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PEER-REVIEWED CONFERENCE REPORT

Excellent Results for Triplet Regimen in FLT3-mutated AML

The triplet combination of azacitidine, venetoclax, and gilteritinib induced high response rates in patients with newly diagnosed or relapsed/refractory *FLT3*-mutated AML in a phase 1/2 study.

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CAR-Hematotox Score Useful in Relapsed/Refractory MM

High CAR-Hematotox scores were associated with an increased risk for severe haematotoxicity, severe infections, and reduced PFS and OS in a retrospective study, suggesting this score can be used to drive risk-adapted management strategies.

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A Non-restricted Diet Is the Preferred Option After SCT

In patients with neutropenia after stem cell transplantation, a non-restrictive diet resulted in comparable infection and death rates as a so-called 'protective' diet, demonstrating that a restrictive diet is an unnecessary burden for these patients.

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Letter from the Editor

Dear Reader,

It is with great pleasure to introduce this peer-reviewed ASH 2022 Medicom Conference Report. It again was organized as a hybrid meeting, a format that currently is available for most medical conferences.

The ASH annual meeting, now held in New Orleans, is a great event to which everyone is looking forward. It offers the opportunity to get informed in benign as well as malignant haematology. Basic, translational, and clinical topics were covered in a wonderful programme. From this years' ASH meeting, we selected a number of interesting abstracts that will most likely change your daily practice now or in the near future. The abstracts are summarised in a way that the information is easy to digest in a rather short time.

The rapidly evolving field of immunotherapy, including bispecific antibody and CAR T-cell treatment applied in a variety of haematological malignancies, got a lot of attention. Gene therapy is emerging, resulting in new treatments for haemoglobinopathies and haemophilia. The further deciphering of the molecular basis of benign and malignant disease by al kind of new technologies is striking.

Treatment of acute myeloid leukemia, a disease in which no new developments emerged for a long time, is rapidly changing with the development of new effective targeted treatments and successful maintenance treatment. Especially in the patients unfit for intensive chemotherapy, new avenues are opened. But also in the other malignant and non-malignant haematological diseases, new drugs are rapidly developed and approved by the regulatory authorities. Measurable residual disease becomes an important surrogate endpoint for outcome in many heamatological malignancies and helps to inform treatment.

You will find snapshots of all these new developments in this report. I can imagine that these are helpful in your daily practice and I am certain that you will enjoy.

Gert Ossenkoppele

Biography

Gert Ossenkoppele is appointed in 2003 as professor of Hematology at the VU University Medical Center in Amsterdam. He obtained his doctorate of medicine at that same University in 1977. He is board certified in Hematology and Internal medicine(1984). The title of his PhD thesis (1990) was: "Differentiation induction in AML". Gert Ossenkoppele has authored over 450 publications in peer-reviewed journals and is invited speaker at many national and international scientific meetings. His research interests is mainly translational and include the (stem cell) biology of AML, leukemic stem cell target discovery, immunotherapy and measurable residual disease (MRD) detection using flow cytometry to inform treatment of AML. He is PI of national and international clinical trials in myeloid malignancies. He is reviewer on a regular basis for many high impact hematological journals (Blood, Leukemia, Haematologica, JAMA Oncology, Lancet Oncology NEJM). He chairs the AML working party of HOVON (Dutch-Belgian Hematology Trial Group) and recently stepped down as vice-chair of the HOVON Executive Board. He is a lead participant of the AML Work package of the European LeukemiaNet(ELN) as well as a board member of the ELN foundation. He co-leads the AML WP of HARMONY. He rotated of as board member of the European Hematology Association and was very recently appointed as vice-chair of the EHA Educational Committee. He just rotated of as chair of the AML Scientific working group of EHA and is now a member of this group. He is member of the Global and EU steering committee of the AMLGlobalPortal an educational portal for hematologists. (www.amlglobalportal.com). He chairs the institutional DSMB of his University. He has now because of retirement an honorary position as hematologist at the Amsterdam University Medical center.

Conflict of Interest Statement:
Prof. Gert Ossenkoppele received research support from Novartis, J&J and BMS-Celgene. He functions as a consultant for J&J, Daiichi-Sanyko, BMS-Celgene, Servier, and Roche. Lastly, he is a member of the advisory boards of Novartis, Pfizer, Abbvie, J&J, Daiichi-Sanyko, BMS-Celgene, AGIOS, Amgen, Astellas, Roche, Jazz pharmaceuticals, and Merus.

Acute Lymphoblastic Leukaemia

Blinatumomab candidate for standard-of-care in newly diagnosed B-ALL

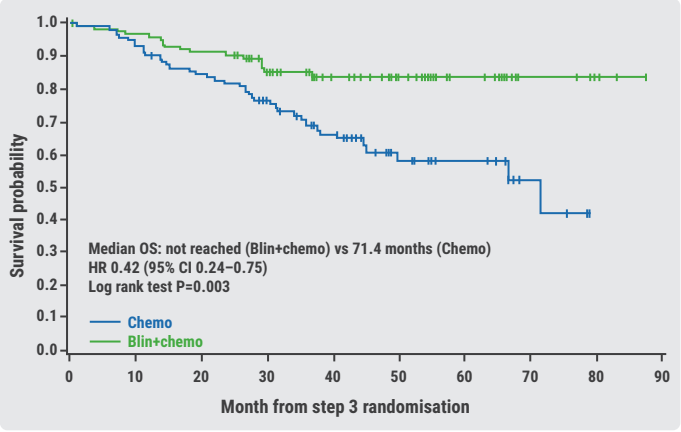
Patients with newly diagnosed B-lineage acute lymphoblastic leukaemia (B-ALL) who were measurable residual disease (MRD)-negative showed an overall survival (OS) benefit if they were treated with a consolidation therapy of blinatumomab plus chemotherapy compared with chemotherapy alone. These results represent a new potential standard-of-care for this group of patients.

The bi-specific CD19 and CD3 T-cell engager blinatumomab is an approved therapy for patients with relapsed/refractory B-ALL and MRD-positive B-ALL. In MRD-negative patients, the therapy had not yet been thoroughly investigated.

The phase 3 ECOG-ACRIN-E1910 NCTN clinical trial (NCT02003222) exposed patients, aged between 30–70 years, with newly diagnosed B-ALL to 2.5 months of Berlin-Frankfurt-Munster (BFM) induction chemotherapy, modified from the UKALL-XII protocol [1,2]. Those with a complete remission (CR) or a complete remission with incomplete count recovery (CRi) received CNS treatment intensification with high-dose methotrexate plus pegaspargase. Hereafter, the MRD status was assessed, and participants were randomised 1:1 to consolidation chemotherapy plus 4 28-day cycles of blinatumomab or to chemotherapy alone. Finally, all randomised participants received 2.5 years of POMP maintenance chemotherapy. The current study aimed to compare the blinatumomab-containing regimen with the chemotherapy-only arm for OS in MRD-negative patients (n=224). Prof. Mark Litzow (Mayo Clinic, MN, USA) presented the results after a median follow-up time of 43 months.

There was a clear OS benefit for participants in the blinatumomab arm compared with those in the chemotherapy alone arm (median OS: not reached vs 71.4 months; HR 0.42; 95% CI 0.24–0.75; log-rank P=0.003; see Figure). Prof. Litzow added that the 3.5-year OS-rates were 83% and 65%, respectively. Similarly, the relapse-free survival comparison favoured the blinatumomab arm over the chemotherapy arm (not reached vs 22.4 months; HR 0.46; 95% CI 0.27–0.78; log rank P=0.004). Finally, according to Prof. Litzow, the combination therapy was well tolerated and no new safety issues were observed.

Figure: Overall survival comparison in MRD-negative patients [2]



OS, overall survival; Blin, blinatumomab; Chemo, chemotherapy.

Consolidation with blinatumomab and chemotherapy thus demonstrated to provide an OS benefit over chemotherapy alone in newly diagnosed patients with MRD-negative B-ALL, potentially representing a new standard-of-care for this population.

1. Rowe JM, et al. Blood. 2005;106(12):3760–3767.
2. Litzow M, et al. Consolidation Therapy with Blinatumomab Improves Overall Survival in Newly Diagnosed Adult Patients with B-Lineage Acute Lymphoblastic Leukemia in Measurable Residual Disease Negative Remission: Results from the ECOG-ACRIN E1910 Randomized Phase III National Cooperative Clinical Trials Network Trial. Late-Breaking Abstract 1, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

High-dose methotrexate or standard interim maintenance in young patients with ALL?

High-dose methotrexate was not associated with a reduction in the risk for CNS relapse compared with standard interim maintenance therapy in children and young adults with acute lymphoblastic leukaemia (ALL) who were enrolled in the phase 3 UKALL 2011 trial.

The UKALL 2011 trial (ISRCTN64515327) included children and young adults up to 25 years of age with ALL. Investigated were the difference of a short (14 days) versus a standard (28 days) induction course of dexamethasone, the CNS relapse risk for high-dose methotrexate compared with a standard

interim maintenance regimen, and the difference between the effect of vincristine/dexamethasone pulses or no pulses on bone marrow relapse rate. At ASH 2017, the results for the dexamethasone induction courses were presented [1]. At ASH 2022, Ms Amy Kirkwood (University College London, UK) presented the maintenance results [2].

In total, 1,570 participants, receiving a backbone therapy according to the risk group they were stratified to, were randomised to 1 of 4 maintenance arms:

- High-dose methotrexate with pulses
- High-dose methotrexate without pulses
- Standard interim maintenance with pulses
- Standard interim maintenance without pulses

After a median follow-up of 72 months, there was no difference between high-dose methotrexate and standard interim maintenance with regard to CNS relapse (HR 0.99; 95% CI 0.65–1.51; P=0.97), with 5-year rates of 5.6% for both treatment regimens. Interestingly, participants who received a short course of induction dexamethasone followed by high-dose methotrexate and no pulses had an inferior event-free survival compared with participants who received short-duration induction dexamethasone followed by either high-dose methotrexate with pulses or standard interim maintenance with or without pulses (survival rate 75.9% vs 83.2–86.0%; P-value for interaction=0.006).

Furthermore, 'no pulses' was non-inferior to 'pulses' regarding bone marrow relapse rates (HR 1.22; 95% CI 0.89–1.67). The corresponding 5-year bone marrow relapse rates were 12.2% for participants who did not receive pulses and 10.2% for those who did receive pulses. Ms Kirkwood added that the 5-year event-free survival rate was slightly higher in participants who received pulses compared with participants who did not receive pulses (86.0% vs 81.7%; P=0.010).

In conclusion, high-dose methotrexate maintenance therapy did not reduce the risk for CNS relapse in young patients with ALL who were enrolled in the UKALL 2011 trial. Omitting pulses did not result in a higher rate of bone marrow relapse in this population.

1. Goulden NJ, et al. Blood. 2017;130(supplement_1):141.
2. Kirkwood AA, et al. High Dose Methotrexate Does Not Reduce the Risk of CNS Relapse in Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoblastic Lymphoma. Results of the Randomised Phase III Study UKALL 2011. Abstract 214, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Acute Myeloid Leukaemia

Excellent results for triplet regimen in *FLT3*-mutated AML

The triplet combination of azacitidine, venetoclax, and gilteritinib induced high response rates in patients with newly diagnosed or relapsed/refractory *FLT3*-mutated acute myeloid leukaemia (AML) in a phase 1/2 study.

Azacitidine plus venetoclax is the standard-of-care for older or unfit patients with *FLT3*-mutated AML. However, the 1-year overall survival (OS) rate is low, at 40–60% [1]. Therefore, researchers tested a regimen of azacitidine, venetoclax, and gilteritinib, an *FLT3* inhibitor that improves OS in patients with relapsed/refractory *FLT3*-mutated AML [2].

Patients with relapsed/refractory *FLT3*-mutated AML (n=20) or newly diagnosed *FLT3*-mutated AML, unfit for intensive chemotherapy (n=27), received a regimen of azacitidine, venetoclax, and gilteritinib (80 or 120 mg, once daily) in a phase 1/2 study. After the phase 1 part of the study, 80 mg was selected as the phase 2 expansion dose. The primary endpoint of the phase 2 part of the trial was complete remission (CR)/ complete remission with incomplete count recovery (CRi). Prof. Nicholas Short (University of Texas, TX, USA) presented the results [3].

CR was achieved in 92% of the participants who were treated with the triplet regimen in the frontline. The 2 remaining participants in this cohort achieved CRi and a morphologic leukaemia-free state (MLFS) response, respectively. Correspondingly, 20% of the participants in the relapsed/refractory cohort reached CR, 15% achieved CRi, and 35% had an MLFS response. In addition, 93% of the participants

in the frontline cohort were on marrow remission after 14 days or had an aplastic marrow. In the relapsed/refractory cohort, the corresponding rate was 63%. Furthermore, MRD-negativity, assessed through flow cytometry, was achieved in 82% and 43% of the participants in the frontline cohort and relapsed/refractory cohort, respectively. The 1-year OS rate was 85% in the frontline cohort and 30% in the relapsed/refractory cohort.

"In the frontline cohort, the regimen was generally well tolerated, with minimal non-haematological toxicity," said Prof. Short. Myelosuppression was common, but manageable with dose adaptations. One patient died due to an infection in this cohort. "In the relapsed/refractory cohort, most adverse events were related to myelosuppression, but mostly manageable with mitigation strategies." In this cohort, there were 4 unsteady deaths, 2 due to an infection, 1 because of an intracranial haemorrhage, and 1 due to disseminated intravascular coagulation.

1. Konopleva M, et al. Clin Cancer Research. 2022;28(13):2744–2752.
2. Perl AE, et al. N Engl J Med. 2019;381(18):728–740.
3. Short NJ, et al. Updated Results from a Phase I/II Study of the Triplet Combination of Azacitidine, Venetoclax and Gilteritinib for Patients with *FLT3*-Mutated Acute Myeloid Leukemia. Abstract 831, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

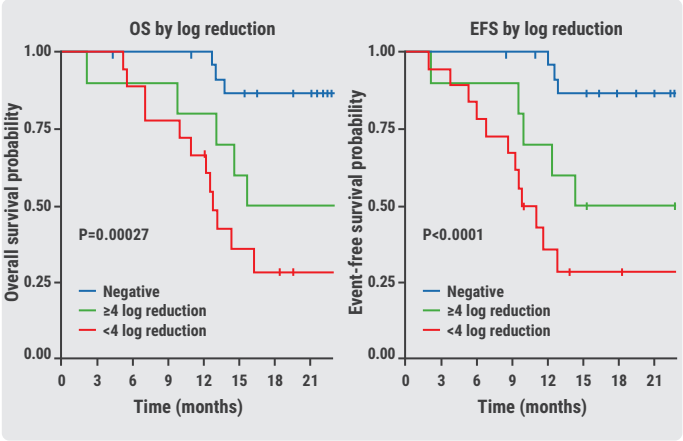
MRD by qPCR prognostic of outcomes in venetoclax-treated *NPM1*-mutated AML

Measurable/minimal residual disease (MRD) assessment by qPCR was strongly associated with clinical outcomes in patients with *NPM1*-mutated acute myeloid leukaemia (AML) who achieved complete remission (CR)/complete remission with incomplete recovery count (CRi) on venetoclax combination therapies.

"Flow cytometric MRD assessment is prognostic of clinical outcomes in venetoclax combinations-treated patients with various AML mutations," stated Mr Jad Othman (Guy's and St Thomas' NHS Foundation Trust, UK) [1,2]. The presented study aimed to determine whether MRD by qPCR is prognostic of clinical outcomes in patients with *NPM1*-mutated AML who achieved CR/CRi in the real-world on venetoclax plus either low-dose cytarabine or a hypomethylating agent.

In a cohort of 55 patients, the best MRD response rates in the first 6 months of therapy were as follows: MRD undetectable (46%), ≥4 log reduction (19%), <4 log reduction (35%). After a median follow-up of 24.3 months, the deepest MRD reduction within the first 6 months was strongly related to overall survival (OS; P=0.00027) and event-free survival (EFS; P<0.0001), favouring those with undetectable MRD over the other subgroups (see Figure). Mr Othman added that an MRD cut-off of <0.005 NPM1 copies/100 ABL was the best discriminator for OS (P<0.0001) and EFS (P<0.0001). Finally, it was noted that peripheral blood MRD, although less sensitive than bone marrow MRD, may be adequately sensitive to predict clinical outcomes.

Figure: Deepest MRD reduction within first 6 months is strongly associated with outcomes [2]



OS, overall survival; EFS, event-free survival.

1. Pratz KW, et al. J Clin Oncol. 2022;40(8):855–865.
2. Othman J, et al. Molecular MRD Assessment Is Strongly Prognostic in Patients with NPM1¬ Mutated AML Receiving Venetoclax Based Non-Intensive Therapy. Abstract 840, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Promising results for triplet therapy with magrolimab in AML

Triplet therapy of azacitidine, venetoclax, and magrolimab was safe as first-line therapy in patients with acute myeloid leukaemia (AML) and displayed encouraging response rates and overall survival rates even in TP53-mutated AML. The randomised phase 3 ENHANCE-3 trial has been initiated to assess whether this triplet combination can outperform the azacitidine and venetoclax doublet.

The overall survival rate of patients with AML treated with azacitidine and venetoclax in the frontline is 35–40% at 2 years [1]. Furthermore, the complete remission (CR)/complete remission with incomplete count recovery (CRi) rate of patients with relapsed/refractory venetoclax-naïve AML is 30–35% [2]. Thus, there is a clear need to improve health outcomes in patients with AML.

Prof. Naval Daver (Anderson Cancer Center, TX, USA) tested the combination of azacitidine, venetoclax, and magrolimab in a high-risk cohort of patients with newly diagnosed

AML (n=43) and in 2 cohorts of patients with relapsed or refractory AML, either venetoclax-naïve (n=18) or venetoclax-experienced (n=18) [3].

In the frontline cohort, the CR/CRi rate was 72% and the CR rate only was 49%. In addition, those with *TP53*-mutated disease and those with *TP53*-wildtype disease had comparable outcomes. After a median follow-up time of 14.5 months, the median overall survival (OS) was not reached in de novo participants (n=33) with *TP53*-wildtype (12-month OS 83%) or *TP53*-mutated AML (12-month OS 53%). In participants with secondary AML (n=10), the median OS was 7.6 months and 9.6 months in those with *TP53*-mutated and *TP53*-wildtype disease, respectively.

Although 90% of the participants had at least 1 grade 3 or higher adverse event (AE), no study treatment discontinuations were reported due to treatment-related AEs. Finally, Prof. Daver noted that anaemia grade ≥3 occurred in 23% of the participants and that this is an issue that should be monitored closely in following studies investigating the triplet combination of azacitidine, venetoclax, and magrolimab.

The phase 3 ENHANCE-3 trial (NCT05079230) will investigate the triplet combination versus azacitidine and venetoclax in newly diagnosed, previously untreated AML patients. In the relapsed/refractory cohorts, the results were not promising (CR/CRi rate venetoclax-naïve [44%]; venetoclax-exposed [11%]) and Prof. Daver mentioned that it is unlikely that the triplet therapy will be further investigated in these patients.

1. Dinardo CD, et al. NEJM. 2020;383:617–629.
2. Dinardo CD, et al. Lancet Haematol. 2020;7(10):e724–e736.
3. Daver N, et al. Phase I/II study of azacitidine, venetoclax and magrolimab for newly diagnosed and relapsed/refractory AML. Abstract 61, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Should we use intensive chemotherapy prior to allo-HCT in relapsed/refractory AML?

In the phase 3 ASAP trial, intensive chemotherapy in advance of allogeneic haematopoietic cell transplantation (allo-HCT) did not lead to improved outcomes or survival benefits compared with watchful waiting followed by sequential conditioning and allo-HCT in patients with relapsed or refractory acute myeloid leukaemia (AML).

A complete remission (CR) in advance to allo-HCT is an advantageous factor for patients with AML. Thus far, it has not been thoroughly investigated whether intensive chemotherapy, with the goal to induce remission, before allo-HCT results in better outcomes than sequential conditioning and allo-HCT in patients with relapsed/refractory AML. To assess this matter, the EATL3-ASAP trial (NCT02461537) randomised 182 patients with relapsed/refractory AML who were eligible for intensive chemotherapy and allo-HCT 1:1 to either:

- High-dose cytarabine and mitoxantrone, followed by allo-HCT; or
- Disease control: recommended watchful waiting but permission of low-dose cytarabine (LDAC) and single doses of mitoxantrone, followed by sequential conditioning, and allo-HCT.

The primary outcome was the CR rate at day 56 after allo-HCT. Prof. Matthias Stelljes (University of Muenster, Germany) presented the results [1].

In total, 76% of the participants in the disease control arm did not need disease-control measures until the start of sequential conditioning. The primary endpoint did not reveal a significant difference between the disease control arm and the chemotherapy arm, with 84.1% and 81.3% of the participants achieving a CR at day 56 after allo-HCT, respectively (non-inferiority P=0.047). Moreover, the 1-year leukaemia-free survival rates following CR at day 56 were 71.5% in the disease control arm and 69.9% in the chemotherapy arm (P=0.8). Finally, the 3-year overall survival rates were comparable, with 51.0% in the disease control arm and 54.2% in the chemotherapy arm (log-rank P=0.47). The disease control strategy resulted in fewer grade ≥3 adverse events than the chemotherapy arm (23% vs 64%; P<0.001). Also, the number of days spent in the hospital prior to allo-HCT was significantly reduced in the disease control arm compared with the chemotherapy arm (19 vs 42; P<0.001).

In conclusion, the current study showed that patients with relapsed or refractory AML did not achieve improved long-term outcomes if they received salvage chemotherapy in advance of allo-HCT, suggesting that a minimal disease burden is not necessarily a pre-requisite for good outcomes after allo-HCT.

1. Stelljes M, et al. In Patients with Relapsed/Refractory AML Sequential Conditioning and Immediate Allogeneic Stem Cell Transplantation (allo-HCT) Results in Similar Overall and Leukemia-Free Survival Compared to Intensive Remission Induction Chemotherapy Followed By Allo-HCT: Results from the Randomized Phase III ASAP Trial. Abstract 4, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Chronic Leukaemia

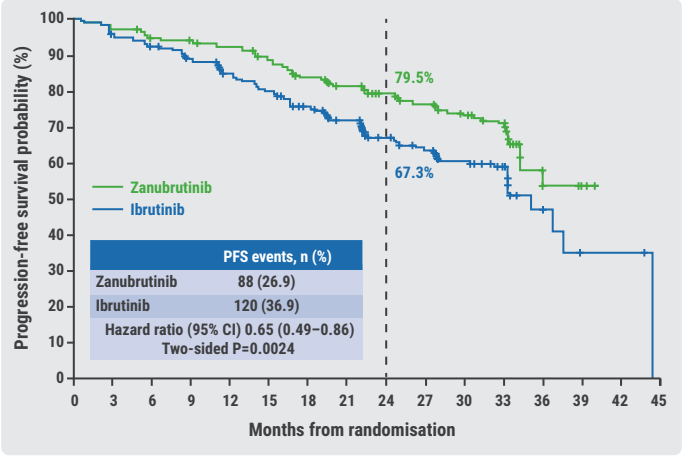
Zanubrutinib wins battle of BTK inhibitors in relapsed or refractory CLL/SLL

Zanubrutinib outperformed ibrutinib with regard to progression-free survival (PFS) in patients with relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL). Furthermore, zanubrutinib was associated with fewer toxicities than ibrutinib in this population.

The second-generation Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib was superior to chemo-immunotherapy in newly diagnosed patients with CLL/SLL without del(17p) [1]. At ASH 2022, Prof. Jennifer Brown (Dana Farber Cancer Institute, MA, USA) presented the final PFS data on zanubrutinib in CLL/SLL from the phase 3 ALPINE study (NCT03734016) [2]. This trial randomised 652 patients with relapsed or refractory CLL/SLL 1:1 to zanubrutinib 160 mg twice daily or to ibrutinib 420 mg once daily.

After a median follow-up of 29.6 months, the PFS was significantly longer in participants who were exposed to zanubrutinib than in those who received ibrutinib (HR 0.65; 95% CI 0.49–0.86; P=0.0024; see Figure). The corresponding 2-year PFS rates were 79.5% and 67.3%. Prof. Brown added that this result was consistent in patients with del(17p) and/or TP53-mutated disease (n=150; HR 0.52; 95% CI 0.30–0.88; P=0.134). The 2-year PFS rates for this subgroup of patients were 77.6% and 55.7%. Additionally, fewer patients died in the zanubrutinib group compared with the ibrutinib group (14.7 vs 18.5%; HR 0.76; 95% CI 0.51–1.11), but this did not reach statistical significance.

Figure: Zanubrutinib significantly superior to ibrutinib regarding PFS [1]



PFS, progression-free survival.

According to Prof. Brown, the safety profile of zanubrutinib was more favourable than that of ibrutinib. Serious adverse events (AEs) occurred in 42.0% of participants on zanubrutinib and in 50.0% of participants on ibrutinib. AEs leading to treatment discontinuation were observed in 15.4% of the participants in the zanubrutinib arm and in 22.2% of the participants in the ibrutinib arm. Importantly, a lower rate of serious cardiac AEs was reported for participants receiving zanubrutinib than for those receiving ibrutinib (1.9% vs 7.7%).

The ALPINE study showed the superiority of zanubrutinib over ibrutinib with regard to PFS in patients with relapsed or refractory CLL/SLL. Moreover, this head-to-head comparison revealed a favourable safety profile of zanubrutinib.

1. Tam CS, et al. Lancet Oncol. 2022;23(8):1031–1043.
2. Brown JR, et al. Zanubrutinib Demonstrates Superior Progression-Free Survival (PFS) Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL): Results from Final Analysis of ALPINE Randomized Phase 3 Study. Late-Breaking Abstract 6, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Ibrutinib plus venetoclax displays long-term benefits in CLL

The 5-year follow-up data of the CAPTIVATE study demonstrated that first-line ibrutinib plus venetoclax delivers deep and durable responses in patients with chronic lymphocytic leukaemia (CLL), showing no difference in disease-free survival after 41 months between patients that continued on placebo or ibrutinib.

The combination of ibrutinib and venetoclax, an oral, once daily, chemotherapy-free regimen, has recently been approved in the EU as treatment for patients with previously untreated CLL. At ASH 2022, Prof. John Allan (Weill Cornell Medicine, NY, USA) presented long-term follow-up data of the phase 2 CAPTIVATE study (NCT02910583), a trial that evaluated the efficacy and safety of this combination, for which the primary results were presented previously [1,2]. After completion of the pre-randomised combination therapy, patients were

randomised 1:1 to continued ibrutinib or placebo. The current analysis focused on the comparison between these arms in a cohort of patients that displayed confirmed undetectable minimal residual disease (uMRD; n=86) after completion of the pre-randomised combination treatment.

Prof. Allan showed that the 3-year disease-free survival rates were high and not significantly different in the 2 arms of the study, with a rate of 85% in the placebo arm and a rate of 93% in the ibrutinib arm (HR 0.44; 95% CI 0.13–1.45; log-rank P=0.16). Furthermore, 36 months after randomisation, MRD negativity was observed in 63% of the participants on ibrutinib and in 58% of those on placebo. The 4-year progression-free survival rates were 95% and 88% in the ibrutinib arm and placebo arm, respectively. Finally, Prof. Allan mentioned that the incidence of adverse events post-randomisation was low and that no new grade ≥3 haemorrhagic events were reported.

In conclusion, the combination regimen of ibrutinib and venetoclax resulted in deep and durable response in newly diagnosed patients with CLL.

1. Allan JN, et al. Treatment outcomes after undetectable MRD with first-line ibrutinib plus venetoclax: fixed-duration treatment (placebo) versus continued ibrutinib with up to 5 years follow-up in the CAPTIVATE study. Abstract 92, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
2. Wierda WG, et al. J Clin Oncol. 2021;39(34):3853–3865.

Multiple Myeloma

Talquetamab further investigated in heavily pre-treated MM after promising phase 2 data

Talquetamab demonstrated a favourable safety profile and promising response rates in a heavily pre-treated group of patients with multiple myeloma (MM) in the phase 1/2 MonumenTAL-1 study, even in those who received prior T-cell redirection therapy. A phase 3 study is initiated to compare this investigational agent with approved therapies.

"Talquetamab is a novel, first-in-class, T cell-redirecting, bispecific antibody, targeting the antigen GPRC5D," said Prof. Ajai Chari (Mount Sinai School of Medicine, NY, USA) [1,2]. In the phase 1 part of the MonumenTAL-1 study (NCT03399799), talquetamab showed an overall response rate (ORR) of 64–70% in patients with relapsed/refractory MM [2]. Prof. Chari presented the results of the phase 2 part of MonumenTAL-1, including 288 patients with MM who had received at least 3 prior lines of therapy and of a cohort of patients who had received prior T-cell redirection therapy (NCT04634552; n=51). Participants were randomised 1:1 to either 0.4 mg/kg talquetamab every week or to a dose of 0.8 mg/kg bi-weekly.

In participants who were triple-class refractory, the ORRs were 72.6% and 71.0% for once weekly dosing and bi-weekly dosing, respectively. Similarly, in penta-drug-refractory participants, the corresponding ORRs were 71.4% and 70.6%. Furthermore, the ORRs in the cohort of participants who had received prior T-cell redirection therapy were 72.2% for those who had received prior CAR-T therapy (n=36) and 44.4% for those who had received prior bispecific antibody therapy (n=18).

As for safety, grade 3/4 anaemia, neutropenia, lymphopenia, and thrombocytopenia were reported in approximately 20–30% of participants in both dosing groups. Prof. Chari commented that cytopenia was generally limited to the first few cycles. Also, grade 3/4 infections occurred in 11.7–16.8% of the participants. Rates of non-haematological adverse events (AEs) of grade 3 or 4 were not higher than 3.5% for a specific event. The most common any-grade AEs were cytokine release syndrome (CRS; 79.0%), skin-related AEs (55.9%), and nail-related AEs (51.7%). "The CRS events were mostly of grade 1 or 2 and occurred predominantly during the step-up phase or during the administration of the first full dose," added Prof. Chari.

Talquetamab showed a manageable safety profile and encouraging efficacy results in the current phase 1/2 study. "The lack of an infection profile and cytopenia make this investigational drug an ideal candidate to combine with other agents," argued Prof. Chari. The phase 3 MonumenTAL-3 study (NCT05455320) will investigate talquetamab in combination with daratumumab and pomalidomide or

talquetamab in combination with daratumumab versus daratumumab, pomalidomide, and dexamethasone.

1. Chari A, et al. Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM): Phase 1/2 Results from MonumenTAL-1. Abstract 157, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
2. Minnema M, et al. J Clin Oncol. 2022;40(16_suppl):8015–8015.

Promising results of elranatamab for MM in phase 2 MagnetisMM-3 trial

Elranatamab displayed a manageable safety profile in patients with relapsed/refractory multiple myeloma (MM) in the phase 2 MagnetisMM-3 trial. Furthermore, the investigational agent demonstrated promising efficacy data, supporting the continued investigation of elranatamab.

Elranatamab is a humanised, bispecific antibody targeting BCMA-expressing MM cells and CD3-expressing T cells [1]. The MagnetisMM-3 study (NCT04649359) tested this agent in 187 patients with relapsed/refractory MM across 2 cohorts [2]. Prof. Nizar Bahlis (University of Calgary, Canada) presented the results of cohort A, including a patient population that had no prior exposure to BCMA-directed therapy (n=123). Notably, 96.7% of the participants was triple-class refractory at baseline. After 2 step-up doses of 12 mg and 32 mg respectively, the participants received 76 mg elranatamab once weekly, subcutaneously administered. The primary endpoint was the objective response rate (ORR) per blinded independent central review.

The confirmed ORR was 61.0%. In addition, 55.3% of the participants had at least a very good partial response and 27.6% had a complete or stringent complete response. Moreover, among partcipants who reached an objective response, the median time to response was 1.2 months. The median progression-free survival and overall survival had not been reached after 10.4 months of follow-up.

According to Prof. Bahlis, the safety profile of elranatamab was manageable. Haematologic events were the most common grade 3 or 4 treatment-emergent adverse events: anaemia (36.6%), neutropenia (48.0%), thrombocytopenia (22.0%), lymphopenia (24.4%). Furthermore, cytokine release syndrome (CRS) occurred in 57.7% of the participants, with all of these events being of grade 1 or 2 severity. Prof. Bahlis added that the step-up priming regimen that was applied in this study mitigated the rate and severity of CRS. Finally, infections were seen in 66.7% of the participants, 35.0% being grade 3 or 4 infections.

So, in the phase 2 MagnetisMM-3 trial, elranatamab was well tolerated and efficacious in patients with relapsed/refractory MM, supporting the further investigation of this agent as monotherapy or in combination with other agents. The phase 3 MagnetisMM-5 trial (NCT05020236) evaluates elranatamab in relapsed/refractory MM and the phase 3 MagnetisMM-7 study (NCT05317416) tests elranatamab in patients with newly diagnosed MM as a post-transplant maintenance therapy.

1. Shah N, et al. Leukemia. 2020;34:985–1005.
2. Bahlis N, et al. Efficacy and Safety of Elranatamab in Patients with Relapsed/Refractory Multiple Myeloma Naïve to B-Cell Maturation Antigen (BCMA)-Directed Therapies: Results from Cohort a of the Magnetismm-3 Study. Abstract 159, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Deep and durable responses for quadruple therapy in smouldering MM

The quadruple therapy of daratumumab, carfilzomib, lenalidomide, and dexamethasone was well tolerated in patients with smouldering multiple myeloma (MM), with similar toxicities as those observed in active MM. Furthermore, many patients were still in deep response at 2 years. Long-term follow-up will provide insights on whether some of these patients can be cured through this regimen.

"Smouldering MM is a so-called precursor condition and patients with this condition have a high risk to progress to active MM," explained Prof. Shaji Kumar (Mayo Clinic, MN, USA). The phase 2 ASCENT trial (NCT03289299) was designed to assess whether an intense, limited duration, quadruple therapy can result in long-term responses or cure patients with smouldering MM and high-risk disease (n=87) [1]. An induction regimen of 6 4-week cycles with daratumumab, carfilzomib, lenalidomide, and dexamethasone was followed by 6 4-week cycles of consolidation therapy and 12 4-week cycles of maintenance therapy with lenalidomide and daratumumab. The primary endpoint was the rate of confirmed stringent complete response (sCR).

The sCR rate was 38% and the CR rate and very good partial response rate were 26% and 30%, respectively. In addition, 84% of the participants achieved marrow MRD-negativity (10^{-5}). The progression-free survival rate at 3 years was 89.9%.

In 81% of the participants a treatment-emergent adverse event (AE) of any grade was observed. Also, 18% of the participants experienced a grade 3 haematological toxicity and 51% had a non-haematological toxicity. A decreased neutrophil count, hypertension, and pneumonia were the most common grade 3 AEs. Finally, 4 deaths were reported, 2 due to COVID-19, 1 because of an RSV infection, and 1 patient died due to disease progression.

"After 2 years, many patients that were included in this study are still in deep response," said Prof. Kumar. "Are we able to actually cure some of these patients? The answer to that question has to come from long-term follow-up."

1. Kumar S, et al. Fixed Duration Therapy with Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone for High Risk Smoldering Multiple Myeloma-Results of the Ascent Trial. Abstract 757, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Ultra-sensitive MRD assessment in MM with BloodFlow

Assessing minimal residual disease (MRD) with BloodFlow in peripheral blood demonstrated to be able to detect MRD with a sensitivity down to 10-8 in patients with multiple myeloma (MM). Furthermore, MRD assessment in peripheral blood was prognostic of disease outcomes if patients followed maintenance therapy or if they were under observation.

"Since bone marrow MRD assessment is an invasive procedure, periodic evaluation is precluded," said Dr Laura Notarfranchi (University of Parma, Italy). "Assessing MRD in peripheral blood could overcome this limitation. However, the sensitivity of peripheral blood assessment needs to be increased to 10-7 or 10-8 to reduce the number of false negatives."

Dr Notarfranchi and colleagues first confirmed that MRD assessment in peripheral blood using next-generation flow (NGF) was prognostic of progression-free survival in patients with MM (cohort of 138 patients with MM) who were enrolled in the GEM2014MAIN trial (NCT02406144]) [1]. However, MRD assessment in bone marrow was more sensitive with 33 MRD-positive patients detected versus 15 on placebo ($P<0.001$).

Next, the researchers assessed MRD in 353 samples of peripheral blood via a novel method called BloodFlow and found this was more sensitive than using NGF, detecting MRD-positive cases with a sensitivity down to 6×10^{-8}. In total, 33 MRD-positive cases were detected via BloodFlow and 14 via NGF. Furthermore, BloodFlow showed a negative predictive value of 77%, with 41 out of 199 paired samples (20.5%) showing a false negative result in BloodFlow compared with NGF in bone marrow. "MRD assessment during induction therapy or intensification of therapy was more frequently associated with false negative results in peripheral blood assessment," explained Dr Notarfranchi.

Finally, a preliminary analysis of 33 patients of the GEM2014MAIN trial that were receiving maintenance therapy or were under observation showed that MRD assessment via BloodFlow in peripheral blood was prognostic of progression-free survival, suggesting that periodic evaluation of MRD via BloodFlow in peripheral blood may help physicians in the monitoring of these patients, although the clinical relevance still has to be proven.

1. Notarfranchi L, et al. Ultra-Sensitive Assessment of Measurable Residual Disease (MRD) in Peripheral Blood (PB) of Multiple Myeloma (MM) Patients Using Bloodflow. Abstract 865, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

CAR-Hematotox score proves useful in relapsed/refractory MM

In patients with relapsed/refractory multiple myeloma (MM) receiving BCMA-directed CAR T-cell therapy, high CAR-Hematotox scores (HT-high) were associated with an increased risk for severe haematotoxicity, severe infections, and a reduced progression-free survival (PFS) and overall survival (OS) in this retrospective study. According to the authors, these results suggest that the CAR-Hematotox score can be used to drive risk-adapted management strategies for these patients.

"Prolonged cytopenia and infectious complications substantially contribute to the toxicity burden of CD19-directed CAR T-cell therapy," explained Dr Kai Rejeski (LMU Munich, Germany). The CAR-Hematotox score was developed to estimate the risk for haematotoxicity, infections, and poor treatment outcomes after CD19-directed CAR T-cell therapy. Whether this tool has utility in patients with relapsed/refractory MM receiving BCMA-directed CAR T-cell therapy had not yet been established. Dr Rejeski and colleagues performed a retrospective analysis on patients with relapsed/refractory MM receiving either ide-cel or cilta-cel to assess the use of the CAR-Hematotox score in this population (n=113) [1].

HT-high scores at baseline were significantly associated with a poor performance status, high disease activity, prior autologous stem cell transplant, poor renal function, and increased bone marrow infiltration. Also, patients with HT-high scores had an increased risk for prolonged neutropenia compared with patients with HT-low scores (mean 9 vs 3 days; P<0.001). Other haematological toxicities were also more common among patients with HT-high scores (see Figure). Furthermore, the rate of severe infections was significantly higher in patients with HT-high scores than in patients with HT-low scores (40% vs 5%; P<0.0001), mostly driven by an increased rate of bacterial infections (34% vs 3%; P<0.0001). Finally, HT-high scores were linked to poorer PFS (median 5.4 vs 14.9 months; P<0.0001) and OS (median 10.5 vs not reached; P<0.0001) outcomes.

Figure:CAR T-mediated haematotoxicity in HT-high and HT-low patients [1]

		CAR-Hematotox score		
Clinical features: CAR T-mediated haematotoxicity	**All patients (n=113)**	**Low (n=63)**	**High (n=50)**	**P**
Severe thrombocytopenia (platelet count >50 G/L)				
Day 0–30	56 (49.6%)	17 (27.0%)	39 (78%)	**<0.0001**
Day 31–100	32 (28.3%)	4 (6.3%)	28 (56%)	**<0.0001**
Severe anaemia (Hb <8 g/dL or requiring transfusion)				
Day 0–30	56 (49.6%)	14 (22.2%)	42 (84%)	**<0.0001**
Day 31–100	30 (26.5%)	6 (9.5%)	24 (48%)	**<0.0001**
Neutropenia				
Severe (ANC <500/µ)				
Day 0–30	82 (72.6%)	40 (63.5%)	42 (84%)	**0.02**
Day 31–100	22 (19.5%)	4 (6.3%)	18 (36%)	**<0.0001**
Protracted, severe (ANC <500/µ for ≥7 days)	28 (24.8%)	5 (7.9%)	23 (46%)	**<0.0001**
Profound (ANC <100/µ) Day 0–100	33 (29.2%)	12 (19.0%)	21 (42%)	**0.01**
Protracted, profound (ANC <100/µ for ≥7 days)	7 (6.2%)	0 (0%)	7 (14%)	**0.003**
Prolonged (ANC <1000/µ measured ≥21 days after CAR-T)	57 (50.4%)	21 (33.3%)	36 (72%)	**<0.0001**

Hb, hemoglobin; ANC, absolute neutrophil count.

1. Rejeski K, et al. The CAR-Hematotox Score As a Prognostic Model of Toxicity and Response in Patients Receiving BCMA-Directed CAR-T for Relapsed/Refractory Multiple Myeloma. Poster 3343, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Head-to-head: VMP versus Rd in transplant-ineligible MM

A head-to-head comparison between bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd) did not show a progression-free survival (PFS) difference between both treatment regimens in transplant-ineligible patients with multiple myeloma (MM). However, a trend was observed that VMP seems to be the better option in high-risk patients.

"VMP and Rd are both standard therapies for patients with untreated MM who cannot receive transplant," explained Dr Sara Bringhen (Università degli Studi di Torino, Italy). "It has not yet been established whether one of the treatment regimens leads to better health outcomes than the other." To investigate this matter, the phase 4 REAL-MM trial (NCT03829371) randomised 231 patients with newly diagnosed MM who were ineligible for transplant 1:1 to VMP or Rd [1]. The primary outcome was PFS.

After a median follow-up of 18.9 months, there was no difference in PFS between participants in the VMP arm and those in the Rd arm (HR 0.82; 95% CI 0.51–1.31; P=0.41), with 2-year PFS rates of 56% and 55%. Although the association was not significant, the data showed that in participants with high cytogenetic risk (n=35), VMP may be preferred over Rd (HR 0.22; 95% CI 0.05–1.07; P=0.06). Dr Bringhen added that there was no PFS difference according to frailty status. Finally, the 2-year overall survival (OS) rates appeared to favour participants who were treated with VMP (89% vs 75%; HR 0.53; 95% CI 0.26–1.07; P=0.076). However, longer follow-up is needed to evaluate whether this trend will lead to a significant OS benefit.

1. Bringhen S, et al. Bortezomib-Melphalan-Prednisone (VMP) Vs. Lenalidomide-Dexamethasone (Rd) in Transplant-Ineligible Real-Life Multiple Myeloma Patients: Updated Results of the Randomized Phase IV Real MM Trial. Abstract 751, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Lymphoma

Ibrutinib added to ASCT improves clinical outcomes in mantle cell lymphoma

In patients with previously untreated mantle cell lymphoma (MCL), autologous stem cell transplantation (ASCT) plus ibrutinib maintenance outperformed ASCT alone with regard to failure-free survival. Furthermore, ASCT alone did not prove to be superior to ibrutinib maintenance, but ibrutinib appeared to be favoured over ASCT in terms of toxicity.

The phase 3 Triangle study (NCT02858258) randomised 870 patients with previously untreated MCL younger than 66 years old 1:1:1 to 3 study arms:

- Arm A: R-CHOP/R-DHAP chemotherapy followed by ASCT and observation
- Arm A+I: R-CHOP/R-DHAP chemotherapy followed by ASCT and 2 years of ibrutinib maintenance therapy
- Arm I: R-CHOP/R-DHAP chemotherapy followed by ibrutinib maintenance therapy

Of note, rituximab maintenance was added to all 3 arms, following national guidelines. The primary endpoint was failure-free survival. Prof. Martin Dreyling (University Hospital Munich, Germany) presented the results [1].

The A+I arm was superior to the A arm in terms of failure-free survival, with 3-year rates of 88% and 72% (HR 0.52; P=0.0008). Next, the A arm did not outperform the I arm: the 3-year failure-free survival rate was 72% in the A arm and 86% in the I arm (HR 1.77; P=0.9979). Prof. Dreyling added that it was too soon to call whether the A+I arm was superior to the I arm. Similarly, the overall survival (OS) data were premature at time of the presentation, with 3-year OS rates of 86%, 91%, and 92% in the A arm, the A+I arm, and the I arm, respectively.

Haematologic adverse events (AEs) of grade 3 or higher appeared to be higher in the A+I arm (50%) than in the I arm (28%) or in the A arm (21%). Likewise, the rate of infection grade ≥3 was elevated in the A+I arm (25%) compared with the I arm (19%) and the A arm (13%).

1. Dreyling M, et al. Triangle: autologous transplantation after a rituximab/ibrutinib/ara-c containing induction in generalized mantle cell lymphoma – a randomized European MCL network trial. Abstract 1, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

High-dose chemotherapy plus ASCT superior to standard immuno-chemotherapy in primary CNS lymphoma

Consolidation high-dose chemotherapy followed by autologous stem cell transplantation (HCT/ASCT) significantly improved overall survival (OS) and progression-free survival (PFS) compared with consolidation non-myeloablative immuno-chemotherapy in patients with primary CNS lymphoma.

The phase 3 MATRix/IELSG43 trial (NCT02531841) included immunocompetent patients with newly diagnosed primary CNS lymphoma to receive 4 cycles of MATRIx immuno-chemotherapy. Hereafter, responders (n=230) were randomised 1:1 to receive 2 cycles of consolidation R-DeVIC immuno-chemotherapy or HCT/ASCT. The chemotherapy regimen consisted of carmustine and thiotepa or busulfan and thiotepa. Prof. Gerald Illerhaus (Klinikum Stuttgart, Germany) presented the PFS results, the primary endpoint of this trial [1].

After a median follow-up of 45.3 months, the PFS was significantly longer in the HCT/ASCT arm than in the R-DeVIC arm (HR 0.41; 95% CI 0.25–0.65; P=0.0002), with corresponding 3-year PFS rates of 79% and 53%. Likewise, OS was improved in the HCT/ASCT arm compared with the R-DeVIC arm (HR 0.46; 95% CI 0.26–0.81; P=0.0077). The 3-year OS rates were 86% and 71%, respectively.

Haematological adverse events (AEs) of grade 3 and 4 appeared to occur more often in the HCT/ASCT arm than in the R-DeVIC arm: neutropenia (75% vs 56%), thrombocytopenia (95% vs 83%), and anaemia (75% vs 69%). Also, grade 3 and 4 infections (53% vs 14%) and oral mucositis (55% vs 0%) were more prevalent in the HCT/ASCT arm.

The current phase 3 trial showed that HCT/ASCT results in improved PFS and OS rates compared with R-DeVIC therapy in patients with newly diagnosed primary CNS lymphoma. In order to reduce adverse events during the induction phase, a shorter induction therapy with R-MTX pre-treatment and 2 cycles of MATRix is currently being investigated in the OptiMATe trial (NCT04931368).

1. Illerhaus G, et al. Effects on Survival of Non-Myeloablative Chemoimmunotherapy Compared to High-Dose Chemotherapy Followed By Autologous Stem Cell Transplantation (HDC-ASCT) As Consolidation Therapy in Patients with Primary CNS Lymphoma - Results of an International Randomized Phase III Trial (MATRix/IELSG43). Late-Breaking Abstract 3, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Odronextamab has considerable anti-tumour effects in relapsed/refractory diffuse large B-cell lymphoma and follicular lymphoma

Odronextamab, an investigational bispecific antibody targeting CD20 and CD3, showed promising anti-tumour activity in heavily pre-treated patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma in a phase 2 study. The agent also had a manageable safety profile.

The phase 1 ELM-1 trial (NCT02290951) evaluated odronextamab in patients with relapsed/refractory DLBCL [1]. The positive results of this trial instigated the pivotal phase 2 ELM-2 trial (NCT03888105) [2]. Here, the study population was divided in 5 disease-specific cohorts. The DLBCL cohort included 140 patients who relapsed after or were refractory to at least 2 lines of therapy. After a 21-day step-up cycle, patients received 160 mg odronextamab once weekly, intravenously administered for 3 cycles. Hereafter, they received 320 mg biweekly. The primary endpoint was the objective response rate (ORR) by independent central review. Prof. Won-Seog Kim (Samsung Medical Center, South Korea) presented the first interim results.

After a median follow-up time of 21.3 months, the ORR was 49.2%, with a complete response (CR) rate of 30.8% and a partial response (PR) rate of 18.5%. Prof. Kim added that results from an expansion cohort of the phase 1 ELM-1 study (n=30) showed that the ORR was 48.4% (CR 32.3%; PR 16.1%) in patients who had received prior CAR T therapy. Furthermore, in the phase 2 study, the median duration of response was 10.2 months, and the median duration of CR was 17.9 months.

A grade ≥3 treatment-emergent adverse event (AE) occurred in 52.9% of the patients. The most common, any grade, treatment-emergent AEs were cytokine release syndrome (CRS; 54.3%), pyrexia (22.1%), neutropenia (20.7%), and anaemia (20.0%). Treatment-emergent AEs led to treatment discontinuation in 7.9% of the participants. Prof. Kim added that the optimised step-up regimen reduced the incidence of grade 2 and 3 CRS events to 13.7% and 1.4%, respectively. Infections of grade ≥3 were seen in 32.9% of the participants. Finally, immune effector cell-associated neurotoxicity syndrome (ICANS) was rare, with only 1 grade 3 event in all participants.

Prof. Tae Min Kim (Seoul National University Hospital, South Korea) presented the results of the cohort of patients with follicular lymphoma who were refractory to or relapsed after ≥2 lines of therapy (n=131) [3]. The ORR by independent central review in this patient population was 81.8% after 22.4 months of follow-up, with a CR rate of 75.2%. Prof. Kim added that the ORR after 12 weeks was comparable in patients who received the 1/20 mg step-up regimen (72.1%) and in patients who were exposed to the 0.4/7/20 mg step-up regimen (75.5%). The results were consistent across high-risk subgroups. Furthermore, the median duration of response was 20.5 months, and the median progression-free survival was 20.2 months. In this population of patients with relapsed/refractory follicular lymphoma, 77.9% of the patients experienced at least 1 grade 3 or higher treatment-emergent AE. The safety profile was comprised of a similar pattern of AEs as in the DLBCL group.

The first results of the phase 2 ELM-2 trial showed the encouraging efficacy and manageable safety profile of odronextamab in patients with either heavily pre-treated DLBCL or heavily pre-treated follicular lymphoma. Phase 3 trials will be initiated to further assess this agent in these disease areas.

1. Bannerji R, et al. Lancet Haematol. 2022;9(5):e327–e339.
2. Kim WS, et al. Odronextamab in Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL): Results from a Prespecified Analysis of the Pivotal Phase II Study ELM-2. Abstract 444, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
3. Kim T, et al. Odronextamab in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) Grade 1–3a: Results from a Prespecified Analysis of the Pivotal Phase II Study ELM-2. Abstract 949, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Excellent results for AFM13-complexed NK cells in CD30-positive lymphoma

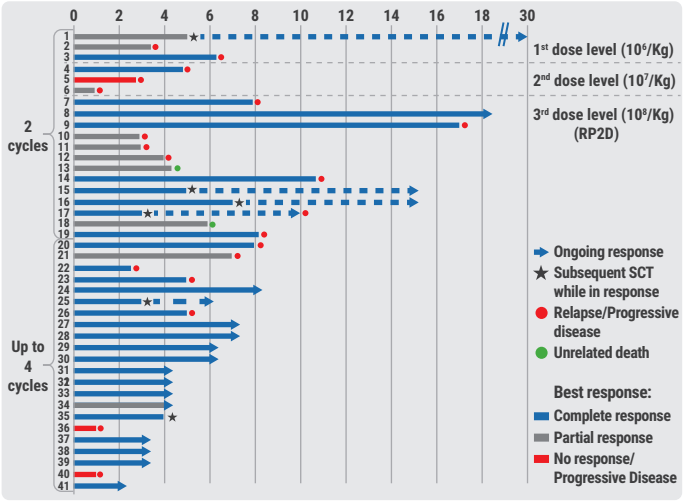
Cord blood-derived, pre-activated, expanded natural killer (NK) cells, pre-complexed with AFM13, was a well-tolerated therapy in patients with double refractory CD30-positive lymphoma, and displayed promising anti-tumour activity at the recommended phase 2 dosing.

"AFM13 is a bispecific antibody targeting CD30 at lymphoma cells and CD16A at NK cells," said Dr Yago Nieto (University of Texas, TX, USA). "Since autologous NK cells of patients with lymphoma are dysfunctional, the current phase 1 study (NCT04074746) pre-complexed allogeneic NK cells with

AFM13 to increase the cytotoxic capacity [1]." Cord blood-derived NK cells were pre-activated with IL-12/IL-15/IL-18, expanded with universal antigen-presenting cells, K562 feeder cells, and IL-2, and pre-complexed with AFM13 (100 µg/mL). Hereafter, patients with relapsed or refractory CD30-positive lymphoma (n=41) received weekly infusions of the AFM13-complexed NK cells at 3 dose levels: 106 NK/kg, 10^7 NK/kg, 10^8 NK/kg. The primary objectives of this study were to evaluate the safety of this approach and to establish the recommended phase 2 dose. Of note, the included patients had received a median number of 7 prior lines of therapy.

The investigational agent was well tolerated, with no cases of cytokine release syndrome, neurotoxicity, or graft-versus-host disease. Grade 3 (30%) or 4 (29%) neutropenia, and grade 3 (15%) or 4 (30%) thrombocytopenia after cycles 3 and 4 were the expected haematological toxicities. However, no bleeding events were reported. According to Dr Nieto, the phase 2 dose level was established at 108 NK/kg. To continue, the 35 patients who were treated at the phase 2 dose achieved an overall response rate of 94.2%. In addition, the complete response rate was 71.4% (see Figure). Furthermore, the 6-month overall survival probability was 85% in the total population and 96% in those who received 4 cycles of the phase 2 dose (n=22).

Figure: Clinical response after first AFM13-complexed NK infusion [1]



RP2D, recommended phase 2 dose.

In conclusion, AFM13-complexed NK cells were well tolerated and resulted in high anti-tumour activity in a heavily pre-treated population of patients with CD30-positive lymphoma, supporting further investigation of this approach.

1. Nieto Y, et al. Innate Cell Engager AFM13 Combined with Preactivated and Expanded Cord Blood-Derived NK Cells for Patients with Double Refractory CD30+ Lymphoma. Abstract 168, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

CAR-Hematotox score predicts toxicity, infections, and clinical outcomes in MCL

Patients with relapsed or refractory mantle cell lymphoma (MCL) and a high CAR-Hematotox score had an increased risk for haematological toxicity, infections, and an inferior progression-free survival and overall survival following treatment with brexucabtagene autoleucel (brexu-cel). According to the authors, stratifying patients for the risk of haematological toxicity may aid physicians to tailor the management of their patients.

CAR T-related haematological toxicity is a frequently occurring phenomenon, and prolonged cytopenia and complications due to infections contribute to the toxicity burden of CD19-directed CAR T therapy [1]. "The CAR-Hematotox score predicts the risk for prolonged neutropenia, severe infections, and poor treatment outcomes after CD19 CAR T-cell therapy," said Dr Kai Rejeski (LMU Munich, Germany) [1,2]. The use of this tool in patients with relapsed/refractory MCL undergoing CD19 CAR T-cell therapy has not yet been established. Therefore, the current international, multicentre, retrospective study analysed the applicability of the CAR-Hematotox score in 103 patients with relapsed/refractory MCL receiving brexu-cel.

At baseline, high CAR-Hematotox scores (HT-high) were related to aggressive disease biology, increased bone marrow infiltration, a higher number of prior treatments, and increased disease activity. It was demonstrated that patients with HT-high had higher risk for haematologic toxicity than patients with HT-low: neutropenia (median 14 vs 6 days; P<0.001); aplastic phenotype (47% vs 0%; P<0.001); severe anaemia (45% vs 11%; P<0.0001); profound (85% vs 46%; P<0.0001) or prolonged cytopenia (66% vs 30%; P<0.0004). Furthermore, severe infections were more common in HT-high patients than in HT-low patients (30% vs 5%; P=0.001), mostly driven by an increase in bacterial infections (28% vs 5%; P=0.002). Finally, after 720 days of follow-up, HT-high scores were associated with poorer progression-free survival (38% vs 79%; P<0.0001) and overall survival (52% vs 90%; P=0.00016).

In summary, HT-high patients had an increased risk to develop severe haematotoxicity and infectious complications

and had a reduced progression-free and overall survival compared with HT-low patients. Dr Rejeski commented that a risk stratification for haematological toxicity and infections should be performed before lymphodepletion in order to initiate prophylactic strategies in time.

1. Rejeski K, et al. Blood. 2021;138(24):2499–2513.
2. Rejeski K, et al. The CAR-Hematotox Score Identifies Patients at High Risk for Hematological Toxicity, Infections and Poor Clinical Outcomes Following Brexucabtagene Autoleucel in Relapsed/Refractory Mantle Cell Lymphoma. Abstract 264, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Myeloproliferative Neoplasms

INCA033989: novel investigational agent for *CALR*-mutated MPN

The novel monoclonal antibody INCA033989 is a potent antagonist of mutant calreticulin (CALR) function, selectively inhibiting the proliferation of *CALR*-mutated haematopoietic stem and progenitor cells (HSPCs), and potentially changing the course of disease in essential thrombocythemia and myelofibrosis by targeting disease-initiating cells. A phase 1 study of INCA033989 is planned to be launched in 2023.

"Myeloproliferative neoplasms (MPN) are a group of chronic myeloid blood cancers that develop following the acquisition of mutations in haematopoietic stem cells that subsequently drive overproduction of cells of the myeloid lineage," outlined Prof. Bethan Psaila (University of Oxford, UK). "The same genetic lesions result in diverse clinical manifestations. Current therapies do not selectively target the MPN clone." She continued to explain that *CALR* mutations are present in a substantial proportion of patients with MPN that do not harbour the *JAK2V617* mutation [1].

INCA033989 is a fully human, mutant CALR-specific monoclonal antibody, antagonising mutant CALR-induced signalling, and oncogenic function. Dr Edimara Reis (Incyte Corporation, DE, USA) discussed the most important findings of the study that evaluated this novel monoclonal antibody [2], summarised as follows:

INCA033989:

- selectively binds to mutant CALR on engineered Ba/F3 cells, reverts mutant CALR-induced TPOR dimerisation on *CALR*-mutated or *HAP1* wildtype cells and inhibits mutant CALR-induced oncogenic signalling.
- selectively inhibits cell proliferation and induces death of *CALR*-mutated cells and selectively inhibits pSTAT5 in primary CD34-positive *CALR*-mutated cells of patients with MPN and inhibits the proliferation of *CALR*-mutated HSPCs from healthy donors or patients with MPN
- In a murine model of essential thrombocythemia, an INCA033989 surrogate restored haematologic and molecular responses and re-established normal megakaryopoiesis in a murine model and selectively targeted *CALR*-mutated disease-initiating clones

According to the authors, these results warrant further investigation of INCA033989 in MPN, especially in patients with myelofibrosis or essential thrombocythemia with *CALR* mutations.

1. Klampfl T, et al. N Engl J Med. 2013;369:2379–2390.
2. Reis E, et al. Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms (MPNs). Abstract 6, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Ruxolitinib mediates clonal evolution of RAS pathway mutations in MPN

The JAK inhibitor ruxolitinib was associated with *RAS*-mutated clonal evolution in myeloproliferative neoplasms (MPN). Mutations could occur in both clones with or without an MPN driver mutation. Presence of *RAS* mutations was associated with worse clinical outcomes in ruxolitinib-treated patients.

"Genetic resistance to targeted therapies in cancer, and especially in haematological cancer, have been well characterised," said Dr Nabih Maslah (Université Paris Cité, France). "The major mechanism of resistance that was revealed was point-mutation of the oncogenic target, but

it was recently demonstrated that downstream activation of the target is another mechanism of resistance in *FLT3*-mutated acute myeloid leukaemia (AML) [1,2]." The current study investigated whether JAK inhibition with ruxolitinib promotes clonal evolution in MPN [3].

In a selection of patients with myelofibrosis and available molecular data of the St Louis cohort (n=73), ruxolitinib treatment was an independent factor of *RAS* pathway mutation acquisition (HR 9.8; 95% CI 1.2–78.9; P=0.031).

To answer the question whether ruxolitinib treatment initiates clonal selection of *RAS*-mutated cells, CD34-positive cells were cultivated from patients with primary MPN known to harbour *RAS* pathway mutations. After 10 days of treatment with ruxolitinib, in cells treated with the JAK inhibitor, there was an increase in *RAS* mutation variant allelic frequency (VAF) and this was associated with a decrease of the MPN driver mutation (*JAK2*, *CALR*, or *MPL*) VAF. This raised the issue of potential co-occurring *RAS* mutations and MPN driver mutations within the same clones. DNA single-cell sequencing subsequently showed that *RAS* mutations can be acquired in either a driver or a non-driver clone.

Furthermore, Dr Maslah showed data that ruxolitinib-treated MPN patients who harboured *RAS* pathway mutations had worse clinical outcomes than patients with unmutated MPN (decreased transformation-free survival: HR 6.7; 95% CI 19–23.2; P=0.003). In patients who did not receive ruxolitinib, this association was not observed. Approximately half of the ruxolitinib-treated patients transformed to AML or myelodysplastic syndrome (MDS), whereas only 1 out of 6 ruxolitinib-untreated patients transformed to AML or MDS [4,5].

These results were further investigated and corroborated in *JAK*-mutated cell lines and murine models. The authors suggest screening for *RAS* mutations before treatment with ruxolitinib to avoid this clonal evolution and subsequent negative clinical outcomes.

1. Quek L, et al. Nat Med. 2018;24(8):1167–1177.
2. McMahon CM, et al. Cancer Discov. 2019;9(8):1050–1063.
3. Maslah N, et al. JAK Inhibition Mediates Clonal Selection of RAS Pathway Mutations in Myeloproliferative Neoplasms. Abstract 326, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
4. Santos FPS, et al. Leukemia. 2020;34(3):799–810.
5. Coltro G, et al. Blood Adv. 2020;4(15):3677–3687.

Immune Thrombocytopenia

Efgartigimod successful in immune thrombocytopenia

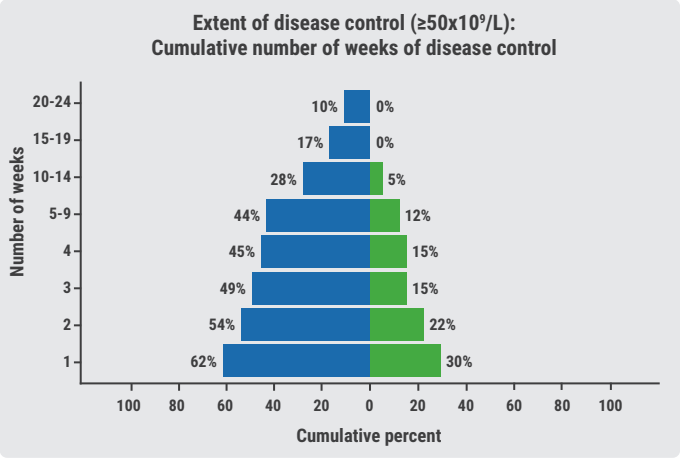
Efgartigimod, a human IgG1 Fc-fragment that prevents recycling of IgG but not albumin, significantly improved platelet counts in patients with primary immune thrombocytopenia (ITP), compared with placebo. Moreover, the phase 3 ADVANCE IV study showed that the study drug was well tolerated by the study participants.

"The effectiveness of the current treatment options for patients with ITP is limited, and better therapies are needed to improve their quality-of-life," said Prof. Catherine Broome (Georgetown University, Washington DC, USA). The ADVANCE trial (NCT04188379) randomised 131 patients with chronic or persistent ITP who had received at least 2 prior ITP treatments, or 1 prior and 1 concurrent treatment, and had platelet counts <30x10^9/L 2:1 to efgartigimod 10 mg/kg once weekly, intravenously administered, or placebo [1]. The dosing of efgartigimod was adjusted according to platelet counts that were performed during the treatment period. The primary endpoint was the proportion of patients with a sustained platelet count response, defined as ≥50x10^9 platelets/L in ≥4 out of 6 visits in week 19–24 of the study, in the absence of intercurrent events.

In total, 21.8% of the participants in the efgartigimod arm and 5.0% of the participants in the placebo arm achieved the primary endpoint, reflecting a significant difference between the arms in favour of the experimental drug (P=0.0316). In addition, the number of cumulative weeks of disease control showed a benefit for the efgartigimod arm over the placebo

arm (mean 6.1 vs 1.5; P=0.0009; see Figure). Prof. Broome added that the results were consistent across subgroups.

Figure: Efgartigimod-treated participants experienced substantially more weeks with disease control [1]



Efgartigimod was well tolerated in this study population and results were consistent with previous data that has been published on the drug [2,3]. Serious adverse events (AEs) were more prevalent in the placebo arm than in the efgartigimod arm (15.6% vs 8.1%). Prof. Broome commented that this was mostly due to an increased rate of bleeding events in the placebo arm (86.7% vs 70.9%). Finally, the infection rate was numerically slightly higher in the efgartigimod arm than in the placebo arm (29.1% vs 22.2%).

To summarise, efgartigimod was efficacious and well tolerated in patients with chronic or persistent ITP. The study results suggest that treatment adjustments can be made based on platelet counts.

1. Broome CM, et al. Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV). Abstract 3, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
2. Howard JF jr, et al. Neurology. 2019;92(23):e2661–e2673.
3. Howard JF jr, et al. Lancet Neurol. 2021;20(7):526–536.

Long-term risk for haematologic disease in persistent, isolated mild thrombocytopenia

Individuals with persistent, isolated mild thrombocytopenia (PIMT) had a much higher long-term risk of progressing towards immune thrombocytopenia (ITP) or haematologic neoplasia than healthy individuals. Furthermore, bleeding events and systemic autoimmunity were more frequently observed in individuals with PIMT than in healthy subjects.

Dr Nardeen Ayad (Massachusetts General Hospital, MA, USA) and colleagues studied the long-term risk of ITP and haematologic neoplasia in adults with PIMT of unknown aetiology over a course of >20 years [1]. The observational cohort study identified 91 patients from the Mass General Brigham research patient data registry who had platelet counts between 100–149 x 10^9/L at ≥3 visitations between 1995 and 2004 and were diagnosed with PIMT of unknown aetiology. They were matched with 364 healthy subjects. The primary outcome of the study was the progression to haematologic disease.

After a median follow-up of 20.5 years, the 25-year cumulative incidence of haematologic disease among individuals with PIMT was 37.0%; the 25-year cumulative incidences of ITP and haematologic neoplasia were 26.0% and 15.7%, respectively. Compared with healthy controls and adjusted for age, the risk for haematologic disease was much higher in the PIMT group, with a sub-distribution HR of 19.0 (95% CI 8.4–43.0; P<0.001). The sub-distribution HRs for developing ITP and haematologic neoplasia were 71.1 (95% CI 9.4–538.7; P<0.001) and 10.3 (95% CI 3.8–28.0; P<0.001), respectively.

Dr Ayad mentioned that ISTH major/CRNM minor bleedings occurred in 26% of the patients in the PIMT arm over the course of follow-up and in 2% of the healthy control subjects. Furthermore, systemic autoimmunity was observed in 13% of the patients in the PIMT group and in 3% of the healthy individuals. Finally, 21% of the patients in the PIMT group and 6% of the healthy individuals died.

"We believe that our findings have significant implications for the initial diagnostic workup of patients with mild thrombocytopenia, as well as for the potential long-term surveillance and prognosis," decided Dr Ayad.

1. Ayad N, et al. Long-Term Risk of Developing Immune Thrombocytopenia and Hematologic Neoplasia in Adults with Persistent, Isolated Mild Thrombocytopenia. Abstract 19, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Various Topics

C1 inhibitor deficiency linked to thrombosis

Hereditary angioedema (HAE) was associated with an increased contact pathway-mediated coagulation and a heightened risk for venous thromboembolic events. Interestingly, C1 inhibitor-deficient mice displayed key aspects of the pro-coagulant phenotype that is associated with HAE, revealing the crucial role of this pathway.

"Congenital C1 inhibitor deficiency causes HAE," stated Dr Steven Grover (University of North Carolina, NC, USA) [1,2]. An epidemiological study, clinical samples, and mouse models were used to assess whether C1 inhibitor deficiency increases contact pathway-mediated activation of coagulation and thrombosis.

The epidemiological study included 239 patients with HAE and 2,383 healthy controls from a Swedish registry [3]. The results showed that there was an increased risk for venous thromboembolic events for patients with HAE compared with healthy controls (OR 3.59; 95% CI 2.17–5.84; P<0.0001). For arterial thromboembolic events, no such association was observed (OR 1.30; 95% CI 0.81–2.09; P=0.28).

Next, the research team investigated the thrombin generation potential of the plasma of patients with HAE (n=19) and of healthy controls (n=20) through automated calibrated thrombography. Patients with severe HAE (C1 inhibitor activation <25%; n=10) had a reduced thrombin generation lag time and an increased thrombin generation peak compared with healthy controls. Dr Grover added that there was no difference in tissue factor-initiated thrombin generation, indicating that severe C1 inhibitor deficiency is associated with a selective enhancement of contact pathway-mediated thrombin generation.

Furthermore, in C1 inhibitor-deficient mice, the investigators found a significantly increased thrombin generation peak compared with control mice. Also, an enhanced risk for venous thrombus formation was observed in mice with severe C1 inhibitor deficiency. In line with the results of the epidemiological study, no such association was found for arterial thrombosis, therefore displaying consistency with the phenotype of HAE.

1. Grover S, et al. C1 Inhibitor Deficiency Results in Increased Activation of Coagulation and Enhanced Venous Thrombosis. Abstract 5, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
2. Davis AE, et al. Thromb Haemost. 2010;104(5):886–893.
3. Sundler Björkman L, et al. Clin Transl Allergy. 2022;12(3):e12135.

Durable responses to gene therapy in haemophilia A

The majority of patients with haemophilia A who received SPK-8011 gene therapy expressed FVIII levels within the 'mild haemophilia A' range after 5 years of follow-up. In addition, a substantial reduction in annualised bleeding rates and FVIII consumption was reported, without major safety issues.

Prof. Stacy Croteau (Harvard Medical School, MA, USA) presented long-term data from the phase 1/2 SPK-8011 study (NCT03003533/NCT03432520), that evaluated the safety and efficacy of adeno-associated virus (AAV)-mediated FVIII gene transfer for patients with haemophilia A with FVIII levels ≤2% [1]. After a 1-hour outpatient intravenous infusion, the included patients (n=24) were followed up for 52 weeks. Hereafter, a 4-year long-term follow-up study was initiated, with visitations every 3 to 6 months.

After a median follow-up of 191 weeks, no FVIII inhibitor developments, thrombotic events, or deaths were reported. One grade 2 transaminitis, related to SPK-8011 treatment, led to hospitalisation for intravenous steroid administration. Other adverse events (AEs) related to SPK-8011 treatment were 11 cases of elevated alanine transaminase and 1 participant who experienced an acute infusion reaction. Also, vector shedding was undetectable after week 12. Prof. Croteau added that durable FVIII activity was observed in most participants, with expression levels within the 'mild haemophilia' range. Furthermore, the annualised bleeding rate was reduced with 82% in participants who received prophylactic FVIII prior to the study and with 99% in participants who were on prior on-demand treatment. Finally, the annualised FVIII infusion rate was 85.5 before infusion with SPK-8011 and 0.3 after infusion.

Prof. Croteau mentioned that there is a need to manage a presumed capsid immune response to further reduce the

variability in FVIII expression following AAV-mediated gene transfer for haemophilia A. Studies that address this issue are ongoing.

1. Croteau S, et al. Long-Term Durable FVIII Expression with Improvements in Bleeding Rates Following AAV-Mediated FVIII Gene Transfer for Hemophilia A: Multiyear Follow-up on the Phase I/II Trial of SPK-8011. Abstract 783, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Long-term benefits from beti-cel in transfusion-dependent β-thalassaemia

Patients with transfusion-dependent β-thalassaemia (TDT) showed durable transfusion independence up to 8 years after a betibeglogene autotemcel (beti-cel) infusion, with an acceptable safety profile. Beti-cel transduction efficiency appeared to be the most predictive attribute of transfusion independence. Moreover, a different study displayed long-term quality-of-life improvements in patients with TDT who had received beti-cel infusion therapy.

Prof. Mark Walters (University of California, CA, USA) presented up to 8 years of follow-up efficacy and safety data of 63 patients with TDT who received beti-cel infusion therapy [1]. Transfusion independence was defined as a haemoglobin (Hb) level ≥9 g/dL without packed red blood cell transfusions for ≥12 months.

The peripheral blood vector copy number (VCN) per cell was stable and durable over time, especially in phase 3 studies, in which patients received optimised beti-cel infusion doses. Similarly, total Hb levels and therapy-derived HbA-T87Q levels were stable and durable (mean of approximately 12 g/dL and 9 g/dL) for patients who were included in phase 3 studies. Prof. Walters showed that the effect was independent of age and genotype. Furthermore, an exploratory analysis suggested that a percentage of 62% transduced cells increased the likelihood of achieving transfusion independence. Finally, 19% of the patients in phase 3 trials had ≥1 adverse event (AE) possibly related to beti-cel infusion therapy. Hepatic veno-occlusive disease occurred in 11% of the patients, but these events were resolved after treatment.

In another presentation, Prof. Franco Locatelli (University of Rome, Italy) reported the 3-year follow-up data of the LTF-303 study (NCT02633943), that investigated patient-reported outcomes in patients with TDT who received beti-cel infusion therapy (n=57) [2]. For patients who had reached transfusion independence, the SF-36 physical component score and mental component score were 55.7 and 56.3 at 3 years, which was a raise from the baseline levels of 53.8 and 50.9, respectively. A slight drop in SF-36 scores was observed in patients who had not achieved transfusion independence. In paediatric patients who reached transfusion independence (n=22), the mean PedsQL total score increased from 78.3 at baseline to 90.6 at 3 years. For those who did not achieve transfusion independence, no change in mean PedsQL total score was reported. Three years after treatment, data showed positive trends in employment/employment seeking rates (67% to 93%), school absence (95% to 50%), and physical activity (+81% improvement).

Thus, durable transfusion independence and quality-of-life improvements were reported in patients with TDT who received beti-cel infusion therapy.

1. Walters MC, et al. Long Term Outcomes of 63 Patients with Transfusion-Dependent β-Thalassemia (TDT) Followed up to 7 Years Post-Treatment with betibeglogene autotemcel (beti-cel) Gene Therapy and Exploratory Analysis of Predictors of Successful Treatment Outcomes in Phase 3 Trials. Abstract 2348, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.
2. Locatelli F, et al. Long-Term Patient-Reported Outcomes Following Treatment with betibeglogene autotemcel in Patients with Transfusion-Dependent β-Thalassemia. Abstract 3665, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Neutrodiet: non-restricted diet is the preferred option after SCT

In patients with neutropenia after stem cell transplantation (SCT), a non-restrictive diet resulted in comparable infection and death rates as a so-called 'protective' diet, demonstrating that a restrictive diet is an unnecessary burden for these patients, altering their quality-of-life.

"Infections are a major cause of morbidity and mortality during neutropenia, following SCT," said Prof. Federico Stella (Università degli Studi di Milano, Italy). Restrictive diets are widely used in centres performing SCT to prevent infections [1]. However, according to Prof. Stella, evidence for the efficacy of these practices is lacking. The non-inferiority, phase 3 Neutrodiet trial aimed to address this issue [2]. Patients who underwent an autologous or allogeneic SCT (n=230) were randomised 1:1 to a protective diet or an unrestricted diet. In the protective diet arm, the patients' food was cooked >80°C unless it was thick peel fruit. Furthermore, yogurt, honey, cold cuts and sausages, raw fish, raw meat, raw vegetables, and raw fruits were forbidden to consume. Patients in the unrestricted diet arm did not receive raw fish or raw meat either. The primary

study endpoint was the rate of grade ≥2 infections during the period of neutropenia.

No difference was observed in the rate of grade ≥2 infections between the protective diet arm and the non-restricted diet arm (65% vs 62%; RR 1.0; 95% CI 0.8–1.3; P=0.8). In addition, severe infections, gastrointestinal infections, sepsis, pneumonia, and fever of undetermined origin occurred equally often in the study arms. One death was reported in the protective diet arm and no deaths were observed in the non-restricted diet arm. Furthermore, the incidence of grade ≥3 graft-versus-host disease did not significantly differ between the two arms, with a rate of 20% in the protective diet arm and a rate of 9.5% in the non-restricted diet arm (P=0.4). Dr Stella mentioned that the mean body weight loss at 1 month was lower in the non-restricted diet arm than in the protective diet arm (2.7 kg vs 3.7 kg; P=0.04). Finally, the non-restricted diet was associated with higher satisfaction rates than the protective diet.

These results support the use of a non-restricted diet in patients with neutropenia after SCT, since a protective diet does not appear to influence infection rates but alters the patients' quality-of-life.

1. Peric Z, et al. Bone Marrow Transplant. 2018;53(8):1030–1037.
2. Stella F, et al. Non-Restrictive Diet Does Not Increase Infections in Patients with Neutropenia after Stem Cell Transplantation: Final Analysis of the Neutrodiet Multicenter, Randomized Trial. Abstract 169, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

Iptacopan offers solution for patients with PNH and residual anaemia after standard-of-care

Iptacopan outperformed standard-of-care in patients with paroxysmal nocturnal haemoglobinuria (PNH) who had residual anaemia after anti-C5 standard-of-care treatment, results from the phase 3 Apply-PNH trial demonstrated. Together with the favourable safety profile of iptacopan, this agent presents itself as a potential practice-changing treatment for this patient group.

In patients with PNH, targeting the terminal complement pathway at C5 with ravulizumab or eculizumab helps to control intravascular haemolysis [1,2]. However, residual anaemia, mostly due to extravascular haemolysis, occurs in up to two-thirds of patients [3]. Iptacopan, a first-in-class, oral, selective factor B inhibitor, targets the complement system proximally, via the alternative pathway [4]. A recently published phase 2 study showed that iptacopan controlled haemolysis in a group of 10 patients with PNH and active haemolysis who did not respond well to eculizumab [5].

To further investigate iptacopan, the Apply-PNH trial (NCT04558918) randomised 97 patients with PNH and residual anaemia despite treatment with standard-of-care 8:5 to iptacopan 200 mg oral, twice daily or to the intravenous anti-C5 standard-of-care they received before randomisation [6]. The primary endpoints were:

- Achieving an increase from baseline in haemoglobin of ≥2 g/dL in the absence of red-blood cell transfusions
- Achieving an increase from baseline in haemoglobin of ≥12 g/dL in the absence of red-blood cell transfusions.

Prof. Régis de Latour (Saint-Louis Hospital, France) presented the primary results after 24 weeks of treatment.

In total, 51 out of 60 patients in the iptacopan arm achieved the first primary endpoint compared with 0 out of 35 in the standard-of-care arm, with a population estimate difference of 80.3% (95% CI 71.3–87.6; P<0.0001). The second primary endpoint was reached by 42 patients in the iptacopan arm and by 0 patients in the standard-of-care arm. The corresponding population estimate difference was 67.0% (95% CI 56.3–76.9; P<0.0001). Furthermore, transfusion could be avoided in 60 out of 62 patients in the iptacopan arm and in 14 out of 35 patients in the standard-of-care arm (population estimate difference 70.3%; 95% CI 52.6–84.9; P<0.0001).

The safety analysis showed an apparent higher incidence of headache (16.1% vs 2.9%) and diarrhoea (14.5% vs 5.7%) in the iptacopan arm, but breakthrough haemolysis was more common in the standard-of-care arm than in the iptacopan arm (17.1% vs 3.2%). Finally, the rate of serious treatment-emergent adverse events seemed to be higher in the standard-of-care arm (14.3% vs 9.7%).

"Iptacopan may represent a practice-changing, oral, outpatient therapy for patients with PNH who do not respond well to ravulizumab or eculizumab," suggested Prof. de Latour.

1. Hillmen P, et al. N Engl J Med. 2006;355:1233–1243.
2. Kulesakararaj AG, et al. Blood. 2019;133(6):540–549.
3. Risitano AM, et al. Front Immunol. 2019;10:1157.
4. Schubart A, et al. Proc Natl Acad Sci USA. 2019;116:7926–7931.
5. Risitano AM, et al. Lancet Haematol. 2021;8(5):e344–e354.
6. de Latour RP, et al. Oral Monotherapy with Iptacopan, a Proximal Complement Inhibitor of Factor B, Has Superior Efficacy to Intravenous Terminal Complement Inhibition with Standard of Care Eculizumab or Ravulizumab and Favorable Safety in Patients with Paroxysmal Nocturnal Hemoglobinuria and Residual Anemia: Results from the Randomized, Active-Comparator-Controlled, Open-Label, Multicenter, Phase III Apply-PNH Study. Late-Breaking Abstract 2, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

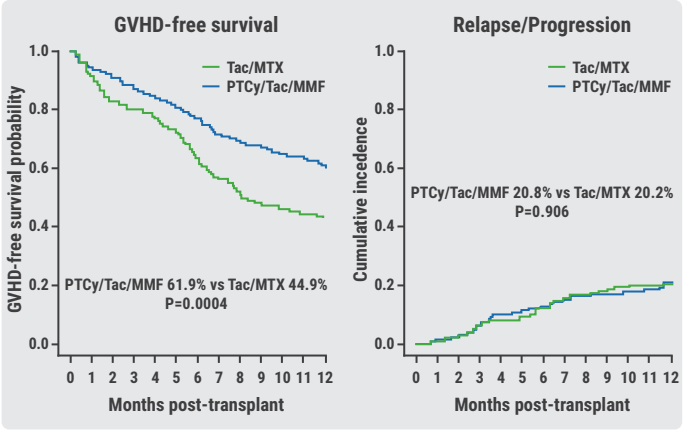
Novel therapy may replace standard-of-care prophylaxis for GVHD

Post-transplant cyclophosphamide/tacrolimus/mycophenolate mofetil (PTCy/Tac/MMF) outperformed tacrolimus/methotrexate (Tac/MTX) as a prophylaxis for graft-versus-host disease (GVHD) in patients with an indication for reduced-intensity conditioning allogeneic stem cell transplantation (RIC ASCT).

The results of the phase 3 BMT CTN 1703 trial (NCT03959241) were presented by Prof. Shernan Holtan (University of Minnesota, MN, USA) [1]. The study included adult patients receiving RIC ASCT (n=431), who were randomised 1:1 to post-transplant PTCy/Tac/MMF or Tac/MTX. The primary endpoint was the 1-year GVHD-free relapse-free survival (GRFS), a composite endpoint of grade III–IV acute GVHD, chronic GVHD requiring systemic immunosuppression, relapse/progression, or death.

The primary endpoint was met, with a 1-year GRFS of 52.7% in the PTCy/Tac/MMF arm and a 1-year GRFS of 34.9% in the Tac/MTX arm (HR 0.64; P<0.001). The effect was driven by a reduction in grade III–IV acute GVHD (6.3% vs 14.7%, respectively; P=0.001) and a decrease in chronic GVHD requiring systemic immunosuppression (12.5% vs 25%, respectively; P=0.001). Prof. Holtan added that relapse/progression rates were similar, with 20.8% in the PTCy/Tac/MMF arm and 20.2% in the Tac/MTX arm (P=0.906; see Figure).

Figure: Improved GVHD outcomes not at expense of relapse [1]



GVHD, graft-versus-host disease; PTCy/Tac/MMF, post-transplant cyclophosphamide/tacrolimus/mycophenolate mofetil; Tac/MTX, tacrolimus/methotrexate.

There were more grade 2–3 infections in the experimental arm (40.0% vs 30.4; P=0.018), mostly explained by an increased rate of grade 2 infections. Also, fewer patients in the experimental arm achieved an absolute lymphocyte count >1,000 (53.8% vs 63.2%; P<0.001). Finally, after 1 year of follow-up, it appeared that patients in the Tac/MTX arm were more likely to die from acute GVHD (14.3% vs 4.2%), whereas patients in the PTCy/Tac/MMF arm were more likely to die from organ failure (22.9% vs 10.7%).

The authors concluded that PTCy/Tac/MMF should become the standard-of-care GVHD prophylaxis in adults receiving RIC ASCT.

1. Holtan S, et al. BMT CTN 1703: A randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation. Late-Breaking Abstract 4, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.

LMWH does not result in higher live birth rates in women with inherited thrombophilia

Low-molecular weight heparin (LMWH) did not increase the live birth rate compared with standard-of-care in women with recurrent miscarriages and inherited thrombophilia, results from the ALIFE2 trial demonstrated.

The ALIFE study (ISRCTN58496168) suggested that LMWH, in combination with aspirin, may reduce recurrent miscarriage in women with inherited thrombophilia. To assess whether LMWH alone may decrease miscarriages in women with inherited thrombophilia, the randomised-controlled ALIFE2 study (NTR3361) was designed [1]. The trial, presented by Prof. Saskia Middeldorp (Radboud UMC, the Netherlands), included 326 women with inherited thrombophilia and a history of at least 2 miscarriages, who were actively trying to conceive or less than 7 weeks pregnant. The participants were randomised 1:1 to standard pregnancy care or to standard pregnancy care plus LMWH once daily until delivery. Aspirin was used as co medication in 11% of the participants. The primary endpoint was the rate of live births.

The rate of live births was comparable for the 2 study arms (LMWH 71.6% vs control 70.9%; adjusted OR 1.08; P=0.770). Furthermore, the rate of adverse events was higher in the LMWH arm than in the control arm (43.9% vs 26.5%; OR 2.17; P=0.0016). According to Prof. Middeldorp, this difference was mostly caused by an increase of bruising, skin reaction at injection site, and minor bleedings in the experimental arm.

In conclusion, the authors do not advise to treat women with inherited thrombophilia with LMWH to prevent miscarriage.

1. Quenby S, et al. Low-Molecular-Weight Heparin Versus Standard Pregnancy Care for Women with Recurrent Miscarriage and Inherited Thrombophilia (ALIFE2): An Open-Label, Phase III Randomized Controlled Trial. Late-Breaking Abstract 5, ASH 64th Annual Meeting, 10–13 December 2022, New Orleans, LA, USA.