EMJ
European Medical Journal

Volume 13 Supplement 2
May 2025
emjreviews.com

Review of EBMT 2025

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Chiara Nozzoli, Alex Rampotas, Esra Gülderen, Christian Chabannon, and Edoardo Campodonico

Congress Feature:
Minimal Residual Disease: Predicting and Preventing Relapse in Myeloma

Hematology
Supplement

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Aims and Scope

EMJ Hematology is an open access, peer-reviewed eJournal committed to publishing the highest quality medical research concerning all aspects of diseases of the blood and bone marrow to help advance the development of this field.

The journal is published annually, approximately six weeks after the European Hematology Association (EHA) Congress, and features highlights from this congress, alongside interviews with experts in the field, reviews of abstracts presented at the congress, as well as in-depth features on congress sessions. The journal also covers advances within the clinical and pharmaceutical arenas by publishing sponsored content from congress symposia, which is of high educational value for healthcare professionals. This undergoes rigorous quality control checks by independent experts and the in-house editorial team.

EMJ Hematology also publishes peer-reviewed research papers, review articles, and case reports in the field. In addition, the journal welcomes the submission of features and opinion pieces intended to create a discussion around key topics in the field and broaden readers' professional interests. The journal is managed by a dedicated editorial team that adheres to a rigorous double-blind peer-review process, maintains high standards of copy editing, and ensures timely publication.

EMJ Hematology endeavours to increase knowledge, stimulate discussion, and contribute to a better understanding of blood disorders. Our focus is on research that is relevant to healthcare professionals in this field. We do not publish veterinary science papers or laboratory studies not linked to patient outcomes. We have a particular interest in topical studies that advance research and inform of coming trends affecting clinical practice in haematology.

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This Publication

Publication Date: May 2025
Online ISSN: 2053-6631

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HEMA NOW

Don’t Miss This Episode

In this must-listen **podcast**, Jonathan Sackier sits down with **Anna Sureda**, President of the **European Society for Blood and Marrow Transplantation (EBMT)** to discuss the **future of blood cancer treatment**.

This episode covers:

- The push for **equitable access** to innovative treatments
- Breakthroughs in **lymphoma therapies**
- The **future of stem cell transplantation**
- Expert **advice for young haematologists**

Anna Sureda
Head of the Clinical Hematology Department, Institut Català d’Oncologia – Hospital Duran i Reynals, Barcelona, Spain

Tune in now

EMJ
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Welcome

Dear Readers,

I am delighted to introduce our coverage of the 51st European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting, a cornerstone event for those working to improve patient outcomes in the field of haematopoietic cell transplantation (HCT) and cellular therapy.

Our review spotlights cutting-edge research updates on a Phase II therapeutic trial in Hodgkin lymphoma, clonal haematopoiesis following HCT in children, and the association between CD19 expression and treatment response in large B cell lymphoma. We also feature several expert interviews with committee members, presenters, and award winners.

> **A cornerstone event for those working to improve patient outcomes in the field of haematopoietic cell transplantation (HCT) and cellular therapy**

Ahead of our 2025 *EMJ Hematology* publication in July, I hope you enjoy this timely insight into the latest breakthroughs in HCT and cellular therapy.

Evgenia Koutsouki
Editor

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EBMT 2025

With over 6,000 attendees, 1,324 submitted abstracts, and representation from 97 countries, this year's congress was a resounding success

Congress Review

Review of the 51st Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT)

Location:	Florence, Italy
Date:	30th March–2nd April 2025
Citation:	EMJ Hematol. 2025;13[Suppl 2]:6-12. https://doi.org/10.33590/emjhematol/IEGI4264

THE 51st Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT) was held this year in the vibrant city of Florence, Italy, from 30th March–2nd April 2025. Renowned for its architectural splendour and rich artistic legacy, Florence provided a stunning and fitting backdrop for this prestigious congress. With over 6,000 attendees, 1,324 submitted abstracts, and representation from 97 countries, this year's congress was a resounding success, further cementing EBMT's role as a global leader in shaping the future of haematopoietic cell transplantation and cellular therapy.

Inside the Fortezza Da Basso Congress, the venue for this year's meeting, there was an undeniable energy as attendees from around the globe gathered. It served as an epicentre for colleagues to connect, collaborate, and engage with the latest research driving innovation in haematology. The opening ceremony, led by the esteemed Congress President, Anna Sureda, Institute Català d'Oncologia – Hospitalet, Barcelona, Spain, included an introduction to the EBMT Patient Advocacy Committee and Nurses Group, followed by a celebratory awards ceremony and several insightful keynote lectures. Sureda extended her heartfelt thanks to the Scientific Committee, speakers, chairs, volunteers, and EBMT team for their unwavering dedication to the congress. She also paid special tribute to Riccardo Saccardi, who sadly passed in 2024: "Riccardo was not only a brilliant clinician and researcher, but also a mentor, a leader, and a deep friend for many of us."

Natasha Bolaños, Lymphoma Coalition, highlighted the ongoing work of the EBMT Patient Advocacy Committee, a group dedicated to keeping EBMT patient-centric as a scientific society. As Bolaños emphasised, patients bring valuable lived expertise that can inform medical innovation, regulatory processes, healthcare programmes, and more. As the President, Michelle Kenyon spoke on behalf of the EBMT Nurses Group, highlighting the vital role nurses play in supporting patients through challenging times. She shared a deeply moving letter from an anonymous patient with acute myeloid leukemia, to their stem cell donor. In it, the patient reflected on the impact of their diagnosis, and the miracle of being matched with a donor. The letter served as a powerful and emotional reminder of the life-saving importance of stem cell transplantation.

Honorary membership was awarded to four individuals as recognition for their dedication to the society and invaluable contributions to haematopoietic stem cell (HSCT) transplantation and cellular therapy. These were Catherine Cordonnier, Henri Mondor University Hospital, Créteil, France; Myriam Labopin, Hospital Saint-Antoine, Paris, France; Nobert Schmitz, Asklepios St. Georg Clinic, Hamburg, Germany; and Gérard Socié, AP-HP Hospital St Louis, Paris, France.

Gianluigi Mancardi, University of Genova, Italy, a long-term colleague and friend of Saccardi, gave a tribute lecture, summarising the instrumental research he and Saccardi conducted into the clinical potential HSCT in multiple sclerosis (MS). The GITMO-NEURO, for example, is a collaborative network of Italian medical centres that investigates the use of autologous HSCT (aHSCT) for MS. A review published in 2017 also concluded that complete suppression of MS activity for 4–5 years has been documented in 70–80% of patients with relapse-remitting MS who have undergone aHSCT.[1] Finally, he spotlighted several promising Phase III trials currently ongoing, including RAM-MS, BEAT-MS, STAR-MS, and NET-MS.

Mancardi also highlighted the decline in transplant-related mortality, which dropped from 5–6% in early cohorts to 1–2% by 2008.[2] This improvement was attributed to several factors, including better patient selection and the growing expertise of both neurologists and haematologists involved in the procedure.

Finally, Franco Locatelli, Director of the Department of Pediatric Hematology and Oncology, IRCCS Ospedale Pediatrico Bambino Gesù Children's Hospital, Rome Italy; and Luigi Naldini, Director, SR-Tiget, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy, each gave an insightful keynote lecture, exploring the journey from bench to bedside for CAR-T cell therapy.

In conclusion, the 51st Annual EBMT Meeting was a powerful reflection of how science, compassion, and collaboration can come together to improve lives. As the field continues to progress, EBMT remains a beacon for innovation and patient-centred care on the global stage.

New Dual Therapy Effective in Hodgkin Lymphoma

PRESENTED by Gunjan L. Shah, Memorial Sloan Kettering Cancer Center, New York, USA, this abstract was awarded the most prestigious EBMT award, the Van Bekkum Award, at the 51st Annual Meeting. It explored a cutting-edge cell therapy combination offering new hope for patients with relapsed or refractory classical Hodgkin lymphoma.[3]

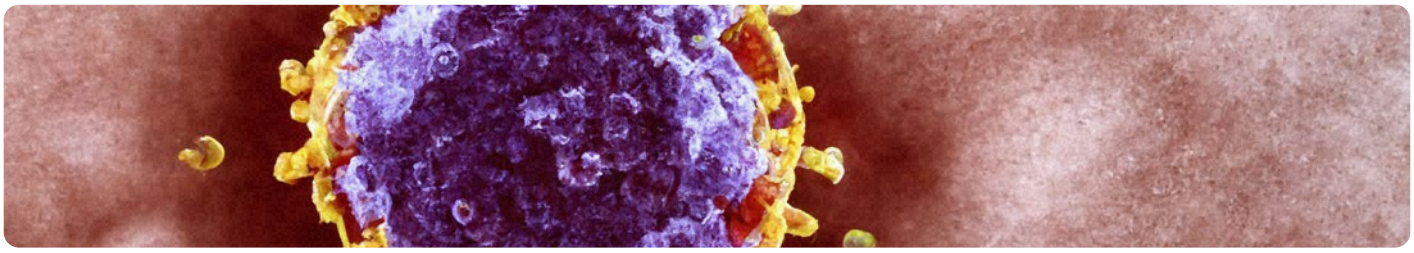
This Phase II study, LuminICE-203, paired acimtamig (AFM13), a bispecific antibody targeting CD30 and CD16A, with AlloNK® (AB-101; Artiva Biotherapeutics, California, USA), a cryopreserved, off-the-shelf natural killer (NK) cell product derived from cord blood. This dual approach is designed to trigger an immune response against CD30+ lymphoma cells in patients who have exhausted standard treatments, including combination chemotherapy, brentuximab vedotin, and programmed cell death protein 1 inhibitors. The primary end point was objective response rate (ORR), with secondary endpoints including safety, tolerability, immunogenicity, complete response rate and duration of response.

The trial enrolled 22 patients in its initial dose-finding phase. These patients, with a median age of 42.5 years and a median of five prior lines of therapy, received varying doses of the drug-cell combination across multiple centres. Treatment was well-tolerated, with no unexpected safety issues and no cases of neurotoxicity or graft-versus-host disease. The most common side effects were mild infusion-related reactions and nausea.

Efficacy results were encouraging. The objective response rate was 86.4%, with more than half of patients (54.5%) achieving a complete response. Notably, responses were seen across all dosing cohorts.

> **Efficacy results were encouraging. The objective response rate was 86.4%, with more than half of patients (54.5%) achieving a complete response**

The researchers emphasised the potential of pairing bispecific antibodies with off-the-shelf NK cell products to provide a scalable and effective treatment for heavily pretreated individuals with classical Hodgkin lymphoma, many of whom currently face limited options. The trial is ongoing, with expansion cohorts now underway to further validate these findings.



Low CD19 Expression Linked to Poor CAR-T Outcomes in Lymphoma

AN INSIGHTFUL study revealed that very low CD19 expression is linked to poor outcomes in patients with large B cell lymphoma treated with CD19-directed CAR-T cell therapy. Presented by Magdalena Corona, Hospital Universitario 12 de Octubre, Madrid, Spain, at the 51st Annual Meeting of EBMT, this study was awarded the prestigious Jian-Jian Award for Lymphoma Transplant Research.[4] It aimed to determine whether genotypic and phenotypic modulation of CD19 influences the efficacy of CD19-directed CAR-T cell therapy in large B cell lymphoma, and whether such modulation remains detectable after treatment.

The research, conducted at a single centre, examined tumour samples from 204 patients with large B cell lymphoma, both before and after CAR-T therapy. A range of advanced techniques were utilised, including flow cytometry, RNA sequencing, and whole-exome sequencing. Researchers categorised patients based on their CD19 expression levels (high, normal/low, and very low) relative to healthy donor B cells.

Flow cytometry, the most commonly used method, showed that 36% of patients had high CD19 levels before CAR-T treatment, while 15% had very low levels. Those with very low CD19 expression were significantly less likely to achieve a complete response (odds ratio: 3.31; 95% CI: 1.02–11.1; p=0.047) and had shorter progression-free survival (PFS).

In a subset of 33 patients, with samples taken before and after treatment, CD19 levels decreased in patients who relapsed after an initial response to CAR-T. However, in those who never responded to CAR-T (primary refractory), CD19 levels remained unchanged. Very low CD19 RNA levels prior to treatment were also linked to shorter PFS compared to normal/high expression. Moreover, gene enrichment analysis identified an inverse relationship between

Gene-set enrichment analysis showed an inverse relationship between CD19 RNA expression and inflammatory pathway expression, notably IFN-γ and IL6-JAK-STAT3. Additionally, DNA analysis showed *CD19* gene gains in some cases but no CD19 mutations, indicating that changes in gene expression, rather than mutation, may play a greater role in resistance.

Additionally, among cases with whole-exome sequencing data (n=63 patients; 58 pre-CAR-T and 15 post-CAR-T samples), *CD19* copy number alterations (primarily gains) were found in 26% of pre-CAR-T samples and 40% of post-CAR-T samples (p=0.3).

In this large single-centre study, reduced CD19 expression, particularly very low levels, was associated with poorer responses and shorter PFS following CD19-directed CAR-T therapy in large B cell lymphoma. These findings suggest that both the level and dynamics of CD19 expression may influence resistance patterns and clinical outcomes.

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Origins of Clonal Blood Mutations After Childhood Transplant

A GROUNDBREAKING study has found that long-term survivors of paediatric haematopoietic cell transplantation (HCT) are significantly more likely to develop clonal haematopoiesis (CH), a condition marked by mutated blood-forming stem cells, than those who have never undergone transplant. It was presented at the 51st Annual Meeting of EBMT by Konradin Müskens, Princess Máxima Center, Utrecht, the Netherlands, and was commended the prestigious Basic Science Award.[5]

Researchers analysed blood samples from 144 long-term (>5 years) paediatric HCT survivors and 258 non-translated controls, discovering that 16% of transplant recipients had detectable CH mutations compared to just 8% of controls. Importantly, larger clones (with higher mutation levels) were only found in the transplant group.

The mutations, most commonly in the *DNMT3A* (80%) and *TET2* (20%) genes, were linked to older stem cell age and the transplant process itself, both of which independently increased CH risk. Using single-cell whole genome sequencing, researchers traced the origins of these mutations, finding they were often present long before transplant, some even as early as during early foetal development.

Interestingly, although CH mutations are often associated with ageing, the mutation patterns in HCT survivors were similar to those seen in normal ageing, rather than caused by transplant-related damage. However, inflammatory events around graft infusion were associated with CH development, highlighting how transplant stress can promote clonal expansion.

Given the long-life expectancy of paediatric HCT survivors, these findings underscore the need for ongoing monitoring and early intervention strategies to manage potential long-term risks linked to CH. The study adds critical insight into how early-life mutations can resurface decades later under selective pressures like transplantation.

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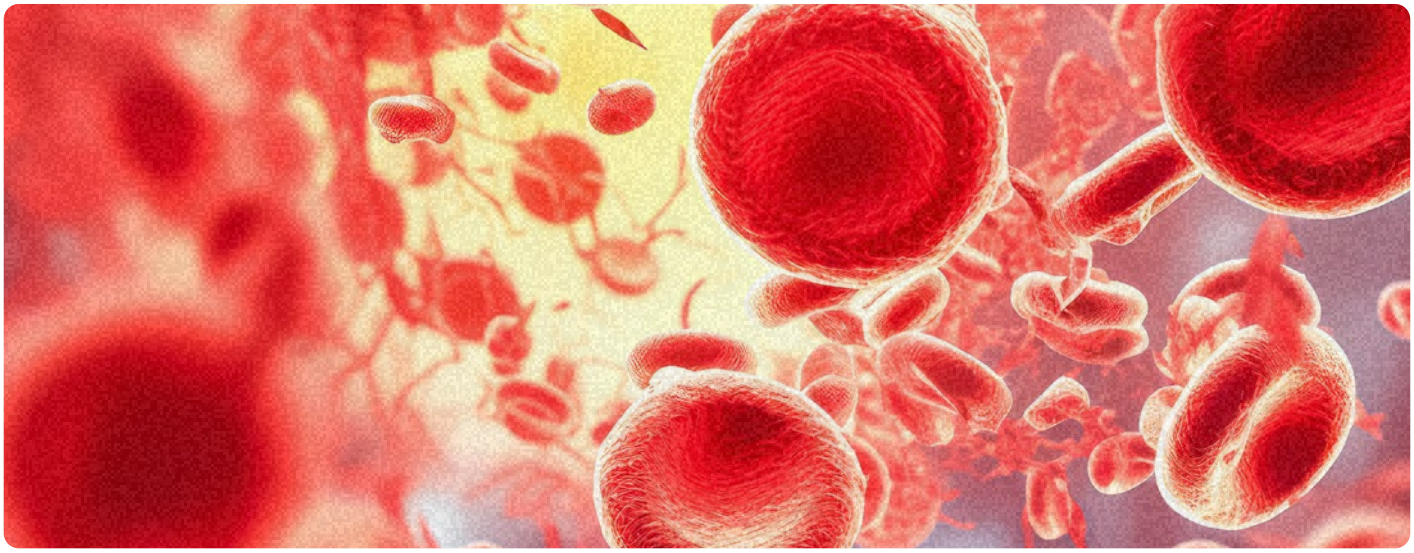

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Minimal Residual Disease: Predicting and Preventing Relapse in Myeloma

Authors: Helena Bradbury, EMJ

Citation: EMJ Hematol. 2025;13[Suppl 2]:13-16. ttps://doi.org/10.33590/emjhematol/ECVO9479

In the evolving landscape of haematologic cancers, the concept of minimal residual disease, also known as measurable residual disease (MRD), has rapidly shifted from a theoretical indicator to a powerful, practice-changing tool. At the forefront of this shift is multiple myeloma (MM), where MRD has emerged as a highly sensitive measure of treatment response and a compelling surrogate marker for long-term outcomes.

MINIMAL RESIDUAL DISEASE AS A SURROGATE MARKER FOR MYELOMA OUTCOMES

Opening this insightful session, Maria-Victoria Mateos, University of Salamanca, Spain, discussed the role of MRD in MM. She initially touched on The International Myeloma Working Group response criteria, a standardised set of parameters used to assess a patient's treatment response for MM. The treatment responses range from stringent complete response to progressive disease. These are based on laboratory values, imaging, and bone marrow analysis.

> **Results showed MRD-CR at 9 or 12 months correlated with longer remission and survival in all groups**

Drawing on her own research published in 2017, Mateos and colleagues evaluated the impact of depth of response in newly diagnosed MM.[1] Data from 609 patients were analysed, with a median follow-up of 71 months. Results showed that MRD-negativity was a stronger prognosis predictor of PFS and OS than complete remission alone. It was therefore recommended that MRD negativity should be a determinant of treatment efficacy and a key goal when treating eligible patients with MM.

With the rise of new treatments and higher complete response rates in MM, the International Myeloma Working Group (IMWG) updated response criteria in 2016 to include MRD negativity.[2] More sensitive techniques, such as flow cytometry, gene sequencing, and imaging were used to define MRD negativity. The IMWG incorporated both next generation flow and next generation sequencing, with studies demonstrating good concordance between the two techniques.[3]

Mateos spotlighted two key initiatives: International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i^{2}TEAMM) and Evaluating Minimal Residual Disease as an Intermediate Clinical Endpoint for Multiple Myeloma (EVIDENCE) Meta-Analysis. i^{2}TEAMM, a collaborative research group advocating for MRD as an early endpoint in clinical trials for MM, published data in 2025. In this analysis, data from over 4,700 patients across 11 clinical trials were analysed to assess MRD-negative complete response (MRD-CR) as an intermediate end point for PFS and OS in three distinct populations: newly diagnosed (ND) transplant-eligible (NDTE), ND transplant-ineligible (NDTinE), and patients with relapsed/refractory MM.[4]

Data from **609 patients** were analysed, with a median follow-up of **71 months**

Results showed MRD-CR at 9 or 12 months correlated with longer remission and survival in all groups.

Similarly, EVIDENCE Meta-Analysis evaluated whether MRD negativity could predict long-term outcomes in MM. Analysing data from 12 randomised trials, eight of which were studies on newly diagnosed multiple myeloma and four of which were studies on relapsed/refractory MM, the findings revealed strong associations between MRD-negativity and improved PFS, supporting its use as an early clinical endpoint to accelerate drug approvals.[5]

Importantly, Mateos offered a balanced perspective by highlighting some current limitations of using MRD as a surrogate endpoint in MM clinical trials. Currently, its acceptance is limited to the USA, where in April 2024 the FDA's Oncologic Drug Advisory Committee (ODAC) endorsed MRD as an acceptable endpoint for accelerated approval. Mateos noted ongoing efforts in Europe to adopt similar regulatory standards. She also emphasised that imaging methods to assess MRD, both inside and outside the bone marrow, are underutilised and should be integrated in future studies. Finally, the concept of sustained MRD negativity remains unexplored. The PERSEUS Phase III trial, evaluating daratumumab plus bortezomib, lenalidomide, and dexamethasone (VRd) in newly diagnosed MM, showed higher rates of sustained MRD negativity (at sensitivities of 10^{-5} and 10^{-6}) compared to the control group.[6,7]

Finally, Mateos cautioned that focusing solely on MRD negativity can overlook important factors such as toxicities and quality of life. She cited the BELLINI study, which tested venetoclax, an oral BCL-2 inhibitor, in combination with bortezomib and dexamethasone in patients with relapsed or refractory MM.[8] Despite improved PFS in the venetoclax group, it also reported a higher mortality rate. Finally, she highlighted that the minimal difference in MRD negative rates between two treatments or therapeutic strategies needed to ensure a (later) significant difference in PFS remains unclear.

MEASURABLE RESIDUAL DISEASE IN MYELOFIBROSIS

Nico Gagelmann, University Medical Center Hamburg-Eppendorf, Germany, subsequently delved into the role of MRD in myelofibrosis (MF), a blood cancer characterised by the abnormal accumulation of scar tissue, or fibrosis in bone marrow.

Gagelmann explored the genetic drivers and molecular pathophysiology of blood cancers, specifically myeloproliferative neoplasms.[9] The most common mutations

"However, when we talk about myelofibrosis, it's always important [to acknowledge] that we don't have only these three mutations"

occur in three driver genes; *JAK2*, calreticulin (*CALR*) and myeloproliferative leukemia virus (*MPL*). "However, when we talk about myelofibrosis, it's always important [to acknowledge] that we don't have only these three mutations," stressed Gagelmann. He pointed to a range of cytogenetic abnormalities and high molecular risk mutations (*IDH1/2, EZH2, DNMT3A, U2AF1, SR5F2, TET2 and ASXL1*), which have been found to have an impact on both overall survival and progression to leukaemia.[9,10]

Quantitative PCR can be used to detect the presence of the three driver mutations (*JAK2*, *CALR,* or *MPL*) in patients with high sensitivity.[11] Drawing on his own research, Gagelmann and colleagues examined mutation clearance post-transplantation in 324 patients with myelofibrosis (73% *JAK2*, 23% *CALR*, 4% *MPL*). Mutations were assessed before transplantation, and at 30-, 100- and 180-days post transplantation. Interestingly, by Day 30, mutation clearance was found in 42% of *JAK2*, 73% of *CALR*, and 54% of *MPL* cases. Moreover, the cumulative incidence of relapse at 1 year was just 6% among patients with mutation clearance at Day 30, compared to 21% in those without.

So, how should we approach relapse? In a 2023 study investigating the effect of donor lymphocyte infusion (DLI) in 37 patients with molecular or haematological relapse after hematopoietic cell transplantation, results showed that molecular monitoring together with DLI allowed for early detection of relapse and was recommended as standard of care for relapsed myelofibrosis after HCT.[11]

TIMING DILEMMAS IN ACUTE MYELOID LEUKAEMIA: MINIMAL RESIDUAL DISEASE MONITORING AND STEM CELL TRANSPLANTATION

To close, Francesco Buccisano, University of Rome Tor Vergata, Italy, spoke on the incorporation of MRD in the different stages of allogeneic stem cell transplantation (allo-SCT). As highlighted by Buccisano, the methods for detection of MRD in acute myeloid leukaemia (AML) have also improved over the last decade.[13] He highlighted how multi-parameter flow cytometry (MFC) can be applied to almost 90% of patients with AML with a fair sensitivity of 10^{-3}–10^{-4}. Real-time quantitative PCR is another established technique, with a higher sensitivity (10^{-4}–10^{-5}) but lower applicability (40–50% of patients with AML) compared to MFC.

Buccisano outlined three key principles for selecting patients with AML for allo-SCT. First, identify those likely to respond well to chemotherapy alone to avoid overtreatment. Second, recognise patients with poor chemotherapy outcomes who would benefit from allo-SCT. Finally, ensure transplantation is feasible by assessing whether it can be performed, and the risk of morbidity and mortality is acceptable.

Data from over **4,700 patients** across **11 clinical trials** were analysed to assess MRD-negative complete response (MRD-CR) as an intermediate end point for PFS and OS

Notably, he discussed the role of MRD and novel agents at different stages of the treatment pathway in AML. Buccisano discussed the strategic use of MRD assessment throughout the allogeneic stem cell transplant process; pre-transplant, peri-transplant, and during post-transplant follow-up. While acknowledging the absence of randomised controlled trials due to ethical concerns around withholding transplants from patient who are MRD-positive, he presented data from hybrid study designs and large cohort analyses.

MRD positivity before transplant is consistently shown to be a strong predictor of relapse and poorer survival. Trials such as FIGARO attempted to intensify conditioning regimens in MRD-positive patients, but failed to improve outcomes, reinforcing the importance of MRD as a prognostic marker.[14] Importantly, the immunological environment, including T cell chimerism, can influence the impact of MRD, suggesting that graft-versus-leukaemia effects play a significant role in disease control.[13]

> **MRD has shown to be a practical, prognostic, and increasingly regulatory tool in multiple myeloma and beyond**

Guidelines increasingly support the use of intensive conditioning for MRD-positive patients and advocate for tailored maintenance strategies post-transplant. Data from a study published in 2025 also demonstrated that MRD positivity before transplant predicts relapse, even in patients who appear MRD-negative at day 100 post-transplant.[15] This highlights the potential benefit of early intervention and maintenance therapy, such as sorafenib, which has shown efficacy in both MRD-negative and MRD-positive settings.

Although the MORPHO trial did not meet its primary endpoint, it supported the use of MRD as both a prognostic and predictive biomarker, particularly for guiding targeted therapies like gilteritinib.[16] Concluding his talk, Buccisano emphasised that MRD assessment, combined with genetic profiling, should guide risk stratification and treatment planning.

CONCLUSION

MRD has shown to be a practical, prognostic, and increasingly regulatory tool in multiple myeloma and beyond. As shown across studies and trials, achieving MRD negativity strongly correlates with better outcomes, offering a clearer path to tailored treatment and earlier decision-making. While challenges remain, its growing role signals a shift toward more precise, response-driven care in haematologic cancers.

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Efficacy and Safety of Tabelecleucel in Epstein-Barr Virus-Associated Relapsed/Refractory Post-Transplant Lymphoproliferative Disease: Update From the Phase III ALLELE Study

This oral presentation took place on 2nd April 2025 as part of the EBMT 51st Annual Meeting held in Florence, Italy.

Co-chairs:	Edoardo Campodonico,[1] Annalisa Ruggeri[2]
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Disclosure:	Chaganti has received honoraria for advisory boards/consultancy from Kite-Gilead, Roche, Abbvie, Pierre Fabre, BMS-Celgene, Amgen, Sobi, and Autolus; speaker fees from Takeda, Kite-Gilead, Incyte, Pierre Fabre, and Roche; and meeting attendance support from Takeda, Kite-Gilead, Abbvie, and Pierre Fabre.
Disclaimer:	The ALLELE study was sponsored by ATARA Biotherapeutics. Prescribing information and adverse events reporting for Ebvallo (tabelecleucel) for UK HCPs can be found here. For those outside the UK please refer to your local country of practice. AE reporting information can be found at the bottom of this article.
Keywords:	Epstein-Barr virus (EBV), haematopoietic stem cell transplantation, lymphoproliferative diseases, organ transplantation, post-transplant complications, post-transplant lymphoproliferative disease (PTLD), tabelecleucel.
Citation:	EMJ Hematol. 2025;13[Suppl 2]:17-21. https://doi.org/10.33590/emjhematol/ANPO6479
Support:	**The publication of this article was supported by Pierre Fabre.**

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Presentation Summary

This presentation was part of the 'CAR-T and other cell therapies' oral presentation session of the EBMT 51st Annual Meeting, held in Florence, Italy on 2nd April. Sridhar Chaganti, Consultant Haemato-oncologist at University Hospital Birmingham, UK, presented updated results from the ongoing Phase III ALLELE trial evaluating the safety and efficacy of tabelecleucel, an off-the-shelf allogeneic T cell immunotherapy, in relapsed/refractory Epstein-Barr virus (EBV)-positive post-transplant lymphoproliferative disease (PTLD). In this latest analysis in a total of 75 patients, the overall response rate (ORR) in recipients of hematopoietic cell transplant (HCT) or solid

organ transplants (SOT) was 50.7%, with median response duration of 23 months and a 12-month overall survival (OS) rate of 78.7% in responders. Tabelecleucel was well tolerated, with no cases of tabelecleucel-related graft-versus-host disease or organ rejection reported.

The Phase III ALLELE Study of Tabelecleucel in Relapsed/Refractory Epstein-Barr Virus + Post-Transplant Lymphoproliferative Disease

PTLDs are a serious complication in patients who have received allogeneic HCT or SOT. They are frequently caused by the presence of EBV that resides in B lymphocytes and can cause uncontrolled B cell proliferation.[1] Current treatments for EBV+ PTLD include a reduction in immunosuppression (RIS) and treatment with anti-CD20 antibody (rituximab) with or without chemotherapy.[1] However, the response rates to these treatments are variable, and in patients with EBV+ PTLD who do not respond, the median OS rates are 0.7 months for those receiving HCT and 4.1 months after SOT.[1] There is an urgent unmet need for new treatment options for this patient population.

Tabelecleucel is an off-the-shelf, non-genetically modified, allogeneic, EBV-specific cytotoxic T cell immunotherapy that targets and eliminates EBV-infected cells in an HLA-restricted manner and has been investigated for multiple EBV-associated malignancies.[2] Tabelecleucel is manufactured from unrelated healthy donor T cells, enriched to recognise EBV antigens, characterised by their HLA restriction and cryo-preserved in a biobank. Each product includes a polyclonal population of highly specific anti-EBV T cells capable of recognizing different EBV-derived peptides: HLA combinations presented on the surface of the infected tumour target cells (HLA restriction). For each patient, a tabelecleucel lot is selected based on an appropriate HLA restriction and matching to optimise anti-tumour activity and recipient compatibility, with the potential to switch lots up to four times if no response is obtained.

The ALLELE study is an ongoing, global, Phase III multicentre, open-label trial investigating the efficacy and safety of tabelecleucel after failure of rituximab ± chemotherapy in patients with EBV+ PTLD following HCT or SOT. Previously reported results from 43 patients (14 HCT; 29 SOT) suggest that tabeleleucel was well tolerated and showed an objective response rate of 50% in the HCT group and 52% in the SOT group.[3] Based on these data, tabelecleucel was approved in Europe in 2022.[4]

Updated Results from the ALLELE Trial

During this oral presentation, Chaganti presented the updated results on efficacy and safety from a larger cohort of 75 EBV+ PTLD patients who have now been treated, 26 post-HCT and 49 post-SOT. They outlined the key eligibility criteria for patients recruited to ALLELE who had a biopsy-proven EBV+ PTLD, had failed treatment with rituximab or rituximab and chemotherapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤3. The primary endpoint of the trial was ORR, and key secondary endpoints were time to response (TTR) and time to best response, overall survival (OS) in responders versus non-responders, progression-free survival (PFS) in responders, and rates of allograft loss/rejection episodes (SOT).

Tabelecleucel was administered in cycles that lasted 5 weeks each, during which patients received intravenous administration of the product at a dose of 2×10^6 T cells/kg patient body weight on Days 1, 8, and 15, with 1-hour monitoring post-injection. Chaganti explained that there was no requirement for pre-medication or lymphodepletion, and most patients received tabalecleucel in the outpatient setting.

Response assessments were performed in Week 5. Patients were allowed to continue with further cycles, and depending on their response, had the option of switching to a different HLA restriction product lot.

Chaganti presented the baseline characteristics of the 75 patients who had been enrolled into the ALLELE study at the cut-off date. Patients' median age was 44 years (range 2–81 years). Overall, 26.5% of patients had an ECOG score ≥2 and a majority had extranodal disease at screening (74.7%). Almost all (92.6%) had an intermediate- or high-risk PTLD prognostic score. Most (69.3%) had PTLD of diffuse large B cell lymphoma morphology.

The median number of previous lines of therapy was one (range 1–5). Of 26 patients in the HCT cohort, all of them had failed prior rituximab treatment and four patients had previously received chemotherapy. There were 49 patients in the SOT cohort, of which 79.6% had already received rituximab and 57.1% had received rituximab and chemotherapy. SOT types included kidney, heart, lung, liver, and multivisceral.

Patients received a median of two cycles of tabelecleucel and had a median treatment duration of 1.9 months. A majority of infusions were carried out in the outpatient setting, with 65.3% of patients receiving one product lot, 30.7% receiving two product lots with different HLA restrictions, and 4% receiving three product lots.

Chaganti went on to present the updated primary endpoint of ORR, which was 50.7% across both HCT and SOT cohorts (38 of 75 patients; Figure 1). Of these 38 patients, 21 (28%) had a complete response and 17 (22.7%) had a partial response (Figure 1). The median duration of response was 23 months and the median time to response was 1.1 months.

Moving on to secondary endpoints, the proportion of responders with PFS at 12 months was 71.9%, and the median PFS among responders of nearly 2 years (23.9 months; Figure 2).

At a median follow-up of 9 months, the 12-month OS was 55.7% for all patients treated and 78.7% for responders to tabelecleucel compared to 28.2% in non-responders (Figure 3). The median OS for all patients was 18.4 months, but this was not evaluable for responders.

Treatment-emergent serious adverse events were not infrequent in this population, but treatment-related serious adverse events were uncommon. There were no reports of infusion-related reactions, immune effector cell-associated neurotoxicity syndrome, tumour flare reaction, cytokine release syndrome immunogenicity, or infection disease transmission. There were three reports of organ rejection in the SOT group, but these were not considered to be related to tabelecleucel.

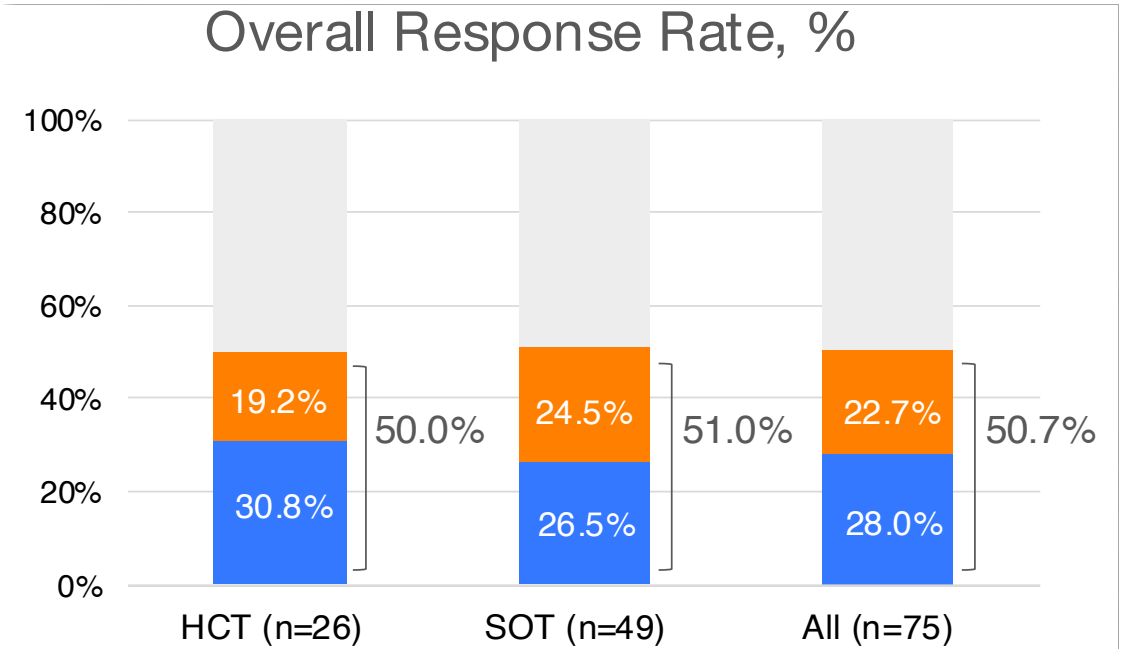
Post-Presentation Question and Answer

Following the presentation, co-chair Campodonico said the study provided 'food for thought' for other EBV-positive diseases. They asked whether there was a difference in ORR between HCT and SOT recipients. Chaganti confirmed that they did not find any difference. The ORR was 50% for patients who received HCT and 51% for patients who received SOT (Figure 1).

Conclusion

In their conclusion, Chaganti summarised that these updated data from the ALLELE study confirm the previously reported benefit of tabelecleucel in relapsed/refractory EBV+ PTLD. They added that tabelecleucel had a promising ORR and OS in this difficult-to-treat patient population and responses were durable, with a median response duration of 23 months. The treatment appeared to be well tolerated, with most treatment-emergent serious adverse events unrelated to tabelecleucel.

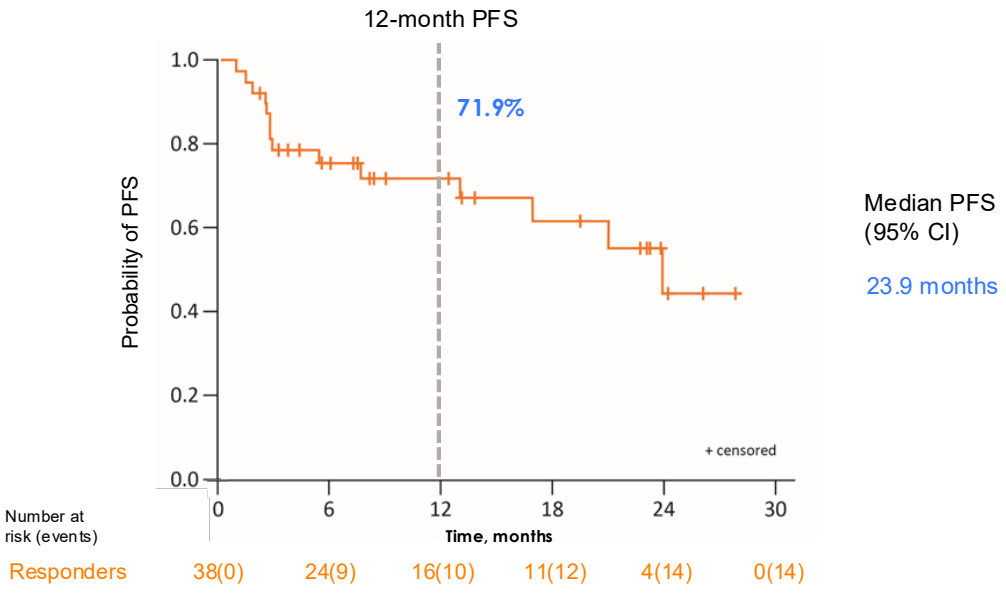
Figure 1: Overall response rate to tabelecleucel assessed per Lugano classification with Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) modification by independent oncologic response adjudication.



Data cutoff date: 9th October 2023.

CR: complete response; HCT hematopoietic cell transplant; PR: partial response; SOT: solid organ transplant.

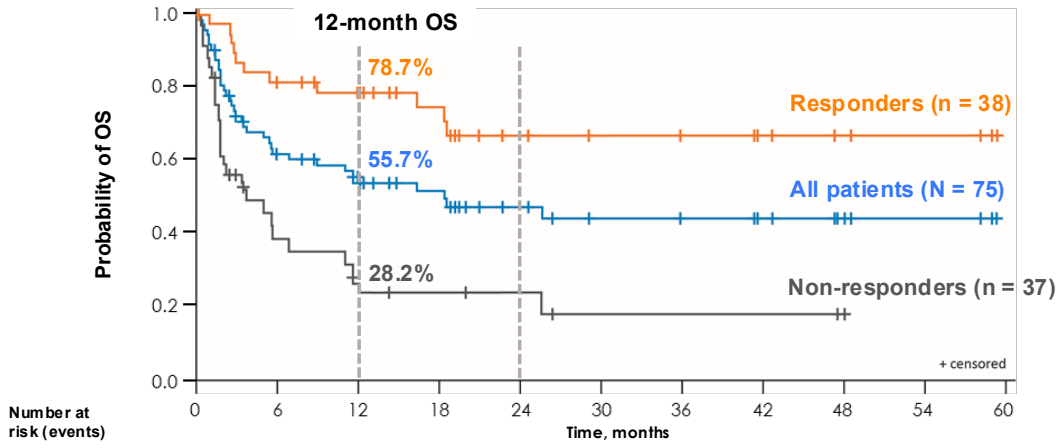
Figure 2: 12-month progression-free survival among responders.



Data cutoff date: 9th October 2023. Median PFS was estimated by the Kaplan–Meier method.

PFS: progression-free survival.

Figure 3: Responders to tabelecleucel had improved 1-year overall survival compared to non-responders.



Number at risk (events)

All patients	75 (0)	41 (27)	33 (31)	24 (33)	16 (35)	12 (36)	11 (36)	9 (36)	5 (36)	3 (36)	0 (36)
Responders	38 (0)	30 (7)	26 (8)	19 (9)	12 (11)	10 (11)	9 (11)	7 (11)	4 (11)	3 (11)	0 (11)
Non-responders	37 (0)	11 (20)	7 (23)	5 (24)	4 (24)	2 (25)	2 (25)	2 (25)	1 (25)	0 (25)	

Median OS (95% CI)

NE (18.6, NE) months

18.4 (5.7, NE) months

3.7 (1.8, 11.0) months

Median follow-up 9.0 months

Data cutoff date: 9th October 2023. OS was estimated by the Kaplan–Meier method. Median follow-up was 9 months.

NE: not estimable; OS overall survival.

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should be reported to Pierre Fabre on 0800 0855292, UKdrug.safety@pierre-fabre.com or https://www.pierre-fabre.com/en/vigilance-form.

Congress Interviews

We had the privilege of speaking with several esteemed members of the European Society for Blood and Marrow Transplantation (EBMT), who shared valuable insights on the latest advancements in stem cell transplantation, highlights from the recent congress, and a range of exciting new initiatives.

Featuring: Chiara Nozzoli, Alex Rampotas, Esra Gülderen, Christian Chabannon, and Edoardo Campodonico

Chiara Nozzoli

Careggi University Hospital, Florence, Italy; EBMT Scientific Committee Co-Chair.

Citation: EMJ Hematol. 2025;13[Suppl 2]:22-23. https://doi.org/10.33590/emjhematol/LJFZ7553

Q1 Can you begin by telling us a bit about your background and what your current role as Head of the Transplant Unit at the Careggi University Hospital, Florence, Italy, entails?

In 2002, I started working in the Blood and Marrow Transplant (BMT) unit at Careggi University Hospital. There, I followed the evolution of transplant procedures and assisted patients affected by both onco-haematological and autoimmune diseases.

For many years now, I have focused my scientific interests on multiple myeloma (MM) through participation and promotion of clinical studies in autologous and allogeneic transplantation. Following the passing of Riccardo Saccardi, I was appointed as Director of the Transplant Unit at the Careggi University Hospital in March 2024, where we perform procedures of autologous and allogeneic stem cell transplantation and CAR-T therapy.

Q2 You have been actively involved in haematopoietic stem cell transplantation (HSCT), particularly in relation to MM. What initially drew you to focus on this condition?

MM is a disease that has seen significant progress in biological knowledge and the therapeutic scenario in recent years. In particular, this is thanks to the use of new proteasome inhibitor drugs, immunomodulators, and immunotherapy, in particular monoclonal antibodies, up to bispecific antibodies, CAR-T, and CAR-NK.

I believe that, particularly in high-risk patients, we can still imagine a role for allogeneic transplantation with the long-lasting graft versus myeloma effect of the donor's immune system, which can represent a treatment platform with immunomodulatory drugs and monoclonal antibodies both in post-transplant maintenance and in relapse.

> **MM is a disease that has seen significant progress in biological knowledge and the therapeutic scenario in recent years**

Q3 How do you see the evolving landscape of personalised medicine impacting the future of MM treatment?

The increasingly in-depth biological knowledge of the disease leads us to the possibility of stratifying patients based on risk and on personalisation of therapy through the identification of cellular antigenic targets for monoclonal antibodies, bispecifics, and cellular therapy, with CAR-T today and CAR-NK cells and trispecific antibodies in the future. It will be important to define an algorithm for the treatment of the disease that identifies the correct sequence of all available therapies. It would be valuable to consider the possibility of anticipating the most effective therapies in the first line of treatment to obtain a significant outcome advantage.

Q4 In the 51st Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT), you are set to chair an oral workshop and an oral session centred on MM. What treatment innovations for MM that are just over the horizon are you most excited about?

The most interesting innovation in MM, in my opinion, will be treatment with trispecific antibodies (TsAb), which can either target two different MM-associated antigens to prevent antigen escape or provide an additional co-stimulatory signal for T cells to prevent CD28-mediated effector cell exhaustion.

Q5 What potential does CAR-T therapy hold for patients with MM, and what challenges persist?

The success of autologous CAR-T cells has changed the treatment landscape in relapsed and refractory MM, resulting in the potential movement of CAR-T cells to the frontline treatment setting. However, one of the greatest weaknesses of this therapy is its autologous nature, which makes it time-consuming, labour intensive, and dependent on the patient's T cell fitness. The development of allogeneic CARs, including CAR-T, CAR-NK, and CAR-iNKT cells, is critical to overcome these challenges and provide patients with an off-the-shelf alternative.

Q6 Are there any other sessions or speakers at the EBMT 2025 Annual Meeting that you're particularly looking forward to?

In my opinion, there are many interesting speakers and sessions, but the ones that I'm particularly interested in are 'New frontiers in acute and chronic GVHD (E03)' and 'Relapse in acute leukemia (P01)'.

Alex Rampotas[1] and Esra Gülderen[2]

1. Academic Clinical Lecturer, University College London (UCL) Cancer Institute, London, UK; EBMT Trainee Committee Co-Chair

2. Resident Physician, Uludag University, Bursa, Turkey; EBMT Trainee Committee Co-Chair

Citation: EMJ Hematol. 2025;13[Suppl 2]:24-29. https://doi.org/10.3390/emjhematol/BAYH3619

Q1 Firstly, congratulations on stepping into the leadership roles as the new Co-Chairs of the European Society for Blood and Marrow Transplantation (EBMT) Trainee Committee. To begin, could you share with us your roles within the committee so far, and reflect on the work Nico Gagelmann and Claire Horgan have done as Co-Chairs?

Gülderen: Thank you. We are both truly honoured to step into these leadership roles and continue the great work initiated by Nico, Claire, and other members, who established the EBMT Trainee Committee in 2021. A fun fact is that Alex and I joined the team at the same time, in June 2022, without knowing each other beforehand. Our first in-person meeting was during the International Transplant Course, in Barcelona, and since then, we have worked closely together on multiple projects. For example, from the start, we have actively joined several initiatives, such as Chimera, a trainee-led educational lecture series covering essential topics in transplantation and cellular therapy. We are also leading some projects stemming from our own committee. Recently, our focus has been on the educational needs in palliative care for transplant and cellular therapy trainees. We conducted a survey to assess the gaps in training and based on the results, are now planning a series of expert-led lectures. We also aim to share our findings as a publication to contribute to the broader discussion on improving palliative care education in haematology, transplantation, and cellular therapy.

We deeply appreciate the outstanding leadership and vision of Nico and Claire, who played a pivotal role in shaping this committee into a dynamic and impactful platform for trainees. Their dedication to fostering education, collaboration, and trainee engagement has set a strong foundation, and we look forward to building upon it in our new roles.

Rampotas: I completely agree with Esra. Nico and Claire started this a few years ago, and it was incredibly important for putting EBMT on the map, especially among young haematologists and trainees. The main focus has been on education and creating connections across the world, which has helped improve transplant and cellular therapy services in many countries, while also training young haematologists in this area. It's been a great opportunity for us to be involved in multiple projects. As Esra mentioned, the Chimera modules were among them. Additionally, we've been heavily involved in meetings like the International Transplant Course, which is a fantastic event where junior haematologists come to learn about the latest advancements in CAR-T cells and transplant. This course is a major educational platform. It's been great to be part of this community, and now, as we take on the chair, we hope to continue the excellent work and solid foundations that Nico, Claire, and the team have built.

> **"I believe we are part of a generation that may soon see even more novel therapies, such as chemotherapy-free regimens, that could cure cancers, especially in haematological malignancies that have relapsed multiple times"**

Q2 What initially drew you to haematology, and how has your career in this field developed over the years?

Rampotas: I've always had an interest in immunology. I graduated in 2014, around the time when CAR-T cell therapies were making headlines in journals as this groundbreaking new approach. The idea of using T cells to specifically target malignant cells really fascinated me. Given my interest in immunology, I realised that haematology was the field where I could apply this knowledge to develop therapeutics and actually treat patients with incredible therapies. The use of monoclonal antibodies and bispecifics was another amazing advancement. I believe we are part of a generation that may soon see even more novel therapies, such as chemotherapy-free regimens, that could cure cancers, especially in haematological malignancies that have relapsed multiple times. This is incredibly exciting. In fact, we may be the only specialty that can claim to use immunotherapy to cure cancer, which I find truly fascinating.

Gülderen: For me, haematology is deeply personal. As a child, I lost my grandfather to cancer, and even at a young age, I felt a strong desire to help people facing similar battles. I always dreamed of becoming a physician–scientist, not only helping my patients in the clinic but also contributing to the field through my research. I pursued my medical education in Ankara, Türkiye, my first summer research internship in a haematopoietic stem cell lab left a strong impression on me. After several electives in the haematology department, I decided this was the path I wanted to pursue. I am the first medical doctor in my family, but I grew up hearing stories about pioneering women in science from my mother, which further inspired me to pursue research and science to improve patient outcomes, particularly in haematology. What fascinates me even more is the way clinical care, basic science, and cutting-edge therapies all come together. I've always dreamed of bridging translational research with clinical practice.

Q3 Haematology has seen significant advancements in recent years. Are there any developments or innovations that you find particularly exciting?

Rampotas: I think haematology has seen so many new trials with incredibly positive results. The more we learn about the molecular mechanisms driving these malignant diseases, the better treatments we can develop. Recently, we've seen that with immunotherapies and tyrosine kinase inhibitors, targeting specific pathways makes tumours and malignancies vulnerable. This has led to those amazing long survival curves that we all strive for.

An additional benefit is that these targeted therapies reduce the morbidity burden caused by the side effects of chemotherapy and transplants because they are more precisely directed at the cancer cells, making them more susceptible to treatment. Ultimately, what we care about is patients living longer and living better. If we use these treatments, especially in the upfront setting with chemotherapy-free

regimens, we can target the molecular mechanisms driving the malignancy, specifically attacking the malignant clones. Even in the relapse setting, these therapies offer a chance for a cure after multiple relapses, which have traditionally been extremely hard to treat.

We used to say that if cancer returns after multiple lines of therapy, it becomes much harder to treat. But now, because we can use these therapies later in treatment, we're offering patients a chance for long-term remission even in later stages. This makes discussions with patients incredibly meaningful. While telling a patient they have cancer is undoubtedly difficult and distressing, it's one of the hardest things anyone can hear, the next part of the conversation is even more hopeful: we have treatments that don't just delay the disease or gain a few months, but actually have the potential to cure them.

Being part of this revolution is fascinating. The availability of these new regimens in recent years for many haematological cancers has been a fantastic development. If I had to pick one breakthrough, it would be CAR-T cell therapies, though I admit I'm biased as this is the field I work in most closely. I find CAR-T cell therapies particularly exciting because they combine targeted treatment with personalised medicine. Essentially, we take the patient's T cells, reprogram them, and direct them to kill the cancer cells.

Gülderen: I completely agree with Alex. I think CAR-T cell therapy is a complete game changer in some haematological malignancies. I would also like to mention about gene editing therapies, they are also offering some creative options for inherited blood disorders, such as sickle cell disease.

> **I think CAR-T cell therapy is a complete game changer in some haematological malignancies**

Q4 As the new Co-Chairs of the EBMT Trainee Committee, how do you plan to continue the work Gagelmann and Horgan have done so far? Are there any specific initiatives you're looking to build on or take forward?

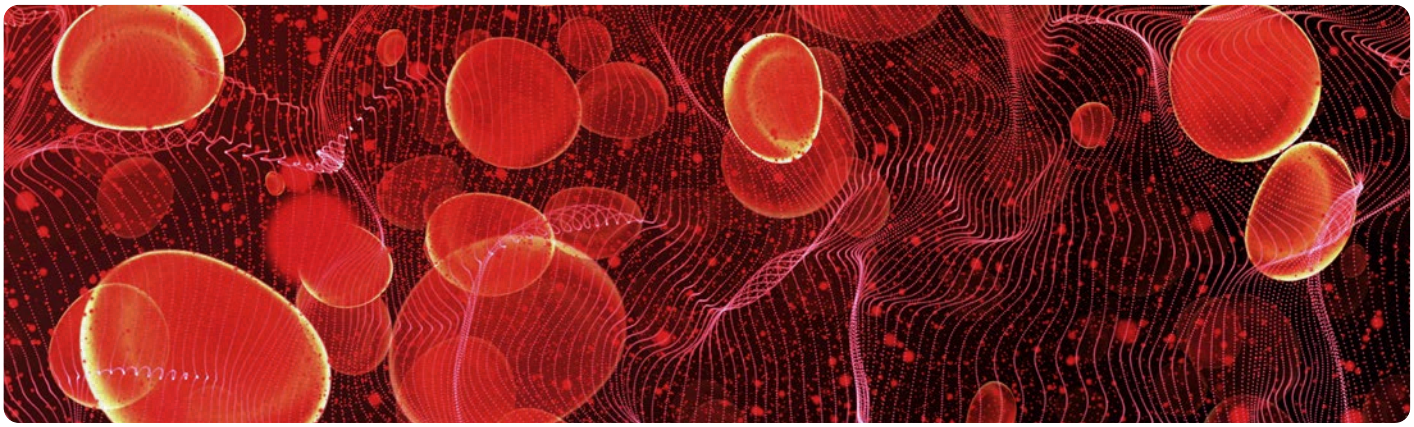
Rampotas: There are big shoes to fill with Nico and Claire are stepping down. We will obviously continue the education purpose of the EBMT Training Committee, and we'll try to get as many as a possible haematology trainees involved in those education aspects of our role. The next thing we are planning to do is to try to blend in the EBMT Training Committee into the various EBMT Working Parties so that they we work more seamlessly with the senior EBMT members.

Additionally, EBMT is expanding internationally, and we want to be part of that growth. We aim to connect with trainees around the world to understand their educational needs and explore how we can meet those needs through EBMT, while also gaining valuable perspectives and experiences from them.

Furthermore, much of EBMT's work is focused on clinical research, clinical guidelines, and best practices. We want to attract molecular biologists, PhD students, and other scientific professionals to help develop a stronger focus on translational research. Hopefully, in collaboration with EBMT, we can build on this and attract more people to the field. EBMT is a great community, and being involved in such an organisation offers valuable opportunities for growth and learning.

Lastly, the EBMT exam is an important certification that EBMT offers, and we believe it's an underutilised resource. It provides a valuable qualification for junior haematologists interested in transplant and cellular therapies, and it also serves as a great training opportunity. I've found that every time I revise for an exam, my understanding of a specific field improves significantly.

Gülderen: Our primary goal is to further strengthen the international and inclusive environment of the EBMT Trainee Committee, ensuring it remains a valuable platform for every trainee, regardless of background or location. We want to encourage and support those who share the same passion for haematology, cellular therapy, and transplantation by providing educational opportunities, enhancing clinical practice, fostering networking, and expanding research collaborations. Building on the strong foundation set by Nico and Claire, we aim to increase trainee involvement in the EBMT and advocate for better access to training opportunities across Europe and beyond, especially for underrepresented groups in our community. Our key priorities include promoting Diversity, Equity, and Inclusion within our trainee network and EBMT as a whole, while continuing to create and expand opportunities for trainees in all aspects of their professional development.



Q5 With the rise of CAR-T therapies in treating haematologic cancers, how do you assess its impact so far, and what do you think the future holds for this treatment in haematology?

Rampotas: The first thing to say is that CAR-T cells are already an established treatment for a few haematological malignancies. It is interesting that in the lab, when we see CAR-T cells, when we culture CAR-T cells, there is nothing in principle that would stop them from being effective against any malignancy; haematological or otherwise.

There are certainly challenges, but CAR-T cell therapy is not just a fixed treatment; it's a cell that can be engineered not only to target cancer cells but also to perform other functions. CAR-T cells have already been established as a treatment for a few haematological malignancies, but in principle, there's no reason they couldn't be effective for other haematological cancers or even solid tumours. In the lab, we know they work amazingly well against a range of different tumours.

Another exciting aspect is that CAR-T cells aren't a one-size-fits-all treatment. They can be engineered to target cancer cells, but they can also be 'armoured' to express other things, such as protection against the immunosuppressive environment or the ability to deliver a therapeutic payload directly to the tumour site. The possibilities here are endless. I believe we'll see CAR-T cell therapies expand to treat myeloproliferative neoplasms, acute myelogenous leukaemia (AML), and even solid tumours. We've already seen successful Phase I trials for CAR-T cells in glioblastoma. In the lab, there's nothing to suggest that CAR-T cells couldn't work against solid tumours.

We're just beginning to explore the full potential of this therapy. We're also seeing trials for autoimmune diseases, which is an unexpected but promising indication for CAR-T cells. People have used them successfully in these cases, and we anticipate that CAR-T cells could eventually become a standardised treatment for many autoimmune diseases. By resetting the immune system, attacking and eliminating the B cells responsible for the autoimmune reaction, patients could recover without the autoimmune tendencies that caused the disease.

It's a fascinating era, and I believe CAR-T cells will be used more frequently in the future. However, there are challenges that remain, particularly around cost and availability. That's why organisations like EBMT can play a critical role in accrediting sites for CAR-T cell therapy, educating healthcare professionals on its use, and fostering collaborations to ensure these therapies are used as effectively as possible.

Gülderen: I think Alex covered everything, but he also mentioned the challenges around access and manufacturing complexities. Additionally, we need to broaden the applications of CAR-T cells, especially in AML, which remains very challenging.

Q6 As you look toward the future of haematology, what emerging trends or breakthroughs are you most excited to see unfold in the next decade?

Gülderen: Several years ago, I attended a talk given by a pioneering physician who shared how, during his early training, the prognosis for multiple myeloma was extremely poor. Yet, with groundbreaking innovations such as targeted therapies, CAR-T therapy and others, patient outcomes have improved dramatically. I hope and strive to contribute to a similar transformation for myeloid malignancies in the years ahead. The next decade in haematology will likely be defined by precision medicine, the deeper integration

of artificial intelligence in diagnostics, and continued breakthroughs in immunotherapy and targeted treatments. Advances will come through an interdisciplinary approach, bridging clinical expertise with cutting-edge research in genomics, immunology, data science, and biotechnology. I believe these developments will not only refine how we diagnose and treat haematologic diseases, but also bring us closer to curative strategies for conditions that remain challenging today.

Rampotas: I think it's fascinating looking back to see how much transplant, for example, is now utilised across many parts of the world. I expect to see that, with protocols becoming more straightforward, and with more collaboration across haematologists across the world, that people in other places in the world will have access to allogeneic stem cell transplant or even CAR-T cell therapy. To be honest, that would have the biggest effect, because if we're missing out places like India, for example, or Pakistan, or places in Africa or South America, then whatever effect you have, even with the curative treatment, is much more limited. So, in the next 10 years, I would expect to see more collaboration. I'm very excited about that, and then I expect to see these places doing those therapies more often, and hopefully with some academic support, they should be able to afford, sometimes the very high prices of these therapies.

In terms of the scientific advancements, I think clonal haematopoiesis is something that's very, very interesting, and this is because haematology may be able to crack another problem after cracking targeting cancer, with immunotherapy, which will be ageing. We consider that ageing is an irreversible process. It's something that just happens. We don't consider it the disease. But if you look at the bone marrow, you can see the signs of ageing on the mutations that stem cells acquire. Hopefully, in the next few years, we'll be able to intervene once we understand this phenomenon a bit better. I also believe that blood and marrow are full of riddles, but they also hold the potential to provide answers to conditions that may currently seem completely untreatable.

Q7 How do you see the role of personalised medicine evolving in the treatment of haematologic conditions?

Rampotas: Autologous CAR-T cell therapy is probably the cradle of personalised medicine, as we're essentially using the patient's own T cells to fight their disease. Now, the limitation of personalised medicine is the cost. Most of the healthcare systems across the world are, to a degree, public/state funded, and hence using such expensive treatments can be extremely challenging to implement. For example, anyone can now check for various diseases in their DNA, but it's still quite an expensive test; or they can monitor other conditions through things like prophylactic MRIs. I think the biggest advancement in personalised medicine will come when the costs of these approaches decrease, and they become accessible to a larger population. The cost of DNA sequencing, for instance, has dropped significantly, which is a step forward. Although it's still prohibitively expensive for many nations, you can now potentially screen all of your DNA for about

1,000 USD or equivalent in other currencies. As the cost continues to decrease, it could become feasible for countries with an average GDP, and that could really change things. So, reducing the cost is the biggest hurdle to applying personalised medicine more broadly.

Gülderen: In the next 10–20 years, personalised medicine will likely become more sophisticated, with greater use of multi-omics data, AI in diagnostics, and real-time monitoring to further refine patient-specific treatment strategies. Treatments will become more personalised and precise, with less toxicity and greater target specificity.

Q8 What's your one can't-miss presentation or event at the EBMT Annual Meeting?

Gülderen: That's a tough question, because the entire program is exceptionally well-designed and filled with fascinating topics. Of course, Trainee Day on Sunday is a must-attend event for all trainees. Beyond that, I'm particularly excited about sessions on relapse in acute leukaemia, the graft manipulation, Chronic Malignancy Working Party session, and optimising transplant in high-risk MDS.

Rampotas: I agree with Esra, and people should definitely attend the EBMT training day. That will be an extremely nice opportunity to interact and meet with the new generation. There would also be opportunities for them to get involved, and we will announce some amazing developments about how they can get involved in the future.

I wouldn't like to pick a particular session. Obviously, my interest is in CAR-T cell therapy, and I know that there are many compelling oral presentations presented at EBMT. This makes me happy, because that means that good CAR-T research will be presented at the EBMT conference. I like that EBMT is expanding into that phase of cellular therapies, because transplant is obviously extremely interesting, and it's probably the most historic cellular therapy, but I like the fact that we will have so many nice presentations on CAR-T.

I would say, just come to the meeting. Enjoy the EBMT trainee day. Interact, and there will be opportunities to discuss and get involved. It's a very nice meeting, so I'll be pleased to interact with everyone and connect.

Q9 What will be participants main takeaways of the Trainee Day that takes place on Sunday?

Rampotas: From my side, I think there are some excellent presentations. I'm particularly looking forward to the presentation on the bone marrow microenvironment and how it creates barriers, but also opens up new opportunities to intervene and improve outcomes, presented by Zoe Wong from Oxford. There are also some great presentations from EBMT trainee members. One of the key takeaways is how this group of people can produce outstanding work, and I think some of this work will be presented there. Of course, another important takeaway is the opportunity to connect with the new generation of EBMT members so that we can continue building on the incredible success that Nico and Claire have achieved and hopefully shape the EBMT Training Committee for the future.

Gülderen: Nothing to add. Enjoy the Trainee Day plus, it's always a great chance for networking with other trainees from around the world, which is an essential part of the experience. Also feel free to reach out to us for future projects!

Christian Chabannon,[1] Edoardo Campodonico[2]

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Citation: EMJ Hematol. 2025;13[Suppl 2]:30-32. https://doi.org/10.33590/emjhematol/CRXL7232

Q1 CAR-T cell therapy has shown immense promise in treating cancers, but its cost remains a barrier for many patients. What do you think can be done to make CAR-T therapy more affordable and accessible to a larger patient population?

Chabannon: We will be in a good position to take action when we better understand cost structures that are associated with the clinical use of CAR-T cells. As expensive as it can be, the cost of acquisition of the medicinal product is only one component. Hospital infrastructures and organisations that are needed for safe and efficient administration also account for a significant share of the cost. Moreover, CAR-T cells are administered as salvage therapies, and one has to consider the cumulated costs of treatments that were administered prior to the infusion of CAR-T cells.

Now manufacturing costs only account for a fraction of the face value of a medicinal product. While manufacturing advanced therapies is way more expensive than manufacturing conventional drugs or biologicals, it still accounts for a fraction of the cost. Other determinants include research and development costs, accounting for all medicinal products that failed during development and the need to recover associated costs, as well as the perception that the price of treatment may, more or less, equal the cost (and thus savings) of standard-of-care for the same indication.

Campodonico: Regarding the accessibility and affordability of CAR-T cell therapy, I mostly agree that the cost of the drug is just one part of the overall treatment expense. The total cost is quite high, especially when considering hospitalisations and the treatment of various complications, which place a significant burden on healthcare systems. To expand the scale of this treatment, in addition to what Christian mentioned, there are some interesting tools, particularly the promotion of academic CAR-T cell therapies. This is an important topic, as academic protocols offer quicker and relatively cheaper products, making them a valuable alternative to standard treatments. These should be encouraged worldwide, as we've seen in examples from Spain and Israel. Some colleagues within EBMT have already paved the way for such treatments, which can complement standard care products and help reduce the costs of external manufacturing. This is an important point to consider. Ultimately, much of the work needs to be done at the level of national healthcare systems. Harmonisation is essential, especially among the various countries that are members of EBMT. In this regard, healthcare authorities should ensure that CAR-T cell therapy is appropriately utilised and implemented, always respecting indications, so that resources are efficiently allocated.

Q2 From a healthcare systems perspective, what are some strategies that could help reduce the financial burden of CAR-T therapies while maintaining their effectiveness?

Chabannon: While the marketing approval is issued at the European level by the European Medicines Agency (EMA), reimbursement is decided at

the national level by Health Technology Assessment (HTA) agencies; harmonisation is further needed in this field. Decreasing the costs of manufacturing through decentralised (point-of-care) manufacturing and the introduction of improved automated engineering techniques and devices are potential ways to decrease costs to the healthcare system, for as long as safety and efficacy are comparable to those measured with commercial CAR-T cells. From this viewpoint, the ongoing comparative trial that is ongoing in the Netherlands with the HOVON cooperative group will produce important information.

Q3 How can we balance the rapid development of CAR-T therapies with ensuring long-term safety and effectiveness for patients?

Chabannon: CAR-T cells are living drugs and may elicit long-term clinical activity, whether favourable or unfavourable, that cannot be detected in registration trials. Thus, the need for high-quality registries that capture long-term follow-up of CAR-T cell treated patients. The recent reports of T cell lymphomas arising in patients treated on both sides of the Atlantic, some of them with detection of the CAR sequence in lymphoma cells, led to promptly re-examining the risk–benefit ratio of CAR-T cells. The rarity of these adverse events is such that the benefit of CAR-T cell therapies is maintained; however, it rang the bell for specialists in the field. CAR-T cell-treated patients must be followed up for their entire lifetime after treatment.

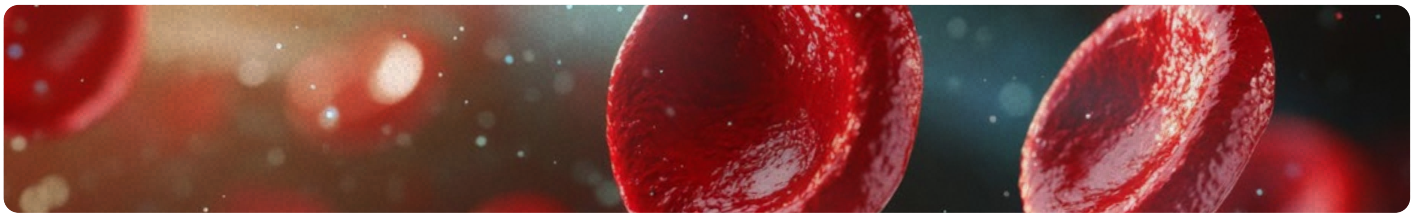
Campodonico: Once again, I believe Christian already highlighted the importance of registries. High-quality registry data is essential, and EBMT does this very effectively, though there's always room for improvement. In times of political instability, it's crucial to avoid over-fragmentation. One key point to remember is the importance of having a centralised registry rather than relying on national ones. A uniform registry with data entries from most centres performing this therapy would enable faster monitoring of severe and unexpected adverse events, which is vital. More generally, adverse event reporting is critical for all practitioners. Additionally, single-centre experiences are valuable, as they help us understand the incidence of specific adverse events, particularly second malignancies. This understanding is essential when determining the emphasis that should be placed on these concerns during patient consultations prior to CAR-T cell therapy.

Q4 Christian, given your involvement with the GoCART Coalition, could you share some background on the initiative and its key objectives?

Chabannon: The GoCART Coalition is an initiative started in 2020, supported both by EBMT and the European Hematology Association (EHA), and was meant precisely to bring all stakeholders around the table to address questions such as costs and affordability, among others. Streamlining the installation of CAR-T cell activities through collective and individual training and qualification is another important avenue.

Q5 Looking ahead, what do you believe is the next major step for CAR-T cell therapy, both in terms of improving patient outcomes and addressing its accessibility and affordability issues?

Chabannon: Without being overly pessimistic, I notice that over the last couple of years, the field has not produced clinical innovations at the same rate as in the years before, particularly if we consider malignant blood diseases and solid tumours. Meanwhile, preclinical developments are blooming, and it is reassuring that European groups and companies are now taking their full share of these



projects. My personal bet would be on *in vivo* reprogramming to generate CAR-T cells; this is a fascinating approach, and some convincing preclinical work has been published in high-profile journals, and early clinical trials recently started.

Campodonico: In terms of improving patient outcomes, I believe the biggest challenge we're facing is extending the CAR-T cell revolution to oncology. While there's much discussion around this, the clinical implementation is lagging behind the promising preclinical data. Currently, the outlook for clinical trials involving solid malignancies remains limited. The expansion and refinement of CAR-T cell therapies, including the addition of new engineering techniques, chimeric stimulator receptors, and combinatorial approaches such as TME modulation, are crucial for breaking through the barrier in oncology and making CAR-T cells applicable to solid tumours.

Regarding accessibility and affordability, a key point is to increase the number of manufacturing facilities. This would ensure that all patients in need of cell therapy can undergo apheresis and benefit from timely product manufacturing. As we know, this is a significant challenge for certain disease indications and geographical regions. By expanding the number of accredited centres for CAR-T cell production, we can improve accessibility for more patients.

> **In terms of improving patient outcomes, I believe the biggest challenge we're facing is extending the CAR-T cell revolution to oncology**

Q6 As CAR-T therapies become more widely used, how do you envision collaboration between clinicians, researchers, and healthcare policymakers to ensure that advancements in CAR-T therapy are both innovative and accessible to all patients who could benefit from them?

Chabannon: The question obviously covers a much broader field than CAR-T cells and immune effector cell-based therapies, and resorts to the balance in public and private expenses dedicated to healthcare in countries with defined gross domestic products. EBMT "historical business", i.e., haematopoietic cell transplantation remains unequally accessible in low-, middle-, and high-income countries after more than 5 decades of medical practice. My expectation is that the same will happen for CAR-T cells, although the hierarchy of low-, middle-, and high-income countries is likely to change on a global scale in these times of political turmoil, and that mitigating inequalities in access requires collaboration and consensus building across all stakeholders: this is essentially the GoCART Coalition mission. CAR-T cells provide a paradigmatic example of a day-to-day collaborative effort that involves healthcare practitioners and institutions along with providers of medical goods; this needs to be reproduced at a global level where managing decisions can be built.

Campodonico: I think it's crucial to have a strong integration between basic researchers and clinicians within tertiary care centres. This is a point that cannot be emphasised enough. From personal experience, I've seen that this communication is often lacking in many centres, where the scientists designing the products don't always engage with the clinicians who will ultimately apply and test these products in humans. On a smaller scale, it's vital that any centre aiming to design new cell-based products foster multidisciplinary collaboration between clinicians and basic researchers.

On a broader scale, this also requires cooperation within scientific societies like the EBMT, and it's especially beneficial to focus on meetings that take a translational approach. For example, the CAR-T cell meeting is a perfect interface where researchers and clinicians come together, giving them the opportunity to discuss and exchange ideas on the latest developments in the field. These kinds of events play a key role in bridging the gap between research and clinical practice, helping to drive the field forward.

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