EHA 2023

Review of the 28th Annual Congress of the European Hematology Association (EHA)

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MALIGNANT haematology and haemoglobinopathies were among the themes of the 28th Annual Congress of the European Hematology Association (EHA), which aims to "elevate progress towards a cure for all blood disorders." In the welcome speech, Elizabeth Macintyre, EHA President, recognised the balanced representation EHA was proud to showcase at this meeting, in the forms of diversity, equity, and inclusion, as well as a hybrid attendance model.

As artificial intelligence continues to play a greater role in modern healthcare, Macintyre fittingly joked that they had written their speech using the famous ChatGPT (OpenAI, San Francisco, California, USA) software. Macintyre was joined by Konstanze Döhner, EHA President Elect and Scientific Committee Chair, to open the annual meeting taking place between the 8th–11th June 2023, in the vibrant city of Frankfurt, Germany.

Located by the River Main, a major financial hub in central Germany, this city provided the perfect setting for a community of haematologists to gather and exchange knowledge in order to "ignite the spark of innovation that drives our profession," as Macintyre put it. Frankfurt's Römerberg Square, famous for hosting bustling Christmas markets, is a short trip on the subway from Messe Frankfurt, one of the largest trade fairs in the world, where EHA 2023 took place.

Döhner introduced the scientific programme available for attendees to access, hoping that it proved both "stimulating and enriching." They drew attention to the YoungEHA and poster sessions as particular highlights, stating: "Together we have created an extraordinary platform," covering a broad spectrum of the specialty, and filled with "a balance of benign and malignant haematology." Alongside these, EHA2023 was packed with over 180 sessions, including debates, workshops, and symposia, ranging in intimacy from large auditorium presentations to smaller case discussions, and spotlight talks featuring speakers from most continents in the world. There were more than 15,000 registrations for this event, and a comprehensive abstract programme was selected, comprising over 2,750 oral and poster presentations combined.

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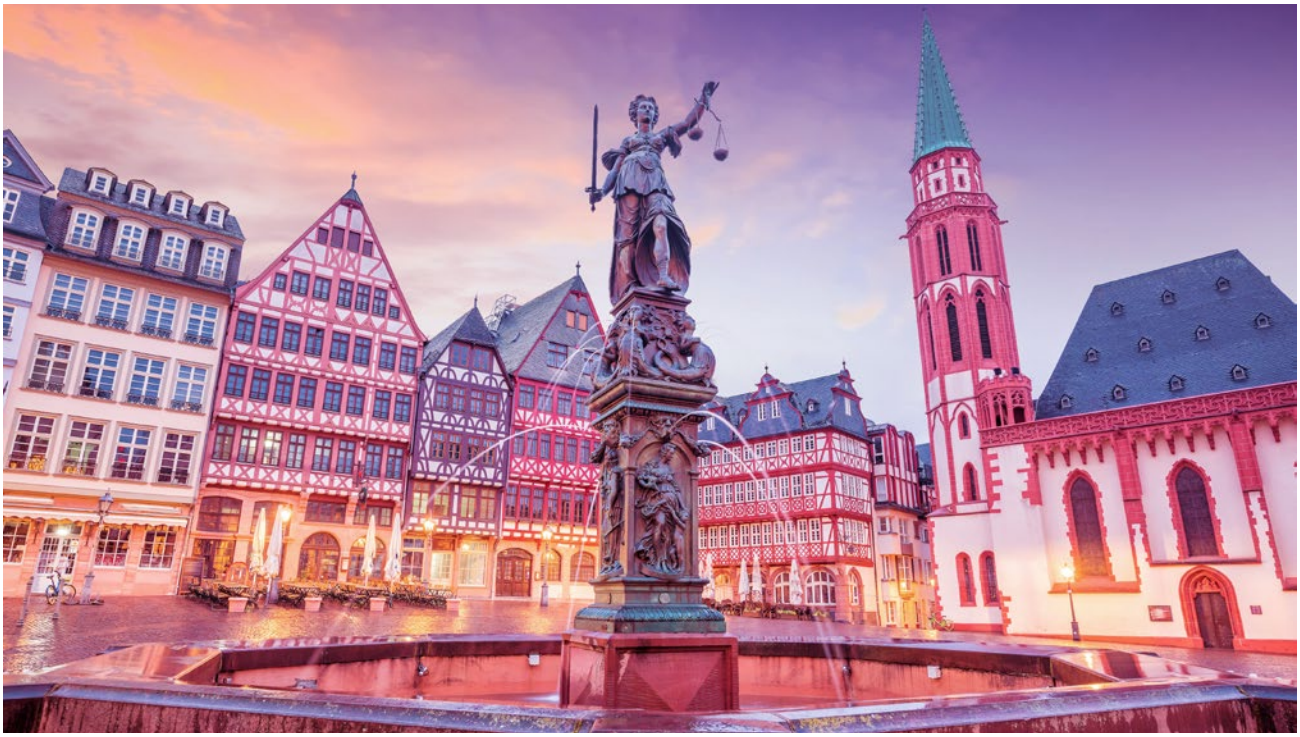

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Jean-Pierre Bourquin, Chair of EHA Fellowship and Grant Committee, was on hand to introduce the 34 researchers from 13 different countries who were awarded EHA Research Grants for their outstanding proposals, more than half of whom were female candidates. These included the Physician Scientists' Research Grant, which was awarded to Jana Ellegast, University Hospital Zürich, Switzerland, and the Topic-in-Focus Research Grants that went to Alkmini Anastasiadi, University of Patras, Greece, and Annamaria Aprile, Fondazione Telethon ETS, Italy, for their projects on haemoglobinopathies. Kick-Off Grants were given to support the initiation of novel concepts, alongside Research Mobility Grants. The coveted Education and Mentoring Award was credited to Gianluca Gaidano, University of Eastern Piedmont, Italy. The David Grimwade Award honouring basic and translational haematology research was given posthumously to Pieter van Vlierberghe, Ghent University, Belgium, who sadly passed away in early 2023. Van Vlierberghe's wife accepted the award on their behalf and gave an emotional speech. A long-time collaborator with van Vlierberghe, Steven Goossens, Ghent University, Belgium, presented some of the work from their research group in an honorary lecture on T cell acute lymphoblastic leukaemia. The José Carreras Award was accepted by Robin Foà, Sapienze University, Rome, Italy, delivering their honorary lecture on Philadelphia chromosome-positive acute lymphoblastic leukaemia.

In one of the final sessions of the in-person congress sessions, António Almeida, Hospital da Luz, Lisbon, Portugal, took over from Macintyre as EHA President, and will guide the association as it focuses now on the EHA2024 meeting that will take place in Madrid, Spain, between the 13th–16th June next year.

This issue of *EMJ Hematology* contains our scientific highlights from the 28th congress of EHA, including a review summarising the cutting edge press releases shared, and abstracts from presenters on topics such as patient blood management and 'haemovigilance', as well as severe haemophilia.

Luspatercept Superior in Treating Anaemia in Lower-Risk Myelodysplastic Syndromes

RESULTS from a Phase III study suggest that patients with lower-risk myelodysplastic syndromes (LR-MDS) suffering from chronic anaemia could benefit from luspatercept therapy. Patients with LR-MDS with chronic anaemia experience iron-overload, increased morbidity, and reduced survival. Furthermore, the current standard of care, erythropoietin-stimulating agents (ESA), produce suboptimal results in these patients. In a pre-planned interim analysis of ESA-naïve patients with LR-MDS, luspatercept demonstrated substantial clinical benefits when compared to the standard treatment, epoetin alfa.

Phase III of the COMMANDS study examined the safety and efficacy of luspatercept and epoetin alfa in 356 ESA-naïve, transfusion-dependent patients with LR-MDS. Primary outcomes investigated during the first 24 weeks include the achievement of red blood cell transfusion independence for ≥12 weeks with a concurrent haemoglobin increase of ≥1.5 g/dL.

Analysis suggested luspatercept outperformed epoetin alfa, as patients treated with luspatercept more commonly achieved red blood cell transfusion independence (59%) than patients treated with epoetin alfa (31%; $p<0.0001$). Further analysis also demonstrated that patients with specific MDS-associated gene mutations, such as *ASXL1*, *SF3B1*, *SF3B1a*, and *TET2*, had superior responses to luspatercept than epoetin alfa. Importantly, luspatercept also exhibited a more favourable safety profile, with patients only reporting mild to moderate treatment-emergent adverse events. These events did not lead to treatment discontinuation, and were generally non-serious. Finally, both treatments resulted in similar overall death rates.

Overall, the results from the COMMANDS study suggest luspatercept may be the more superior treatment option for patients with LR-MDS with anaemia, who require transfusions. Luspatercept's improved outcomes, favourable safety profile, and broad applicability across a range of genetic profiles is encouraging. The research team from Humanitas University and Research Hospital, Milan, Italy, hope these results have the potential to establish a new standard of care for patients with LR-MDS who have not yet received ESAs. ●

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Targeting ADGRE2 and CLEC12A as a Novel Therapy for Acute Myeloid Leukaemia

AT EHA 2023, Sascha Haubner, Memorial Sloan Kettering Cancer Center, New York City, USA, presented promising preclinical outcomes for a novel combinatorial chimeric antigen receptor (CAR) concept called ADCLEC.syn1 for the therapy of acute myeloid leukaemia (AML).

ADCLEC.syn1 utilises cooperative receptors that target *ADGRE2* and *CLEC12A* to efficiently eliminate AML, while minimising haematologic toxicities. This has been demonstrated in a comprehensive series of *in vivo* efficacy and toxicity models, prompting the development of a Phase I clinical trial for ADCLEC.syn1 in AML.

CAR therapies for AML face challenges due to clonal heterogeneity and similarities to normally early haematopoiesis, potentially resulting in antigen escape and haematological toxicities.

Haubner and colleagues performed a quantitative analysis of target expression profiling on the surface of AML and normal tissues to determine therapeutic avenues for novel combinatorial CAR designs. The unique CAR therapy, ADCLEC.syn1, was developed to simultaneously target *ADGRE2* and *CLEC12A* for selective elimination of AML cells with low levels of *ADGRE2*, while preserving normal haematopoietic stem and progenitor cells.

The research team correlated target antigen expression with efficacy and CD33-CAR T cells, using patient-derived or humanised AML xenograft models. This demonstrated a high expression of ADGRE2 and CD33 within the AML fraction enriched for leukaemic stem cells. Comparatively, *ADGRE2* expression was significantly less abundant in normal haematopoietic cells compared with CD33.

ADCLEC.syn1 induced durable remissions in multiple human AML cell line xenograft models representative of phenotypes found in patients with relapsed/refractory AML. A control CD33-CAR also demonstrated effectiveness against AML cell lines in engrafted mice. However, when AML-engrafted mice were reconstituted with normal human haematopoietic cells, only ADCLEC.syn1 exhibited a response, not CD33-CAR. In an AML patient-derived xenograft model, mice treated with CD33-CAR experienced relapse with functional leukaemic stem cells, which were effectively eliminated by ADCLEC.syn1.

The findings emphasise the importance of quantitative CAR target profiling in AML and normal tissues to guide CAR design, and highlight the need for further investigation into how antigen expression on normal bystander cells can impact CAR therapy efficacy. Notably, ADCLEC.syn1 is set to undergo a first-in-human Phase I clinical trial for relapsed/refractory AML. ●

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Combination Therapy Improves Survival Rate in Acute Promyelocytic Leukaemia?

STUDY findings presented at EHA 2023 in Frankfurt, Germany, discussed overall survival (OS) outcomes in patients with acute promyelocytic leukaemia (APL) treated with all-trans retinoic acid and arsenic trioxide (ATRA-ATO) combination therapy.

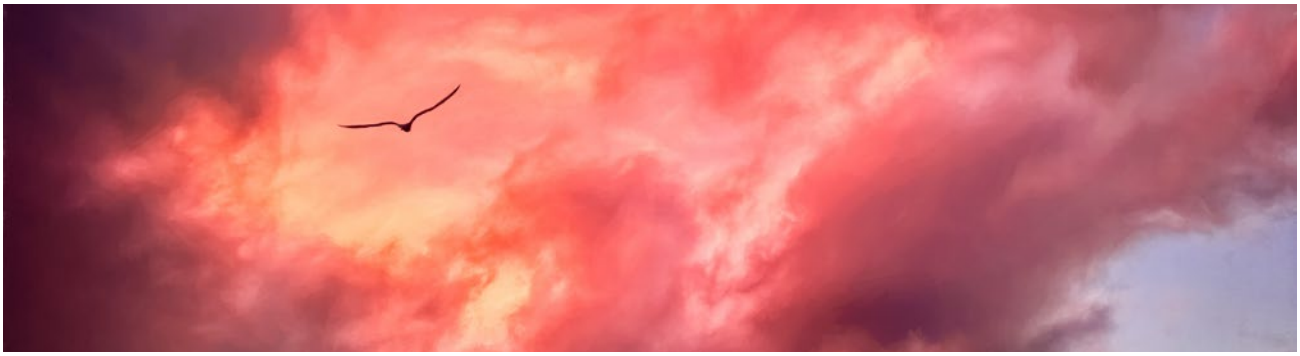
Maria Teresa Voso, Department of Biomedicine and Prevention, University of Rome Tor Vergata, and Neuro-Oncohematology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCSS) Fondazione Santa Lucia, Rome, Italy, and colleagues, used data from the HARMONY registry to retrospectively assess OS in patients with APL treated with chemotherapy-free regimen, ATRA-ATO, compared with those treated with ATRA-idarubicin (AIDA).

The HARMONY registry comprised 1,868 patients with a diagnosis of APL who had been involved in two clinical trials (n=536), UK AML-17 and GIMEMA APL0406, as well as patients with APL from national registries in six countries (n=401) who had received diagnosis between 2007–2020. A total of 937 of these patients met the data quality criteria for inclusion in the study; 380 (40.6%) received ATRA-ATO, 509 (54.3%) received AIDA, and treatment received was not available for 48 patients. The cohort consisted of 483 males (51.5%) and 454 females (48.5%), and the median follow-up was 5.66 years.

Following data analysis, researchers found that 10-year OS rate was significantly improved in patients treated with ATRA-ATO at 92% compared with 75% for those treated with AIDA ($p<0.001$). Despite this, early death rates, defined as death within 30 days of diagnosis, were similar between both groups (3.4–5.7%). Following risk stratification using the Sanz risk score, the survival benefit was seen across risk groups. Additionally, the authors also found that age had a significant role in OS, with patients <50 years of age experiencing better outcomes.

> **"Researchers found that 10-year OS rate was significantly improved in patients treated with ATRA-ATO."**

The researchers concluded that the findings confirm, in a large international cohort, that chemotherapy-free ATRA-ARO combination treatment confers a survival advantage in patients with APL, and that this survival advantage is consistent irrespective of risk profile. In terms of limitations, high-risk patients were under-represented in the analysis, and therefore the findings will need to be confirmed in this cohort in the future.



Effective Treatment Found for Chronic Lymphocytic Leukaemia

A LONG-TERM study has confirmed that an effective treatment for chronic lymphocytic leukaemia (CLL) has been found in venetoclax-obinutuzumab. Researchers from the CLL14 study, a prolonged and groundbreaking investigation into the treatment of CLL, presented updated evidence on long-term outcomes of this drug combination at EHA 2023, held in Frankfurt, Germany, and online.

The aim of the CLL14 study is to investigate the long-term safety and efficacy of fixed-duration B-cell lymphoma 2 inhibition with venetoclax when combined with the CD20 antibody obinutuzumab, in previously untreated patients with CLL. Results showed evidence of sustained efficacy, as well as safety, and potentially pave the way for venetoclax-obinutuzumab to become a preferred therapy option for patients with CLL, including those who have co-existing conditions.

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The study, which is ongoing, included 432 patients with CLL who were previously untreated. The group were randomly assigned either venetoclax-obinutuzumab or chlorambucil-obinutuzumab. After the median follow-up period (76.4 months), venetoclax-obinutuzumab demonstrated higher progression-free survival (PFS) rates in comparison to chlorambucil-obinutuzumab (median PFS: 76.2 versus 36.4 months, respectively), and a significantly longer time-to-next-treatment (6-year time-to-next-treatment: 65.2% versus 37.1%, respectively). Researchers estimated that PFS after 6 years would be 53.1% for venetoclax-obinutuzumab versus 21.7% for chlorambucil-obinutuzumab.

Results were replicated across all risk groups, which included patients who had high-risk characteristics for CLL. Venetoclax-obinutuzumab also showed excellent minimal residual disease response; 7.9% of patients had undetectable levels of minimal residual disease after a 5-year follow-up, compared with 1.9% of patients treated with chlorambucil-obinutuzumab.

The CLL14 study has shown convincing evidence thus far regarding the long-term benefits of using venetoclax-obinutuzumab in patients with CLL, including those who are defined as high-risk. It offers patients high rates of undetectable minimal residual disease, prolonged time-to-next-treatment, and sustained remission; over half of patients treated with venetoclax-obinutuzumab in this study remained in remission for 5 years following treatment completion. The majority of patients also did not require any second-line treatment.

Venetoclax has been approved to treat patients who are previously untreated and who have been diagnosed with CLL or small lymphocytic lymphoma, by the U.S. Food & Drugs Administration (FDA, 2019), and the European Medicines Agency (EMA, 2020). To conclude, researchers believe that a treatment regimen of venetoclax-obinutuzumab for a 1-year period is an effective option for patients with CLL.

Potential One-Time Cure for Patients with Transfusion-Dependent β-Thalassaemia

EXAGAMGLOGENE autotemcel (exa-cel) has potential as a one-time cure for patients with transfusion-dependent β-thalassaemia, according to interim findings presented at EHA 2023. Franco Locatelli, Catholic University of the Sacred Heart, Bambino Gesù Children's Hospital, Rome, Italy, revealed the results of CLIMB THAL-111, a Phase III study.

Exa-cel is a non-viral cell therapy that uses *ex vivo* clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 gene editing. This targets *BCL11A* in autologous CD34⁺ haematopoietic stem and progenitor cells, and reactivates synthesis of foetal haemoglobin.

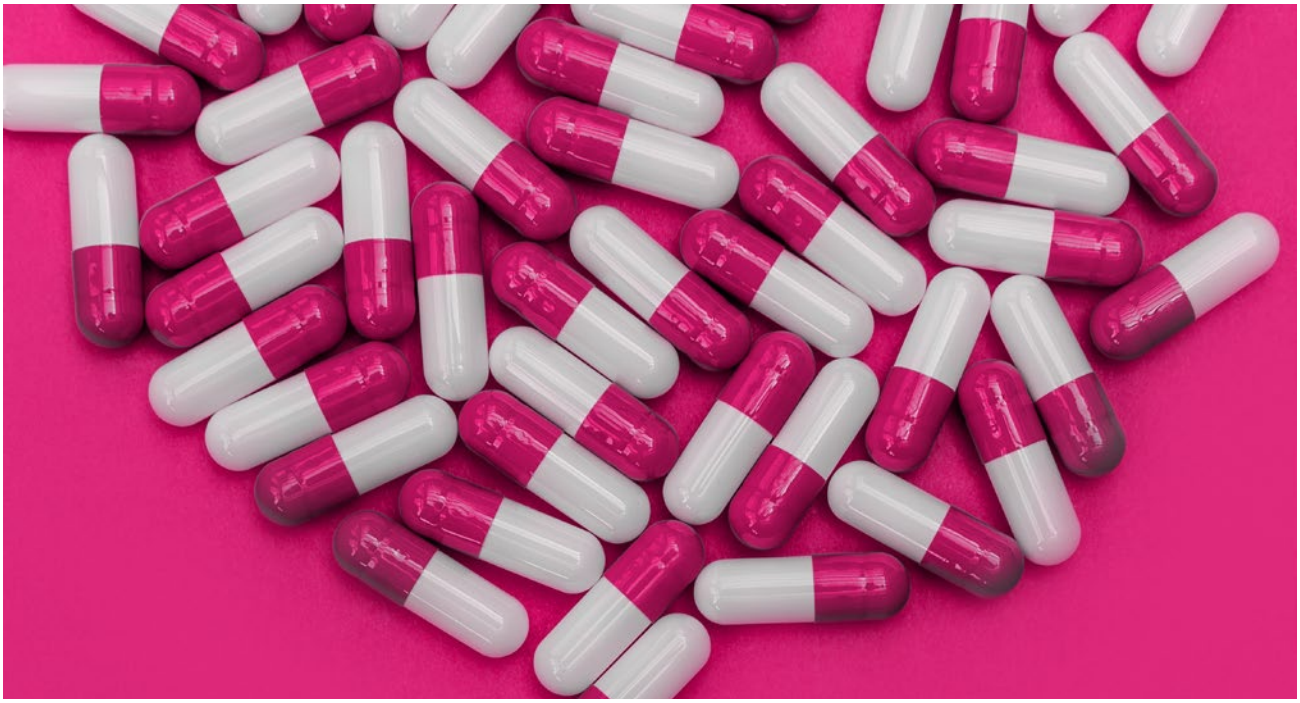
"Only 27 could be evaluated during the pre-specified interim analysis for study endpoints."

While the study included 48 patients with transfusion-dependent β-thalassaemia, only 27 could be evaluated during the pre-specified interim analysis for study endpoints. Of these, 88.9% maintained an average weighted haemoglobin of ≥9 g/dL, without the need of transfusion for ≥12 months. After exa-cel infusion, patients who were transfusion-independent for ≥12.0 months remained transfusion-free for up to 40.7 months, and had a mean time to last transfusion of 37 days.

Edited *BCL11A* alleles in the patients' bone marrow CD34⁺, haemoglobin levels, and peripheral blood nucleated cells remained stable. Furthermore, exa-cel's safety profile proved to be consistent with autologous transplantation procedures and the myeloablative busulfan-based conditioning regime.

No patients discontinued the study or died, all serious adverse events were resolved, and there were no malignancies. Locatelli also reported that the study showed significant improvements in patient quality of life. Moreover, the CLIMB THAL-111 study observed successful neutrophil and platelet engraftments in all patients.

The results of the CLIMB THAL-111 study indicate that exa-cel has potential as a one-time cure for patients with transfusion-dependent β-thalassaemia. It shows that patients can achieve transfusion independence, thus improving their quality of life and haemoglobin levels. This marks a significant advancement in treating transfusion-dependent β-thalassaemia.



Gilterinib Promising as Post-transplant Maintenance Therapy

TREATMENT with tyrosine kinase 3 inhibitor gilteritinib has shown potential as a post-transplant maintenance therapy in patients with acute myeloid leukaemia with an internal tandem duplication mutation of *FLT3*. The MORPHO study, which investigated whether this treatment would improve relapse-free survival, was presented by Mark Levis, John Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, USA, at EHA 2023.

In this Phase III, randomised, double-blind, placebo-controlled trial, participants were randomised to receive either 120 mg of gilteritinib daily for 24 months, or a placebo. The primary endpoint was relapse-free survival, while secondary endpoints included overall survival; graft-versus-host-free relapse-free survival; event-free survival; non-relapse mortality; incidence of infections; acute and chronic graft-versus-host disease; and effect of pre- and post-haematopoietic cell transplantation with detectable measurable residual disease on relapse-free survival and overall survival. Results showed that patients receiving gilteritinib had a higher 2-year relapse-free survival rate (77.2%), compared with the placebo group (69.9%); however, this was not statistically significant (p=0.0518). Overall survival rates were similar in both groups, but in patients with detectable measurable residual disease, gilteritinib had a more pronounced effect, suggesting that the treatment could be beneficial for this population.

There was a higher incidence of treatment-emergent adverse events, such as chronic graft-versus-host disease and myelosuppression, in those treated with gilteritinib, with a higher number of dose interruptions and reductions.

> **"In patients with detectable measurable residual disease, gilteritinib had a more pronounced effect."**

The team concluded that gilteritinib should be a standard-of-care for patients with measurable residual disease pre- or post-haematopoietic cell transplant. These results could improve outcomes for these patients, and aid the challenges of relapse. Further research will need to optimise patient selection and refine treatment protocols. ●