposia, abstract presentations, and debates to cover the full discipline of haematology from the laboratory to the clinic, including leukaemias and lymphomas, red and white cell disorders, haemoglobinopathies, and transfusion medicine. EHA guideline sessions shared summary updates for practising clinicians, including joint sessions with the European Society for Medical Oncology (ESMO) and other partner associations for detailed and practical education.

More than 1,800 abstracts were submitted to EHA 2021 to share insights across the

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sub-disciplines of haematology. The authors of several standout abstracts from the congress have provided summaries of their research, shared in this issue of *EMJ Hematology*. These include the clinical experience at a haematological centre of patients with COVID-19 and acute leukaemia, as well as an analysis comparing the value of different formulas to discern iron deficiency anaemia from β-thalassaemia minor.

Stand-out highlights from the congress, sharing hot-topic research news, are summarised in our following congress review. These include a French national registry analysis of the efficacy of chimeric antigen receptor T cell therapy in diffuse large B-cell lymphoma, the results of treatment efficacy studies in multiple myeloma, and genetic insights in juvenile haemochromatosis, among others. EHA 2021 highlighted the findings from these studies as of highest impact for current and upcoming practice in haematology, and summaries of these findings are shared to allow *EMJ Hematology* to continue the conversation from EHA 2021. We also interviewed EHA 2021 Chair of Scientific Program Committee Ruud Delwel, who gave the opening address for the congress; he outlined for us how his goals for EHA 2021 shaped the delivery of the congress.

While many expert and valued haematologists were celebrated at the congress, highlighting their research work or sharing their career insights, three major awards were presented as part of EHA 2021. The David Grimwade Award was presented to Olivier Bernard to recognise his role as a leading and active basic and translational researcher, particularly for his work in delineating the role of JAK2 and TET2 in oncogenesis and their impact on haematopoiesis. The José Carreras Award winner for 2021 was Elias Campo, recognising his contributions to haematologic translational and clinical research as a clinical pathologist pioneering genetic understanding in modern haematological practice. Finally, the prestigious Jean Bernard Lifetime Achievement Award honoured the work of Christine Chomienne for her 25-year career in clinical haematology, translational research, and active impact in EHA including in her term as EHA President 2013–2015.

While the hope this year had been to walk the Ringstrasse in Vienna, Austria, alongside haematology colleagues, the virtual format did not diminish the fantastic delivery and atmosphere of this key event in haematology care. Read on for our key scientific insights from EHA 2021, and we look forward to sharing in this community again, hopefully in-person, in Vienna in 2022. ■

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EHA 2021 REVIEWED →

Efficacy of CAR T Therapy in Patients with Diffuse Large B-Cell Lymphoma

DESCAR-T is the French national registry for patients treated with commercial chimeric antigen receptor (CAR) T cells across all haematological malignancies, with the goal to collect real-world data, including safety and effectiveness, up to 15 years after CAR T cell infusion. In a new study, a team led by Steven Le Gouill, Assistant Professor in Clinical Hematology, Nantes University Hospital, France, sought to investigate CAR T efficacy in patients with diffuse large B-cell lymphoma (DLBCL) who were registered in the DESCAR-T database. The results of this study were presented as part of an oral session at EHA 2021.

Phase II clinical trials have demonstrated that CAR T cells can provide long-term disease control in relapsed/refractory patients with B-cell acute lymphoblastic leukaemia or DLBCL. The French Health Authority (HAS) commissioned specific real-world data on this; they stated the data had to be characteristic of the CAR-T-eligible population in the 'intention-to-treat' category, have long-term follow-up of 15 years, and include previous therapy description. To fulfil this need for a national registry, DESCAR-T was created in 2019.

The DESCAR-T database saw approximately 50 new patients registered each month, indicating the success of CAR T therapy for patients. Of the patients in the database, CAR T cells were ordered for 607 patients and 550 had been infused. The median time from CAR T order to infusion was 50 days. Of the patients who completed CAR T therapy, 350 patients were infused with axicabtagene and 200 received tisagenlecleucel. Patient characteristics and clinical outcomes of 537 patients with DLBCL who were registered in the DESCAR-T database were measured in this study. In an analysis of the response data from 460 infused patients, the authors found that 40% achieved complete remission and 30% achieved partial remission by Day 30. The progression-free survival at 6 months calculated from the time of CAR-T infusion was 44.5% (39.6–49.2) months.

"The DESCAR-T registry confirmed the clinical trial efficacy of CAR T therapy in the real world."

The authors concluded the analysis by stating that the DESCAR-T registry confirmed the clinical trial efficacy of CAR T therapy in the real world. ■

Humoral Response of COVID-19 Vaccine in Haematopoietic Cell Transplantation and CAR-T Therapy

COVID-19 has been linked to the occurrence of other severe disease and increased mortality rates in patients who have undergone hematopoietic cell transplantation (HCT). The approved Pfizer/BioNTech BNT162b2 vaccine has proven to be necessary for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, especially in patients with health conditions associated with immunosuppression. Despite the benefits of the BNT162b2 vaccine, the efficacy and safety of this vaccine in patients undergoing immunologic cell therapy has not been effectively recorded. A new study presented on 12th June 2021 during EHA 2021 assessed BNT162b2 vaccine immunogenicity and safety in patients who underwent HCT and chimeric antigen receptor therapy (CAR-T).

The study, presented by Ron Ram, BMT Unit, Tel Aviv Sourasky Medical Center, Israel, observed the humoral immune response of 79 patients who had recently been vaccinated with BNT162b2 at the medical centre. There were 66 patients in the HCT group and 14 patients in the CAR-T therapy group. All participants were vaccinated according to the European Society for Blood and Marrow Transplantation (EBMT) guidelines. Generally, the vaccine was effective and any adverse effects resolved, apart from one graft rejection that is currently under examination.

Humoral antibody response was observed in only 36% of patients who underwent CAR-T therapy compared with 81% of patients who received allogeneic HCT. Patients diagnosed with B cell aplasia as well as those who received the vaccine shortly after CAR-T therapy were less likely to develop antibodies.

In conclusion, the results demonstrated that the humoral response to the BNT162b2 vaccine displayed a good response in patients who had undergone allogeneic HCT but diminished in those patients receiving CAR-T. ■

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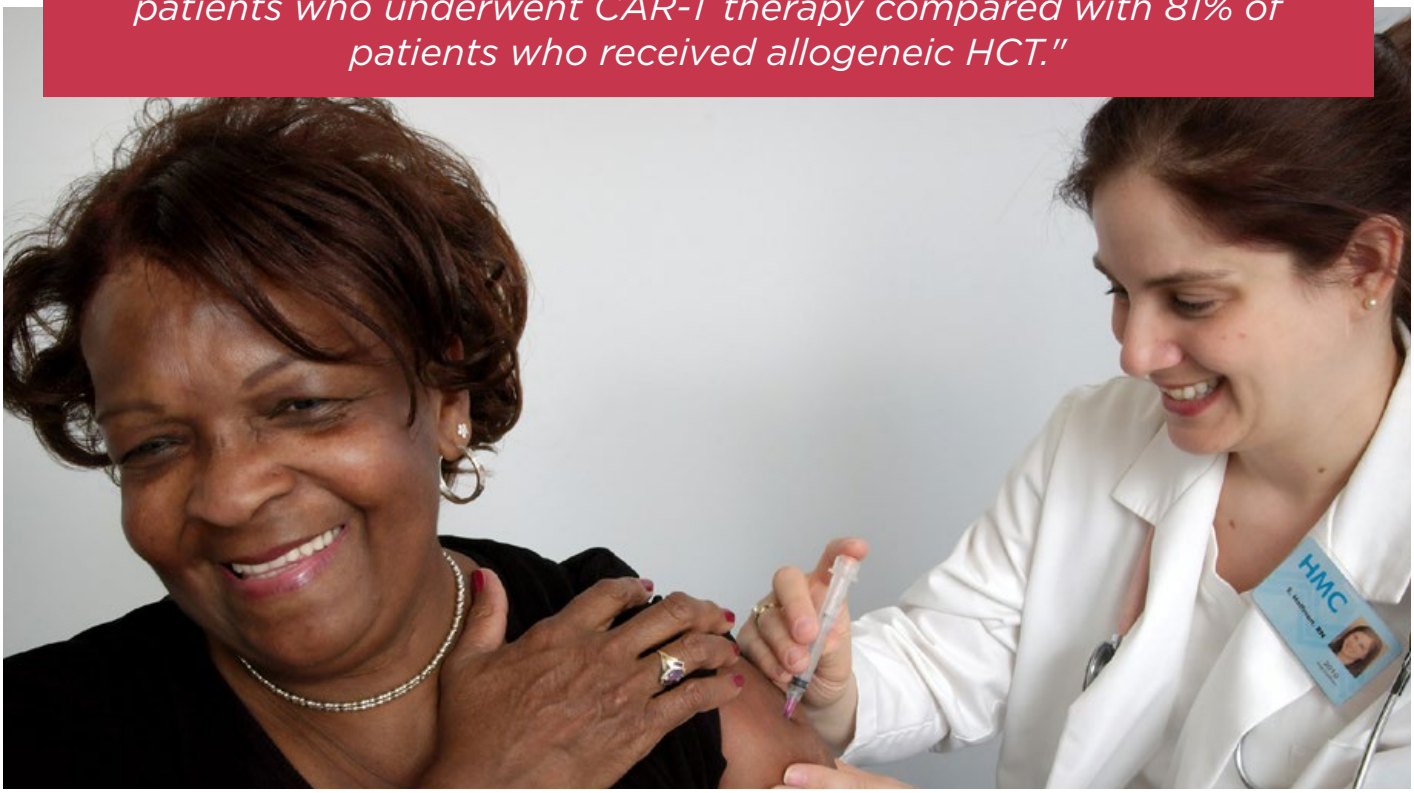

Improved Progression-Free Survival Shown in Myeloma by Adding Daratumumab to Treatment

THE FRONT-RUNNER of novel treatments for newly diagnosed multiple myelomas (NDMM) is a modern initiative that incorporates daratumumab. This addition to bortezomib, thalidomide, and dexamethasone (D-VTd) induction/consolidation was compared with velcade, thalidomide, and dexamethasone (VTd) alone in a French study. D-VTd demonstrated superior efficacy in combination with autologous stem cell transplantation (ASCT) by producing longer progression-free survival (PFS) rates, most beneficial in patients who had previously received VTd induction/consolidation.

This two-part study led by Philippe Moreau, spanning 2 years, revealed significantly improved post-ASCT outcomes in patients with NDMM and lays strong foundations for the development of further maintenance strategies in this field. Labelled the CASSIOPEIA trial, the current Phase III study included 1,085 participants with transplant-eligible NDMM in its first stage, with a randomised, open-label, active-controlled, parallel-group design. In this step, D-VTd induction/consolidation demonstrated superior depth of response, better minimal residual disease negativity scores, and prolonged PFS in comparison with VTd.

The second section of the study was an interim analysis comparing D-VTd and VTd treatments using observation treatment, conducted in 886 responders progressing from the previous stage of investigation. This brought forward evidence that patients maintained longer PFS in the daratumumab arm; however, stratification showed that this benefit was exclusive to patients previously treated with VTd in the first stage of the trial.

The researchers acknowledge that further longitudinal study is required to assess the potential the findings bring for overall survival and long-term PFS2. The evidence is promising for patients with myeloma and there is no doubt that ongoing studies, such as GRIFFIN, PERSEUS, and AURRIGA, will build on the strategies investigated to bring us closer to an optimal maintenance strategy; the next steps are expected to combine daratumumab with lenalidomide. ■

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Addition of Daratumumab Improved Overall Survival in Multiple Myeloma

MULTIPLE Myeloma (MM) is a life-threatening bone marrow cancer that is more prevalent in elderly patients. Those diagnosed have a shorter life expectancy by approximately ten years. Individuals who are not diagnosed early have a much poorer prognosis of only six months. Therefore, there is great interest in exploring novel therapeutics to increase overall survival of patients.

A Phase III multicentre study that took place from March 2015 to January 2017 evaluated the difference in efficacy between the immunomodulatory drugs lenalidomide and dexamethasone (Rd) versus Rd plus daratumumab (D-Rd). Researchers recruited 737 eligible patients who could not have high-dose chemotherapy or were transplant-ineligible. Patients were given either Rd or D-Rd in a randomised 1:1 ratio in cycles of 28 days. The doses of Rd were the same in both groups (R: 25 mg; d: 40 mg); patients receiving D-Rd were given an additional 16 mg of daratumumab. The results showed that in patients receiving D-Rd there was a 44% decrease in the risk of disease progression and death after treatment compared with Rd alone. Further to this, 32% of patients in the D-Rd group had a significant reduction in risk of death compared to the Rd group.

"D-Rd significantly improved overall survival and response rate (93% versus 82%) compared to Rd alone."

5-year overall survival was higher in the D-Rd group (66.3%) in comparison to the Rd group (53.1%). Interestingly, the overall survival rate was maintained, with a 47% reduction in disease progression or death (hazard ratio: 0.53; 95% confidence interval: 0.43–0.66; p<0.0001). Adverse events reported were similar in both groups and there were no new safety concerns.

The researchers concluded that there was greater treatment efficacy when daratumumab was added to Rd. The promising data showed that D-Rd significantly improved overall survival and response rate (93% versus 82%) compared to Rd alone. The next steps could involve considering how to achieve the same desirable outcomes with fewer moderate-severe adverse events. Nonetheless, this research allows us to be optimistic for future treatment for patients with MM. ■

Terbutaline and Restoration of T Helper Cell Dysregulation in Immune Thrombocytopenia

IMMUNE thrombocytopenia is an autoimmune pathology characterised by a low platelet count. Dysregulation of T helper (Th) cells, specifically the Th1 and Th17 subsets, plays a central role and is associated with the production of autoantibodies against platelets. Recent studies showed that the β2-adrenergic receptor (β2-AR) is the primary adrenergic receptor on immune cells. Furthermore, the nervous system was found to directly modulate Th cell polarisation. For this reason, Xiao-Hui Zhang, Peking University People's Hospital, Beijing, China, and collaborators explored the regulation of the sympathetic nervous system on Th cell polarisation and the role of β2-AR signalling in immune cell development and pathways during immune thrombocytopenia. The results of this study were presented during the Presidential Symposium at this year's EHA 2021, 9th–17th June 2021.

Using 6-hydroxydopamine, the researchers chemically depleted the sympathetic nerves in an active immune thrombocytopenia mouse model. Sympathectomised mice displayed a significantly longer platelet recovery time, lower survival, and expressed more Th1 genes compared with non-sympathectomised mice. Subsequent injection of terbutaline, a β2-AR agonist, stimulated β2-AR signalling and improved platelet counts in both groups of mice. Moreover, terbutaline also restored the immune imbalance of Th cells to control levels.

Finally, peripheral blood mononuclear cells, isolated from people with immune thrombocytopenia, were treated with terbutaline. Treatment of these cells with the β2-AR agonist had no effect on the proliferation of $CD4^+$ or $CD8^+$ T cells. Notably, stimulation of these cells with terbutaline inhibited the differentiation of Th1 cells while promoting the differentiation of Th2 and regulatory T cells.

In conclusion, impaired sympathetic innervation and Th dysregulation is crucial for driving the pathogenesis of immune thrombocytopenia. However, this can be reversed by terbutaline administration, which potentially represents a novel therapeutic approach for the treatment of this blood disorder. ■

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Pegcetacoplan Shows Sustainable Promise in Paroxysmal Nocturnal Haemoglobinuria

A PHASE III study spanning 48 weeks has demonstrated favourable results for pegcetacoplan as a therapeutic option for treating paroxysmal nocturnal haemoglobinuria (PNH). This haematopoietic stem cell disorder has previously been combatted using eculizumab, which was found to produce lower haemoglobin (Hb) levels in a randomised controlled study compared to pegcetacoplan. The findings of the study from the University of Paris, France, were shared at EHA 2021 and in a press release from the congress dated 12th June 2021.

Split into two branches of treatment, the study included adults with PNH and haemoglobin <10.5 g/dL after stable treatment with eculizumab for 3 months. A 4-week run-in period was followed by 16 weeks of monotherapy, randomised to either pegcetacoplan (41 participants) or eculizumab (39 participants). A further 32 weeks of open-label pegcetacoplan treatment was then prescribed for all participants, and notably patients switching at this stage displayed improved Hb levels at Week 48. Clinical parameters also improved in this switched group, with 75% remaining free from transfusion, comparable to the unswitched pegcetacoplan arm.

Overall, patients with a suboptimal response to eculizumab experienced a durable improvement when switched to pegcetacoplan. However, It should be mentioned that 6% of participants experienced adverse events possibly related to pegcetacoplan and 15% discontinued treatment as a result of this. Further study will focus on methods to reduce these treatment-emergent adverse events.

The study findings are positive for prevention of anaemia in PNH, especially as 72% of eculizumab-treated patients currently experience chronic anaemia and 36% require at least one blood transfusion per year. Following these positive findings, more countries may follow in the footsteps of the USA in approving pegcetacoplan for the treatment of PNH in adults. ■

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Juvenile Haemochromatosis Caused by Mutations in the *PIGA* Gene

HEREDITARY haemochromatosis, a condition characterised by enhanced gastrointestinal iron absorption, is the most common genetic disorder among the Caucasian population. If untreated, excess iron deposition causes multiple organ dysfunction in ageing patients. In addition to the late-onset adult form of haemochromatosis, rare subtypes have been described with severe iron overload in children. Oriana Marques, Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University, Germany, and colleagues have found a novel subtype of juvenile haemochromatosis resulting from mutations in the *phosphatidylinositol glycan class A* (*PIGA*) gene, which encodes a protein involved in the biosynthesis of glycosylphosphatidylinositol (GPI) lipid anchors. The research findings were shared during the Presidential Symposium at EHA 2021, 9th–17th June 2021.

Initially, three juvenile patients with neurological deficits were diagnosed with systemic iron overload and *PIGA* mutations. To further investigate the pathomechanism associated with iron accumulation, the researchers applied CRISPR/Cas-mediated gene deletion of *PIGA* in a liver cell line. *PIGA* deletion was found to prevent cell membrane attachment of haemojuvelin, which facilitates the formation of an active bone morphogenetic receptor complex that signals to increase hepcidin, the key regulator of systemic iron homeostasis. Therefore, a lack of *PIGA* reduces hepcidin levels and ultimately causes the body to store excess iron. Moreover, ceruloplasmin, a ferroxidase involved in cellular iron export, is also GPI-anchored. Consequently, *PIGA* depletion will substantially decrease ceruloplasmin to enhance intracellular iron accumulation and exacerbate the iron overload.

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These results identify not only a novel form of juvenile hereditary haemochromatosis but also its underlying molecular mechanism. The function of two GPI-anchored proteins, haemojuvelin and ceruloplasmin, involved in maintaining iron homeostasis, is impaired in patients with germline *PIGA* mutations. Identifying these mutations may allow for clinical assessment of potential and future iron overload in affected individuals. ■

Comparison of Zanubrutinib to Ibrutinib Uncovers Improved Treatment Profile

HARNESSED to treat chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL), zanubrutinib has demonstrated a more selective inhibition of bruton tyrosine kinase (BTK) to achieve improved safety and efficacy, compared to ibrutinib. At EHA 2021, Peter Hillmen, St James's University Hospital, Leeds, UK, shared the findings of a Phase III randomised controlled trial, the ALPINE study, in a press release dated 11th June 2021, revealing that zanubrutinib significantly outperformed ibrutinib with relation to response rates, survival rates, and safety outcomes.

For a cohort of 415 patients with CLL/SLL, with inclusion criteria including lymphadenopathy on CT or MRI, analysis at 12 months highlighted an overall response rate of 78% with zanubrutinib but only 63% with ibrutinib. Intervention groups received either 160 mg zanubrutinib twice daily or 420 mg ibrutinib once daily. Concerning safety, zanubrutinib performed better than ibrutinib in terms of episodes of atrial fibrillation, major bleeding, and adverse events leading to discontinuation, as well as demonstrated a more selective and efficacious inhibition of BTK.

The only areas in which ibrutinib remained superior were with the ease of taking one dose per day and the rate of neutropenia (zanubrutinib: 28%; versus ibrutinib: 22%). Improved response rates, progression-free survival, and lower rates of atrial flutter support that zanubrutinib offers a superior treatment to patients with CLL and SLL.

These findings present an exciting development in the ongoing challenge of addressing B cell malignancies. While inbrutinib is currently considered first-in-class for CLL/SLL and is approved for use in >80 countries, these data prompt future consideration for the role of zanubrutinib in further research and clinical practice. ■

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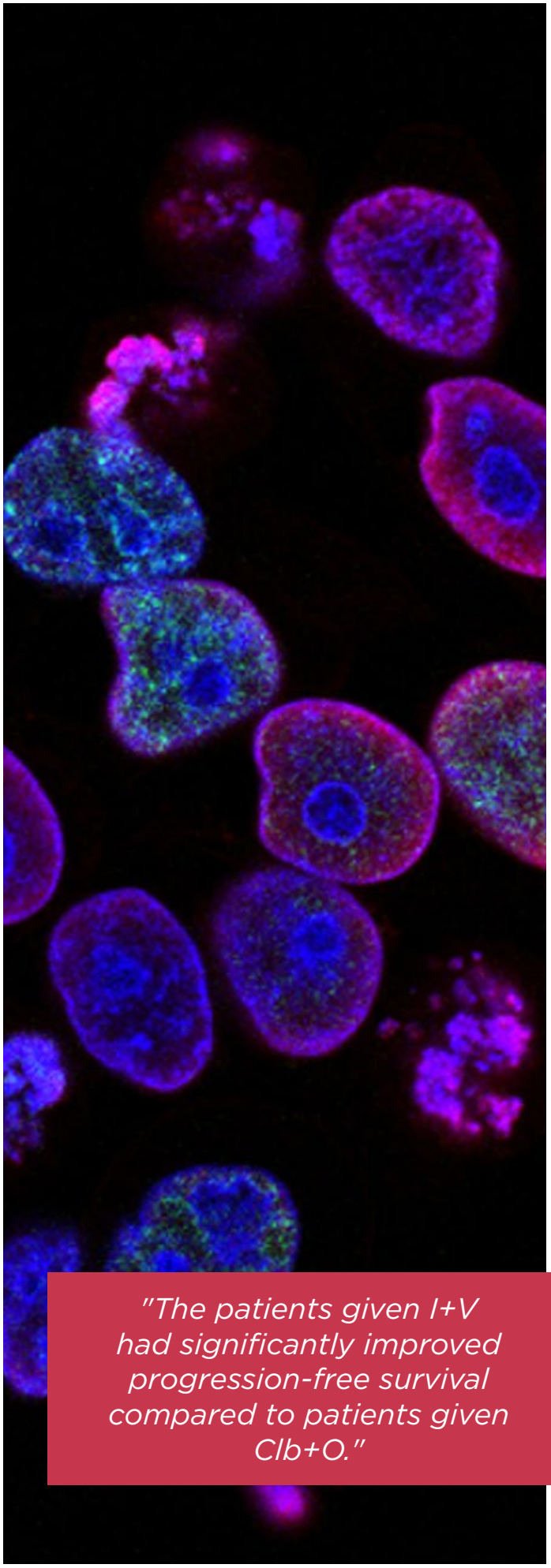
Improved Overall Survival in Patients Taking Ibrutinib and Venetoclax

CHRONIC lymphocytic leukaemia (CLL) is a serious cancer that causes the over-production of white blood cells, namely lymphocytes. This cancer predominately affects middle-aged and elderly patients. Symptoms include fatigue, shortness of breath, and repeated infections. CLL has a poor prognosis: 2–3 years life expectancy after diagnosis. Therefore, there is an urgent need to improve therapeutics and progression-free survival.

Arnon Kater, Amsterdam Medical Center, University of Amsterdam, the Netherlands, shared the findings of a recent clinical trial at EHA 2021 in a press release dated 12th June 2021. The study evaluated the combination of ibrutinib and venetoclax (I+V) compared with combined chlorambucil and obinutuzumab (Clb+O). Researchers predicted the former combination would produce promising results due to their complementary mechanisms: ibrutinib prevents the mobility of CLL cells and venetoclax then destroys the immobilised circulating cancer cells.

Researchers recruited 211 eligible patients who were then either treated with I+V or Clb+O in a randomised 1:1 ratio with a 27.7 month follow-up. The patients given I+V had significantly improved progression-free survival compared to patients given Clb+O. Further to this, the study found the rate of undetectable minimal residual disease in bone marrow and blood examination was significantly higher in patients receiving I+V, which could suggest that there are fewer circulating cancer cells in I+V patients. Furthermore, 84.5% of I+V patients went on to maintain this low rate of minimal residual disease.

These results suggest that a careful combination of inhibitors could improve prognosis and overall survival in CLL. Future research with a larger sample size could reinforce these results, and may evaluate other combinations of inhibitors that may be equally effective with fewer adverse events. ■



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Luspatercept for Anaemia in Non-transfusion-dependent β-Thalassaemia

COMPROMISED production of haemoglobin results from an inherited blood disorder in non-transfusion-dependent (NDT) β-thalassaemia. This disorder presents with mild–moderate chronic anaemia and iron overload, which could lead to the development of serious morbidities in several organs and reduced quality of life, regardless of transfusion-dependence. Currently, there are no therapies approved for the treatment of anaemia in NTD β-thalassaemia. However, a new study suggests luspatercept, an approved treatment of anaemia in transfusion-dependent β-thalassaemia, could be useful for patients diagnosed with NTD β-thalassaemia. The results of the BEYOND study, a randomised, double-blind, placebo-controlled Phase II study that enrolled 145 patients diagnosed with NTD β-thalassaemia, was presented by Ali Taher, American University of Beirut Medical Center, Lebanon, at the EHA 2021 congress.

The aim of the study was to compare the effectiveness and safety of luspatercept with placebo in the treatment of NTD β-thalassaemia. All participants received supportive care and were followed to 24 weeks after treatment. Participants treated with luspatercept showed significant improvement, with an increase in the production of haemoglobin and decrease in anaemia compared to the placebo-treated group. Additionally, approximately 90% of the patients treated with luspatercept did not require transfusion throughout the 24-week study. Alongside an increase in haemoglobin in the luspatercept-treated group, it was noted that quality of life improved, with reduced clinical symptoms associated with anaemia such as fatigue and weakness.

The occurrence of adverse events caused by the treatment were comparable between the luspatercept and placebo groups, and there were no thromboembolic or thrombophlebitis incidents during the trial. Overall, luspatercept was found to be safe and effective over the 24-week study and demonstrated significant improvements for anaemia and anaemia-associated symptoms in NTD β-thalassaemia. ■

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