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PEER-REVIEWED
CONFERENCE REPORT



CARTITUDE-4 Brings Good News to Lenalidomide-Refractory MM

Cilta-cel was superior to the standard of care in patients with lenalidomide-refractory multiple myeloma, results from the phase 3 CARTITUDE-4 trial showed. A new standard of care?

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Ziftomenib in Relapsed/Refractory *NPM1*-Mutated AML

Ziftomenib displayed encouraging clinical activity in heavily pre-treated patients with relapsed/refractory *NPM1*-mutated acute myeloid leukaemia. Is ziftomenib a candidate for combination therapy?

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REVIVE: Rusfertide Meets Primary Endpoint in PV

Compared with placebo, rusfertide was associated with improved response rates in patients with polycythaemia vera. The drug met all the efficacy endpoints and was well-tolerated.

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COLOPHON

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Letter from the Editor



Dear colleagues,

It is a great pleasure to introduce this peer-reviewed EHA2023 Medicom Conference Report. The EHA annual meeting held in Frankfurt this year was a great event everyone looked forward to. The Scientific Program Committee of the EHA has taken care of what, in my opinion, turned out to be a wonderful programme.

The conference was again organised as a hybrid meeting, a format that currently is available for most medical conferences, and offered the opportunity to gather knowledge in benign as well as malignant haematology. Basic and translational research, but also a special focus on clinical topics were presented in many parallel sessions. From this year's EHA Medicom Conference Report, we selected several abstracts that will most likely change your daily practice now or soon. The abstracts are summarised in a way that the information is easy to digest in a rather short time.

Highlights of the conference and report include the striking rapidly evolving field of immunotherapy including bispecific antibody and CAR T-cell treatment applied in a variety of haematological malignancies. Also, the ongoing further deciphering of the molecular basis of benign and malignant disease by all kinds of new technologies paving the way for new treatment options is covered in this report. Read about the treatment of AML, a disease in which no new developments emerged for a long time, which is rapidly changing with the development of new effective targeted treatments and successful maintenance treatment. Especially in patients unfit for intensive chemotherapy, new avenues are opened. Finally, the report also covers other malignant and non-malignant haematological diseases, for which new drugs are rapidly developed and approved by the regulatory authorities.

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

Best wishes,
Gert Ossenkoppele

Biography

Gert Ossenkoppele is a professor of Hematology at the Amsterdam UMC, location VUMC, since 2003. He obtained his doctorate of medicine at that same University in 1977. He is board certified in Hematology and Internal medicine since 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 an invited speaker at many national and international scientific meetings. His research interests are mainly translational and include the (stem cell) biology of AML, leukaemic stem cell target discovery, immunotherapy and measurable residual disease (MRD) detection using flow cytometry to inform the treatment of AML. He is the principal investigator of many national and international clinical trials in myeloid malignancies and regularly functions as a reviewer for many high-impact haematological journals (Blood, Leukemia, Haematologica, JAMA Oncology, Lancet Oncology, NEJM). He is a member and fulfils a mentorship of the AML working party of HOVON (Dutch-Belgian Hematology Trial Group) and former vice-chair of the HOVON Executive Board. He co-leads the AML WP of HARMONY, is a lead participant in the AML Work package of the European LeukemiaNet (ELN) and is a board member of the ELN foundation. Until recently, he was a board member of the EHA and is now vice-chair of the EHA Educational Committee. Subsequently to his former position as chair of the AML Scientific working group of EHA, he is now a member of this group. He is a member of the Global and EU steering committee of the AMLGlobalPortal an educational portal for hematologists (www.amlglobalportal.com). During his current retirement, he maintains an honorary position as a haematologist at the Amsterdam UMC.

Conflict of Interest Statement:

Prof. Gert Ossenkoppele 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, and Jazz pharmaceuticals.

Multiple Myeloma

Can we combine teclistamab and nirogacestat for the treatment of RRMM?

High and deep response rates were observed for the combination of teclistamab and nirogacestat in patients with relapsed/refractory multiple myeloma (RRMM). Although the safety profile improved with delayed administration of lower-dose nirogacestat, evaluation is warranted when combining B-cell maturation antigen (BCMA)-targeted bispecific treatments with a gamma-secretase inhibitor.

Dr Jeffrey Matous (Colorado Blood Cancer Institute, Colorado, USA) presented the results from one arm of the phase 1b MajesTEC-2 trial ([NCT04722146](#)), evaluating the combination of teclistamab and nirogacestat in participants with RRMM [1]. Teclistamab is a bispecific antibody, targeting the B-cell maturation antigen and CD3 (approved for the treatment of triple-class exposed RRMM), and nirogacestat is an investigational gamma-secretase inhibitor. The 28 participants were assigned to one of three dose levels:

- teclistamab 0.72 mg/kg, every week plus 100 mg nirogacestat, twice daily (n=8)
- teclistamab 0.72 mg/kg, every week plus 100 mg nirogacestat, once daily (n=7)
- teclistamab 1.5 mg/kg, every week plus 100 mg nirogacestat, once daily (n=13)

The overall response rate was 74.1%, with a complete or stringent complete response rate of 51.9%. The time-to-first-response was 1.18 months and 87.2% of the participants maintained a response after 12 months of follow-up.

At low-dose teclistamab plus nirogacestat, twice daily, 3 dose-limiting toxicities were reported for 2 participants: one participant experienced grade 3 gastrointestinal bleeding plus grade 3 diarrhoea and another participant had grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS). At the other two dose levels, no dose-limiting toxicities were observed. Dr Matous mentioned that there were 5 grade 5 events: sepsis, septic shock, COVID-19, cardiac arrest, and pneumonia. After a median follow-up of 14.7 months, 60.7% of all participants had discontinued nirogacestat due to adverse events (AEs). Teclistamab

was discontinued by 7% of the participants due to AEs. Furthermore, grade 3 or 4 neutropenia was seen in 75% of the participants. The most common non-haematologic AEs were cytokine-release syndrome (75.0%), diarrhoea (64.3%), injection site erythema (53.6%), and decreased appetite (50.0%). “The rates of grade 3 or 4 AEs were relatively low, except for diarrhoea and pneumonia, which occurred in 25% and 21% of the participants, respectively,” added Dr Matous.

1. Offner F, et al. Teclistamab + nirogacestat in relapsed/refractory multiple myeloma: the phase 1b MajesTEC-2 study. MM clinical: new combinations and novel targets, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Encouraging results for low-dose belantamab mafodotin plus nirogacestat in patients with RRMM

Low-dose belantamab mafodotin plus nirogacestat showed encouraging efficacy results in patients with relapsed/refractory multiple myeloma (RRMM) in the phase 1/2 DREAMM 5 platform study. Further exploration of this combination therapy is warranted.

Belantamab mafodotin, a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate, was approved in Europe for the treatment of patients with MM who had received 4 or more prior lines of therapy and were refractory to a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. Nirogacestat is an investigational gamma-secretase inhibitor that has displayed encouraging preclinical results in MM.

The phase 1/2 DREAMM 5 platform study ([NCT04126200](#)) assessed whether the combination of low-dose belantamab mafodotin plus nirogacestat resulted in a similar efficacy but an improved ocular safety profile compared with belantamab mafodotin monotherapy [1]. 81 participants were analysed: 10 from the dose-exploration cohort, 34 from the cohort expansion phase receiving combination therapy, and 37 from the monotherapy arm. The primary endpoint was the overall response rate (ORR). Prof. Sebastian Grosicki (Medical University of Silesia, Poland) presented the findings.

The reported ORRs were 29% in the combination therapy group and 38% in the monotherapy group. Incorporating

posterior probability distribution resulted in median ORR values of 36% and 33%, respectively. The safety profile of the combination therapy was consistent with the known safety profiles per monotherapy agent. Although the rates of ocular events were similar between participants in the combination therapy (71%) and the monotherapy group (78%), high-grade events were more common in the monotherapy group than in the cohort expansion group (grade 1: 21% vs 5%; grade 2: 21% vs 14%; grade 3: 29% vs 59%; combination vs monotherapy, respectively).

In conclusion, these data support further exploration of low-dose combination therapy belantamab mafodotin plus nirogacestat in patients with RRMM

1. Grosicki S, et al. Low-dose belantamab mafodotin (belamaf) in combination with nirogacestat vs belamaf monotherapy in patients with relapsed/refractory multiple myeloma (RRMM): Phase 1/2 DREAMM-5 platform sub-study 3. P913, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

CARTITUDE-4: Cilta-cel meets expectations in lenalidomide-refractory MM

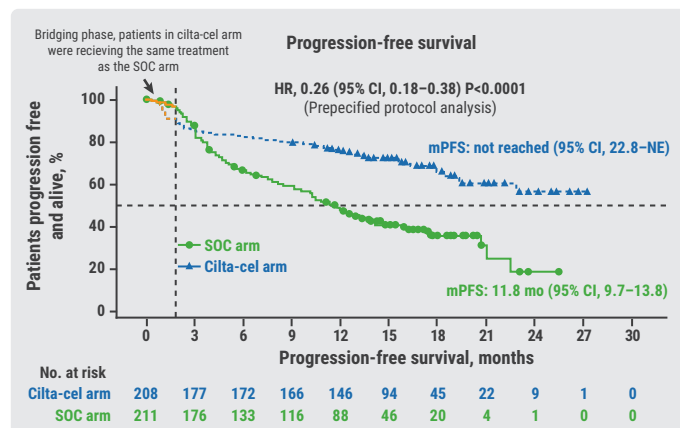
Cilta-cel was superior to the standard of care in patients with lenalidomide-refractory multiple myeloma (MM), results from the phase 3 CARTITUDE-4 trial showed. According to the authors, cilta-cel has the potential to become the new standard of care for patients with lenalidomide-refractory MM after a first relapse.

Cilta-cel is a dual-binding B-cell maturation antigen (BCMA)-directed CAR T-cell therapy, which has demonstrated a median progression-free survival of approximately 3 years in patients with MM who had received at least 3 prior lines of therapy in the previous CARTITUDE-1 trial ([NCT03548207](#)) [1]. Progressing from there, Dr Hermann Einsele (University of Würzburg, Germany) presented the primary results of the current phase 3 CARTITUDE-4 trial ([NCT04181827](#)), which tested cilta-cel against standard of care in earlier lines of therapy. The trial randomised 419 participants with lenalidomide-refractory MM who had received 1-3 prior lines of therapy 1:1 to cilta-cel or to the standard of care therapy by physician's choice (DPd or PVd) [2]. The primary outcome measure was progression-free survival (PFS).

After a median follow-up of 15.9 months, the primary endpoint was met: PFS was significantly improved in

participants in the cilta-cel arm compared with standard of care (HR 0.26; 95% CI 0.18–0.38; $P < 0.0001$, see Figure). The corresponding 12-month PFS rates were 76% and 49%. This result was consistent across pre-defined subgroups. Dr Einsele added: "Importantly, the data suggest that participants who had received only 1 prior line of therapy may benefit more from cilta-cel than participants having received 2 or 3 prior lines of therapy". Overall response rates were 84.6% versus 67.3% and the complete response rate was 73.1% in the cilta-cel versus 21.8% in the standard of care arm, respectively. In an as-treated analysis, the complete response rate was even higher in the as-treated population (99.4% vs 86.4%).

Figure: Primary endpoint of progression-free survival from the CARTITUDE-4 trial [2]



SOC, Standard of care; HR, hazard ratio; CI, confidence interval; mo, months; mPFS, mean progression-free survival; No., number; NE, not estimable.

Looking at safety, 85%–90% of the patients experienced neutropenia. These events were almost exclusively grade 3 or 4 events, but mostly resolved to low-grade events by day 30. The grade 3 or 4 infection rate was similar for the 2 arms, with 26.9% in the experimental arm and 24.5% in the control arm. Cytokine release syndrome was seen in 76.1% of the 'as-treated with cilta-cel' population, but only 2 cases were grade 3 or 4 events. Finally, neurotoxicity was reported in 20.5% of the participants, including 5 cases that were of grade 3 or 4.

1. Berdeja JG, et al. *Lancet*. 2021;398(10297):314–324
2. Einsele H, et al. Phase 3 results from CARTITUDE-4: Cilta-cel versus standard of care (PVd or DPd) in lenalidomide-refractory multiple myeloma. Plenary abstracts session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Lymphoma

Radiotherapy or not in patients with PMBCL after immunochemotherapy?

Omission of mediastinal radiotherapy in patients with primary mediastinal B-cell lymphoma (PMBCL) who had a complete metabolic response after first-line immunochemotherapy appeared safe, results from the IELSG37 trial demonstrated. The progression-free survival (PFS) and overall survival rates were comparable for patients who received radiotherapy and for those who did not.

There is conflicting evidence regarding the effectiveness of radiotherapy in patients with PMBCL [1,2]. The IELSG37 trial ([NCT01599559](#)) assessed whether mediastinal radiotherapy can be safely omitted in participants with PMBCL who had a complete metabolic response after standard immunochemotherapy [3]. All PET-negative participants after immunochemotherapy (n=268) were randomised 1:1 to mediastinal radiotherapy (30 Gy) or observation. The primary endpoint was PFS at 30 months. Dr Maurizio Martelli (University Sapienza Roma, Italy) presented the results.

The 30-month PFS rates were 98.5% in the radiotherapy arm and 96.2% in the observation arm (Log-rank P=0.27), demonstrating that there is no difference between the two study arms. The 30-month overall survival rates were 99.2% and 99.3%. Dr Martelli concluded that the omission of radiotherapy is safe in participants with PMBCL who had a complete metabolic response after first-line immunochemotherapy.

1. [Jackson MW, et al. Am J Hematol. 2016;91\(5\):476-480.](#)
2. [Dunleavy K, et al. N Engl J Med. 2013;368:1408-1416.](#)
3. Martelli M, et al. Omission of radiotherapy in primary mediastinal B-cell lymphoma patients following complete metabolic response to standard immunochemotherapy: results of the IELSG37 randomized trial. Plenary abstracts session, EHA 2023 Annual Congress, 8-11 June, Frankfurt, Germany.

Durable responses for loncastuximab tesirine in relapsed/refractory DLBCL

Loncastuximab tesirine displayed durable, long-term responses in patients with heavily pre-treated diffuse large B-cell lymphoma (DLBCL), the phase 2 LOTIS-2 trial showed. Moreover, no new safety issues were reported during the long-term follow-up.

“Patients with DLBCL who relapse after stem cell transplantation or CAR T-cell therapy, or who are refractory to second-line therapy have a poor prognosis,” said Dr Paolo Caimi (Cleveland Clinic, Ohio, USA). “There is an unmet need for accessible therapies with manageable toxicity profiles that have displayed long-term disease control in patients with relapsed or refractory DLBCL.” The phase 2 LOTIS-2 trial (n=145, [NCT03589469](#)) investigated the anti-tumour activity of the anti-CD19 monoclonal antibody-drug conjugate (conjugated drug: loncastuximab tesirine) in participants with relapsed/refractory DLBCL in [1] and Dr Caimi presented the long-term efficacy and safety results of this trial [2].

The overall response rate was 48.3% and the complete response rate was 24.8%. In the complete study population, the duration of response was 13.4 months, whereas the duration of response was ‘not reached’ in the subset of participants who had a complete response (n=36). The corresponding results for the median progression-free survival were 4.9 months and ‘not reached’. Also, the median overall survival was ‘not reached’ in the subset of participants who had a complete response and accumulated to 9.5 months in the overall study population.

According to the authors, no new safety signals emerged during the long-term follow-up. The most frequently reported grade ≥ 3 treatment-emergent adverse events were neutropenia (26%), thrombocytopenia (18%), increased gamma-glutamyl transferase (17%), and anaemia (10%).

Durable responses of loncastuximab tesirine were reported for participants with RR DLBCL during the long-term follow-up of the LOTIS-2 trial.

1. [Caimi PF, et al. Lancet. 2021;22\(6\):790-800.](#)
2. Caimi PF, et al. Long-term responses with loncastuximab tesirine: updated results from LOTIS-2, the pivotal phase 2 study of patients with relapsed/refractory diffuse large B-cell lymphoma. P1132, EHA 2023 Annual Congress, 8-11 June, Frankfurt, Germany.

Zandelisib promising in relapsed/refractory indolent B-cell NHL

Zandelisib displayed a high response rate in heavily pre-treated patients with relapsed/refractory indolent B-cell non-Hodgkin's lymphoma (RR iB-NHL), including patients

with poor prognoses. The safety analysis revealed a low rate of grade ≥ 3 adverse events of special interest.

Zandelisib is a selective oral PI3K δ inhibitor that has been studied in patients with RR follicular lymphoma, chronic lymphocytic leukaemia, and marginal zone lymphoma [1–3]. Dr Takahiro Kumode (Kindai University, Japan) presented the findings of the current phase 2 MIRAGE trial ([NCT04384770](https://clinicaltrials.gov/ct2/show/study/NCT04384770)), which evaluated the efficacy and safety of zandelisib, administered by intermittent dosing, in 61 Japanese participants with RR iB-NHL [4]. The primary endpoint was the overall response rate (ORR).

The ORR was 75.4%, with a complete response rate of 24.6% and a partial response rate of 50.8%. Dr Takahiro added that the ORRs were also high in participants who were refractory to their last therapy (ORR 70.0%), participants who had a bulky disease (ORR 62.5%), or those who had 'progression of disease within 2 years' (ORR 65.5%). Furthermore, the median time-to-response was 58 days.

The most common adverse events were a decreased neutrophil count (43%) and diarrhoea (36%). Grade ≥ 3 adverse events of special interest, such as pneumonia, increased AST (aspartate aminotransferase) and ALT (alanine aminotransferase), or hepatic function abnormalities were all below 5%. Finally, the discontinuation rate due to adverse events was 14.8%.

These data demonstrate favourable safety and efficacy profiles of zandelisib in Japanese patients with RR iB-NHL.

1. [Pagel JM, et al. Lancet Oncol. 2022;23\(8\):1021–1030.](#)
2. [Goto H, et al. Int J Hematol. 2022;116\(6\):911–921.](#)
3. [Zelenetz AD, et al. JCO. 2022;40.16_suppl.7511.](#)
4. Kumode T, et al. Efficacy and safety of zandelisib administered by intermittent dosing in patients with relapsed/refractory indolent B-cell non-Hodgkin's lymphoma: primary analysis of the phase 2 study MIRAGE. P1086, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

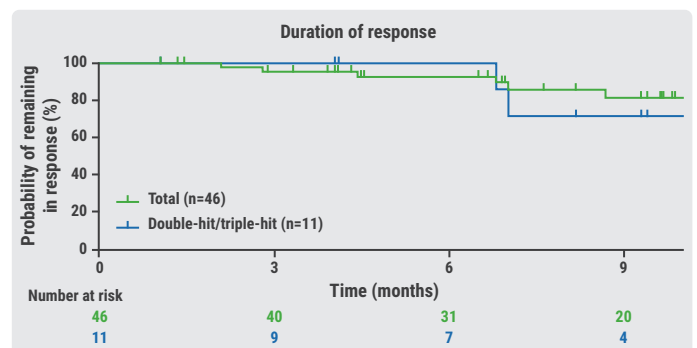
Promising data for epcoritamab plus R-CHOP in untreated DLBCL

The combination of epcoritamab plus R-CHOP resulted in high response rates in patients with untreated high-risk diffuse large B-cell lymphoma (DLBCL), including double-hit/triple-hit patients. A phase 3 trial is underway to further evaluate this combination as first-line therapy for patients with DLBCL.

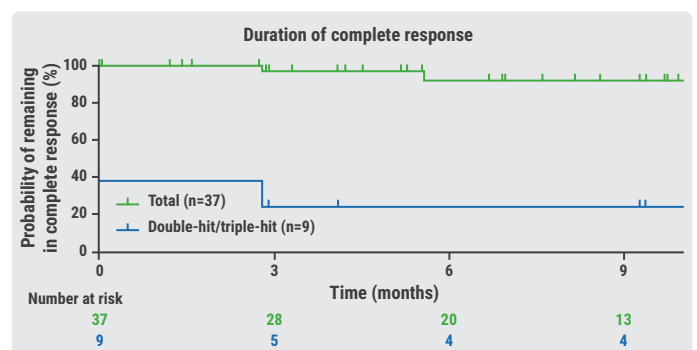
For patients with newly diagnosed DLBCL, R-CHOP remains the standard of care. However, about 45% of the patients do not reach a curative state and the 4-year overall survival rate is only 55% [1,2]. Epcoritamab is a bispecific antibody targeting CD3 and CD20, which has demonstrated efficacy and safety in patients with relapsed or refractory DLBCL as a single agent [3]. Dr Michael Clausen (Lillebaelt Hospital, Denmark) presented the updated results from arm 1 of the phase 1b/2 EPCORETM NHL-2 trial ([NCT04663347](https://clinicaltrials.gov/ct2/show/study/NCT04663347)) [4]. This arm of the trial included 47 participants with untreated DLBCL and evaluated the safety and efficacy of epcoritamab (weekly in R-CHOP cycles 1-4, every 3 weeks in cycles 5–6, every 4 weeks in cycle 7 for a total of 1 year) plus R-CHOP (21-day cycles). Anti-tumour activity was the primary endpoint.

The overall response rate was 100% in the study population and therefore also 100% in double-hit/triple-hit participants (n=11). The complete metabolic response rate was 80% and the partial metabolic response rate was 20%. Of those participants who completed therapy, 95% achieved and maintained a complete response after 9 months of follow-up (see Figure).

Figure: Median duration of response and of complete response for participants treated with epcoritamab plus R-CHOP [4]



Median duration of response



Median duration of complete response

Neutropenia (67%), anaemia (62%), and cytokine release syndrome (CRS; 59%) were the most common adverse events. There was only one grade 3 CRS event reported.

In conclusion, these promising data of epcoritamab plus R-CHOP support further evaluation of this combination regimen in patients with DLBCL.

1. [Sehn LH, et al. Blood. 2007;109\(5\):1857–1861.](#)
2. [Susanibar-Adaniya S, et al. Am J Hematol. 2021;96\(5\):617–629.](#)
3. [Phillips T, et al. Blood. 2022;140 \(supplement 1\): 8022–8023.](#)
4. Clausen M, et al. High complete metabolic response rates with epcoritamab + R-chop in previously untreated patients with high-risk diffuse large B-cell lymphoma, including double/triple-hit: epcore NHL-2 update. P116, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Non-Malignant Haematology

Investigational agent OMS906 performs well in PNH

The MASP-3 inhibitor OMS906 appeared safe and displayed encouraging signs of efficacy in the interim analysis of a phase 1b trial involving patients with treatment-naïve paroxysmal nocturnal haemoglobinuria (PNH). Several trials are underway to further evaluate this agent in the PNH population.

“Established therapies for PNH come with the risk of extravascular haemolysis,” said Dr Jens Panse (University of Aachen, Germany). The investigational agent OMS906 selectively targets MASP-3, which is a key activator of the alternative complement pathway. “Since this agent inhibits the alternative complement pathway proximally, it may block intravascular haemolysis and prevent extravascular haemolysis,” added Dr Panse. He presented the findings of the phase 1b trial ([NCT05889299](#)) which evaluated OMS906 in treatment-naïve participants with PNH who received 4-weekly subcutaneous injections of the agent up to 13 times. Safety was the primary endpoint [1].

OMS906 was well-tolerated in participants with PNH. “There were no cases of clinical breakthrough haemolysis, no major adverse vascular events, no serious adverse events or discontinuations,” stated Dr Panse. Low-grade headache or itching was observed in 20% and 30% of the participants, respectively, and 3 participants with underlying bone marrow failure showed evidence of cytopenia.

All participants had an increase in haemoglobin of at least 2g/dL after 1 injection and participants without myelodysplastic syndrome (n=8) achieved sex-normal haemoglobin levels.

LDH normalisation was achieved in 7 out of 10 participants and reticulocyte normalisation was reached in 9 out of 10 participants.

The interim results of the current phase 1b trial demonstrate that OMS906 is a promising candidate to target PNH.

1. Karnabeda O, et al. OMS906, a mannan-binding lectin-associated serine protease-3 (MASP-3) inhibitor, normalizes hemoglobin levels in treatment-naïve PNH patients: interim data from a proof-of-concept clinical trial. Late-breaking oral session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Robust platelet responses with cevidoplenib in ITP

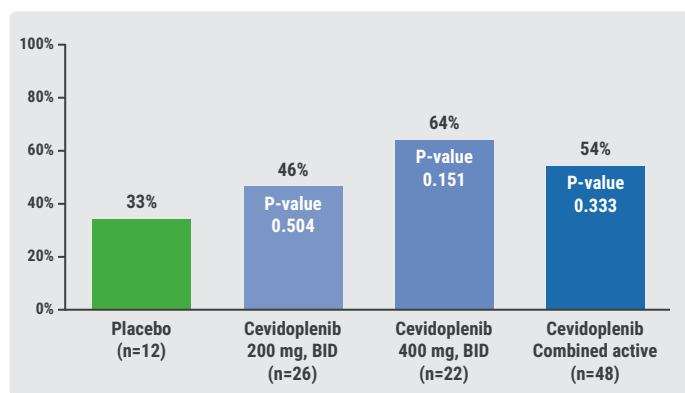
Cevidoplenib was associated with robust platelet responses in patients with persistent and chronic immune thrombocytopenia (ITP) who had received at least one prior therapy. The agent was well-tolerated, and no new safety signals emerged in the current phase 2 trial.

Thrombopoietin receptor agonists are common second-line therapies for patients with ITP. “However, 30% of the patients do not respond to these agents. Next to the emerging therapies rilzabrutinib and efgartigimod, cevidoplenib, an investigational SYK inhibitor is being evaluated for the ITP population.” introduced Dr Jun-Ho Jang (Samung Medical Center, South Korea). He presented the findings of the phase 2, multicenter, randomised, double-blind, placebo-controlled trial ([NCT04056195](#)), which assessed the SYK inhibitor cevidoplenib in 60 participants with persistent and chronic ITP who had failed at least 1 prior therapy [1]. The participants were randomised 1:2:2 to placebo, 200 mg cevidoplenib (twice daily), or 400 mg cevidoplenib (twice daily). The

primary endpoint was the participant's platelet response at any visit during the 12-week treatment period, defined as a platelet count $\geq 30,000/\mu\text{L}$ and doubling the baseline count.

The primary endpoint was achieved by 33% of the participants in the placebo arm and by 54% in the cevidoplenib arms ($P=0.333$, see Figure). The rate of participants who reached

Figure: Primary efficacy results (platelet response) [1]



BID, bis in die, twice daily.

the primary endpoint was numerically higher in the 400 mg dose group than in the 200 mg dose group (64% vs 46%). Participants on cevidoplenib were more likely to achieve the secondary endpoint of reaching ≥ 2 consecutive platelet counts $\geq 30,000/\mu\text{L}$, irrespective of the dosing, than participants receiving a placebo (38% vs 50% vs 8%).

Grade 3 or 4 adverse events occurred in 16.7% of the participants on placebo and 7.7% and 22.7% of the participants on 200 mg and 400 mg cevidoplenib, respectively. The most common treatment-related adverse events were ALT increase (alanine aminotransferase, 8.3%), AST increase (aspartate aminotransferase, 6.3%), and nausea (6.3%).

“Further evaluation of cevidoplenib in a larger number of patients for an extended period is needed to confirm the durability of the observed clinical benefits,” concluded Dr Jang.

1. Jang J-H, et al. Cevidoplenib, a selective inhibitor of SYK, in persistent and chronic ITP: phase 2 study. Late-breaking oral session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Leukaemia

QuANTUM-First: updated results on quizartinib in AML with FLT3-ITD

Treatment with quizartinib resulted in an improved overall survival (OS) in patients with acute myeloid leukaemia (AML) with internal tandem duplications of the *FLT3* gene (FLT3-ITD), regardless of whether they received allogeneic haematopoietic cell transplantation (HCT) in first clinical remission, results from the QuANTUM-First trial demonstrated.

Although allogeneic HCT in first clinical remission improves survival in patients with FLT3-ITD mutated AML, relapse rates remain high [1]. To improve outcomes for the FLT3-ITD mutated AML population, Dr Richard Schlenk (University of Heidelberg, Germany) and his team investigated the benefits of adding quizartinib, a second-generation type 2 FLT3 inhibitor, to the treatment regimen: the phase 3 QuANTUM-First study ([NCT02668653](https://clinicaltrials.gov/ct2/show/study/NCT02668653)) included 539

participants with FLT3-ITD mutated AML who had received standard high-dose cytarabine and/or HCT and assessed the safety and efficacy of the addition of quizartinib to standard induction and consolidation chemotherapy, followed by up to 3 years of continuation therapy with quizartinib [2]. The current analysis investigated the impact of allogeneic HCT in the first clinical remission and the interplay with quizartinib.

In total, 157 participants received allogeneic HCT in the first clinical remission. Including allogeneic HCT in first clinical remission as a time-dependent variable in a multiple regression analysis resulted in a hazard ratio of 0.42 ($P<0.0001$) for overall survival (OS), favouring those who had received allogeneic HCT over those who had not. On top of that, treatment with quizartinib was an independent factor for improving OS (HR 0.77; $P=0.028$), irrespective of whether participants had received allogeneic HCT or not.

For patients with FLT3-ITD mutated AML, quizartinib may thus present a promising treatment option substituting HCT.

1. Schlenk RF, et al. *Blood*. 2014;124(23):3441–3449.
2. Schlenk RF, et al. Impact of allogeneic hematopoietic cell transplantation in first complete remission plus FLT3 inhibition with quizartinib in acute myeloid leukemia with FLT3-ITD: results from QuANTUM-First. AML clinical studies and risk stratification, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Promising data for ziftomenib in relapsed/refractory *NPM1*-mutated AML

Ziftomenib displayed encouraging clinical activity in a population of heavily pre-treated patients with relapsed/refractory (RR) *NPM1*-mutated acute myeloid leukaemia (AML). The agent was well-tolerated and the lack of predicted adverse drug-drug interactions suggests that ziftomenib could be explored in combination with other agents.

“*NPM1*-mutant AML is a large genetic subset with a high unmet need,” stated Dr Amir Fathi (Massachusetts General Hospital, Massachusetts, USA). “The 5-year overall survival rate is approximately 50% and in the second line, the median overall survival is only 7.8 months [1,2]. Also, there is no FDA-approved *NPM1*-mutation-specific therapy for the AML population.” To address the unmet need in this *NPM1*-mutated AML population, the phase 1/2 KOMET-001 study ([NCT04067336](#)) evaluated the use of ziftomenib, which targets the menin-KMT2A pathway, an important target in *NPM1*-mutated AML. Dr Fathi presented the results of the phase 1b part of the trial, where 20 participants with RR-*NPM1*-mutated AML received 600 mg ziftomenib daily [3].

The overall response rate was 45% and the complete remission rate was 35%. The median duration of response was 8.2 months. Dr Fathi added that co-mutations in *FLT3* and *IDH1/2* did not appear to affect the responsiveness to ziftomenib.

The most common adverse events were diarrhoea (45%), hypokalaemia (40%), nausea (30%), anaemia (30%), and back pain (30%). Thrombocytopenia (20%) and anaemia (25%) were the most frequently reported grade ≥ 3 events. As a treatment-related adverse event, the differentiation syndrome was observed in 20%, but only 1 of the 4 cases was a grade 3 event. Treatment-related nausea was seen in 20% of the participants. “These findings are in line with previously reported publications on this agent,” commented Dr Fathi.

These encouraging results warrant further evaluation of ziftomenib in combination with other agents in AML.

1. Angenendt L, et al. *JCO*. 2019;37(29):2632–2642.
2. Issa GC, et al. *Blood Adv*. 2023;7(6):933–942.
3. Fathi AT, et al. Activity, tolerability and resistance profile of the menin inhibitor ziftomenib in adults with relapsed or refractory *NPM1*-mutated AML. Late-breaking oral session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

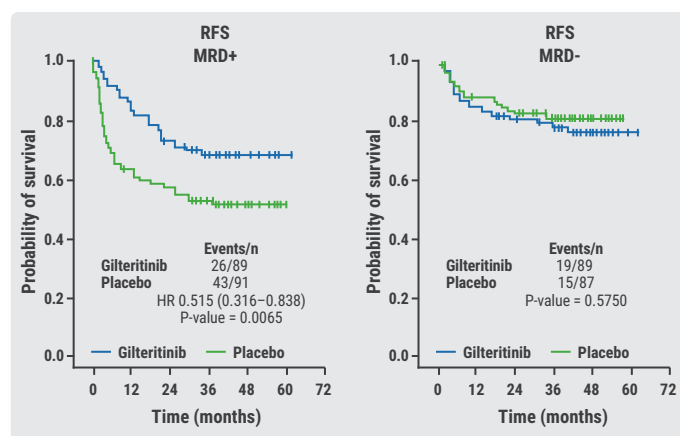
MRD-positive patients with FLT3-ITD AML may benefit from post-transplant gilteritinib

Although gilteritinib as post-haematopoietic transplant (HCT) maintenance therapy for patients with *FLT3*-internal tandem duplication (*FLT3*-ITD) acute myeloid leukaemia (AML) did not significantly outperform placebo, MRD status was predictive of the responsiveness to gilteritinib.

“The risk of relapse is high in patients with *FLT3*-ITD-mutated AML,” said Dr Mark Levis (Johns Hopkins Hospital, Maryland, USA). “Although *FLT3* inhibitors are often administered as post-HCT maintenance therapy, the evidence for the usefulness of these agents in *FLT3*-ITD-mutated AML is inconclusive.” Dr Levis and colleagues investigated whether post-HCT maintenance therapy with gilteritinib, a potent *FLT3* inhibitor, could provide a clinical benefit for patients with this form of AML. Additionally, they evaluated whether the tumour’s MRD status could facilitate the selection of patients who should receive post-HCT gilteritinib. The MORPHO trial ([NCT02997202](#)) randomised 356 participants 1:1 to 24 months of gilteritinib maintenance therapy or placebo post-HCT [1]. Relapse-free survival was the primary endpoint.

Considering the complete study population, the primary endpoint of relapse-free survival was not met, but a numerical benefit was observed for participants who were treated with gilteritinib (HR 0.68; 95% CI 0.46–1.01; $P=0.052$). Overall

Figure: Effect of detectable pre-HCT MRD on relapse-free survival per study arm [1]



RFS, relapse-free survival; HR, hazard ratio.

survival did not differ significantly between treatment groups (HR 0.85; P=0.44). MRD status at randomisation (thus pre-HCT) was, however, predictive of gilteritinib response: In the MRD-positive subset of participants, the primary endpoint was met (HR 0.52; 95% CI 0.32–0.84; P=0.0065, see Figure).

“We did not observe an increase in acute graft-versus-host-disease (GVHD), but chronic GVHD appeared to be more common in the gilteritinib arm than in the placebo arm (52.2% vs 42.4%),” explained Dr Levis. Drug-related adverse events of grade 3 or higher (61.2% vs 25.4%), and drug-related adverse events leading to treatment discontinuation (15.2% vs 7.9%) were more frequently observed in the experimental arm. Myelosuppression was the predominant cause of adverse events.

Overall, the authors concluded that post-HCT gilteritinib could be particularly beneficial for patients who are MRD-positive pre- or post-HCT.

1. Levis M, et al. BMT-CTN 1506 (MORPHO): a randomized trial of the FLT3 inhibitor gilteritinib as post-transplant maintenance for FLT3-ITD AML. Late-breaking oral session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Deep responses with asciminib in CML-CP

Asciminib was an efficacious treatment for patients with chronic myeloid leukaemia in chronic phase (CML-CP) who had received at least 2 prior tyrosine kinase inhibitors (TKI), long-term results of the phase 3 ASCEMBL trial showed, further supporting that this agent is a new standard of care for this population.

Asciminib is the first BCR::ABL1 inhibitor that specifically targets the ABL myristoyl pocket. The ongoing phase 3 ASCEMBL trial ([NCT03106779](#)) randomised 214 participants with CML-CP 2:1 to asciminib (40mg twice daily) or bosutinib (500mg once daily). In the published primary analysis of the ASCEMBL trial, asciminib was superior to bosutinib regarding efficacy and safety in participants who had received ≥ 2 prior TKIs (n=84) [1]. The current analysis aimed to characterise the efficacy of asciminib versus bosutinib and to examine factors associated with response [2]. Prof. Timothy Hughes (University of Adelaide, Australia) presented the findings.

At week 96, the asciminib group comprised more patients who achieved $BCR::ABL1^{IS} < 1\%$ after having received at least 1 prior TKI than in the bosutinib group (47.2% vs 23.5%).

The major molecular remission (MMR) rate was higher in asciminib-treated participants than in bosutinib controls (37.5% vs 21.1%) at week 96. The corresponding results for participants who had received at least 2 TKIs were similar. Among participants receiving asciminib with $BCR::ABL1^{IS} > 0.1\%$ by week 24 who remained on asciminib beyond week 24 (n=56), the cumulative incidence of MMR was 17.9% by 1 year and 37.9% by 2 years, showing that MMR could still be achieved by later timepoints.

Finally, the cumulative incidence of MMR and deep molecular response (DMR) was higher in the asciminib arm than in the bosutinib arm in the subset of participants who discontinued their last TKI due to a lack of efficacy.

No new on-treatment deaths were reported since the primary analysis.

These data further support asciminib as a standard of care for patients with CML-CP who had received at least 2 prior TKIs.

1. Réa D, et al. [Blood. 2021;138\(21\):2031–2041.](#)
2. Hughes TP, et al. Rapid and deep responses with asciminib in patients with chronic myeloid leukemia in chronic phase after ≥ 2 prior tyrosine kinase inhibitors in the phase 3 ASCEMBL study. P665, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

QUIWI: First results suggest a clinical benefit of quizartinib in AML

Preliminary results of the QUIWI study indicate that the addition of quizartinib to the ‘3+7’ regimen may prolong survival in untreated patients without internal tandem duplications of the *FLT3* gene (*FLT3*-ITD wild-type) acute myeloid leukaemia (AML).

The addition of quizartinib, a selective FLT3 inhibitor, to standard chemotherapy with or without allogeneic hematopoietic cell transplant, improved overall survival in AML patients with *FLT3*-ITD mutations [1]. The current phase 2 QUIWI trial ([NCT04107727](#)) the effectiveness of quizartinib in *FLT3*-ITD wild-type AML by randomising 273 participants with untreated *FLT3*-ITD wild-type AML 2:1 to ‘3+7’ plus FLT3 inhibitor quizartinib, or ‘3+7’ plus a placebo [2]. In the experimental arm, quizartinib was administered during induction, consolidation, and maintenance therapy. The primary endpoint was event-free survival (EFS). Dr Pau Montesinos (University of Valencia, Spain) presented the findings of a preplanned interim analysis.

After a median follow-up of 17 months, the median EFS was 16.6 months in the quizartinib arm and 10.6 months in the placebo arm (HR 0.73; 95% CI 0.52–1.02; P=0.062). The median overall survival (OS) was not reached in the quizartinib arm and 15.0 months in the placebo arm (HR 0.56; P=0.004). Corresponding 2-year OS rates were 63.5% and 47.0% for quizartinib and placebo, respectively. Disease-free survival was not reached in the quizartinib arm versus 15.4 months in the placebo arm (HR 0.64; P=0.050).

These findings suggest that quizartinib, on top of standard chemotherapy, may improve EFS and OS even in patients with newly diagnosed FLT3-ITD wild-type AML.

1. [Erba H. et al. Lancet. 2023;401\(10388\):1571–1583.](#)
2. Montesinos P, et al. Preliminary results of QUIWI: a double blinded, randomized clinical trial comparing standard chemotherapy plus quizartinib versus placebo in adult-patients with newly diagnosed FLT3-ITD wild-type AML. Novel combinations in the treatment of AML, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Miscellaneous

COMMANDS trial: A paradigm shift in LR-MDS-associated anaemia

Luspatercept was superior to epoetin alfa in treating anaemia in erythropoiesis-stimulating agent (ESA)-naïve patients with transfusion-dependent lower-risk myelodysplastic syndromes (LR-MDS). The safety profile of luspatercept was manageable and predictable.

Luspatercept has been shown to improve erythropoiesis and increase platelet and neutrophil counts in patients with LR-MDS [1,2]. Dr Matteo Della Porta (Humanitas Cancer Centre Milan, Italy) presented the results of an interim analysis of the phase 3 COMMANDS trial ([NCT03682536](#)), which compared luspatercept with ESAs in ESA-naïve participants with transfusion-dependent LR-MDS [3]. The study randomised 356 participants 1:1 to luspatercept or epoetin alfa for the treatment of anaemia. The primary endpoint was red blood cell transfusion independence for at least 12 weeks during the 24-week treatment period with a concurrent mean haemoglobin increase of at least 1.5 g/dL.

Luspatercept outperformed epoetin alfa for the primary endpoint: 58.5% of the participants in the experimental arm achieved the primary endpoint versus 31.2% in the control arm (P<0.0001). All subgroup analyses favoured treatment with luspatercept over epoetin alfa, except for the subgroup of participants without ring sideroblasts. Dr Della Porta highlighted the results of an exploratory analysis where participants with *SF3B1*, *SF3B1a*, *ASXL1*, and *TET2* mutations were likely to benefit significantly more from luspatercept than from epoetin alfa.

The treatment discontinuation rate was 44% in the luspatercept and 60% in the epoetin alfa arm. Lack of efficacy was the main reason for treatment discontinuation in the luspatercept (15.7%) and epoetin alfa arm (32.4%). Finally, treatment-emergent adverse events were balanced between the two arms, including low rates of progression to acute myeloid leukaemia.

1. [Fenaux P. et al. N Eng J Med. 2020;382:140–151.](#)
2. [Garcia-Manero G. et al. Blood. 2022;139\(4\):624–629.](#)
3. Della Porta MG, et al. Luspatercept versus epoetin alfa for treatment of anemia in ESA-naïve lower-risk myelodysplastic syndromes patients requiring RBC transfusions: data from the phase 3 COMMANDS study. Plenary abstracts session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

REVIVE: Rusfertide meets the primary endpoint in PV

Compared with placebo, rusfertide was associated with improved response rates in patients with polycythaemia vera (PV). The drug met all the efficacy endpoints and was well-tolerated.

“The peptide hormone hepcidin regulates iron homeostasis and controls the availability of iron for the formation of red blood cells,” explained Dr Marina Kremyanskaya (Mount Sinai, New York, USA). She presented the results of the phase 2 REVIVE trial ([NCT04057040](#)), which assessed the safety and efficacy of the hepcidin mimetic rusfertide in participants with PV who had a high phlebotomy burden while they were treated with standard of care therapy [1]. After completion of the phase 1 part of the trial, participants were randomised to placebo or to maintain their last dose of rusfertide. The

primary endpoint was the combination of maintaining a haematocrit <45% and not reaching phlebotomy eligibility. In total, 53 participants entered the 12-week randomised withdrawal period and were included in the primary efficacy analysis.

“There was a meaningful reduction in phlebotomy frequency following rusfertide administration,” said Dr Kremyanskaya. 69.2% of the participants in the rusfertide arm and 18.5% in the placebo arm met the primary endpoint, representing a significant benefit for the rusfertide arm (P=0.0003). This result was comparable for participants who were previously treated with phlebotomy alone and those who received phlebotomy plus cytoreductive therapy.

The drug was generally well-tolerated. Grade 1 or 2 injection site reactions were the most common treatment-emergent adverse events. Symptoms associated with PV, like fatigue (31.4%), pruritis (25.7%), and headache (22.9%) were observed. 2 participants discontinued rusfertide, due to mild thrombocytosis and recurrent grade 1 injection site erythema, respectively.

Rusfertide and its effect on the absence of phlebotomy eligibility are currently being validated in the large phase 3 VERIFY trial ([NCT05210790](https://clinicaltrials.gov/ct2/show/study/NCT05210790)).

1. Kremyanskaya M, et al. Targeted therapy of uncontrolled erythrocytosis in polycythemia vera with the hepcidin mimetic rusfertide: blinded randomized withdrawal results of the REVIVE study. Late-breaking oral session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

Mapping healthy HPSC variations to diagnose haematopoietic abnormalities

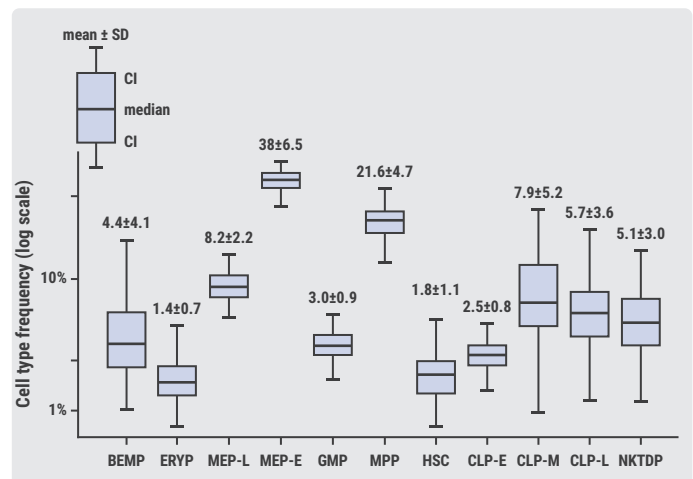
Researchers generated a first-of-its-kind single-cell RNA sequencing atlas of healthy circulating haematopoietic stem and progenitor cells (HSPCs). This atlas serves amongst others as a reference map for the creation of blood-based diagnostics and analytics for various haematopoietic abnormalities.

“The haematopoietic system is constantly formed by the differentiation of stem cells into specialised cells,” started Dr Nili Furer (Weizmann Institute of Science, Israel). “While we have established reference values for matured cells, we do not have relevant reference values for progenitor states. We need to capture these values to know which values are part of healthy variation and what values may be related to diseases.” For this purpose, Dr Furer and co-investigators

analysed HSPCs from peripheral blood samples from 99 individuals [1].

In total, 360,000 single cells were retrieved and categorised as common lymphoid progenitors or multipotent myeloid progenitors. Dr Furer commented that the inter-individual variation in circulating HPSCs is large in healthy individuals (see Figure), whereas intra-individual cell type frequencies were stable across time. The generated data was then applied as a healthy reference map. Using HSPCs derived from blood samples of 100 cytopenic study participants and an additional 100 healthy participants, they validated their atlas and compared healthy and diseased states. Indeed, the additional set of 100 samples from healthy individuals fitted in the healthy variation of the reference map, whereas progressive dissimilarities were seen in cytopenic patients, validating their unique dataset.

Figure: Inter-individual variation in circulating HSPC compositions in healthy individuals [1]



BEMP, basophil eosinophil mast progenitor; ERY-P, primitive erythroid cells; MEP(-L-E), megakaryocyte-erythroid progenitors (-L-E); GMP, granulocyte-macrophage progenitors; MPP, multipotent progenitors; HSC, hematopoietic stem cells; CLP(-E-M-L), common lymphoid progenitors (-E-M-L); NKTD-P, natural killer- T-and dendritic cell progenitors.

1. Furer N, et al. Natural and age-related variation in circulating human hematopoietic stem cells. Plenary abstracts session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.

High risk of death for individuals with C282Y/C282Y hereditary haemochromatosis and diabetes

Individuals with C282Y/C282Y genotypes, a hereditary cause of haemochromatosis, have an increased risk of diabetes, even if they have normal levels of iron, transferrin saturation, or ferritin. Also, the risk of death

is two times higher for C282Y homozygotes than in wild-type individuals with diabetes. These were the main outcomes of a large Danish cohort study.

“There are several genetic variants that can affect hepcidin levels in the context of hereditary haemochromatosis,” explained Dr Mathis Mottelson (Copenhagen University Hospital, Denmark). “Today I will focus on two genotypes: wildtype/wildtype individuals, who have normal hepcidin levels and normal iron uptake, and C282Y/C282Y individuals, who generally show lowered hepcidin levels and increased iron uptake.” Dr Mottelson and colleagues hypothesised that C282Y homozygotes have an increased risk of diabetes and death even with normal levels of iron and transferrin saturation. The study included 132,542 individuals. Plasma iron, transferrin saturation, ferritin, and haemochromatosis genotype were measured for each individual and all participants were followed prospectively for up to 28 years [1].

The risk for diabetes was increased in C282Y homozygotes

(n=422) compared with wildtype individuals (n=87,313; HR 1.66; 95% CI 1.20–2.31; P=0.002), even when C282Y homozygotes presented with normal iron levels (HR 1.67; P=0.007), normal transferrin saturation (HR 2.49; P=0.002), or normal ferritin (HR 4.35; P=0.001, all compared with wildtype individuals). While the risk of death for C282Y homozygotes and wildtype individuals was comparable for individuals without diabetes, the risk of death in C282Y homozygotes with diabetes was significantly higher than in wildtype individuals with diabetes (HR 4.39 vs 2.26; P=0.008). Dr Mottelson added that the population-attributable fraction of all deaths of diabetes was 27.3% in the group of C282Y homozygotes with diabetes.

“Future research should focus on how to improve the testing and treatment specifically for individuals with C282Y/C282Y hereditary haemochromatosis,” concluded Dr Mottelson.

1. Mottelson M, et al. Individuals with HFE C282Y homozygosity and diabetes have almost two-fold risk of death compared to non-carriers with diabetes: a prospective study of a 132,542-individual general population cohort. Plenary abstracts session, EHA 2023 Annual Congress, 8–11 June, Frankfurt, Germany.