Medicom International Conference Series in Haematology

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European Hematology Association

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PEER-REVIEWED

CONFERENCE REPORT

Isa-VRd as new standard for transplant-ineligible multiple myeloma?

Isatuximab plus VRd significantly improved progression-free survival and measurable residual disease negativity rates compared with VRd alone in transplant-ineligible multiple myeloma the IMROZ trial.

read more on PAGE 3

ENERGIZE: Mitapivat boosts haemoglobin and reduces fatigue in thalassaemia

In the ENERGIZE phase 3 trial, mitapivat significantly improved haemoglobin levels and reduced fatigue in non-transfusion-dependent thalassaemia participants.

read more on PAGE 12

New hope for Richter's transformation: epcoritamab

Epcoritamab demonstrated significant efficacy and a manageable safety profile in high-risk Richter's transformation participants, with impressive response rates supporting further evaluation in the EPCORE™ CLL-1 trial.

read more on PAGE 17

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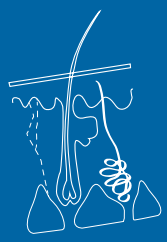

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Letter from the Editor

Dear colleagues,

It is my pleasure to introduce this peer-reviewed EHA 2024 Medicom Conference Report. The annual EHA meeting is still growing. This year's number of attendants was 15,000 in person and another 2,000 virtually. The Scientific Program Committee of the EHA has taken care of what, in my opinion, turned out to be a wonderful programme.

From this year's EHA, we selected several interesting abstracts that will likely change your practice now or soon. The abstracts are summarised in a way that the information is easy to digest in a rather short time.

The number of new drugs steadily increases, resulting in a better prognosis for many haematological diseases. Many new combinations of these drugs were discussed during the meeting.

The increase in abstracts focussing on immunotherapy including bispecific antibody and CAR T-cell treatment applied in a variety of haematological malignancies, which we have observed at previous meetings, was maintained in this year's event. New treatments for haemoglobinopathies and haemophilia and other benign haematological disorders are rapidly being developed.

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

Best regards,
Gert Ossenkoppele

Biography

Professor Gert Ossenkoppele was appointed in 2003 as Professor of Haematology 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 Haematology and Internal medicine (1984). The title of his Ph.D. thesis (1990) was: "Differentiation Induction in acute myeloid leukaemia (AML)". Gert Ossenkoppele has authored over 480 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/ myelodysplastic syndrome (MDS), leukaemic stem cell target discovery, immunotherapy, and measurable residual disease (MRD) detection using flow cytometry to inform treatment of AML/MDS. He was the PI of national and international clinical trials in myeloid malignancies. He was associate editor of HemaSpere the official journal of EHA and the European Journal of Haematology and regularly reviewed for many high-standard haematological journals (Blood, Leukemia, JCO, Haematologica, Oncotarget, NEJM). He recently rotated off as chair of the AML working party of HOVON (Dutch-Belgian Hematology Trial Group) and is past vice-chair of the HOVON Executive Board. He rotated off in 2024 as a lead participant of the AML Work package of the European LeukemiaNet (ELN) as well as a board member of the ELN foundation. He is the key opinion leader of WP2 AML of the HARMONY project. He rotated off as a board member of the European Haematology Association (EHA) and was chair of the EHA Educational Committee. He further rotated off as chair of the Global and EU steering committee of the AMLGlobalPortal an educational portal for haematologists. (www.amlglobalportal.com). Recently he retired and now functions as emeritus professor of haematology at the Amsterdam University, location VUmc.
In 2022 he received the Jean Bernard Lifetime Achievement Award at the EHA Annual meeting in Vienna. Recently he stopped most of his professional activities.

Conflict of Interest Statement:
Prof. Gert Ossenkoppele has no conflicts of interest to declare.

Multiple Myeloma

Isa-VRd proves its value in newly diagnosed MM in the IMROZ trial

Isatuximab (Isa) combined with bortezomib, lenalidomide, and dexamethasone (VRd) yielded better health outcomes than VRd alone for the first-line treatment of transplant-ineligible participants with newly diagnosed multiple myeloma (MM) in the phase 3 IMROZ study.

The anti-CD38 monoclonal antibody isatuximab was added to VRd (Isa-VRd) to challenge the current standard frontline VRd treatment for patients with newly diagnosed MM. The phase 3 IMROZ trial (NCT03319667) randomised 446 participants with transplant-ineligible, newly diagnosed MM 3:2 to Isa-VRd or VRd alone. Progression-free survival (PFS) was the main outcome and Prof. Thierry Facon (University of Lille, France) presented the findings of the current interim analysis [1].

After a median follow-up of 5 years, the median PFS was not reached in the experimental arm and 54.3 months in the control arm (HR 0.60; 98.5% CI 0.41–0.88; log-rank P=0.0005). The corresponding 60-month PFS rates were 63.2% and 45.2%, respectively. "These findings reflect a reduction of 40.4% for disease progression or death," commented Prof. Facon. Furthermore, the measurable residual disease negativity (10^{-5}) rates were 58.1% and 43.6%, respectively, favouring the experimental over the control arm. Although the overall survival data was immature, there was a favourable trend for the Isa-VRd arm compared with the VRd arm, with 60-month overall survival rates of 72.3% and 66.3% (HR 0.78; 99.97% CI 0.41–1.48).

Serious adverse events were seen in 70.7% and 67.4% of participants in the experimental arm and control arm, respectively. Grade ≥3 infections (44.9 vs 38.1%), grade ≥3 cataracts (15.6 vs 11.0%), and grade ≥3 diarrhoea (7.6 vs 8.3%) were common side effects in both arms.

"The improved efficacy of isatuximab plus VRd, combined with a consistent safety profile, provides an important frontline treatment, supporting Isa-VRd as a new standard of care for patients aged ≤80 years with transplant-ineligible, newly diagnosed MM," concluded Prof. Facon.

1. Facon T, et al. Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ). S100, EHA congress 2024, 13–16 June, Madrid, Spain.

PERSEUS: High MRD negativity rates with D-VRd and consolidation therapy and D-R maintenance in MM

In the PERSEUS trial, approximately half of the participants with newly diagnosed transplant-eligible multiple myeloma (MM) in the daratumumab plus bortezomib, lenalidomide, and dexamethasone (D-VRd) arm achieved sustained measurable residual disease (MRD) negativity at the 10^{-6} level, signifying a potential cure for these patients.

"Achieving (sustained) MRD negativity at 10^{-6} translates into very long survival outcomes for patients with MM and standard risk features," outlined Prof. Pieter Sonneveld (Erasmus University Medical Center, the Netherlands) [1]. The earlier, primary analysis of the PERSEUS study (NCT03710603; n=709) demonstrated that induction and consolidation with D-VRd followed by maintenance with daratumumab-lenalidomide (D-R) maintenance was superior to induction and consolidation with VRd alone and lenalidomide (R) maintenance concerning progression-free survival and other health outcomes [2]. Prof. Sonneveld presented the most recent data from the trial, focussing on MRD outcomes [1].

"Participants who had received at least 24 months of D-R maintenance therapy and reached a complete response and 12 months of sustained MRD negativity (10^{-5}) were allowed to stop daratumumab," mentioned Prof. Sonneveld. At the end of consolidation, MRD negativity (10^{-6}) was achieved by 34.4% of the participants on D-VRd, whereas VRd participants reached this endpoint in 16.1% of the cases. At 36 months of follow-up, this rate increased to 63.9% in the experimental and 30.8% in the control arm, demonstrating the efficacy of D-R maintenance therapy. Furthermore, sustained MRD negativity rates (10^{-6}; ≥12 months) were 47.3% and 18.6% in the D-VRd arm and VRd arm, respectively. For participants with high-risk disease (n=152), the corresponding sustained MRD negativity rates were 30.3% and 14.1% for experimental and control regimens. Prof. Sonneveld highlighted that 56.7% of the participants in the D-VRd arm who were MRD positive at the end of consolidation converted to MRD negativity (10^{-6}) during D-R maintenance. This percentage was only 25.2% in the control arm.

"These data further highlight the benefit of D-VRd and D-R maintenance as a new standard of care for transplant-eligible patients with newly diagnosed MM," concluded Prof. Sonneveld.

1. Sonneveld P, et al. Daratumumab plus bortezomib/lenalidomide/dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma: analysis of minimal residual disease in the Perseus trial. S201, EHA congress 2024, 13–16 June, Madrid, Spain.
2. Sonneveld P, et al. New Engl J Med. 2024;390(4):301–313

Post-intensification data confirm superiority of quadruple therapy in MM

An interim analysis of the phase 3 GMMG-HD7 study showed that the addition of isatuximab to lenalidomide, bortezomib, and dexamethasone (VRd) ameliorated clinical remission and measurable residual disease (MRD) negativity rates after intensification by high-dose therapy (HDT) and allogeneic stem cell transplantation (allo-SCT) in transplant-eligible participants with previously untreated multiple myeloma (MM).

The phase 3 GMMG-HD7 trial (NCT03617731) previously demonstrated that the anti-CD38 monoclonal antibody isatuximab plus VRd is more successful in inducing MRD negativity than VRd alone in transplant-eligible participants with newly diagnosed MM (50.1% vs 35.6%; P<0.001; n=660) [1]. The current interim analysis, presented by Prof. Marc Raab (University Hospital Heidelberg, Germany), looked at MRD negativity rates after intensification [2].

At least 1 intensification was administered to 598 participants and 179 received a second intensification. Clinical remission rates (43.5% vs 34.0%; P=0.013), and partial response rates (82.8% vs 68.7%; P<0.0001) after intensification were significantly higher in the isatuximab arm. Similarly, more participants achieved MRD negativity (10^{-5}) after intensification in the isatuximab arm than in the VRd alone arm (66.2% vs 47.7%; OR 2.13; 95% CI 1.56–2.92). Finally, 52.8% and 36.8% of the participants converted from MRD positive after induction to MRD negative after intensification in the isatuximab and VRd arms, respectively.

Isatuximab plus VRd improved MRD negativity and clinical remission rates after intensification as compared with VRd alone in transplant-eligible newly diagnosed participants with MM. The trial is ongoing and will investigate the role of isatuximab in combination with lenalidomide as maintenance therapy after a second randomisation.

1. Goldschmidt H, et al. Lancet Haematol. 2022;9(11):e810–821.
2. Raab MS, et al. Isatuximab, lenalidomide, bortezomib, and dexamethasone for newly diagnosed, transplant-eligible multiple myeloma: post-transplantation interim analysis of the randomized phase 3 GMMG-HD7 trial. S202, EHA congress 2024, 13–16 June, Madrid, Spain.

Promising phase 1 results for novel CAR T-cell therapy in MM

Anitocabtagene autoleucel (anito-cel) yielded excellent efficacy results in a heavily pre-treated population of participants with relapsed or refractory multiple myeloma (RRMM) in a phase 1 study. Phase 2 and 3 studies are initiated to further investigate this novel CAR T-cell therapy in MM.

The autologous B-cell maturation antigen (BCMA)-directed CAR T-cell therapy anito-cel was tested at 2 dose levels in a phase 1 trial among participants with RRMM who had received at least 3 prior lines of therapy. The lower dose level was administered to 32 participants, and 6 received the higher dose. Dr Binod Dhakal (Medical College of Wisconsin, WI, USA) shared findings concerning safety and efficacy [1].

The overall response rate was 100%, with a stringent complete remission (sCR)/CR rate of 76%. This result was consistent among participants with extramedullary disease (n=13) and those with high-risk cytogenetics (n=11). Dr Dhakal added that the median progression-free survival was not reached after a median follow-up of 26.5 months. The corresponding 24-month progression-free survival rate was 56%. Furthermore, 25 out of 28 evaluable participants were measurable residual disease negative (10^{-5}). "Remarkably, these findings are consistent in participants with extramedullary disease, a feature associated with notoriously poor prognosis," stressed Dr Dhakal.

The toxicity profile was more favourable in the lower dose group, whereas the efficacy of the lower dose appeared to be similar to the higher dose. "We did not observe any delayed neurotoxicity, Guillain-Barre syndrome, cranial nerve palsy, or Parkinsonian-like syndrome," highlighted Dr Dhakal. Also, there were no grade 3 cytokine release syndrome cases in the low-dose group and only 1 case of grade 3 immune effector cell-associated neurotoxicity syndrome.

Altogether, anito-cel delivered encouraging results in a heavily pre-treated population of participants with RRMM in a phase 1 trial, supporting further assessment of this novel CAR T-cell therapy in RRMM.

1. Frigault M, et al. Phase 1 study of CAR-T-ddBCMA for the treatment of patients with relapsed and/or refractory multiple myeloma: results from a least 1-year follow-up in all patients. S207, EHA congress 2024, 13–16 June, Madrid, Spain.

DREAMM 8: Belantamab mafodotin offers hope for patients with RRMM

Belantamab mafodotin plus pomalidomide and dexamethasone (B-Pd) outperformed pomalidomide plus bortezomib and dexamethasone (P-Vd) for progression-free survival (PFS) in participants with relapsed or refractory multiple myeloma (RRMM). Seeing the manageable safety profile and ease of administration, the authors suggest that B-Pd can become a new standard of care for the population.

Belantamab mafodotin is an anti-B-cell maturation antigen (BCMA) antibody-drug conjugate and its efficacy and safety have previously been confirmed among participants with RRMM in the DREAMM-7 study, where B-Vd led to an improved PFS compared with daratumumab plus Vd [1].

The current phase 3 DREAMM 8 study (NCT04484623) compared the addition of belantamab mafodin versus bortezomib in regimes of B-Pd versus P-Vd in participants with RRMM (n=302) [2]. Participants were eligible if they had received at least one prior line of therapy, including lenalidomide. The primary endpoint was PFS and Prof. Meletious Dimopoulos (University of Athens, Greece) presented the late-breaking results.

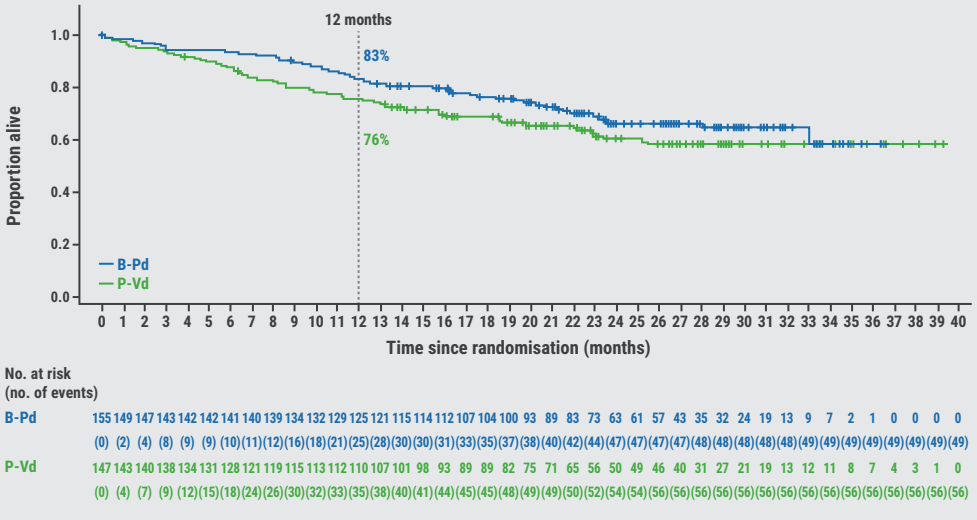
After a median follow-up of 21.8 months, participants in the B-Pd arm had a significant PFS benefit over participants in the P-Vd arm (HR 0.52; 95% CI 0.37–0.73; P<0.001). The corresponding 12-month PFS rates were 71% and 51%, respectively. This result was consistent across subgroups, including lenalidomide-refractory and anti-CD38 therapy-refractory participants. The authors also noted a positive trend in overall survival, favouring B-Pd over P-Vd (HR 0.77; 95% CI 0.53–1.14). The 12-month overall survival rates were 83% and 76% (see Figure).

"The exposure-adjusted safety profiles of the 2 treatment regimens were overall comparable," explained Prof. Dimopoulos. Ocular events were seen in 83% of the participants on B-Pd. However, most of these events were manageable by dose holds and reductions in dosing frequency. In 9% of the cases, ocular events led to treatment discontinuation.

"The robust efficacy, manageable safety, and ease of administration of B-Pd support that this treatment regimen could become the new standard of care for patients with RRMM," concluded Prof. Dimopoulos.

1. Mateos MV, et al. J Clin Oncol. 2024;42(36 suppl):439572–439572.
2. Dimopoulos MA, et al. Results from the randomized phase 3 DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone vs pomalidomide plus bortezomib and dexamethasone in relapsed/refractory multiple myeloma. LB3440, EHA congress 2024, 13–16 June, Madrid, Spain.

Figure: Survival of participants receiving B-Pd versus P-Vd [2]



Interim OS	B-Pd (n=155)	P-Vd (n=147)
Events, n (%)	49 (32)	56 (38)
Median OS (95% CI), months	NR (33.0–NR)	NR (25.2–NR)
HR (95% CI)	0.77 (0.53–1.14)	

Subsequent antimueloma therapy, n (%)	B-Pd (n=155)	P-Vd (n=147)
Steroids	37 (24)	59 (40)
Anti-CD38 antibodies	23 (15)	49 (33)
Proteasome inhibitor	26 (17)	36 (24)
Immunomodulator	14 (9)	29 (20)
BCMA-targeting therapy	1 (<1)	20 (14)
Chemotherapy	16 (10)	25 (17)
Transplant	1 (<1)	5 (3)

B-Pd, belantamab mafodotin plus pomalidomide and dexamethasone; CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; P-Vd, pomalidomide plus bortezomib and dexamethasone.

Prof. C. Ola Landgren
University of Miami, FL, USA

Meet the Trialist:

Prof. C. Ola Landgren discusses MRD as a key haematological cancer trial endpoint

To better understand the use of measurable residual disease (MRD) as a surrogate marker in myeloma and other haematological cancers, Medicom interviewed Prof. C. Ola Landgren (University of Miami, FL, USA).

What is the rationale for measurable residual disease (MRD) as an endpoint in clinical trials evaluating treatments for patients with multiple myeloma or other haematological cancers?

"The reason why MRD has become an important endpoint is because the historical endpoints have become obsolete. A long time ago, overall survival was the only endpoint. This was at a time when there were no effective therapies. So, if you could prove the patient lived longer, that was a success story, and you could use that to get drugs approved. But as drugs improved and could make a patient live longer and longer, it would take a very long time to prove superiority.

So, the FDA adopted progression-free survival many years ago. Progression-free survival means that patients who either die or progress, count as an event. If you could show that a new therapy had a longer progression-free survival, you could get it approved. Now, the problem is that current drugs cannot cure patients. There is no established cure. About 40% of patients don't live 5 years or longer. There is a huge unmet need. However, with this endpoint, if you were to design a study for newly diagnosed patients, you need to consider the statistical framework required to show superiority.

Firstly, you need to have a randomised study. Secondly, you need sufficient numbers to statistically test the hypothesis that the new therapy is superior to an old one. That would require large sample size, usually hundreds of patients. Identifying and enrolling all those patients would typically take at least 2 years. Then, to prove in the newly diagnosed setting that there is an improved progression-free survival, the dataset needs to mature, which takes about 10 years from randomisation.

Considering that there is still no cure for the disease, and about 40% of patients don't survive 5 years or longer, this creates a huge barrier for drug development. Patients need new drugs, but it takes 2 years to enrol patients and then over 10 years for the dataset to mature.

I saw this coming over 15 years ago when I worked at the National Cancer Institute (NCI) at the National Institutes of Health (NIH). I established contacts within the the NIH, National Cancer Institute, and the National Heart, Lung, and Blood Institute. We formed an interagency agreement with the FDA and worked together to form a task force within the federal government. After a few years, we had strong evidence that testing for MRD after about a year would be a very strong predictor of what would happen many years later.

The model was basically: if you enrol patients for 1 year and check after 1 year. If a patient has a deep response, you are very close to predicting what will happen 10 years later. My idea was if we could test all the patients 1 year out in both arms of the study, we would have a very strong prediction of the outcome. That is the background rationale."

Would you say that blood cancers have the edge on most solid tumours, where MRD is still an emerging concept?

"Every disease has rules for determining a response. Over 20 years ago, we agreed that if you could reduce the disease by half using a biomarker in the blood, that would be called a partial response. If the bone marrow was also free from disease, it was a complete response. So, if you had at least a partial response, it was counted as an overall response.

The FDA decided that for relapsed refractory disease, you could use overall response as an [...]

Curious?
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Leukaemia

PhALLCON: Third-generation TKI superior to first-generation TKI in Ph+ ALL

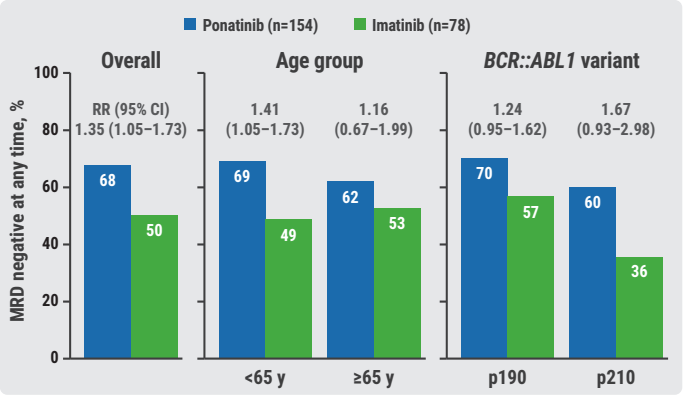
Ponatinib outperformed imatinib in participants with previously untreated Ph+ acute lymphoblastic leukaemia (ALL) in progression-free survival (PFS) and measurable residual disease (MRD) negativity rates. These findings were consistent across age and *BCR::ABL1* variant subgroups.

The phase 3 PhALLCON trial (NCT03589326) compared the third-generation *BCR::ABL1* tyrosine kinase inhibitor (TKI) ponatinib to the first-generation variant imatinib in participants with newly diagnosed Ph+ ALL. Enrolled participants (n=245) were randomised 2:1 to ponatinib or imatinib plus reduced-intensity chemotherapy. A previous analysis demonstrated that the primary endpoint, MRD-negative clinical remission rate at the end of induction, favoured the ponatinib arm (34.4% vs 16.7%) [1]. In the current analysis, Prof. Jose Maria Ribera (Josep Carreras Leukaemia Research Institute, Spain) shared additional efficacy data, outcomes in subgroups, and results from participants who proceeded to stem cell transplantation [2].

After a median follow-up of 19.4 months, the median PFS was significantly longer for participants receiving ponatinib than for imatinib controls (20.2 months vs 7.5 months; HR 0.52; 95% CI 0.36–0.73). This result was consistent with the higher rates of participants who were MRD negative at any time in the ponatinib group, even when subdivided per age (younger or older than 65 years), and *BCR::ABL1* subgroups (p190 or p210; see Figure). Fewer participants in the ponatinib arm proceeded to stem cell transplantation at any time (36% vs 47%). This finding was consistent in the MRD-negative subgroup of participants (32% vs 56%).

The safety profiles of the 2 agents were very comparable, although more participants in the ponatinib arm had dose interruptions due to unspecified reasons (73% vs 41%). "Of note, the exposure time was more than 2-fold longer in the ponatinib arm than in the imatinib arm among participants who did not proceed to stem cell transplantation, whereas the adverse event rates remained similar," emphasised Prof. Ribera.

Figure: MRD negativity at all time rates for participants receiving ponatinib vs imatinib [2]



CI, confidence interval; MRD, measurable residual disease; RR, relative risk; y, years of age.

Additional data from the PhALLCON trial confirmed the superior efficacy of ponatinib over imatinib plus chemotherapy in participants with newly diagnosed Ph+ ALL. Also, the exposure-adjusted safety profile of ponatinib appears to be more acceptable than the imatinib profile.

1. Jabbour E, et al. JAMA. 2024;331(21):1814–1823.
2. Ribera J-M, et al. Ponatinib versus imatinib in patients with newly diagnosed Ph+ acute lymphoblastic leukemia in the phase 3 PhALLCON trial: in-depth responder analysis. S115, EHA congress 2024, 13–16 June, Madrid, Spain.

APOLLO: ATRA plus ATO meets expectations in high-risk APL

All-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) was superior to ATRA-chemotherapy for event-free survival in participants with high-risk acute promyelocytic leukaemia (APL) in the phase 3 TUD-APOLLO-064 trial.

"ATRA plus ATO is the first-line standard of care for patients with low- or intermediate-risk APL," said Prof. Uwe Platzbecker (Leipzig University Hospital, Germany) [1,2]. "However, in high-risk APL, ATRA plus chemotherapy is still the standard of care and ATRA plus ATO has not yet been assessed" [1]. The phase 3 TUD-APOLLO-064 study (NCT02688140) included 133 participants with newly diagnosed high-risk APL, who were randomised 1:1 to the ATRA plus ATO or the ATRA plus chemotherapy arm. The primary endpoint was event-free survival at 2 years follow-up.

The incidence of relapse at 2 years was significantly higher in the chemotherapy arm than in the ATO arm (14.0% vs 1.6%; P=0.011). In line with that, the 2-year event-free survival rate was higher in the ATO arm than in the chemotherapy arm (88% vs 70%; P=0.02). The overall survival data was not yet mature at 2 years of follow-up but suggested an advantage for participants randomised to ATO (93% vs 87%).

"Haematologic toxicities were more prevalent in the chemotherapy arm than the ATO arm, particularly during the consolidation phase," evaluated Prof. Platzbecker. Thrombocytopenia and grade 3 or 4 neutropenia were almost non-existent in the ATO group during consolidation but were seen in up to 56% of the participants on chemotherapy. The occurrence of non-haematologic toxicities did not differ substantially between the 2 study arms.

ATRA plus ATO outperformed ATRA plus chemotherapy in participants with previously untreated high-risk APL in terms of event-free survival. Further analysis is awaited and will reveal whether ATRA plus ATO should be the new standard of care for this high-risk APL population.

1. Platzbecker U, et al. A randomized phase III study to compare arsenic trioxide (ATO) combined to ATRA and idarabucin versus standard ATRA and anthracycline-based chemotherapy (AIDA regimen) for patients with newly diagnosed, high-risk acute promyelocytic leukemia. S102, EHA congress 2024, 13–16 June, Madrid, Spain.
2. Lo-Coco F, et al. N Engl J Med. 2013;369:111–121.

Excellent phase 3 results for asciminib in chronic myeloid leukaemia

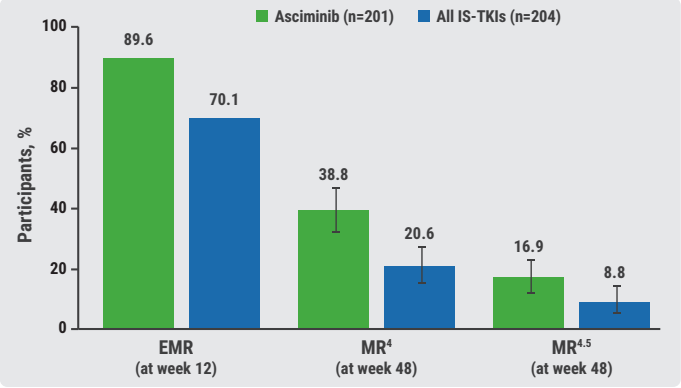
Asciminib was superior to all other tested first-line tyrosine kinase inhibitors (TKIs) in participants with chronic myeloid leukaemia (CML). Also, asciminib treatment was associated with fewer adverse events than the standard-of-care TKIs in the ASC4FIRST trial.

"Many newly diagnosed patients with CML do not achieve an optimal response with standard TKIs," opened Prof. Andreas Hochhaus (Jena University Hospital, Germany) [1]. "Moreover, long-term use of TKIs has been linked to renal failure, pleural effusion, and other adverse events." The phase 3 ASC4FIRST trial (NCT04971226) randomised 405 participants with untreated CML in the chronic phase 1:1 to the new-generation *BCR::ABL1* TKI inhibitor asciminib or an investigator-selected standard-of-care TKI.

Treatment with the first-generation TKI imatinib, or one of the second-generation TKIs bosutinib, dasatinib, or nilotinib was permitted for ≤2 weeks before randomisation. Prof. Hochhaus presented the results and noted that randomisation was stratified by pre-randomisation TKI selection and the European Long-Term Survival (ELTS) risk category. The primary endpoints were major molecular response (MMR) at week 48 and MMR within the imatinib stratum.

The first primary endpoint was met: 67.7% of the participants in the asciminib and 49.0% in the control arm reached an MMR at week 48 (Δ 18.9; 95% CI 9.6–28.8; P<0.001). In addition, MR4.5 (*BCR::ABL1* ≤0.0032%) was seen in 16.9% of participants in the asciminib arm compared with 8.8% in the control arm (see Figure). In the imatinib stratum, the MMR rates were 69.3% and 40.2%, in favour of the asciminib arm, meeting the second primary endpoint (Δ 29.6; 95% CI 16.9–42.2; P<0.001). Of note, the difference in MMR between the asciminib arm (66.0%) and control arm (57.8%) within the second-generation TKI stratum was less pronounced (95% CI -5.1 to 21.5).

Figure: More participants achieved early/deep molecular responses with asciminib as compared with investigator-selected TKIs [1]



EMR, early molecular response; IS, investigator-selected; MR, molecular response; TKIs, tyrosine kinase inhibitors.

Fewer grade ≥3 adverse events were documented in the asciminib arm (38.0%) compared with participants who received imatinib (44.4%) or second-generation TKIs (54.9%). Similarly, the adverse events-related treatment discontinuation rate was lower (4.5% vs 11.1% and 9.8%) on asciminib. "We saw less neutropenia, anaemia, and lymphopenia with asciminib," added Prof. Hochhaus. Also, diarrhoea, nausea, and muscle spasms were less common in the asciminib arm.

Asciminib displayed a favourable safety profile and provided better efficacy outcomes than first-line standard-of-care TKIs in newly diagnosed participants with CML in the chronic phase.

1. Hochhaus A, et al. Asciminib provides superior efficacy and excellent safety and tolerability vs tyrosine kinase inhibitors in newly diagnosed chronic myeloid leukemia in the pivotal ASC4FIRST study. S103, EHA congress 2024, 13–16 June, Madrid, Spain.

AUGMENT-101: Revumenib trial in *KMT2Ar* leukaemia stopped early for efficacy

In a heavily pretreated population of participants with *KMT2A* rearranged (*KMT2Ar*) acute leukaemia, revumenib displayed encouraging anti-tumour activity. Moreover, the phase 2 study was terminated early for efficacy.

The investigational menin-KMT2A interaction inhibitor revumenib was tested in the phase 2 AUGMENT-101 trial (NCT04065399) among 94 participants with *KMT2Ar* acute leukaemia, either myeloid leukaemia (n=78) or lymphoblastic/mixed phenotype leukaemia (n=16). The participants had received a median of 2 lines of prior therapy. The primary outcomes were safety and the rate of complete remission (CR) plus CR with partial haematologic recovery (CRh). Dr Ibrahim Aldoss (City of Hope National Medical Center, CA, USA) presented the findings of the interim analysis [1].

After a median follow-up of 6.1 months, 23% of participants in the efficacy population (n=57) reached the primary endpoint of CR plus CRh (95% CI 12.7–35.8). The median duration of response was 6.4 months. The overall response rate was 63% and responses appeared consistent across participants with common co-mutations. Dr Aldoss mentioned that 70% of participants who reached CR plus CRh also achieved measurable residual disease negativity. Finally, 39% of the responders proceeded to haematopoietic stem cell transplant.

Grade ≥3 treatment-related adverse events were documented in 54% of the participants, with differentiation syndrome (16%), febrile neutropenia (14%), and QTc prolongation (14%) as the most commonly observed events of these higher grades. Dr Aldoss noted that 6% of the participants had discontinued therapy due to treatment-related adverse events.

Overall, revumenib provided high overall response rates, CR plus CRh rates, measurable residual disease negativity rates and the possibility to proceed to haematopoietic stem cell transplant in heavily pretreated participants with *KMT2Ar* leukaemia.

1. Aldoss I, et al. Revumenib monotherapy in patients with relapsed/refractory KMT2AR acute leukemia: topline efficacy and safety results from the pivotal AUGMENT-101 phase 2 study. S131, EHA congress 2024, 13–16 June, Madrid, Spain.

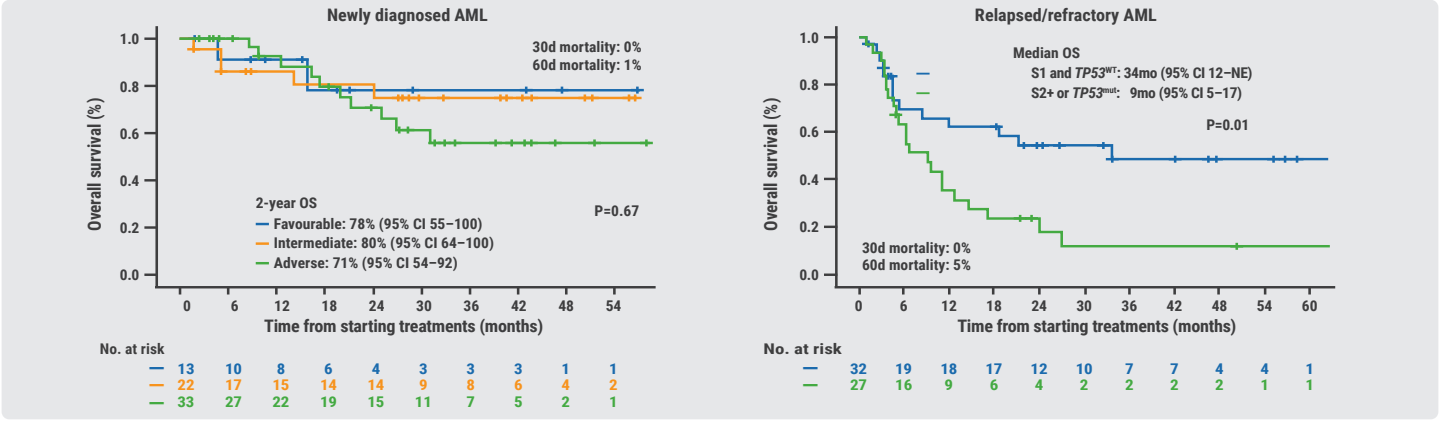
FLAG-Ida plus venetoclax induces high MRD-negativity rates in AML

Treatment with fludarabine plus cytarabine, idarubicin and granulocyte colony-stimulating factor (FLAG-Ida) chemotherapy plus venetoclax led to high measurable residual disease (MRD) negativity rates across the European LeukaemiaNet (ELN) subgroups in participants with newly diagnosed acute myeloid leukaemia (AML). Results showed that FLAG-Ida plus venetoclax may also be an efficacious salvage therapy for participants with relapsed/refractory (RR) AML.

The current phase 2 trial (NCT03214562) assessed the efficacy and safety of FLAG-Ida plus venetoclax in 127 participants with newly diagnosed (n=68) or RR AML (n=59). The primary outcome was the objective response rate (ORR) defined by the ELN. Dr Wei-Ying Jen (MD Anderson Cancer Center, TX, USA) presented the results [1].

In the participants with newly diagnosed disease, the ORR was 99% and MRD negativity (10^{-4}) was reported in 89%. These findings were consistent across ELN risk groups. The 2-year overall survival (OS) rate was 75% (see Figure). Notably, those who received stem cell transplantation in their first clinical remission had a survival benefit over those who did not proceed to stem cell transplantation. In contrast, the ORR was 70% in

Figure: Overall survival with FLAG-IDA plus venetoclax in participants with newly diagnosed and relapsed/refractory AML [1]



AML, acute myeloid leukaemia; CI, confidence interval; d, day; mut, mutant; NE, not estimable; OS, overall survival; S1, in first salvage; S2, in second salvage; WT, wild-type.

participants with RR AML and the 2-year OS rate was 40% in this subgroup. "Participants with *TP53* wild-type disease appeared to respond better to this therapy," added Dr Jen.

The most common adverse events were infections. Infections of grade 3 or higher occurred in 80% of the participants, and gastrointestinal toxicity or bleeding was observed in 16% of participants with newly diagnosed AML and 7% of those with RR AML.

In conclusion, FLAG-Ida plus venetoclax was associated with high MRD-negativity rates in newly diagnosed participants with AML. It also appeared to be an efficacious salvage treatment for participants with RR AML, especially those with *TP53* wild-type disease.

1. Jen W-Y, et al. FLAG-IDA + venetoclax in newly diagnosed or relapsed/refractory AML. S136, EHA congress 2024, 13–16 June, Madrid, Spain.

CD40/CD47 inhibitor shows promise in high-risk MDS and AML

The combination of the investigational agent SL-172154 with azacitidine delivered promising efficacy results among participants with newly diagnosed acute myeloid leukaemia (AML) or higher-risk myelodysplastic syndrome (MDS) in a phase 1b trial.

SL-172154 is a bifunctional fusion protein targeting CD40 and CD47. In a phase 1b study, this agent was tested in combination with azacitidine as a combination regimen for patients with previously untreated AML or higher-risk MDS. The current interim analysis presented findings from 2 dose expansion cohorts, including 23 participants with high-risk MDS and 21 with *TP53*-mutated AML. Prof. Amer Zeidan (Yale University, CT, USA) presented safety and efficacy data from this assessment [1].

The overall response rate was 67% in the MDS group and 43% in the AML participant group. In the MDS group, the complete remission rate was 42% compared with 29% in the AML group. After 5.3 months of follow-up in the MDS group and 4.2 months in the AML group, the median duration of overall response, complete remission, and overall survival had not been reached.

There were 9 cases of SL-172154-related serious adverse events, including infusion-related reactions (n=3) and cytokine release syndrome (n=2). Dr Zeidan and colleagues noted that the safety profile of the combination regimen was comparable to that of azacitidine alone, except for any grade infusion-related reactions (42%), any grade fatigue 10–17%, and cytokine release syndrome in the MDS arm (8%).

Dr Zeidan concluded that SL-172154 plus azacitidine had an acceptable safety profile and promising anti-tumour activity in these participant cohorts with poor prognostic features.

1. Zeidan AM, et al. Phase 1B study of SL-172154, a bi-functional fusion protein targeting CD47 and CD40, with azacitidine, in previously untreated acute myeloid leukaemia and higher-risk myelodysplastic syndromes. P773, EHA congress 2024, 13–16 June, Madrid, Spain.

ENHANCE: Magrolimab does not ameliorate health outcomes in high-risk MDS

A benefit of magrolimab plus azacitidine over azacitidine alone could not be found for participants with high-risk myelodysplastic syndrome (MDS), the final analysis of the phase 3 ENHANCE trial showed. According to the authors, this finding highlights the challenge of developing efficacious therapies for this heterogeneous disease.

The phase 3 ENHANCE trial (NCT04313881) compared a regimen of the standard of care azacitidine in combination with CD47 inhibitor magrolimab versus azacitidine plus a placebo among 539 participants with high-risk MDS [1].

"The final analysis of 'best response of clinical remission (CR)' did not show a difference between the experimental arm [21.3%] and the control arm [23.6%]," concluded Dr David Sallman (Moffitt Cancer Center, FL, USA). In *TP53*-mutated participants, the CR rate was lower for participants treated with magrolimab than their placebo control (17.7% vs 32.8%). Fewer participants in the experimental arm proceeded to stem cell transplantation (20.9% vs 35.4%). The overall survival (OS) data at this final analysis did not display a difference between the experimental arm and control arm either (median OS 15.9 months vs 18.6 months). "This finding was consistent across subgroups," added Dr Sallman.

"Unfortunately, we noticed a higher percentage of treatment-emergent adverse events leading to discontinuation in the magrolimab arm," expressed Dr Sallman (24.0% vs 12.1%). "Anaemia and, to a lesser extent, thrombocytopenia were more common adverse events in the experimental than in the control arm."

The ENHANCE study did not meet the primary efficacy endpoints, and more safety issues were observed when

adding magrolimab to azacitidine. "High-risk MDS is a heterogeneous disease with a high unmet need," said Dr Sallman. "Developing successful anti-CD47 therapies for this disease remains a challenge."

1. Sallman D, et al. Magrolimab plus azacitidine vs placebo plus azacitidine in patients with untreated higher-risk myelodysplastic syndromes: phase 3 ENHANCE study final analysis. S181, EHA congress 2024, 13–16 June, Madrid, Spain.

Can MRD-guided azacitidine treatment improve outcomes in AML and MDS?

Azacitidine may be an efficacious pre-emptive therapy to prevent or delay haematologic relapse in patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) who displayed measurable residual disease (MRD)-positivity after achieving a first clinical remission, results of the phase 2 RELAZA2 study revealed.

"Patients with AML or MDS who reach clinical remission after receiving disease-specific therapy or transplant are observed until a haematological relapse occurs in common practice," opened Dr Anne Sophie Kubasch (University of Leipzig, Germany) [1]. "In the phase 2 RELAZA2 study [NCT01462578], we assessed whether azacitidine is efficacious in participants who become MRD positive after reaching clinical remission following conventional chemotherapy or allogeneic transplant."

All participants without haematological relapse, displaying CD34 donor chimerism <80% or an *NPM1* mutational load >1% were considered MRD positive and eligible for azacitidine treatment. The final analysis included 357 participants, of whom 119 were MRD-positive and 95 were eligible for azacitidine treatment. The median follow-up duration was 22.5 months and the primary endpoint was relapse-free survival at 6 months.

The study's primary endpoint was reached by 63% of the participants. Of the responders, 65% displayed a major MRD and 35% a minor MRD response. "We observed that a favourable European LeukemiaNet [ELN] risk group, a longer time to last therapy, and a lower MRD level were predictive factors influencing the response to azacitidine therapy. Also, participants with a major MRD response presented with an improved overall survival over non-responders. Finally, 51% of the participants with a major MRD response were alive and relapse-free at the time of the analysis. This compares with 24% of participants with a minor MRD response who were alive and relapse-free. "Our results illustrate the importance of achieving MRD negativity," commented Dr Kubasch.

In conclusion, azacitidine appeared to be safe and efficacious in preventing or delaying haematological relapse in participants with AML or MDS.

1. Kubasch AS, et al. Azacitidine to treat measurable-residual disease in MDS and AML patients: long-term follow-up results of the RELAZA2 study. S265, EHA congress 2024, 13–16 June, Madrid, Spain.

Can WGTS replace standard-of-care diagnostics in AML?

Whole-genome and -transcriptome sequencing (WGTS) proved useful for the diagnosis and risk stratification of participants with acute myeloid leukaemia (AML). The agreement between results from standard-of-care (SoC) techniques and WGTS was overall good, albeit with some variation in the detection of subclonal features.

Dr Anna Staffas (University of Gothenburg, Sweden) and colleagues investigated whether WGTS reaches the sensitivity and specificity to replace SoC methods in AML diagnostics [1]. The research team analysed data from 129 *de novo* participants with AML, who mostly received both SoC diagnostics (G-band, FISH, fragment, Sanger, NGS-panel) and WGTS.

WGTS was associated with improved detection of risk-classifying rearrangements, detecting 6 rearrangements that were missed by SoC techniques, in addition to all the rearrangements that were detected by SoC techniques. Whole-transcriptome sequencing confirmed the findings of whole-genome sequencing (WGS). Next, most large copy number variations that were detected by SoC techniques were also detected by WGS. Yet, some subclonal events were detected solely by SoC techniques whereas others were only spotted by WGS. Furthermore, *FLT3*-ITD status was missed with WGS in 11 out of 42 participants (26%).

"Overall, we noticed a good concordance in AML classification between SoC diagnostics and WGTS, with a 5–7% increase in genetically defined entities with WGTS," said Dr Staffas. "WGTS detects fusions that are missed with current SoC techniques, whereas (low-frequency) *FLT3*-ITD may be missed with WGS, indicating that parallel targeted analysis is required," she concluded.

1. Staffas A, et al. Whole-genome and -transcriptome sequencing as a comprehensive precision diagnostic test in acute myeloid leukemia: a report from the national initiative genomic medicine Sweden. S338, EHA congress 2024, 13–16 June, Madrid, Spain.

Non-malignant Haematology

ENERGIZE: Mitapivat meets primary efficacy endpoint in thalassaemia

Mitapivat improved haemoglobin (Hb) levels and fatigue in participants with non-transfusion-dependent alpha (α)- or beta (β)-thalassaemia (NTDT) in a phase 3 study. These improvements were seen in all subgroups and the agent had a manageable safety profile.

The phase 3 ENERGIZE trial (NCT04770753) randomised 194 participants with α-NTDT (n=62) or β-NTDT (n=132) 2:1 to 24 weeks of 100 mg twice daily mitapivat or placebo. Subsequently, all participants received mitapivat for up to 5 years. The primary endpoint was Hb response from week 12 to week 24 compared with the baseline. Prof. Ali Taher (American University of Beirut, Lebanon) presented the results [1].

"Mitapivat demonstrated a statistically significant improvement in Hb response versus placebo," expressed Prof. Taher. In the mitapivat arm, 42.3% of participants had a Hb response, compared with 1.6% in the placebo arm (P<0.0001; see Figure). The average Hb response among responders was 1.56 g/dL. Importantly, the researchers reported an improvement in the mean FACIT-Fatigue Scale for participants on mitapivat compared with placebo controls (+4.85 vs +1.46; P=0.0026). "We also observed improvements in markers of haemolysis and erythropoietic activity," added Prof. Taher.

Serious adverse events (AEs) were seen in 6.2% of the participants on mitapivat and none of the participants on placebo. In addition, 3.1% discontinued the study drug due to AEs. Headache (22.5%), insomnia (14.0%), nausea (11.6%), and upper respiratory tract infection (10.9%) were the most common 'any grade' AEs in the experimental arm.

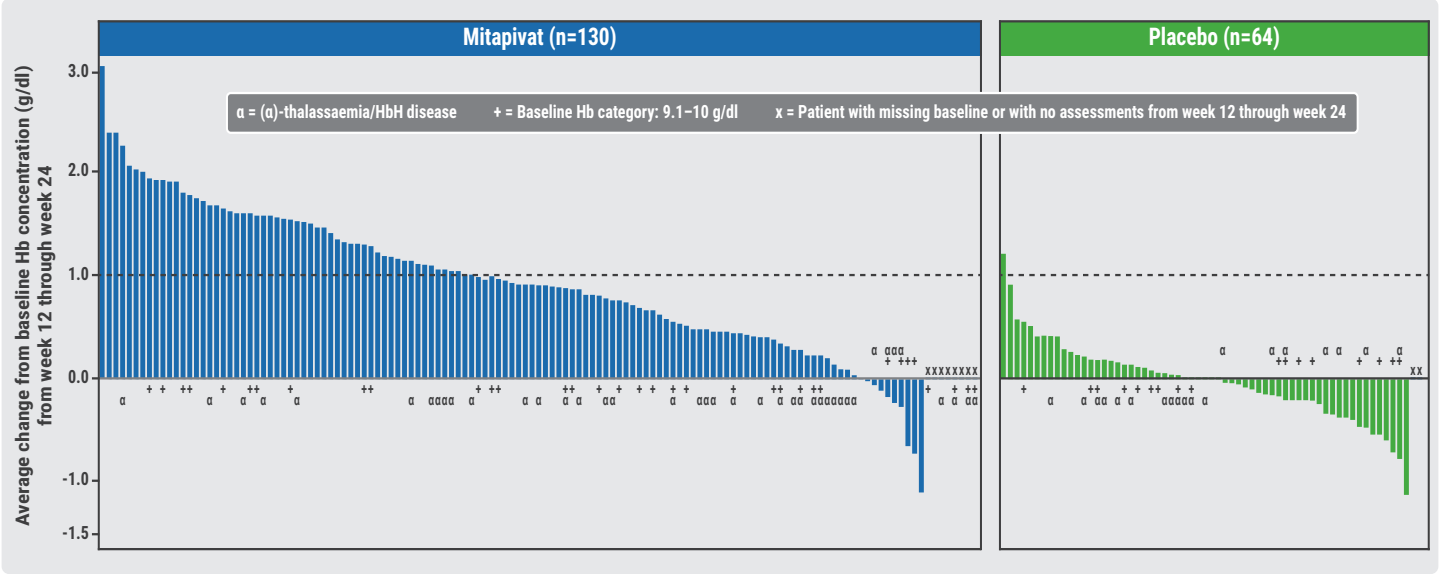
Mitapivat met the primary and key secondary endpoints in the ENERGIZE trial, realising Hb and fatigue improvement in participants with α- or β-NTDT.

1. Taher AT, et al. ENERGIZE: a global, phase 3 study of mitapivat demonstrating efficacy and safety in adults with alpha- or beta-non-transfusion-dependent thalassemia. S104, EHA congress 2024, 13–16 June, Madrid, Spain.

Sovleplenib delivers durable responses and QoL improvements in primary ITP

Sovleplenib was associated with early and durable platelet responses in participants with primary immune thrombocytopenia (ITP) who had received at least 1 prior line of therapy in the phase 3 ESLIM-01 trial. Combined

Figure: Haemoglobin response per participant, mitapivat versus placebo [1]



Hb, haemoglobin; HbH disease, haemoglobin H disease.

with the acceptable safety profile and quality-of-life (QoL) improvements, this agent may be a valuable treatment for this patient population.

The spleen tyrosine kinase inhibitor sovleplenib was assessed for efficacy and safety in the phase 3 ESLIM-01 trial (NCT05029635). Participants (n=188) with primary ITP, previously treated with at least 1 therapy, were randomised 2:1 to sovleplenib or placebo. After 24 weeks, Prof. Renchi Yang (Chinese Academy of Medical Sciences, China) and colleagues assessed the durable response rate, defined as platelet counts ≥50*10^9 platelets/L on at least 4 out of 6 scheduled visits between weeks 14 and 24, not influenced by rescue therapy [1].

Participants treated with sovleplenib achieved a durable response in 48.4% of the cases, compared with none in the placebo arm (P<0.0001). The researchers reported a higher overall response rate (at least 1 platelet count ≥50*10^9 platelets/L) in the sovleplenib arm during the study (70.6% vs 16.1%; P<0.0001).

In total, 25.4% (experimental arm) and 24.2% (control arm) experienced grade ≥3 treatment-emergent adverse events. Upper respiratory tract infection (28.6%), COVID-19 infection (23.8%), and increased blood lactate dehydrogenase (23.8%) were common events in the sovleplenib arm. Finally, Prof. Yang noted that physical functioning and fatigue had improved significantly in the sovleplenib arm.

In conclusion, the safety and efficacy results of the current phase 3 trial indicate that sovleplenib could be a potential treatment option for patients with primary ITP who have received at least 1 prior line of therapy.

1. Yang R, et al. Efficacy and safety of the SYK inhibitor sovleplenib (HMPL-523) in adult patients with primary immune thrombocytopenia in Chine (ESLIM-01): a randomized, double-blind, placebo-controlled phase 3 study. S316, EHA congress 2024, 13–16 June, Madrid, Spain.

Avatrombopag successful in children with chronic ITP

Avatrombopag proved to be an efficacious and well-tolerated agent to treat paediatric participants with chronic immune thrombocytopenia (ITP) in the phase 3 AVA-PED-301 trial. Moreover, avatrombopag's ease of use helps to reduce the treatment burden.

The thrombopoietin receptor agonist avatrombopag was tested in the phase 3 AVA-PED-301 trial (NCT04516967) among paediatric participants with chronic ITP who had an insufficient response to prior therapies. "The agent can be administered orally with food, has no substantial hepatotoxicity, and comes with a low immunogenicity risk compared with parenterally administered agents," explained Dr Rachael Grace (Harvard Medical School, MA, USA) [1].

Participants (n=75) were randomised 3:1 to avatrombopag or a placebo for 12 weeks. The primary efficacy endpoint was a durable platelet response, defined as achieving ≥50*10^9 platelets/L in 6 out of 8 weekly platelet counts without rescue therapy during the last 8 weeks of the treatment period. The alternative primary efficacy endpoint was a platelet response, which comprised at least 2 consecutive platelet assessments ≥50*10^9 platelets/L during the 12-week treatment period without rescue therapy.

The primary efficacy endpoint was met by 27.8% of the participants in the avatrombopag arm and none in the placebo arm (P=0.0077). The alternative primary efficacy endpoint also favoured the avatrombopag arm (81.5% vs 0%; P<0.0001). The proportion of participants requiring rescue therapy was higher in the placebo arm than in the active arm (42.9% vs 7.4%; P=0.0008).

Dr Grace highlighted that the incidence of treatment-emergent adverse events was somewhat higher in the experimental arm than in the control arm (92.6% vs 76.2%), with the most common side effects being petechiae, epistaxis, ecchymosis, and headache. "We did not see any thromboembolic events during the study," added Dr Grace.

"Avatrombopag demonstrated to be efficacious and well-tolerated in children with chronic ITP who did not respond adequately to previous treatments," summarised Dr Grace. "The ease of oral dosing and the absence of dietary restrictions are additional advantages of this agent regarding monitoring and administration."

1. Grace RF, et al. A phase 3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of avatrombopag for the treatment of children with chronic immune thrombocytopenia (AVA-PED-301). S318, EHA congress 2024, 13–16 June, Madrid, Spain.

RUBY: Promising data for first AsCas12a gene-editing therapy in sickle cell disease

Renizgamglogene autogedtemcel (reni-cel) established a swift and durable normalisation in haemoglobin (Hb) and improved haemolysis markers in participants with severe sickle cell disease, supporting further evaluation of this first AsCas12a gene-edited cell therapy.

Reni-cel is a gene-edited stem cell therapy of CD34+ cells, edited at the γ-globin gene (*HBG1* and *HBG2*) promoters. The reasoning for this therapy is that these edits will induce the production of foetal Hb (HbF), which is an important factor in reducing sickle cell disease. The phase 1/2 RUBY trial (NCT04853576) exposed 18 participants with severe sickle cell disease to a single infusion of reni-cel. Dr Rabi Hanna (Cleveland Clinic, OH, USA) shared findings from an interim analysis of this study [1].

After a mean post-infusion follow-up of 6.2 months, none of the participants had experienced a vaso-occlusive event (VOE), compared with a mean of 5.2 severe VOEs per year in the 2 years before the reni-cel infusion. The mean Hb levels increased rapidly and were sustained at 14.4 g/dL from month 5. Dr Hanna added that the mean percentage of foetal Hb was 48.0% at month 4. Likewise, F-cells and mean HbF concentration/F-cell increased quickly and these changes were maintained over time. Key markers of haemolysis indicated improvement and/or normalisation in all participants treated with reni-cel.

The safety profile of reni-cel was comparable with myeloablative conditioning with busulfan and there were no adverse events directly related to reni-cel.

Reni-cel induced a swift and sustained normalisation of Hb, an early increase in foetal Hb, and improvements in key markers of haemolysis. Combining the VOE-free status of the participants after infusion and the favourable safety profile, the results suggest that this promising gene-editing therapy should be further investigated in larger cohorts of patients with sickle cell disease.

1. Hanna R, et al. Reni-cel, the first AsCas12a gene-edited cell therapy, led to hemoglobin normalization and increased fetal hemoglobin in severe sickle cell disease patients in an interim analysis of the RUBY trial. S285, EHA congress 2024, 13–16 June, Madrid, Spain.

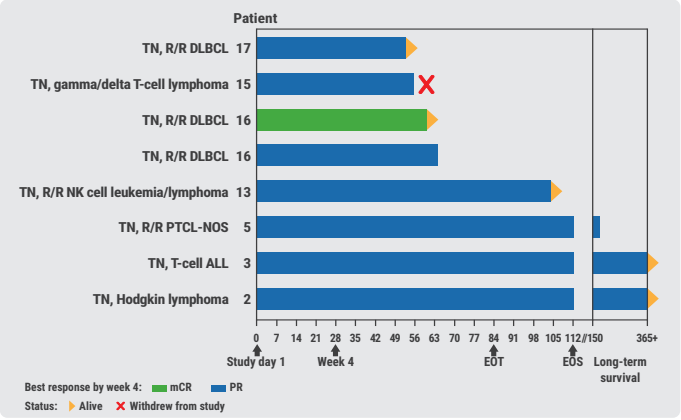
Encouraging data for ELA026 to treat secondary haemophagocytic lymphohistiocytosis

The investigational drug ELA026 improved survival and yielded a manageable safety profile in participants with secondary haemophagocytic lymphohistiocytosis (HLH) in a phase 1 study, warranting further investigation of the agent.

The investigational agent ELA026 targets signal regulatory protein (SIRP)-α/β1 on myeloid cells and SIRPγ on T-lymphocytes. Dr Abhishek Maiti (MD Anderson Cancer Center, TX, USA) and colleagues tested ELA026 among patients with secondary HLH in a phase 1 study (NCT05416307) [1]. During the current presentation, Dr Maiti discussed findings from 8 treatment-naïve participants with malignancy-associated HLH exposed to ELA026. "These participants stemmed from the refined study population cohort," said Dr Maiti. For the safety analysis, data from cohorts 1 and 2 was involved, including participants with refractory or relapsed disease.

After 4 weeks of therapy, all 8 participants presented with at least a partial response. The observed 2-month survival rate of 88% on ELA026 was substantially higher than the 2-month survival rate from natural history malignancy-associated HLH cohorts (50%; see Figure).

Figure: Therapy response and survival upon ELA026 administration to participants with treatment-naïve malignancy-associated HLH [1]



AITL, angioimmunoblastic T-cell lymphoma; ALL, acute lymphoblastic leukaemia; DLBCL, diffuse large B-cell lymphoma; EOS, end of study; EOT, end of treatment; mCR, marrow complete remission; NK cell, natural killer cell; PR, partial remission; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; R/R, relapsed/refractory; TN, treatment-naïve.

Thrombocytopenia (35%), neutropenia (24%), and infusion-related reactions (18%) were among the most commonly observed adverse events (AEs) in the 17 participants included in the safety analysis. "A third of the neutropenia and thrombocytopenia was already established at baseline," highlighted Dr Maiti.

"ELA026 appeared well-tolerated and was associated with improved survival outcomes among treatment-naïve participants with malignancy-associated HLH," concluded Dr Maiti. "This promising therapy may help to control the cytokine storm from any trigger that is the main driver of early mortality in patients with secondary HLH."

1. Maiti A, et al. ELA-026 targeting of SIRP+ immune cells results in a high response rate and improved 2-month survival of treatment-naïve malignancy associated hemophagocytic lymhohistiocytosis in a phase 1 study. LB3442, EHA congress 2024, 13–16 June, Madrid, Spain.

Lymphoma

The landscape of *TP53* mutations and their prognostic impact in CLL

A comprehensive study into the role of *TP53* mutations in chronic lymphocytic leukaemia (CLL) revealed various clinical implications of *TP53* mutations and their prognostic value for targeted therapies.

Dr Consuelo Bertossi (University Hospital Ulm, Germany) and colleagues investigated the prognostic impact of *TP53* mutations in CLL in the context of other genetic markers and different treatment regimens [1]. For this purpose, they analysed the expression patterns of tumour cells of 10,051 participants with CLL through denaturing high-performance liquid chromatography, Sanger sequencing, next-generation sequencing, and variant interpretation according to ERIC guidelines and Seshat.

Of the total study population, 1,368 participants had *TP53* mutations. Overall, 1,824 *TP53* variants were detected, of which 1,273 (69.8%) were missense mutations, 244 (13.4%) were of the frameshift type, 131 (7.2%) were nonsense mutations, 125 (6.9%) were splice site mutations, 20 (1%) were classified as synonymous mutations, and 31 (1.7%) were categorised as 'other'. The same distribution and number of mutations were reported for participants with or without del(17p). However, it was noted that del(17p) was associated with higher variant allele frequency (44% vs 20%; P<0.001).

The efficacy cohort of the study included 3,713 participants from 9 different clinical trials, of whom 9% had *TP53* mutations. Participants with *TP53* mutations had worse progression-free survival (HR 2.61; 95% CI 1.80–2.37; P<0.001) and overall survival (HR 2.82; 95% CI 2.38–3.34; P<0.001) outcomes than those with *TP53* wild-type disease. Dr Bertossi added that both minor (variant allele frequency <10%) and major *TP53* mutations negatively impacted progression-free and overall survival, whereby the impact of major mutations appeared to be more pronounced.

"We also noted that pathogenic, deleterious, and truncating *TP53* mutations affected overall survival outcomes, whereas variant of uncertain significance mutations associated with similar outcomes as observed for *TP53* wild-type disease," according to Dr Bertossi. Furthermore, the prognostic impact of *TP53* mutations was independent of del(17p) and immunoglobulin heavy chain gene (IGHV) status. Finally, all participants displayed improved survival outcomes with venetoclax or ibrutinib compared with chemo-immunotherapy; those with wild-type disease had better outcomes than those with mutated disease, irrespective of administered therapy.

1. Bertossi C, et al. The landscape of TP53 mutations and their prognostic impact in chronic lymphocytic leukemia. S101, EHA congress 2024, 13–16 June, Madrid, Spain.

Can golcadomide plus R-CHOP become the first-line standard of care in high-risk BCL?

Golcadomide plus R-CHOP delivered a high rate of durable complete metabolic responses (CMR) regardless of the cell of origin in participants with aggressive B-cell lymphoma (BCL). The progression-free survival data of this phase 1b study were promising at 12 months follow-up and the safety profile was manageable.

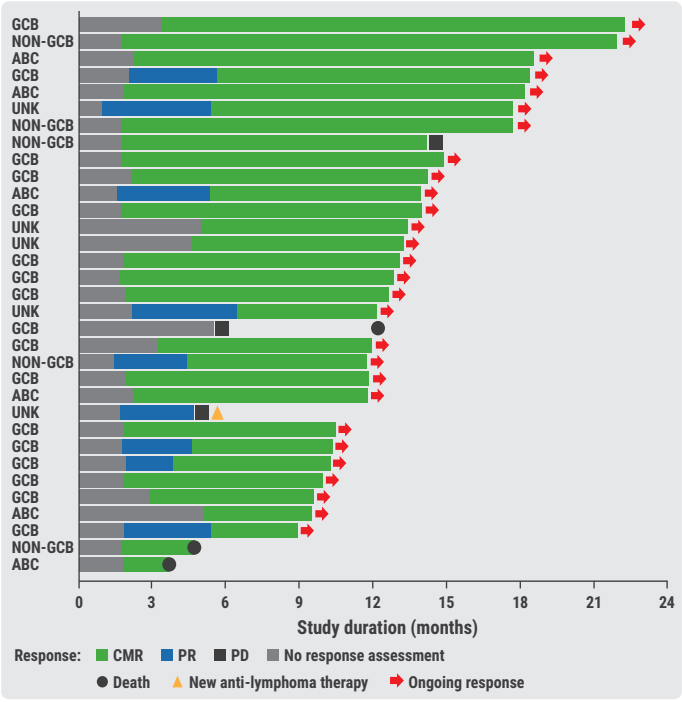
Golcadomide is an orally administered cereblon E3 ligase modulator, that degrades target proteins to produce dual immunomodulatory and direct cell-destructing anti-tumour activity [1]. The phase 1b CC-220-DLBCL-001 trial (NCT04884035) investigated the safety and efficacy of golcadomide plus R-CHOP in participants with untreated aggressive BCL. Safety was the primary endpoint of this study. Dr Marc Hoffman (The University of Kansas Cancer Center, KS, USA) presented the 12-month follow-up results [2].

Participants received ≤6 x 21-day cycles of golcadomide plus R-CHOP therapy and were randomised to 0.2 mg or 0.4 mg golcadomide at days 1 to 7 of each treatment cycle during the dose expansion phase. Of the 78 included participants, most had Ann Arbor stage III–IV (83.3%), 82% had high-risk disease, and 82% had diffuse large BCL with a histological diagnosis of "not otherwise specified".

Grade 3 or 4 treatment-emergent adverse events (TEAEs) were seen in 91% of the participants, predominantly neutropenia (87%) and thrombocytopenia (42%). Serious TEAEs were reported in 46% of the participants, of which febrile neutropenia (19%) was the most common AE.

In the highest dose group (n=33), the CMR rate was 88% at the end of therapy and all participants were progression-free. This result was consistent across risk and cell of origin subgroups. At 12 months follow-up, the progression-free survival rate was 85% in the high-dose group and 75% in the low-dose group, with similar rates in biologically distinct molecular subtypes germinal centre B-cell (GCB) and activated B-cell (ABC; see Figure, diffuse large BCL only).

Figure: Treatment response and treatment follow-up per patient participant receiving the high golcadomide dose (0.4 mg) [2]



ABC, activated B-cell diffuse large BCL; CMR, complete metabolic response; (non-)GCB, (non-) germinal centre B-cell diffuse large BCL; PD, progressive disease; PR, partial response; UNK, unknown.

These findings support the currently recruiting GOLSEEK-1 trial (NCT06356129), an upstarting phase 3 study comparing golcadomide plus R-CHOP to R-CHOP alone as first-line treatment for participants with high-risk large BCL.

1. Matyskiela ME, et al. J Med Chem. 2018;61(2):535–542.
2. Hoffman M, et al. Golcadomide, a potential first-in-class oral CELMOD agent, plus R-chop in patients with untreated aggressive B-cell lymphoma: safety and 12-month efficacy results. S235, EHA congress 2024, 13–16 June, Madrid, Spain.

High survival rates following atezolizumab consolidation in DLBCL

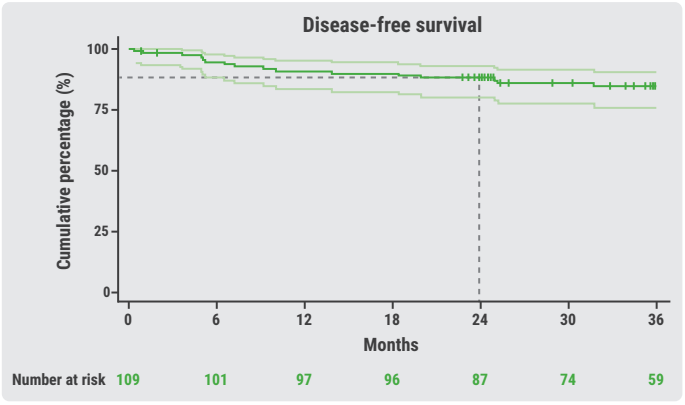
Participants with high-risk diffuse large B-cell lymphoma (DLBCL) and a complete metabolic response (CMR) after R-CHOP benefitted from atezolizumab consolidation therapy. The final analysis of the HOVON 151 study showed improved disease-free survival (DFS) and overall survival.

"The 5-year progression-free survival (PFS) rate for patients with high-risk DLBCL is around 60%," opened Dr Marcel Nijland (University Medical Center Groningen, the Netherlands) [1]. He shared that the incidence of relapse is around 25% for high-risk patients in clinical remission after R-CHOP and that lenalidomide maintenance and polatuzumab vedotin added to R-CHOP improve PFS but not overall survival [2,3].

The phase 2 HOVON 151 study (NL6335204217) investigated the efficacy of consolidation therapy with the PD-L1 inhibitor atezolizumab in participants with high-risk DLBCL who had a CMR after R-CHOP therapy (n=109). The participants received 1,200 mg of atezolizumab, intravenously administered every 3 weeks, for up to 18 cycles. The primary endpoint was DFS and Dr Nijland presented the study's final analysis [1].

The 2-year DFS rate was 87.9% (90% CI 81.5–92.1), meeting the primary endpoint (see Figure) and surpassing the 2-year DFS rate from a historical cohort (≤79%) [4]. Moreover, the 2-year overall survival rate was 96.3% [1]. Dr Nijland added that 13 of the 15 relapsing participants received salvage chemotherapy, of whom 77% experienced a second CMR.

Figure: Kaplan-Meier curve of disease-free survival in HOVON 151 [1]



Adverse events were reported in 79% of the participants, most commonly being infections (25%), musculoskeletal and connective tissue disorders (9%), and nervous system disorders (9%). The research team noted 10 cases of endocrinopathy and 3 ocular toxicities during the study.

Atezolizumab consolidation therapy after R-CHOP yielded excellent results in participants with high-risk DLBCL who achieved a CMR on R-CHOP. The remarkable 2-year overall survival outcomes and the fact that most participants were chemo-sensitive at relapse support atezolizumab as a consolidation therapy for this population.

1. Nijland M, et al. Feasibility and clinical efficacy of atezolizumab consolidation in high risk diffuse large B-cell lymphoma: final analysis of the HOVON 151. S236, EHA congress 2024, 13–16 June, Madrid, Spain.
2. Thieblemont C, et al. J Clin Oncol. 2017;35(22):2473–2481.
3. Tilly H, et al. N Engl J Med. 2022;386(4):351–363.
4. El-Galaly TC, et al. J Clin Oncol. 2015;33(34):3993–3998.

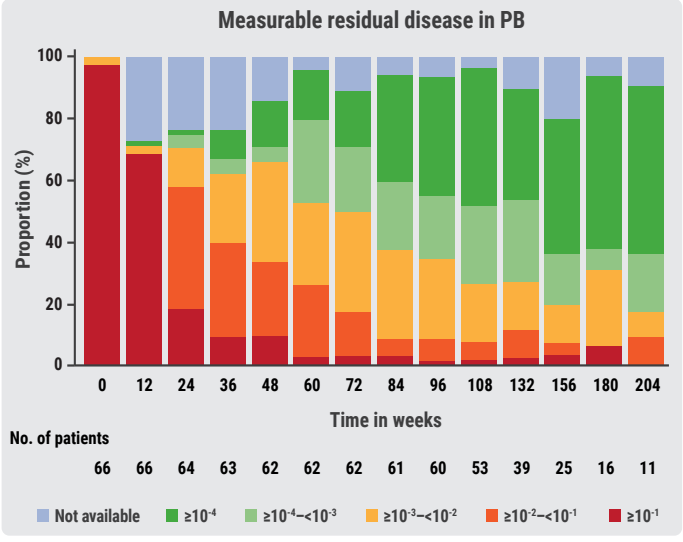
First results for zanubrutinib plus venetoclax in del(17p)/*TP53*-mutated CLL/SLL

The combination of zanubrutinib and venetoclax was associated with deep and durable responses in participants with previously untreated high-risk chronic lymphocytic leukaemia (CLL)/ small lymphocytic lymphoma (SLL) and del(17p) and/or *TP53* mutations, first results of the SEQUOIA trial showed.

Arm D of the phase 3 SEQUOIA trial (NCT03336333) exposed 66 participants with CLL/SLL and del(17p) and/or *TP53* mutations to the combination regimen of Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib plus the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax. Prof. Paolo Ghia (University Vita-Salute San Raffaele, Italy) presented the preliminary results of this study [1].

After a median follow-up of 31.6 months, the overall response rate was 100% and the complete remission (CR) plus CR with incomplete count recovery rate was 48%. Importantly, the best undetectable measurable residual disease ($<10^{-4}$) rate was 59% in at least 1 peripheral blood sample (see Figure). The median progression-free survival was not reached at the time of presentation of the results, but the estimated 24-month progression-free survival rate was 94%.

Figure: Measurable residual disease rates in peripheral blood increased with longer treatment duration [1]



MRD, measurable residual disease; PB, peripheral blood.

COVID-19 (55%), diarrhoea (39%), nausea (30%), contusion (29%), and fatigue (23%) were the most frequently observed adverse events with the combination regimen. "The safety profile was overall favourable and we did not see any unexpected issues," commented Prof. Ghia.

In conclusion, zanubrutinib plus venetoclax delivered promising preliminary efficacy results in participants with newly diagnosed CLL/SLL with del(17p) and/or *TP53* mutations.

1. Ma S, et al. Combination of Zanubrutinib plus venetoclax for treatment-naïve CLL/SLL with del(17p) and/or TP53: preliminary results from SEQUOIA arm D. S160, EHA congress 2024, 13–16 June, Madrid, Spain.

EPCORE™ CLL-1: Promising data for epcoritamab in high-risk Richter's transformation

Epcoritamab delivered encouraging efficacy data and a favourable safety profile in participants with high-risk Richter's transformation (RT), supporting further evaluation of this agent in RT.

Prof. Arnon Kater (University of Amsterdam, the Netherlands) and co-investigators tested the bispecific antibody epcoritamab (targeting CD3 on T-cells and CD20 on B-cells) in participants with high-risk RT [1]. The EPCORE™ CLL-1 trial (NCT04623541) included 42 participants with RT who had received fewer than 3 lines of therapy for RT and were ineligible for chemotherapy. All participants received epcoritamab until disease progression. The primary endpoint was the independent central review's objective response rate (ORR).

The ORR was 60% in participants who received epcoritamab as first-line therapy (n=20), a good result according to Prof. Kater. Moreover, the complete response rate was 50% in this subset of participants. For relapsed disease (n=18), the ORR was 44% and the complete response rate was 33%. "The median time to response was 1.4 months and the median time to complete response was 2.5 months," added Prof. Kater. Furthermore, the median duration of response was 9.6 months.

Cytokine release syndrome (83%), infections (66%), thrombocytopenia (46%), anaemia (42%), and neutropenia (40%) were the most common side effects. "Cytokine release syndrome events were predictable, mostly following the first full dose, and predominantly of grade 1 or 2," added Prof. Kater.

Overall, epcoritamab showed promising anti-tumour activity and had a manageable safety profile in this participant

population with high-risk RT. Other cohorts of the EPCORE™ CLL-1 trial are currently investigating epcoritamab in combination with other agents for participants with RT or chronic lymphocytic leukaemia.

1. Kater AP, et al. Single-agent epcoritamab leads to deep responses in patients with Richter's transformation: primary results from the EPCORE CLL-1 trial. S163, EHA congress 2024, 13–16 June, Madrid, Spain.

Updates from the EBMT Lymphoma Working Group: outcomes after allo- and auto-SCT for T-cell lymphoma subtypes

A large retrospective study from the EBMT Lymphoma Working Group revealed different outcomes of autologous (auto-) versus allogeneic (allo-) stem cell transplantation (SCT) across major T-cell lymphoma subtypes. These results suggest that patients should be followed up according to their T-cell lymphoma entity after transplantation if feasible.

Dr Evgenii Shumilov (University of Münster, Germany) and colleagues aimed to investigate whether outcomes of allo- and auto-SCT differ between major T-cell lymphoma entities [1]. The current analysis included participants with peripheral T-cell lymphoma not otherwise specified (PTCL NOS; n=4,029), angioimmunoblastic T-cell lymphoma (AITL; n=2,838), and anaplastic lymphoma kinase rearranged (*ALK*)-positive (n=430) or *ALK*-negative (n=1,103) anaplastic large cell lymphoma (ALCL). Auto-SCT was performed in 7,099 and allo-SCT was conducted in 1,292 participants.

The 2-year overall survival rates of participants undergoing auto-SCT showed that participants with *ALK*-positive (85.3%) or *ALK*-negative ALCL (83.8%) lived significantly longer than those with PTCL NOS (66.0%) or AITL (68.9%; P<0.001; see Figure). For the group that underwent allo-SCT, only participants with *ALK*-positive ALCL had better 2-year survival rates (79.9%) compared with *ALK*-negative ALCL (63.3%), AITL (59.4%), or PTCL NOS (53.3%; P<0.001) cases. Although the survival rates of participants with 1 of the 3 latter entities were similar, the 4 investigated entities differed in 2-year relapse incidence rates (*ALK*-positive ALCL 23.2%; *ALK*-negative ALCL 36.2%; PTCL NOS 30.3%; AITL 13.4%) and non-relapse mortality rates (*ALK*-positive ALCL 11.6%; *ALK*-negative ALCL 14.4%; PTCL NOS 21.4%; AITL 30.0%).

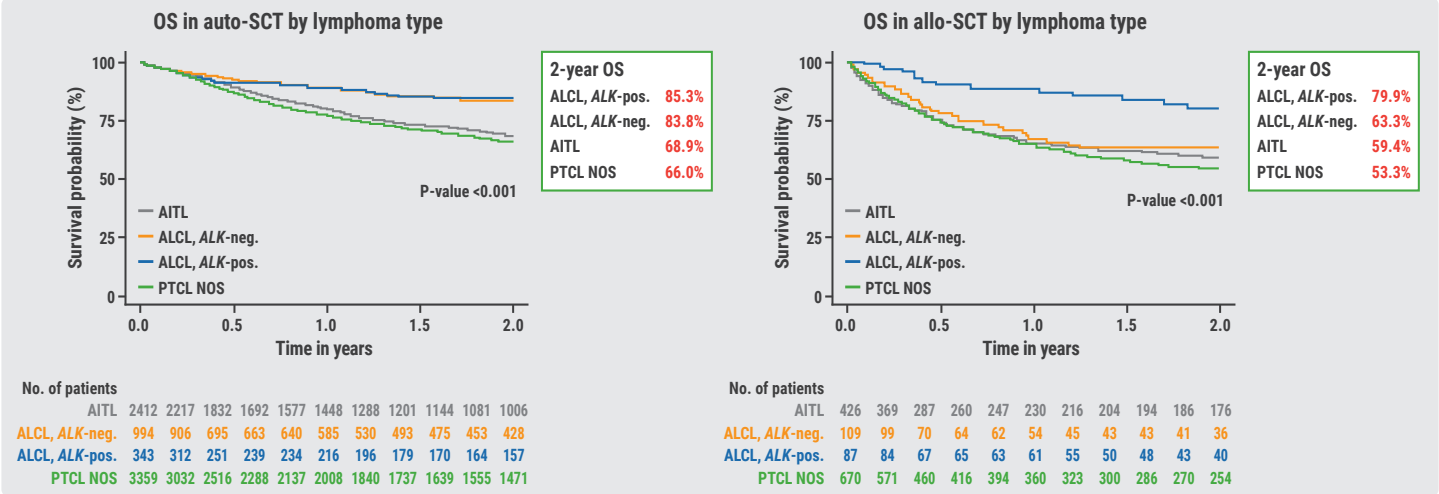
"These outcomes indicate that patients with PTCL NOS, AITL, *ALK*-negative ALCL, and *ALK*-positive ALCL disease should be analysed separately after transplantation whenever possible," concluded Dr Shumilov.

1. Shumilov E, et al. Outcomes of autologous and allogeneic stem cell transplantation for T-cell lymphoma: an updated analysis of the EBMT lymphoma working party. S245, EHA congress 2024, 13–16 June, Madrid, Spain.

ECHO: Can we expect a novel standard of care in newly diagnosed MCL?

A first-line treatment regimen of acalabrutinib added to bendamustine and rituximab (BR) decreased the risk of disease progression or death compared with a regimen of BR and a placebo in older participants with mantle cell lymphoma (MCL) in the phase 3 ECHO trial.

Figure: Overall survival after auto- and allo-SCT according to lymphoma subtype [1]



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; allo-SCT, allogeneic stem cell transplantation; *ALK*, anaplastic lymphoma kinase rearranged; auto-SCT, autologous stem cell transplantation; OS, overall survival; PTCL NOS, peripheral T-cell lymphoma not otherwise specified.

"Although intensive frontline therapies can deliver durable responses in patients with MCL, these treatments are not suited for older patients due to poor tolerability," elaborated Prof. Michael Wang (University of Texas, TX, USA) [1]. Thus, BR is therefore the most frequently administered first-line therapy in this population. Recently, the addition of the BTK inhibitor acalabrutinib to BR delivered promising safety and efficacy results in a phase 1 study (NCT02717624) [2].

To further evaluate this combination therapy, the current phase 3 ECHO trial (NCT02972840) randomised 598 participants over 64 years of age with newly diagnosed MCL 1:1 to BR plus acalabrutinib or BR plus placebo. The primary endpoint was progression-free survival (PFS). "Participants in the placebo arm were permitted to cross over to acalabrutinib if they had disease progression," noted Prof. Wang [1].

After a median follow-up of 45 months, PFS was improved in the acalabrutinib arm compared with the placebo arm (HR 0.73; 95% CI 0.57–0.94; P=0.016). The median PFS was 66.4 months in the acalabrutinib and 49.6 months in the placebo arm. Of note, 69% of the participants in the placebo arm received BTK inhibitors as a subsequent treatment. According to Prof. Wang, there was also a positive trend in OS, with a hazard ratio of 0.86 (95% CI 0.65–1.13; P=0.27). "If we censor for COVID-related deaths the OS trend was even more positive," emphasised Prof. Wang (HR 0.75; 95% CI 1.04; P=0.08; see Figure).

The safety profiles of the 2 treatment regimens did not differ substantially. Atrial fibrillation occurred in 6.1% of the participants on acalabrutinib and in 4.4% of placebo. Hypertension (12.1% vs 15.8%) and major bleeding (2.4% vs 5.4%) were slightly more common in the placebo arm, whereas infections (78.1% vs 71.0%) were more frequently reported in the acalabrutinib arm.

"The data from ECHO indicate that acalabrutinib plus BR may be a new first-line standard of care for older patients with MCL," concluded Prof. Wang.

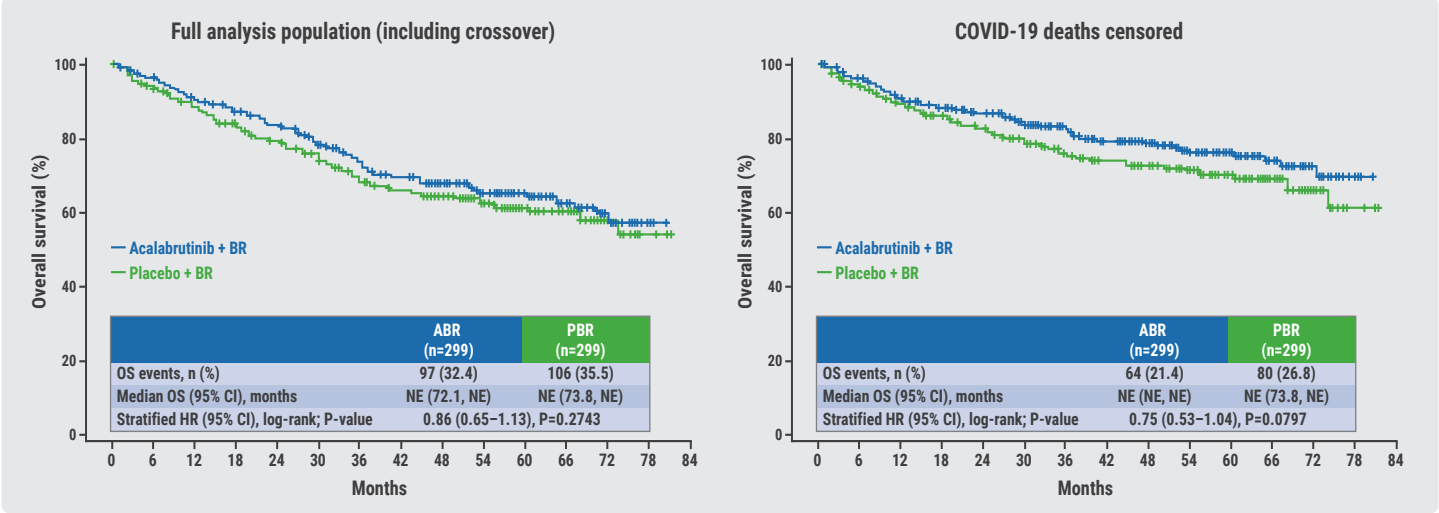
1. Wang M, et al. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma: results from the phase 3, double-blind, placebo-controlled ECHO trial. LB3439, EHA congress 2024, 13–16 June, Madrid, Spain.
2. Phillips TJ, et al. J Clin Oncol. 2023;41(16 suppl):7546.

Clinically meaningful outcomes for mosunetuzumab across follicular lymphoma subgroups

High-risk participants with heavily pre-treated relapsed or refractory follicular lymphoma (R/R FL) benefitted from mosunetuzumab for clinical remission and survival outcomes in a phase 1/2 study. The benefit of mosunetuzumab was consistent in participants who had disease progression within 2 years.

The phase 1/2 study (NCT02500407) recently demonstrated high complete response (CR) rates with the CD20/CD3 T-cell engaging bispecific antibody mosunetuzumab among patients with R/R FL [1]. Dr Sarit Assouline (Jewish General Hospital, Canada) presented the current subgroup analysis of this study after 3 years of follow-up [2]. All participants

Figure: A pre-specified sensitivity analysis of OS with and without COVID-19 deaths [1]



ABR, acalabrutinib plus bendamustine and rituximab; BR, bendamustine and rituximab; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo plus bendamustine and rituximab.

received mosunetuzumab in the third line or later and progression of disease within 24 months (POD24) was observed in 52% of participants.

After 3 years of therapy, CR was seen in 60% of participants with POD24, a figure consistent with the overall study population (also 60%). Similarly, CR rates in participants older than 64 years (67%) and those who received mosunetuzumab as fourth-line therapy or later (55%) were comparable with the general trial population. In addition, the median duration of CR was not reached in participants with POD24 or older participants but was 33 months in 'fourth-line-or-higher' participants. The 3-year progression-free survival rates were 44% in the POD24 subgroup, 47% in participants over 64 years, and 43% in the overall population. In fourth-line-or-higher participants, this rate appeared lower at 36% compared with third-line participants (54%).

The safety profile of mosunetuzumab was manageable and consistent across subgroups. The observed adverse events were cytokine release syndrome (44%), neutropenia (29%), and serious infections (20%).

"The consistent results of mosunetuzumab across subgroups of participants with R/R FL and the manageable safety profile support outpatient administration of this agent," concluded Dr Assouline.

1. Budde LE, et al. Lancet Oncol. 2022;23(8):1055–1065.
2. Assouline S, et al. Mosunetuzumab demonstrates clinically meaningful outcomes in high-risk patients with heavily pre-treated R/R FL after ≥3 years of follow-up: subgroup analysis of a pivotal phase 2 study. S233, EHA congress 2024, 13–16 June, Madrid, Spain.

Myelofibrosis

Navitoclax plus ruxolitinib leads to spleen volume reductions in myelofibrosis

JAK inhibitor-naïve participants with myelofibrosis benefitted from a regimen of navitoclax plus ruxolitinib compared with ruxolitinib and a placebo in the phase 3 TRANSFORM-1 trial.

The phase 3 TRANSFORM-1 trial (NCT04472598) randomised 252 participants with untreated intermediate- or high-risk myelofibrosis and measurable splenomegaly to the Bcl-2 inhibitor navitoclax or placebo plus ruxolitinib. All participants received the JAK inhibitor ruxolitinib. The primary endpoint was a 35% spleen volume reduction (SVR35) at week 24 and Prof. Naveen Pemmaraju (MD Anderson Cancer Center, TX, USA) presented the findings [1].

The primary endpoint was met by 63% of the participants in the navitoclax arm and 32% in the placebo arm (P<0.0001). "This finding was consistent across subgroups," highlighted Prof. Pemmaraju. Almost 50% of the included participants had high molecular risk profiles. In this subgroup of participants, the primary endpoint was met by 59% and 41%, favouring the navitoclax over the placebo arm. Also, variant allele frequency reductions of at least 20% at any time were seen in 57% of the navitoclax and 42% of the placebo receivers. Survival data was presented for the high molecular risk profile participants and the median progression-free survival was 25.2 months in the experimental arm versus 22.9 months in the placebo arm.

The most frequently occurring adverse events in the navitoclax arm were thrombocytopenia, anaemia, diarrhoea, and neutropenia, all observed in >30% of the participants. Finally, serious adverse events were seen in 28% of the participants on navitoclax and 38% on placebo.

Navitoclax plus ruxolitinib resulted in a 2-fold improvement of SVR35 at week 24 compared with placebo plus ruxolitinib in this population with myelofibrosis, without showing new safety signals.

1. Pemmaraju N, et al. Efficacy and safety of navitoclax in combination with ruxolitinib versus ruxolitinib plus placebo in patients with untreated myelofibrosis in the phase 3 randomized, double-blind TRANSFORM-1 study. S222, EHA congress 2024, 13–16 June, Madrid, Spain.

Is pelabresib plus ruxolitinib the paradigm-shifting combo therapy for myelofibrosis?

Treatment with pelabresib plus ruxolitinib improved all 4 hallmarks of myelofibrosis, results of the phase 3 MANIFEST-2 trial showed.

The phase 3 MANIFEST-2 study (NCT04603495) evaluated pelabresib, an investigational bromodomain and extra-terminal domain (BET) protein inhibitor, in combination with JAK inhibitor ruxolitinib for treating myelofibrosis. The 430 participants with myelofibrosis were randomised to pelabresib or placebo plus ruxolitinib. The primary endpoint was a 35% spleen volume reduction (SVR35) at week 24. Dr Raajit Rampal (Memorial Sloan Kettering Cancer Center, NY, USA) presented the latest trial results [1].

At week 24, 65.9% and 35.2% of the participants in the pelabresib arm and placebo arm, respectively, achieved the primary endpoint (P<0.001). Dr Rampal addressed that the mean absolute change in total symptom score at week 24 was -15.99 in the pelabresib and -14.05 in the placebo arm, reflecting a numerical benefit for the pelabresib arm (P=0.055). Haemoglobin responses were seen in 10.7% and 6.0% of the participants in the experimental and placebo arm, respectively.

Furthermore, significant improvements in bone marrow fibrosis (at least 1 grade) were documented for 38.5% on pelabresib and 24.2% on placebo (OR 2.09; 95% CI 1.14–3.93).

As for safety, the most common treatment-emergent adverse events in the experimental and placebo arms were anaemia (43.9% vs 55.6%), thrombocytopenia (32.1% vs 23.4%), decreased platelet count (20.8% vs 15.9%), and diarrhoea (23.1% vs 18.7%).

In conclusion, the treatment regimen of pelabresib plus ruxolitinib was associated with significant spleen responses, improved anaemia and bone marrow fibrosis, and a trend towards improved symptoms, compared with a treatment regimen of ruxolitinib and placebo in a population of patients with myelofibrosis.

1. Rampal RK, et al. Safety and efficacy of pelabresib in combination with ruxolitinib for JAK inhibitor treatment-naïve patients with myelofibrosis: latest data from the phase 3 MANIFEST-2 study. S221, EHA congress 2024, 13–16 June, Madrid, Spain.