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European Hematology Association

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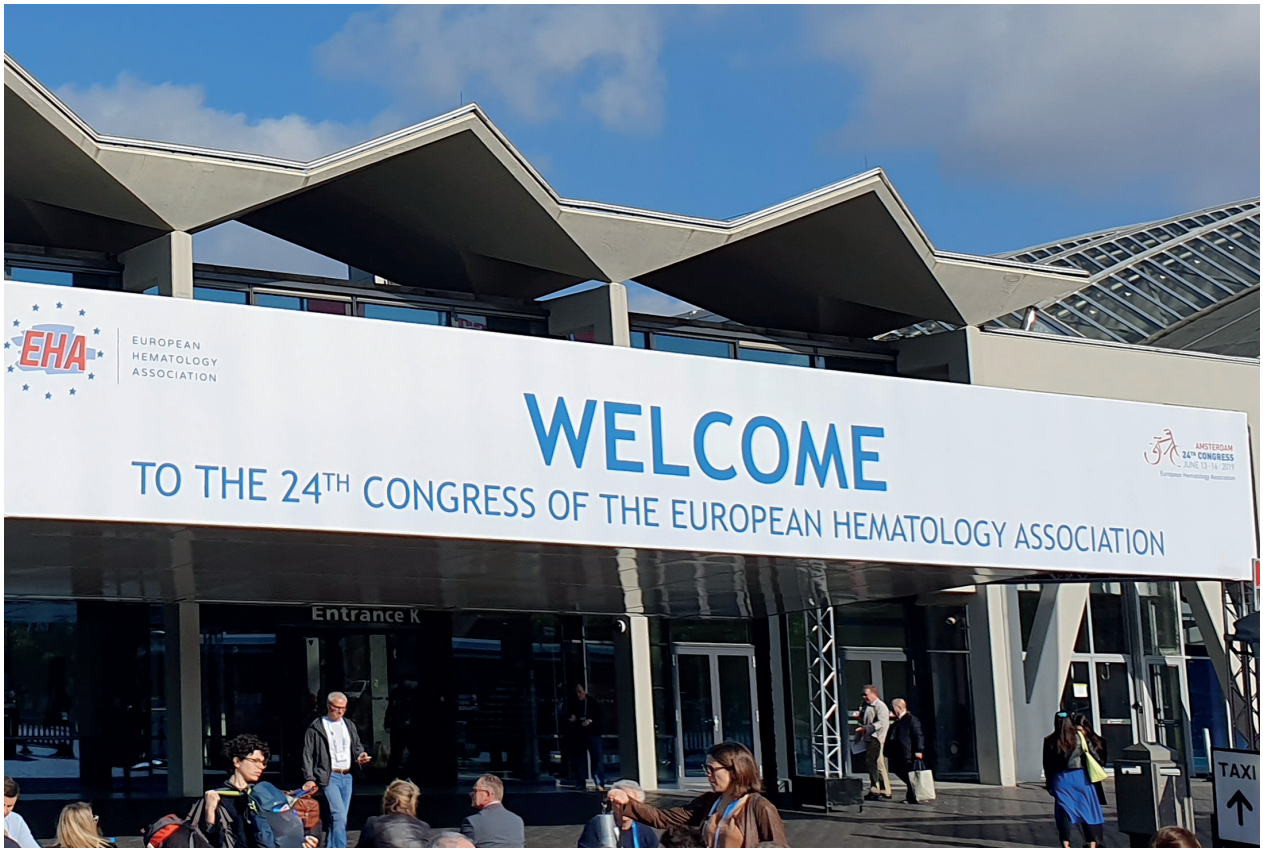

Gilteritinib Benefits Relapsed/Refractory AML

The ADMIRAL phase 3 trial of gilteritinib, a selective FLT3 inhibitor, for relapsed or refractory AML report favourable outcomes with increased complete response rate and improved overall survival.

read more on PAGE 3

CAR-T Therapies

Advances and challenges with CAR-T therapy: Results from trials in acute lymphocytic leukaemia, diffuse large B cell lymphoma, and multiple myeloma.

read more on PAGES 9 &14

Voxelotor Beneficial in Sickle Cell Disease

The phase 3 HOPE trial of voxelotor in adults and adolescents with sickle cell disease shows 60% patients improve anaemia and haemolysis.

read more on PAGE 19

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Contents

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MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

Introduction

Dear Reader,

More than 12,600 haematology professionals from around the world (41 countries in Europe/ 82 countries outside of Europe) met together for the 24th European Hematology Association (EHA) Congress in Amsterdam, The Netherlands, from 13-16 June, 2019.

The 4-day program combined a broad range of topics from the rapidly evolving field of haematology. Updates on the diagnosis and management of patients with haematological disorders, as well as presentations on the cutting edge of basic, translational and clinical research were presented in over 400 sessions of invited presentations, abstract presentations and sponsored sessions from EHA's industry partners. Original unpublished data formed the core of the program, with some large clinical trials pushing the evidence-base of primary clinical relevance, with likely practice-changing outcomes.

Two topics-in-focus were highlighted as well at this meeting, because of their impending high-impact in this field: advances in haemoglobinopathies and immunotherapy. Within the area of haemoglobinopathies, several promising developments in sickle cell disease management will bring changes to daily practice in the near future. For immunotherapy, CAR-T-cell therapy has been marked by particularly rapid success in the clinic, with steadily better results, as we start to understand the safety profile and underlying biology modulating response. This year was the start of implementing such focussed programs aimed at raising awareness, providing education, furthering research, and building a network of experts with the ultimate goal to improve patient care. This Conference Report aims to bring the conference to the physician, by summarising the main points of interest in a peer-reviewed and balanced manner.

Enjoy the read!
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Professor Gert Ossenkoppele

Editor Biography

Professor Gert Ossenkoppele was appointed in 2003 as professor of Hematology at the VU University Medical Center in Amsterdam. Gert Ossenkoppele has authored over 390 publications in peer-reviewed journals and is an invited speaker at many international scientific meetings. His research interests are mainly translational and include the (stem cell) biology of AML, leukemic stem cell target discovery, immunotherapy, and measurable residual disease (MRD) detection using flow cytometry to inform treatment of AML. He is the PI of various clinical trials in myeloid malignancies. He chairs the AML working party of HOVON (Dutch-Belgian Hematology Trial Group) and is appointed as vice-chair of the HOVON Executive Board. He is a lead participant of the AML Work package of the European LeukemiaNet (ELN) as well as a board member of the ELN foundation. He is recently appointed as chair of the EHA Educational Committee. He chairs the AML Scientific working group of EHA, and he is chair of the Global and EU steering committee of the AMLGlobalPortal an educational portal for hematologists (www.amlglobalportal.com).

Conflict of Interest
Statement: Prof. Ossenkoppele is consultant for Novartis and BMS.

Interview with EHA President **Prof. Pieter Sonneveld,** MD, PhD,

conducted on 24 June 2019 by Dr Rachel Giles

Prof. Pieter Sonneveld, MD, PhD serves as Head of the Department of Hematology at the Erasmus Medical Center in Rotterdam, the Netherlands. Prof. Sonneveld was a founder of the European Myeloma Network and serves as its Chairman. He serves on the scientific advisory boards of the International Myeloma Foundation, the International Myeloma Working Group and the International Myeloma Society.

Can you tell us about the focus topics the EHA wanted to place in the spotlight this year?

The annual EHA meeting this year had two topics-in-focus highlighting haemoglobinopathies -diseases of red blood cells like thalassemia and sickle cell disease- and immune therapy of haematologic diseases. There are several new immune therapies like antibodies but also drugs that influence immune competent cells like the checkpoint inhibitors. Last but not least the cellular therapies like CAR T cell therapies. Those main approaches were highlighted during the conference across several disease domains.

What did you consider some of the promising developments that were featured at EHA2019?

Very many promising studies were presented at the Plenary sessions and at the Presidential Symposium. Although many of the talks presented exciting data, I would like to mention two talks that were particularly exciting. Firstly, the use of combination therapy venetoclax with obinutuzumab for a fixed duration of time in elderly patients with chronic lymphocytic leukaemia demonstrated that this is a very competent combination. Secondly, another breakthrough talk I would like to highlight was the use of new drugs in sickle cell disease which increased the haemoglobin content of the cells and thereby reduced symptoms in patients with this disease.

What are the challenges for the upcoming year in this field?

In a much wider sense, I would like to mention that EHA is committed to education, and promotes basic, translational and clinical research in haematology with the aim to stimulate new partnerships. As the largest haematology professional association in Europe, the EHA has the largest impact on education and communication of topics in haematology. In addition, the EHA held the 3rd European Hematology Exam on-site during the 24th EHA Congress in Amsterdam, and held parallel exams in Greece, Portugal, Spain, Switzerland and Turkey at the same moment. This exam is an important step in the harmonisation of haematology training/education in Europe, and will support professional mobility, and I anticipate that this will be expanded over the next several years.

Another challenge I think we need to address is the high cost of the novel drugs and therapies. Access and availability will be restricted as a consequence, and these options will not be available to many patients, especially in lesser developed countries. The EHA takes this task seriously to try and make all these drugs and treatments available, also to patients in developing countries. We also try to approach this by working together with many other organisations in the European Community to highlight the importance of haematology; for example, we work with laboratory organisations, patient organisations and many others to facilitate the process.

You are passing on the EHA Presidency; what was your experience and what wisdom do you pass on to your successor?

The next EHA President will be Prof. John Gribben from London, UK. Over the past two years during my Presidency, I have been able to expand many activities of the EHA both in the organisation itself but also in the countries where the EHA is active in Europe and beyond. I am pleased to have been able to increase the connection of the EHA with the scientific communities in haematology throughout Europe via the scientific working groups. Of course these are just one or two of the many activities I have been involved with, but I would like to highlight those. To my successor I would say: keep on supporting the ongoing scientific and clinical collaborations as well as our various efforts in education, and the EHA will continue to grow and expand and increase its relevance in the haematology world.

Myeloid Malignancies

Residual disease in AML patients prior to stem cell transplant increases relapse risk

For patients with acute myeloid leukaemia (AML), the presence of measurable residual disease (MRD) prior to stem cell transplant significantly increases the risk of relapse among patients who receive a reduced-intensity conditioning regimen, compared with those with no MRD. This suggests that patients with evidence of MRD should receive higher-intensity conditioning, say researchers reporting a new analysis from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901 [1].

In the late-breaking abstracts session, Dr Christopher Hourigan (NIH, USA) presented the results of preconditioning samples from 188 AML patients in the 0901 trial. The patients were well matched with respect to baseline characteristics, including age, sex, disease risk, donor type, donor match, and graft type.

A previous analysis of this study compared the outcomes of AML patients in remission, following 1 of 2 forms of pre-transplant preparative therapy, either high-intensity myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC), relapsed within 18 months after transplant [2]. They found that 31% of patients in the high-intensity myeloablative group and 33% in the reduced-intensity group had no genomic variants indicative of MRD. Subsequent survival rates did not differ among those groups (3-year overall survival: 58% vs 65%; P=0.98). However, among the patients with detectable variants indicative of MRD prior to conditioning, the 3-year overall survival rate was significantly better for the patients in the high-intensity conditioning group than for those in the reduced-intensity group (61% vs 44%; P=0.02).

The researchers assessed MRD using a next-generation, ultra-deep, error-corrected genomic sequencing technology that is currently available only for research purposes, Dr Hourigan explained. However, he said the findings underscore a role for MRD testing in the future. Overall, 76% of patients who experienced relapse had at least 1 detectable variant prior to conditioning. After adjusting for factors that included the level of disease risk and donor group, patients with detectable variants indicating MRD who went on to receive the reduced-intensity conditioning had a nearly 6 times greater risk for relapse (HR 5.98; 95% CI 3.19-11.26; P<0.001).

For these patients, disease-free survival was significantly decreased (HR 2.80; 95% CI 1.76-4.44; P<0.001), as was overall survival (HR 2.16; 95% CI 1.30-3.60; P=0.003), when compared with the higher-intensity conditioning group. Although in the original trial mortality related to toxicity from the treatment itself was significantly higher among the patients who received the high-intensity regimen, the new findings suggest the risk/benefit balance may be offset by this MRD finding, said Dr Hourigan.

"As a physician who treats acute leukaemia patients, these findings for me open up many interesting questions and some obvious opportunities for potentially improving the therapeutic outcomes for our AML patients," Dr Hourigan concluded.

1. Hourigan C, et al. Abstract LB2600, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Scott BL, et al. J Clin Oncol. 2017 Apr 10;35(11):1154-1161.

Gilteritinib prolongs overall survival in patients with FLT3-mutated relapsed/refractory AML

Dr Alexander Perl (University of Pennsylvania, USA) presented the data from the phase 3 ADMIRAL trial of gilteritinib, a selective FLT3 inhibitor, for relapsed or refractory acute myeloid leukaemia (AML). Patients were randomised 2:1 to receive either gilteritinib or one of 4 standard salvage chemotherapy treatments. The investigators report favourable outcomes of gilteritinib observed in this trial with increased complete response rate and improved overall survival for relapsed/refractory AML [1].

FLT3 mutations (FLT3MUT+) occur in approximately 30% of patients with AML and are often associated with poor survival. Results from the ADMIRAL trial show the median overall survival for relapsed/refractory FLT3MUT+ AML patients who received gilteritinib was 9.3 months vs 5.6 months for patients who received salvage chemotherapy (HR 0.637; 95% CI 0.490-0.830; P=0.007); 1-year survival rates were 37% for patients

Table: The gilteritinib arm had superior response rates across all 4 major co-mutation cohorts in the ADMIRAL trial

Patients	CR/CRh (%)		Median overall survival			
	Gilteri-tinib	SC	Gilteri-tinib	SC	HR	P Value
ITT population (n=371)	37.0	17.3	9.3	5.6	0.637	<0.0007
Co-mut+ cohorts						
NPM1 (n=173)	32.2	12.1	8.3	5.1	0.419	<0.0001
DNMT3A (n=115)	37.3	12.5	9.1	5.5	0.504	0.0031
DNMT3A/ NPM1 (n=86)	40.0	9.7	10.8	5.0	0.252	<0.0001
WT1 (n=65)	35.6	5.0	9.1	3.4	0.309	0.0001

ITT, intention to treat; CR/CRh, complete remission/with partial haematological recovery; SC, salvage chemotherapy; HR, hazard ratio. Permission granted by Dr Perl to use abbreviated Table.

who received gilteritinib vs 17% for patients who received salvage chemotherapy (see Table).

The most common treatment-emergent adverse events of any grade occurring in ≥10% of patients during the first 30 days of treatment with gilteritinib were anaemia (33%), increased transaminases (24%), febrile neutropenia (21%), thrombocytopenia (19%), constipation (17%), pyrexia (15%), fatigue (15%), decreased neutrophil count (14%), increased blood alkaline phosphatase (13%), nausea (13%), hypokalaemia (11%), cough (11%), headache (10%), and diarrhoea (10%).

Dr Perl concluded that the clinical benefit of gilteritinib was maintained regardless of the presence of *NPM1*, *DNMT3A*, or *WT1* co-mutations (see Table). Relative to the other co-mutated cohorts, patients with both *NPM1* and *DNMT3A* co-mutations had the greatest survival benefit with gilteritinib. "We are very encouraged by the findings of the ADMIRAL trial," said Dr Perl. "Patients with relapsed/refractory *FLT3* mutation-positive AML generally have a poor prognosis and short survival. Until just recently, they had few treatment options." This experimental therapy is an oral drug that can be given on an outpatient basis, while salvage chemotherapy patients mostly are admitted for a couple of weeks in the hospital. Even if the outcome would have been equal, it offers an enormous advantage for the patient. "These findings are practice changing for this patient population."

1. Perl A et al. Abstract S876. 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

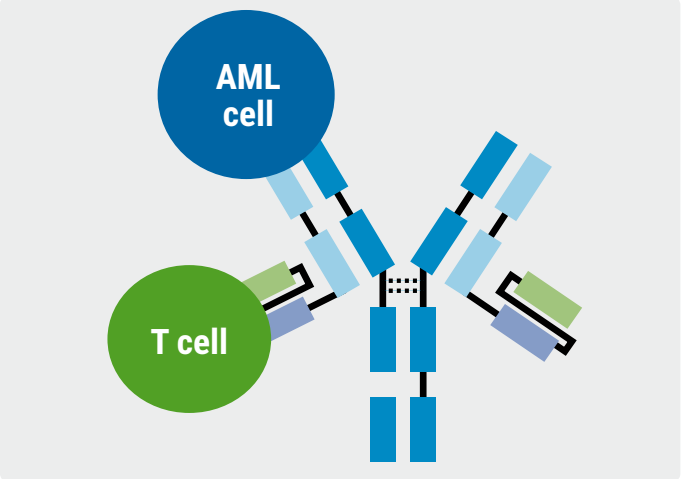
Initial data on AMV564 in patients with relapsed/refractory AML

AMV564-101 is a phase 1, first-in-human, dose escalation and dose expansion trial designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of AMV564 in patients with relapsed or refractory acute myeloid leukaemia (AML) after 1-2 prior induction regimens (with a standard anthracycline-based regimen or hypomethylating agent) and no more than 2 prior salvage regimens. Prof. Gail Roboz (Weill Cornell Medicine, USA) highlighted initial data from the dose-escalation portion of data from 33 patients treated within 9 cohorts, demonstrating favourable safety profile and initial efficacy data that AMV564 is active [1].

AMV564 is a bivalent, bispecific CD33/CD3 T cell engager with 2 binding sites for CD3 (expressed on T cells) and 2 binding sites for CD33 (highly expressed in myeloid-derived suppressor cells and on >95% of AML blasts). AMV564 brings T cells together with the CD33+ AML blast cell (see Figure) leading to T cell activation, proliferation and differentiation as well as cytokine release and T cell-mediated cell death of the CD33+ cells without affecting monocytes and neutrophils.

"While this is a phase 1 study," Prof. Roboz said, "we believe that AMV564 has demonstrated promising monotherapy activity, including a CR, CRi, and PR, and evidence of durability in a high-risk, older patient population on a 14-day dosing

Figure: Bivalent binding action of AMV564, a bispecific antibody for CD33/CD3. Modified from [2]



regimen. The data shows that AMV564 is well tolerated with no dose-limiting toxicities in doses up to 250 µg and only grade 1 and grade 2 cytokine release syndrome distinguishing the safety of AMV564 from other drugs in development for myeloid malignancies."

There were only limited grade 1 and 2 events. A lead-in dose schedule is now being utilised to continue the escalation up to 450 µg. Some responses and stabilisation of the disease for up to 7 months were observed.

1. Westerveldt P, et al. Abstract S877. 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Hoseini SS, et al. Blood Advances 2018, 2(11), 1250-1258.

Overcoming the "don't eat me" signal in AML and MDS

Antileukaemic activity was observed with anti-CD47 macrophage checkpoint inhibitor 5F9, both as monotherapy and in combination with azacytidine, in patients with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS), as presented by Dr David Sallman (Moffitt Cancer Center, USA) [1].

5F9 is a novel form of immunotherapy that targets CD47 to restore innate immunity, the first line of defence against cancer cells. CD47 provides the notorious "don't eat me" signal displayed by many types of cancer cells that enables macrophage immune evasion by preventing phagocytosis. CD47 is the dominant macrophage checkpoint that is overexpressed in most cancer cells, and increased CD47 expression has been associated with poorer prognosis. In addition, azacitidine can upregulate the pro "eat-me" signals, and in an aggressive AML xenograft preclinical model, the combination of 5F9 and azacitidine significantly improved overall survival vs either azacitidine or 5F9 alone [2].

Therefore, the 5F9005 study compared the activity of 5F9 administered alone or in combination with azacitidine in patients with AML or MDS. In addition to patients with relapsed/refractory AML, the study enrolled patients with previously untreated AML who were ineligible for induction chemotherapy and untreated MDS patients at intermediate to very high risk by IPSS-R criteria. Ten patients with relapsed/refractory AML received sole 5F9 at 30 mg/kg intravenous (IV) twice weekly, and 36 treatment-naïve patients were treated with the standard regimen of azacitidine (75 mg/m^2 on days 1 to 7) plus a priming dose of 5F9 of 1 mg/kg followed by ramp-up to 30 mg/kg given IV weekly. The priming dose was used to mitigate on-target anaemia, caused by the clearance of aging red blood cells by the CD47-blocking effects of 5F9. An initial priming dose causes a transient mild decline in haemoglobin and a temporary reticulocytosis that soon resolves. Haemoglobin levels return to baseline even with continued 5F9 at doses much higher than the priming dose.

In the cohort of patients with relapsed/refractory disease, 6 patients with AML and 4 with MDS received 5F9 monotherapy. These patients had received a median of 2 (range 1 to 6) prior therapies. In the cohort of patients with untreated AML or MDS, 5F9 was administered with azacitidine as first line to 22 patients with AML and 17 patients with MDS. In the respective combination therapy arms, the median patient age was 74 and 71 years. Fifty-five percent of patients with AML also had underlying myelodysplasia. Among MDS patients, 41% of patients were high risk and 12% of patients were very high risk according to IPSS-R.

The safety analysis showed 5F9 was well tolerated both as monotherapy (n=10) and in combination (n=36). The maximum tolerated dose was not reached in either treatment arm, and the safety profile of 5F9 combined with azacitidine was similar to that of single-agent azacitidine. In the combination arm, 1 dose-limiting toxicity, grade 4 haemagglutination, was observed, but resolved within 24 hours. One patient discontinued combination treatment due to an adverse event. No cytopenia, infections, or autoimmune adverse events were observed, and no deaths occurred within the initial 60 days of treatment.

Antileukaemic activity was observed with 5F9 monotherapy and in combination in patients with AML and MDS. Among the 10 patients in the relapsed/refractory AML cohort receiving 5F9 monotherapy, the objective response rate was 10%, which represented marrow complete response (CR); 70% of patients demonstrated stable disease, and 20% experienced disease progression.

In the cohort of 14 patients with AML and 11 patients with MDS receiving 5F9 plus azacitidine as first line therapy, the ORR was 64% and 100%, respectively. In the AML subgroup, the responses included 5 (36%) patients with CR, 2 (14%) patients with morphologic complete remission with incomplete blood count recovery, and 2 (14%) patients with marrow CR. Stable response was seen in 36% of patients, and no patients had disease progression. Of the 11 responding patients with MDS,

6 (55%) patients had CR, 4 (36%) had marrow CR, and 1 (9%) patient showed haematologic improvement. Again, no disease progression occurred. The time to response was more rapid at 1.9 months with the combination than that observed with azacitidine alone.

The median duration of response was not reached (range 0.03+ to 8.3+ months). In patients with MDS treated with the combination, 43% had a complete cytogenetic response, and 20% showed minimal residual disease negativity. Median duration of response was not reached (range 0.5+ to 4.3+). The median follow-up in both groups was short, approximately 3.8 months, and is ongoing. "The longest patient in response is in CR for 9+ months in therapy and ongoing," Dr Sallman noted. "Combination treatment also eliminated leukemic mutations in some AML patients." The clinical value has not been established, as longer follow-up will need to be studied.

1. Sallman D, et al. Abstract S878. 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Liu J,et al. PLoS One. 2015 Sep 21;10(9):e0137345.

Asciminib plus imatinib in patients with heavily pre-treated chronic myeloid leukaemia

In a phase 1 trial of asciminib in combination with imatinib in heavily pre-treated patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP), 60% (9/15) of participants achieved a molecular response rate <1% in the asciminib+imatinib arm [1].

Asciminib binds the myristate-binding pocket of the Bcr-Abl kinase domain. In the current study, presented by Prof. Jorge Cortes (University of Texas MD Anderson Cancer Center, USA), patients ≥18 years of age had a confirmed diagnosis of CML-CP. Patients had to be on a minimum of 2 years treatment with imatinib first line for CML-CP, BCR-ABL1 levels had to be >0.01% International Scale (IS) and ≤ 1% IS at the time of study entry as confirmed with a central assessment at screening and must not have achieved molecular response (MR)[4] IS at any time during prior imatinib treatment.

The primary outcome was MR[4.5] rate between asciminib+imatinib and imatinib alone at 48 weeks. The preliminary results showed that among patients who at baseline did not achieve BCR-ABL1 IS <1%, by 48 weeks, 42% (8/19) achieved major MR with asciminib plus imatinib with median treatment exposure of 54.6 weeks. Furthermore, no patients with major MR at baseline lost response due to the combination therapy. The combination showed a tolerable safety profile in heavily pre-treated CML patients. The most common any-grade adverse events were nausea (32%), increased lipase (20%), as well as abdominal pain, peripheral oedema, and vomiting (16% each).

1. Cortes J, et al. Abstract S883. 24th Congress of the European Hematology Association. June 13-16, Amsterdam, the Netherlands.

Guadecitabine vs treatment of choice in AML

The phase 3 ASTRAL-1 study compared the use of guadecitabine to treatment of choice (ToC) in patients with acute myeloid leukaemia (AML) who had not received prior treatment and who were not eligible for intensive chemotherapy.

This study failed to meet the primary endpoint of a statistical difference in complete response (CR) and overall survival (OS) between guadecitabine and ToC. However, Prof. Pierre Fenaux (Hôpital Saint-Louis, France) presented data that a benefit was observed in patients who received >4 cycles, indicating that treatment duration is crucial to response. Around 40% of patients in both arms did not receive the minimum of 4 cycles to see the maximum of treatment benefit [1].

Guadecitabine is a next-generation hypomethylating agent designed to be resistant to degradation by cytidine deaminase and prolong the exposure of tumour cells to the active metabolite decitabine. For this phase 3 study, the largest trial in treatment-naïve patients with AML, participants were randomised 1:1 to either guadecitabine (n=401, 60mg/m^2 dose subcutaneously administered over 5 days) or ToC (n=392). In the ToC arm, the investigators could choose between decitabine, azacitidine, or low-dose cytosine arabinoside. Most patients were unfit and 75 years or older. In the subgroup analysis, there were no differences between treatment arms based on age, sex, cytogenetic risk, ECOG score, or race. The exception was that *TP53* mutations were more common in the control arm (ToC).

Primary endpoint analysis in the intention-to-treat (ITT) population demonstrated no difference in median OS at 12 or 24 months (P=0.73; HR 0.97; 95% CI 0.83-1.14) or complete response (P=0.48). However, the survival analysis (see Table) shows improved outcome for patients responding to ≥4 cycles or ≥6 cycles guadecitabine compared with ToC. This superior survival was more pronounced when patients received

Table: Subgroup analysis of ASTRAL-1. Survival of patients with a response who received ≥4 cycles and ≥6 cycles of guadecitabine vs treatment of choice. Data derived from [1]

	Guadeci-tabine	ToC	P-value
More than 4 cycles (n=476)			
Median survival	15.6 months	13.0 months	0.02
12-month survival	60%	52%	HR 0.78 (95% CI 0.64–0.96)
24-month survival	29%	20%	
More than 6 cycles (n=375)			
Median survival	19.5 months	14.9 months	0.002
12-month survival	75%	62%	HR 0.69 (95% CI 0.54–0.88)
24-month survival	37%	24%	

CI, confidence interval; HR, hazard ratio; ToC, treatment of choice.

>6 cycles (P=0.002) compared with >4 cycles (P=0.02) of guadecitabine. These results indicate that prolonged exposure to guadecitabine is necessary to observe clinical benefit. Approximately 41% and 54% of patients did receive less than 4, or 6 cycles, respectively.

The most common grade 3 and 4 adverse events occurring in ≥20% of patients in either group were febrile neutropenia, pneumonia, thrombocytopenia, neutropenia, and anaemia. In relation to safety, both guadecitabine and all 3 ToC options were comparable, though higher rates of febrile neutropenia and pneumonia were noted in the guadecitabine arm. Adverse events leading to discontinuation of treatment were higher in the guadecitabine arm (10.2%) vs the ToC arm (6.6%).

1. Fenaux P. et al. Abstract S879, 24th Congress of the EHA. June 13-16, Amsterdam, the Netherlands.

Lymphoid Malignancies

Venetoclax/obinutuzumab combination elicits high response rates in CLL

Previously untreated patients with chronic lymphocytic leukaemia (CLL) and coexisting conditions who received fixed-duration 12-month venetoclax plus obinutuzumab had better survival outcomes compared with fixed-duration 12-month chemoimmunotherapy, showed results from the international, open-label, phase 3 CLL14 trial [1,2].

Dr Kirsten Fischer (University of Cologne, Germany) presented data from the CLL14 trial, which included 432 previously untreated patients with CLL. Patients were randomly assigned treatment with fixed-duration venetoclax plus obinutuzumab (n=216) or fixed-duration chlorambucil plus obinutuzumab (n=216). Venetoclax rapidly induces apoptosis of CLL by selective inhibition of BCL2, a protein that regulates cell death and is overexpressed in CLL cells. Obinutuzumab is an anti-CD20 monoclonal antibody that is able to bind malignant CLL cells, facilitating their destruction. Pre-clinical data suggests added benefit for venetoclax when combined with obinutuzumab.

The overall response rate was significantly higher for the venetoclax plus obinutuzumab arm compared with the chlorambucil plus obinutuzumab arm (84.7% vs 71.3%; P<0.0007); the complete response rate was also significantly higher (49.5% vs 23.1%; P<0.001). At a median follow-up of 28 months, the median progression-free survival (PFS) favoured the venetoclax plus obinutuzumab arm over the chlorambucil plus obinutuzumab arm (HR 0.35; 95% CI 0.23-0.53; P<0.001). The venetoclax plus obinutuzumab arm also had a superior 24-month PFS rate compared with the chlorambucil plus obinutuzumab arm (88% vs 64%; median PFS not reached in both arms). Importantly, the PFS benefit was seen regardless of *IGHV* or *TP53* mutational status. Furthermore, 3 months after the completion of treatment, 76% of the patients in the venetoclax plus obinutuzumab group were confirmed negative for minimal residual disease (MRD) in the blood; the MRD-negative response rate was more than doubled when compared with a negativity rate of 35% of the patients in the standard arm.

The most common grade 3/4 infection was pneumonia, affecting 4% in each arm. The venetoclax plus obinutuzumab arm had a higher incidence of fatal adverse events compared with the chlorambucil plus obinutuzumab, but this difference was not statistically significant (8% vs 4%). "The increased number of events occurred after completion of therapy," Dr Fischer added.

In conclusion, fixed-duration targeted therapy with venetoclax/obinutuzumab can be administered safely to elderly patients with CLL and co-existing comorbidities and provides a superior outcome compared with chlorambucil and obinutuzumab regarding:

- progression-free survival,
- overall response rate,
- complete response rate, and
- MRD-negative responses.

These outcomes were in all relevant subgroups including *IGVH*-unmutated, del(17p), or *TP53*-mutated patients.

1. Fischer K, et al. Abstract S149, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Fischer K, et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236.

Unmutated *IGHV* as predictive factor for venetoclax/obinutuzumab benefit in frontline CLL

Findings from an analysis of genetic aberrations and mutations in patients with chronic lymphocytic leukaemia (CLL) participating in the CLL14 trial were presented by Dr Eugen Tausch (University of Ulm, Germany) [1]. Although both del(17p) and *TP53* mutations remain adverse prognostic factors for progression-free survival (PFS) with venetoclax/obinutuzumab treatment, unmutated *IGHV* was associated with a 3.5-fold improvement in patient response.

Dr Tausch explained: "Genomic aberrations, *IGHV* mutation status and mutations in genes such as *TP53* are established prognostic factors in CLL in the context of chemoimmunotherapy. Their role is less well established when using chemotherapy-free treatments." In summary, the CLL14 trial (n=432) showed that the venetoclax combination reduced the risk of disease progression or death by 65% vs obinutuzumab plus chlorambucil (HR 0.35; 95% CI 0.23-0.53; P<0.001). The overall response rate (ORR) was 85% with venetoclax/obinutuzumab vs 71% in the control arm. The complete response (CR) or CR with incomplete haematologic recovery rates were 50% vs 23%, respectively.

Dr Tausch and colleagues assessed the incidence of genomic aberrations and evaluated their impact on outcomes in the CLL14 trial. The investigators used florescence in situ hybridisation to determine the cytogenetics in 418 patients, the *IGHV* status with <98% homology cut-off in 408, and used a custom next-generation sequencing panel to evaluate the mutations in 13 genes in 421 of 432 patients in the intention to treat (ITT) population.

The incidence of genomic aberrations was del(17p) in 7% of patients, del(11q) in 18%, +(12q) in 18%, and del(13q) in 53%. Unmutated *IGHV* was detected in 61% of patients. Regarding gene mutations, the incidence of the following genes was determined: *TP53* (10%), *NOTCH1* (23%), *SF3B1* (16%), *ATM* (13%), *MYD88* (2%), *POT1* (5%), *BIRC3* (4%), *XP1* (6%), *NFKB1E*, (4%), *BRAF* (4%), *EGR2* (4%), *RPS15* (5%), and *FBXW7* (1%).

Across all genetic variants assessed, the ORR was approximately 80% with venetoclax/obinutuzumab compared with approximately 60% with chlorambucil/obinutuzumab. However, the ORR was reduced in patients with del(17p), del(11q) *TP53* mutations, *ATM* mutations, and *BIRC3* mutations treated with the chlorambucil combination. None of these alterations impacted the venetoclax ORR.

Notably, the ORR was approximately 82% in patients with unmutated *IGHV* with the venetoclax combination, which when taken in multivariate analysis generated a HR of 3.475 (95% CI 1.96-6.15; P<0.001) for the relationship between unmutated *IGHV* and mutated *IGHV*. In the venetoclax/obinutuzumab arm, the HR was 1.16 (P=0.73) for patients with unmutated *IGHV* versus mutated *IGHV*. The HR was 3.45 (P<0.001) for the same comparison in the chlorambucil arm.

PFS was assessed according to the genetic variables. With median follow up of 29 months, 107 PFS events and 37 OS events had occurred in the ITT population. Del(17p) significantly impacted PFS with both venetoclax and chlorambucil; in the venetoclax arm, the HR was 4.42 (P=0.001) for the comparison of no deletion vs deletion and in the chlorambucil arm the HR was 4.64 (P<0.001) for the comparison of no deletion vs deletion. *TP53* mutations also affected PFS with both treatments; with venetoclax no *TP53* mutation vs *TP53* mutation the HR was 3.08 (P=0.01) and with chlorambucil, the HR was 2.74 (P=0.001) for no *TP53* mutation vs *TP53* mutation.

The PFS of chlorambucil was adversely affected by mutated vs nonmutated *BIRC3* (HR 4.0; P=0.001), *NOTCH1* (HR 1.74; P=0.03), and *ATM* (HR 1.77; P=0.06); however, these mutations did not significantly affect PFS with venetoclax. Mutations in the other investigated genes had no effect on either venetoclax or chlorambucil efficacy.

All the genetic subgroups showed more favourable PFS outcomes with venetoclax/ obinutuzumab than with obinutuzumab; these subgroups included patients with del(17p), del(11q), and *TP53, NOTCH1, SF3B1*, and *ATM* mutations. High coincidence was found for del(17p) and *TP53* mutations. "Both del(17p) and *TP53* mutations remain adverse prognostic factors for PFS with venetoclax/ obinutuzumab treatment," Dr Tausch summarised. "Venetoclax was particularly effective in patients with *IGHV* unmutated; these findings establish *IGHV* as a predictive rather than prognostic marker."

1. Tausch E et al. Abstract S105, 24th Congress of the EHA. June 13-16, Amsterdam, the Netherlands.

CAR-T cell therapy in ALL as breakthrough advance

Prof. Mohamad Mohty (Saint-Antoine Hospital and University Pierre & Marie Curie, France) gave a state-of-the-art lecture about the recent advances and challenges in chimeric antigen receptors T cell (CAR-T) therapy in acute lymphocytic leukaemia (ALL) [1].

The key take-home messages were (1) if minimal residual disease (MRD) negativity is achieved after CAR-T cell therapy, the majority of patients will be cured; (2) allogenic transplantation after CAR-T cell therapy grants patients an even better survival; (3) success of CAR-T cell therapy seems to be mostly dependent on the post-infusion expansion of CAR-T cells; and (4) the challenges, such as cytokine release syndrome (CRS) or CD19-negative relapse, require internationally coordinated homogeneous criteria.

The pivotal single-arm phase 2 ELIANA study infused 63 heavily pre-treated patients (half had had one or more stem cell transplantations) and showed >80% complete response (CR) including MRD negativity. This study placed CAR-T cells firmly in the spotlight as a novel therapeutic modality. Most of the first studies focussed on children and young adults <25 years old. Collectively, although the numbers are small, the consistent CR rate of 80-90% across studies, coupled with the fact that the majority of patients will proceed to MRD negativity, suggests that CAR-Ts can offer long-term survival in many patients (see Table for overview of all CAR-T trials in ALL). It also became evident that the use of CAR-T cells is associated with some severe and serious complications, namely cytokine release syndrome (CRS) and neurotoxicity; at least one-third of the patient will experience severe CRS, and another 25-33% will experience neurotoxicity [2].

In the study with the longest follow-up (median follow-up 29 months), older patients (up to 60 years) also demonstrated that more than half of ALL patients -despite their age- will achieve CR and MRD negativity [3]. This outcome appears to be dependent on the *in vivo* expansion of the CAR-T cells; using a lymphodepletion regimen based on fludarabine and cyclophosphamide is important to create the right environment to allow the expansion of the CAR-T cells, supported by co stimulatory molecules 4-1BB and CD28.

What are the factors associated with durable event-free survival after CAR-T cells in adult ALL? Hay and colleagues recently published their trial FH2639, a phase 1-2 study of defined composition CD19 XAR-T cells for relapse/refractory B cell malignancies [4]. Forty-five of the 53 treated patients

Table: Overview of all CAR-T studies performed to date in ALL patients [1]

	Co-stimulatory molecule	Patient Population (n)	CR %	MRD-neg %	CRS	CRES
Maude et al. NEJM 2014	41BB	Paediatric (25), adults (5)	90	78	100 27 (severe)	43
Davila et al. STM 2014	CD28	Adults (16)	88	75	43 (severe)	25 (severe)
Lee et al. Lancet 2015	CD28	Paediatric and young adults (21)	67	57	76 28 (severe)	29 0 (severe)
Turtle et al. JCI 2016	41BB	Adults (30)	97	93	83 23 (severe)	50 (severe)
Gardner et al. Blood 2017	41BB	Paediatric and young adults (43)	93	93	93 23 (severe)	49 21 (severe)
Maude et al. NEJM 2018	41BB	Paediatric and young adults (75)	81	81	77 46 (severe)	40 13 (severe)
Park et al. NEJM 2018	CD28	Adults (53)	83	60	85 26 (severe)	44 42 (severe)

CR, complete response; CRES, CAR-T related encephalopathy syndrome; CRS, cytokine release syndrome; MRD-neg, negative for minimal residual disease.

went into MRD-negative CR (85%). The take-home message from the ALL cohort of this paper was that the number of prior lines of therapy affects the outcome, i.e. the worse the disease burden, the worse the outcome. The most predictive value that came out of this study was the level CAR-T expansion after infusion. In contrast to what we hear about from lymphoma or myeloma, ALL patients can have a robust and long-term expansion of CAR-T cells. In terms of survival, the vast majority of MRD-negative patients appear to be cured, with a mean follow-up of 30.9 months. Although these data are a bit controversial, most data support that patients who received a transplant after CAR-T cells have a better 24-month survival (P=0.014) survival.

There are 2 major challenges:

1. Toxicities. The symptoms frequently observed in CRS are fever, hypotension, capillary leak, coagulopathy, multi-organ failure, and MAS/HLH. Among the neurological toxicities we observe headaches, confusion, delirium, seizures, and focal/non focal deficits. The learning curve has improved management and timely intervention for these. Importantly, measures are being taken to create consensus within and among professional societies on how best to diagnose and treat CRS [5,6] adopting homogeneous criteria.

2. Duration of response is determined by a lack of long-term persistence of CAR-T cells. Around 80-90% patients achieve MRD negativity but only about 50% achieve a cure. One explanation for this discrepancy is the lack of persistence. In addition, up to 20% of ALL patients receiving CD19-specific CAR-T cells will experience a CD19-negative relapse after CAR-T cell therapy. Possible mechanisms of loss of CD19 frameshift mutations clustered in *CD19* exon 2 leading to expression of the Δex2 isoform not recognised by CAR-T cells [7]. Alternatively, it has been postulated that a full myeloid switch can occur in an MLL-rearranged ALL patient, which has been modelled in mice as well [8].

Prof. Mohty concluded, "We still hesitate about the positioning of CAR-T therapy within the ALL treatment, even ignoring accessibility and affordability aspects. Assuming all options are available, the question should be which strategy/algorithm? Should this be an option for consolidation in lieu of SCT? Or perhaps as a bridge to ASCT? Or as salvage therapy after ASCT (half of the patients receiving CAR-T cells underwent ASCT)? How should we sequence with blinatumomab, inotuzumab, or combinations? Should we treat CRS pre-emptively with early intervention tocilizumab? When it comes to duration of response, optimisation of CAR-T cell functionality should be researched, in particular *in vivo* persistence. Furthermore, immunogenicity reduction should be achievable with human/humanised scFv because antibodies can be detected against the murine construct."

1. Mohty M. 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Jackson HJ, et al. Nat Rev Clin Oncol. 2016 Jun;13(6):370-83.
3. Park JH et al. N Engl J Med. 2018 Feb 1;378(5):449-459.
4. Hay KA, et al. Blood. 2019 Apr 11;133(15):1652-1663.
5. Lee DW et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638.
6. Kansagra AJ et al. Bone Marrow Transplant. 2019 May 15.
7. Sotillo E et al. Cancer Discov. 2015 Dec;5(12):1282-95.
8. Gardner R et al. Blood. 2016 May 19;127(20):2406-10.

Brentuximab vedotin continues to demonstrate superior clinical activity in classical Hodgkin lymphoma

Additional analysis and 3-year update of results from ECHELON-1, a frontline phase 3 trial evaluating brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (AVD) compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in stage III or IV frontline classical Hodgkin lymphoma (HL) patients, resulted in a statistically significant improvement in modified progression-free survival (PFS) for the brentuximab vedotin + AVD arm vs the control arm of ABVD, as assessed by independent review [1].

Brentuximab vedotin is an antibody-drug conjugate directed to CD30, a defining marker of classical HL and expressed on the surface of several types of peripheral T-cell lymphomas. The intention-to-treat analysis examined PFS outcomes per investigator assessment in the population of 1,334 patients <60 years old at 3 years, by cycle 2 positron-emission tomography (PET2). The ECHELON-1 trial achieved its primary endpoint with the combination of brentuximab vedotin plus AVD resulting in a statistically significant improvement in modified PFS vs the control arm of ABVD, as assessed by independent review facility (HR 0.77; P=0.035). Modified PFS was defined as time to progression, death, or evidence of non-complete response after completion of frontline therapy per independent review facility followed by subsequent anticancer therapy. Key findings from this updated analysis include:

- The 3-year PFS for all patients in the brentuximab vedotin + AVD arm was 83.1% compared with 76% in the ABVD arm (HR 0.70), a difference of 7.1%.

- PFS benefit at 3 years for brentuximab vedotin + AVD was observed for all patients independent of PET2 status, including in patients <60 years old.
  - PET2-scan was negative in 85.8% in the brentuximab vedotin + AVD arm compared with 79.5% in the ABVD arm (HR 0.69), a difference of 6.3%.
  - PET2-scan result was positive in 67.7% in the brentuximab vedotin + AVD arm compared with 51.5% in the ABVD arm (HR 0.59), a difference of 16.2%.
- Consistently higher PFS was observed among patients treated with brentuximab vedotin + AVD compared with ABVD across most pre-specified subgroups, including disease stage, age, and prognostic score.
- In the brentuximab vedotin + AVD arm, peripheral neuropathy events were observed in 67% of patients compared with 43% in the ABVD arm. The 3-year analysis shows that among patients with peripheral neuropathy, 78% of in the brentuximab vedotin + AVD arm and 83% in the ABVD arm reported complete resolution or improvement at last follow-up.

1. Horwitz S, et al. Abstract S820, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Infectious complications mild and not common in patients receiving CAR-T therapy for diffuse large B cell lymphoma

Dr Roberta Di Blasi (Hospital Saint-Louis, France) studied infection complications of chimeric antigen receptors T cells (CAR-T) treatment in diffuse large B cell lymphoma (DLBCL) patients [1]. She concluded that febrile neutropenia is a frequent complication and that it can be difficult to distinguish infections from beginning cytokine release syndrome (CRS). Bacterial and viral infection have low incidence and fungal infections did not occur in this cohort at all. Infectious complications appear mild and not fatal. Longer follow-up for immune recovery/infectious complications is needed, as well as broader studies to better define infectious risk in this subset of patients.

CAR-T efficacy was demonstrated in DLBCL patients by the JULIET and ZUMA1 trials [2]. Consistent with other CAR-T studies, the main toxicities observed were CRS and neurotoxicity, as well as some early and late onset haematologic toxicities such as neutropenia, thrombopenia, and B cell aplasia. Neutropenia occurred in 22-80% of patients across studies to date.

The objective of the study by Dr Di Blasi and colleagues was to establish the infection risk in DLBCL patients (n=29) treated with CAR-T cell therapy, especially gathering data from the first 30 days from the injection. The median age of patients was 50 (23-77) years, of whom 28% had had prior stem cell transplantation, and the median number of previous lines of treatment was 4. Out of 29 patients, 27 required a bridging chemotherapy while their CAR-T cells were being manufactured; immunochemotherapy was provided for most of these patients. All patients were treated with a fludarabine-containing lymphodepletion regimen. Prophylaxis was performed in 28/29 patients for *Pneumocystis jirovecii* and viral infections.

Neutropenia, lasting a median of 6 days, was present in 90% of the patients (24/29), which was complicated by fever in 76% of the patients. At day 30, 3 patients (10%) had severe neutropenia <500. Empirical antibiotics were given to 22/24 (92%) patients with for a mean duration of 10 days (range 4-22 days), and 5/29 patients presented with infection (17%) from whom 8 microbiologically confirmed specimens were derived: 4 were bacterial, 4 were viral, and 0 were fungal; 2 patients had 2 or more concomitant infections. Of the bacterial infections identified, 1 patient had a polymicrobial gram + blood stream infection (BSI) consisting of *E.fecalis* + *S.epidermidis* attributable to cholangitis, and this same patient also had *C.difficilis* enteritis. Another patient had *S.epidermidis* BSI with concomitant deep venous catheter infection, while yet another patient had *E.coli* pneumonia.

There were 4 isolates confirming viral infections in 3 patients, 1 patient had Rhinovirus upper respiratory tract infection, 1 patient had Norovirus enteritis, and 1 patient had CMV reactivation + BK virus cystitis. Interestingly, all 5 patients with infections presented with non-severe CRS (grade <2).

Of all febrile patients, 42% (10/24) were transferred to the ICU, with a mean stay of 7 days (3-12). Poor outcomes were observed in 2 of the 24 patients at day 30; 1 had progressive disease and infection (BSI) and died, and another patient had a CMV-positive PCR test at day 30 was treated with foscarnet. 19/24 patients without microbiological documentation of infection showed spontaneous improvement and resolution of their febrile event. No mortality was attributable to infections complications alone.

Dr Di Blasi continued with the data for 90-day follow-up, reported here for the first time. After the patients went

home, they were in the care of their family doctor. Of the 28 living patients, 1 upper respiratory tract infection (not microbiologically documented) was treated with antibiotics at home, and 1 patient developed *P.jirovecii* pneumonia (no prophylaxis). 20/29 patients had persistent response with regard to their haematological disease (not retreated) at day 90. 8/20 patients (40%) had at least one episode of grade 3-4 neutropenia between 30-60 days after infusion.

1. Di Blasi R, et al. Abstract S1641, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Neelapu SS, et al. N Engl J Med. 2017 Dec 28;377(26):2531-2544.

Obinutuzumab/polatuzumab in follicular lymphoma

Prof. Wojciech Jurczak (Jagiellonian University, Poland) presented the history of trials in high-risk relapsed/refractory follicular lymphoma (FL), focussing on a pre-planned interim analysis of a recent phase 1b/2 study [1,2].

This open-label, single-arm trial assessed the safety and preliminary efficacy of polatuzumab vedotin in combination with obinutuzumab and lenalidomide (Pola-G-Len) in patients with relapsed/refractory FL (n=52). Polatuzumab vedotin is a first-in-class antibody-drug conjugate that targets CD76b, a protein expressed in FL and diffuse large B cell lymphoma (DLBCL). Polatuzumab vedotin in combination with rituximab and bendamustine was recently approved for the treatment of relapsed or refractory DLBCL.

The primary efficacy endpoint of the trial was complete response (CR) at the end of induction treatment, as assessed by an independent review committee based on PET-CT scans. Patients received Pola-G-Len induction treatment (six 28-day cycles). At a median follow-up of 16.6 months (range 3.2-25.1), the median progression-free survival (PFS) had not been reached, with a 12-month PFS rate of 90%. Two out of 17 responders have experienced progressive disease; the remaining patients have ongoing responses (longest one > 21 months).

No new safety signals were recorded, overall safety was comparable with previous reports in DLBCL. A grade 3 or higher neutropenia was reported in 30% of patients; 18% were febrile, and 9% had thrombocytopenia. Treatment was discontinued by 11% of patients due to AEs after receiving 1–5 cycles, and 8% of patients had a pola dose reduction.

The results of this phase 1b-2 trial indicate Pola-G-Len treatment has a manageable toxicity profile and leads to promising response outcomes in relapsed/refractory follicular lymphoma.

1. Jurczak W. 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Diefenbach, C. et al. Abstract 7505, 2019 ASCO Annual Meeting, Chicago, Illinois, USA.

Exciting survival data for ibrutinib vs placebo in treatment-naïve, early-stage CLL

Patients with early-stage, asymptomatic, newly diagnosed chronic lymphocytic leukaemia (CLL) showed improved survival outcomes with ibrutinib monotherapy compared with placebo, according to results from phase 3 CLL12 study presented by Dr Petra Langerbeins (University of Cologne, Germany).

"So far, treatment of asymptomatic, early-stage CLL patients has not been proven beneficial; ibrutinib is a Bruton tyrosine kinase inhibitor with impressive clinical efficacy in advanced or relapsed CLL that has not been tested in treatment-naïve, early-stage CLL," Dr Langerbeins explained. To address this gap, Dr Langerbeins and the German CLL Study Group conducted the double-blind, randomised, placebo-controlled, phase 3 CLL12 trial evaluating whether ibrutinib prolonged event-free survival (EFS; primary endpoint) in patients with early-stage CLL and increased risk of progression, as defined using a score system newly developed by this group.

Median EFS was not reached in the ibrutinib arm compared with 47.8 months in the placebo group (HR 0.25; 95% CI 0.14-0.43; P<0.0001). Median progression-free survival (PFS) was also not reached with ibrutinib vs 14.8 months with placebo (HR 0.18; 95% CI 0.12-0.27; P<0.0001). The time to next treatment was longer in the ibrutinib arm vs the placebo arm (HR 0.21; 95% CI 0.11-0.39; P<0.0001), with a median observation time of 31 months.

The trial enrolled treatment-naïve, asymptomatic Binet A patients with intermediate, high, or very high risk of progression. Of these, 182 were randomly assigned to receive ibrutinib at 420 mg per day and 181 were randomised to placebo. The median patient age in both cohorts was 64 years, and approximately 89% of patients were ECOG PS 0. In the ibrutinib and placebo arms, 75.8% and 82.9% of patients, respectively, had thymidine kinase >10 U/L, and fewer than 10% of patients in either arm had mutated *TP53* or 17p deletions. In the ibrutinib and placebo arms,

11.5% and 10.5% of patients, respectively, had 11q deletions. The primary endpoint was EFS and secondary endpoints included PFS and time to next treatment. The 152 patients with low-risk disease were not included in the primary endpoint analysis. Dr Langerbeins noted that EFS, PFS, and TTNT improvement were consistent across all risk groups analysed, except in the very high-risk group where there were just 8 patients.

The safety evaluation included 185 patients on ibrutinib and 178 patients on placebo and noted no differences in most adverse events for ibrutinib compared with placebo. The incidence of any grade adverse events (AEs) was 82.2% vs 84.8% with ibrutinib and placebo, respectively. AEs leading to treatment interruption occurred in 41.6% vs 21.3% of patients, respectively. The most commonly reported AEs in the respective cohorts leading to interruption included cardiac arrhythmias (18 vs 0 patients), bleeding (8 vs 1 patients), diarrhoea (4 vs 3 patients), and neoplasia (4 vs 3 patients). Treatment discontinuation was reported for 34.1% of ibrutinib vs 45.9% of placebo patients, respectively; the primary cause of discontinuation was disease progression in 2 and 45 patients, respectively. AEs were the primary cause of discontinuation in the ibrutinib arm (n=53).

Six deaths on study occurred in the ibrutinib arm, and 5 deaths occurred in the placebo arm. "The results of this study allow us to conclude that ibrutinib significantly improves EFS, PFS, and time to next treatment in asymptomatic patients with treatment-naïve early stage CLL when compared with placebo," concluded Dr Langerbeins.

1. Langerbeins P, et al. Abstract LB2602, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

ASCEND study: Acalabrutinib improves progression-free survival in relapsed/refractory CLL

Dr Paolo Ghia (Vita-Salute San Raffaele University, Italy) presented the findings from the phase 3 ASCEND study of the Bruton's tyrosine Kinase inhibitor (BTKi) acalabrutinib in relapsed or refractory chronic lymphocytic leukaemia (CLL). The study demonstrated that acalabrutinib had superior progression-free survival vs rituximab with idelalisib or bendamustine [1].

The ASCEND trial was a global, multicentre, open-label, phase 3 study that randomised 310 patients to receive either acalabrutinib monotherapy or the physician's choice of either idelalisib plus rituximab or bendamustine.. Acalabrutinib is a highly selective, potent inhibitor of BTK that has previously demonstrated substantial activity and improved tolerability in patients with CLL, similar to ibrutinib. In this study, acalabrutinib monotherapy significantly improved progression-free survival, with a more tolerable safety profile, compared with idelalisib plus rituximab or bendamustine in patients with relapsed or refractory CLL, reducing the risk of disease progression or death by 69% at a median follow-up of 16.1 months (HR 0.31; 95% CI 0.20-0.49, P<0.0001). At 12 months, 88% of patients on acalabrutinib showed no disease progression compared with 68% for the control arm, with tolerability consistent with the known profile.

These results are significant because there is a need for an effective but also well-tolerated BTKi for patients with CLL. In addition, no new safety signals were identified for acalabrutinib. The ASCEND study results indicate that acalabrutinib has the potential to change current practice by providing a well-tolerated, highly effective BTKi treatment option.

Dr Ghia concluded: "This is the first randomised study to directly compare a BTK inhibitor as monotherapy with standard chemoimmunotherapy or idelalisib and rituximab combinations. With a significant improvement in progression-free survival and a favourable safety profile, acalabrutinib may become an important choice for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia."

1. Ghia P, et al. LB2601, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Myeloma

CASSIOPEIA trial: Phase 3 results of daratumumab + bortezomib/thalidomide/ dexamethasone in multiple myeloma

The addition of daratumumab to the triplet bortezomib, thalidomide, and dexamethasone (VTd) induction and consolidation in transplant-eligible patients with newly diagnosed multiple myeloma improved both the depth of response and progression-free survival (PFS) compared with VTd alone [1].

Prof. Phillippe Moreau (University Hospital of Nantes, France) discussed the findings from the randomised, open-label, multicentre, phase 3 CASSIOPEIA trial and the potential role for daratumumab in patients with newly diagnosed multiple myeloma in combination with standard-of-care VTd for patients who are candidates for autologous stem cell transplantation (ASCT).

Patients (n=1,085) were enrolled and randomly assigned to VTd induction and consolidation either with (n=543) or without (n=542) the addition of daratumumab (Dara-VTd) followed by high-dose melphalan and ASCT. The stringent complete response rate was 28.9% with the combination compared with 20.3% in the VTd-alone arm. The median PFS rate at 18 months was 92.7% with daratumumab vs 84.6% without (HR 0.47; 95% CI 0.33-0.67; P<0.0001). Although the data for overall survival is still immature and the median overall survival was not reached in either arm, at 24 months the overall survival rate was 97% with added daratumumab vs 93% without. Death occurred on study in 14 vs 32 patients (HR 0.43; 95% CI 0.23-0.80).

Administering daratumumab in combination with VTd both before and after SCT did not demonstrate additional safety concerns in this setting. The most common grade 3/4 treatment-emergent adverse events noted with the addition of this agent included neutropenia (27.6% with daratumumab vs 14.7% with VTd alone), lymphopenia (17.0% vs 9.7%, respectively), stomatitis (12.7% vs 16.4%), and thrombocytopenia (11.0% vs 7.4%).

In a different session, Prof. Moreau also reported for his colleague Dr Hervé Avet-Loiseau that the minimal residual disease negativity (10^{-5} sensitivity threshold)., as measured by deep sequencing, was achieved in 64% vs 44% (P<0.0001) [2].

CASSIOPEIA is a 2-part study; the second part of this trial will randomise patients to receive either daratumumab maintenance or no maintenance. The second phase of the trial is currently ongoing, and the researchers expect that a follow-up of at least 1 year is needed.

1. Moreau P et al. Abstract S145, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Avet-Loiseau H, et al. Abstract S874, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Chimeric antigen receptor T cell therapy in multiple myeloma

Prof. Hermann Einsele (University of Würzburg, Germany) discussed CAR-T therapy in the multiple myeloma (MM) treatment pathway [1]. The take-home message of Prof. Einsele's presentation was that CAR-T therapy be indicated in MM in the following three scenarios: (1) in patients who are not eligible for autologous transplant, CAR-T may consolidate or maintain remission; however, safety is a concern; (2) in patients who are eligible for autologous transplant there are 2 main groups who may benefit – those with adverse cytogenetics and those who progress early. In both populations, the long-term efficacy needs to be shown; and (3) heavily pre-treated patients (double-penta refractory) may also obtain some benefit, but the efficacy of CAR-T in this population must be shown with minimal residual disease (MRD)-negativity for prolonged PFS.

Patients with an MRD-negative state appear to have the same prognosis, regardless of whether they have standard or high-risk disease. However, even though MRD-negativity can be achieved in around 50% of patients with standard risk disease, this figure is significantly lower in those with high-risk features, e.g. concomitant t(4;14) or del(17p) [2]. Therefore, the aim should be to increase the rate of MRD-negativity in high-risk patients. Although adding daratumumab can increase rates of MRD-negativity and improve PFS, this is still within a subset of patients without adverse cytogenetics. Thus, CAR-T therapy

may be beneficial as a consolidation therapy based on their long persistence and could potentially replace maintenance therapy.

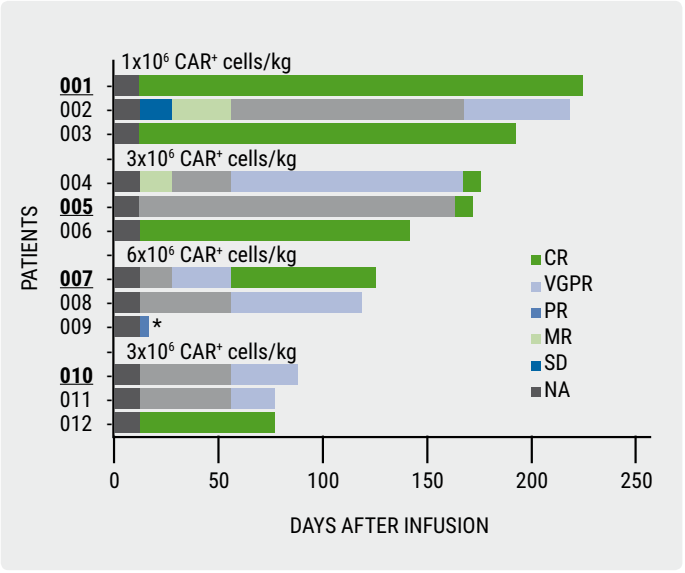
Several immunotherapy targets have been identified for CAR-T cells in MM with ongoing clinical trials investigating anti-CD19, anti-CD138, and anti-BCMA CAR-T cells with others targeting SLAMF7 (CARAMBA study: phase 1-2a study in the relapsed setting), CD38, and CD44v6-CAR (EURE-CART study). In the bb2121 trial, heavily pre-treated patients were enrolled and received anti-BCMA CAR-T cells. The toxicity profile was milder than in the lymphoma CAR-T products and at the highest dose of >150 x 10^6 there was a 95.5% ORR with 50% CR. A median PFS of 17.7 months was also seen in 16 patients who were MRD-negative; all 33 patients (100%) tested MRD-negative at one or more time points [3]. The length of the PFS reported in this heavily pre-treated population was a notable advance.

Another ongoing trial is the LEGEND-2 study, using LCAR-B38M with two BCMA-targeting domains leading to high avidity binding. These patients had a median of 3 lines of prior therapy. The toxicity profile was consistent with other BCMA-targeted CAR-T cell therapy, with cytokine release syndrome (CRS) ≥grade 3 experienced by 7% of patients and neurotoxicity in 2%. With an average 12-month follow-up, in 57 patients, the median duration of response was 16 months (95% CI 12–not reached [NR]) and increased to 22 months (95% CI 14–NR) in MRD-negative patients [4].

Shi et al. presented updated data at ASH 2018 where they used both anti-BCMA and anti-CD19 CAR-T in patients with high-risk, heavily pre-treated MM. They showed MRD-negative status can be achieved in this dual approach, despite the high-risk features of the patients they were treating. This approach also showed a high efficacy with over 50% CR rate and a manageable safety profile [5].

Current CAR-T trials in MM have shown an improved safety profile when compared to the lymphoma setting with lower CRS and neurotoxicity rates. Additionally, even in a heavily pre-treated group of patients, there is a high rate of CR/MRD negativity. A study evaluating JCARH125 –a fully human binder with a low affinity for surface BCMA and a modified spacer to increase binding to BCMA– is ongoing, with the hope that decreasing the immunogenicity of CAR-T therapy will improve survival of the CAR-T cells, and therefore the ORR. Dr Chunrui Li (Huazhong University of Science and

Figure: Efficacy data showing an ORR of 100%, CR of 64%, and a VGPR of 36% [6]



CR, complete response; MR, molecular response ; NA, not available; ORR, objective response rate; PR, partial response; SD, stable disease; VGPR, very good partial response.
Bold and underlined patient numbers indicate patients having relapsed from a previous CAR-T therapy. Data cut-off date: 22 May 2019.

Technology, China) presented a study of patients receiving a fully humanised CAR-T CT103A [6]. As of the data cut-off date of 22 May 2019, the ORR was 100% (CR 64%, very good partial response 36%, median follow-up 40 weeks) with strong persistence and high expansion of the CAR-T *in vivo* (see Figure). All patients (100%) experienced CRS within 2 to 5 days (median 2.6), which resolved within 14 days. CRS was routinely managed with tocilizumab and sometimes steroids. Interestingly, the 12-patient study included 4 patients having previously relapsed from a prior CAR-T therapy, a murine anti-BCMA CAR-T. "Relapsed/refractory multiple myeloma is associated with a poor prognosis," said Dr Li. "Many who receive CAR-T treatments have relapsed, and with a non-human scFv, retreatment may not be an option due to immunogenicity. With a fully human BCMA scFv, CT103A provides an effective option for these patients. This data suggests they should not be excluded from future CAR-T trials."

Prof. Einsele pointed to the remaining challenges to tackle: lack of persistence and immunogenicity. Other causes for CAR-T cell therapy failing include malignant stem cells expressing different surface antigens in the bone marrow (which is rare) and the upregulation of inhibitory receptors. These resistance mechanisms are more pronounced in patients with a higher tumour load.

Based on the results presented at EHA, it could be argued that CAR-T therapy should be moved into an earlier line of therapy as using CAR-T upfront in high-risk patients has shown impressive efficacy results. If the toxicity profile can be shown to be acceptable, then CAR-T may be feasible for elderly patients who are ineligible for ASCT as an upfront consolidation therapy and potentially maintenance therapy. Beyond the second line, whilst CAR-T has been shown to be effective and provide a prolonged PFS, the cost-benefit ratio needs to be analysed. For patients who relapse early following ASCT and those with high-risk cytogenetics, CAR-T may provide a long term PFS improvement.

1. Einsele H. 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Arana P, et al. Leukemia. 2018 Apr;32(4):971-978.
3. Raje N, et al. N Engl J Med. 2019 May 2;380(18):1726-1737.
4. Zhao WH, et al. J Hematol Oncol. 2018 Dec 20; 11:141.
5. Shi X, et al. Abstract 1009. ASH 60th Annual Meeting and Exposition, San Diego, CA.
6. Li WH, et al. Abstract S827, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Higher levels of treatment satisfaction without compromising efficacy: subcutaneous daratumumab in RRMM

Results of a phase 3 study of daratumumab monotherapy administered subcutaneously (SC) compared with intravenous (IV) administration in patients with relapsed/refractory multiple myeloma (RRMM) showed no significant differences in efficacy or pharmacokinetic endpoints [1].

The IV formulation of daratumumab, a monoclonal antibody targeting CD38, has been approved as either monotherapy or in combination with standard-of-care regimens for patients with RRMM, or when combined with bortezomib/melphalan/dexamethasone for transplant-ineligible, newly diagnosed patients with MM. However, IV daratumumab is typically infused over hours and is associated with infusion reactions in a substantial percentage of patients.

In the open-label, multicentre, phase 3 COLUMBA trial, 522 adult patients with RRMM were randomly assigned in a 1:1 ratio to receive an SC formulation of daratumumab, including recombinant human hyaluronidase to temporarily break down the hyaluronan barrier to allow for the more rapid administration of large volumes of drug. The formulation was a fixed dose of 1,800 mg once weekly in cycles 1 and 2, every 2 weeks in cycles 3 to 6, and every 4 weeks in cycle 7 and beyond, with each cycle lasting 4 weeks, and administered using alternating left/right abdominal site injections. This was compared with the IV formulation (16 mg/kg once weekly in cycle 1 and 2, every 2 weeks in cycle 3 to 6, and every 4 weeks in cycle 7 and beyond).

The co-primary endpoints of the study were overall response rate and the maximum pre-dose trough concentration of daratumumab on day 1 of cycle 3, with both endpoints analysed for noninferiority. Patient characteristics and disease-related characteristics of the study population included a median age of 67 years, a median of 4 previous lines of therapy, as well as prior treatment with both an immunomodulatory drug and a proteasome inhibitor in all patients.

At a median follow-up of 7.5 months, the overall response rates were 41.1% and 37.1% for patients receiving SC and IV formulations, respectively. In addition, the ratio of the maximum pre-dose trough concentration of daratumumab on day 1 of cycle 3 for SC daratumumab over IV daratumumab was 108%. Furthermore, median PFS was 5.6 months vs 6.1 months for patients receiving the SC and IV formulations of daratumumab, respectively (P=0.9258).

Anaemia, neutropenia, thrombocytopenia, and diarrhoea were the most common treatment-emergent adverse events reported in the study. The 2 study arms showed generally comparable safety profiles, although rates of grade 3/4 neutropenia were slightly higher for patients receiving SC daratumumab (13%) compared with IV daratumumab (8%). The rates of treatment discontinuation due to an adverse event were 7% and 8% for those receiving SC and IV daratumumab, respectively. While 34.5% of patients receiving IV daratumumab experienced infusion reactions, these were reported in only 12.7% of those receiving SC daratumumab. Injection-site reactions occurred in approximately 7% of patients receiving SC daratumumab. Importantly, the median duration of injection for SC daratumumab was 5 minutes compared with infusion times of 421 minutes, 255 minutes, and 205 minutes for patients receiving the first, second, and subsequent infusions of IV daratumumab. A striking difference was noted in assessments of treatment satisfaction over time of patients in the 2 study arms, showing higher levels of satisfaction with treatment for patients receiving SC daratumumab compared with IV daratumumab.

1. Mateos M-V, et al. Abstract S823, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Adding isatuximab to pomalidomide and dexamethasone improves PFS and ORR in RRMM

Results from the randomised, phase 3 ICARIA-MM trial, presented by Prof. Michel Attal (University Institute Cancer Toulouse Oncopole, France), showed that the addition of isatuximab to pomalidomide and low-dose dexamethasone significantly improved progression-free survival (PFS) and the overall response rate in patients with relapsed or refractory multiple myeloma (RRMM) [1].

Isatuximab, an investigational anti-CD38 monoclonal antibody, was previously found to be safe and effective in the treatment of RRMM when combined with pomalidomide and dexamethasone in a phase 1b study. Based on this finding, investigators launched the phase 3 study, which enrolled 307 patients with RRMM who had received at least 2 prior lines of therapy with lenalidomide and a proteasome inhibitor. The patients were then randomised to receive isatuximab and pomalidomide/dexamethasone or pomalidomide/dexamethasone therapy.

Researchers found that at a median follow up of 11.6 months, the median PFS was significantly longer in the isatuximab and pomalidomide/dexamethasone arm compared with the pomalidomide arm (11.5 compared with 6.5 months; HR 0.5; 95% CI 0.44-0.81; P<0.0001). Though median overall survival was not reached in either arm of the trial, a clinically meaningful trend toward improvement was seen with the combination therapy (72% vs 63%).

Also of note, isatuximab combination therapy demonstrated a significantly greater overall response rate, compared with pomalidomide/dexamethasone alone (60% vs 35%, P<0.0001). In additional analyses, isatuximab combination therapy compared with pomalidomide/dexamethasone alone showed a treatment benefit consistent across multiple subgroups, including patients 75 years and older, patients with renal insufficiency, and patients who were refractory to lenalidomide. The results presented above were based on an independent review committee assessment.

In addition, the following results favoured isatuximab combination therapy:

- Isatuximab combination therapy demonstrated significantly higher very good partial response rate compared with pomalidomide/dexamethasone alone (31.8% vs 8.5%, respectively, P<0.0001) and a longer duration of response compared to pomalidomide/dexamethasone alone (median 13.27 vs 11.07 months, respectively). Among patients who achieved a response, isatuximab combination therapy demonstrated faster median time to first response compared with pomalidomide/dexamethasone alone (35 days vs 58 days, respectively).
- Time to next treatment was longer with isatuximab combination therapy compared pomalidomide/dexamethasone alone (median not reached vs 9.1 months; HR 0.538).
- Data at the time of analysis showed a trend towards an overall survival benefit associated with isatuximab combination therapy. Final data on overall survival will be reported when available.

The combination treatment was generally manageable, reported Prof. Attal, though the addition of isatuximab to pomalidomide/dexamethasone did increase rates of grade 3 or higher treatment-emergent adverse events (86.8% in isatuximab plus pomalidomide vs 70.5% in pomalidomide). Additionally, isatuximab combination therapy compared with pomalidomide/dexamethasone showed: 7.2% vs 12.8% of patients discontinued due to adverse events, respectively; 7.9% vs 9.4% patients died due to adverse events, respectively; infections of grade ≥3 were seen in 42.8% vs 30.2% of patients, respectively; and grade ≥3 neutropenia was seen in 84.9% (febrile 11.8%) vs 70.1% (febrile 2.0%) of patients, respectively. Infusion reactions were reported in 38.2% (2.6% grade 3-4) of isatuximab combination therapy patients.

1. Attal M et al. Abstract 824, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Subcutaneous daratumumab + cyclophosphamide, bortezomib, and dexamethasone in patients with newly diagnosed amyloid light chain amyloidosis

Prof. Raymond Comenzo (Tufts University, USA) presented 1-year follow-up data from the phase 3 ANDROMEDA trial; the combination of subcutaneous daratumumab with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) led to high overall and complete response (CR) rates in patients with newly diagnosed amyloid light chain (AL) amyloidosis.

In the safety run-in single arm phase of ANDROMEDA, 28 patients (median age 68 years; range 35-83 years) with previously untreated AL amyloidosis received daratumumab 1,800 mg (formulated with recombinant human hyaluronidase PH20) administered subcutaneously once a week during cycles 1 and 2, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter for up to 2 years. Patients also received CyBorD, with cyclophosphamide 300 mg/m2, bortezomib 1.3 mg/m2, and dexamethasone 40 mg, administered once weekly for up to 6 treatment cycles. Researchers followed patients for a median of 341 days (range 17-449 days), with median treatment duration of 11 months (range 0.2-14 months).

The primary endpoint was overall complete haematologic response rate, evaluated every 4 weeks during cycles 1 through 6 and every month thereafter. All but one patient (n=27; 96%) responded to treatment with daratumumab plus CyBorD. Most responders achieved at least a very good partial response (VGPR; 82%), with 10 achieving a CR. The median times to CR and VGPR were 85 days (range 29-226 days) and 22 days (range 7-228 days), respectively.

The one patient whose disease did not respond to treatment eventually experienced disease progression while on the study. However, "all 10 patients who achieved a CR continue to respond to treatment," Dr Comenzo reported. The median duration of CR had not been reached. Six participants went on to receive subsequent autologous haematopoietic cell transplantation; 4 of these patients have died (2 due to disease progression and 2 due to events following transplant). The most common treatment-related adverse events included diarrhoea (64%), fatigue (50%), and peripheral oedema (50%)

1. Comenzo RL et al. Abstract S875, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Venetoclax for multiple myeloma: effective but some safety concerns

Despite promising progression-free survival (PFS) and response data with venetoclax in combination with bortezomib and dexamethasone, roughly twice the number of deaths due to infection in the experimental arm cast fears over the overall survival findings in patients with relapsed/refractory multiple myeloma, according to results of the double-blind, multicentre, randomised, phase 3 BELLINI trial [1].

In BELLINI, patients were treated with bortezomib/dexamethasone with venetoclax or placebo; the FDA has now called for a halt in enrolment because of increased risk of death (not applicable for approved indications of venetoclax). In the late-breaking abstracts session, the trial data showed a median follow-up of 18.7 months; the median PFS was nearly doubled at 22.4 months with the venetoclax combination compared with 11.5 months with the placebo arm (HR 0.630; P=0.01). More patients demonstrated a response with venetoclax than placebo; the overall response rate was 82% vs 68%, respectively (P<0.01), and a very good partial or better response (≥VGPR) was seen in 59% vs 36% of patients (P<0.01). Regarding the parameter of undetectable minimal residual disease (uMRD [10-5]), the uMRD rates were 13% compared with 1% with the respective treatments. The median duration of response was not reached with venetoclax, compared with 12.8 months with placebo.

However, at the interim analysis, the FDA found that for overall survival, there were 41/194 (21.1%) deaths found in the venetoclax arm compared with 11/97 deaths in the placebo arm (HR 2.03; 95% CI 1.04-3.94), "increasing the relative risk of death by approximately 2-fold compared with the placebo arm," according to the FDA. The FDA noted, however, that this alert does not apply to indications for which venetoclax is currently FDA-approved, including chronic lymphocytic leukaemia, small lymphocytic lymphoma, and as part of a combination treatment for acute myeloid leukaemia. Additionally, patients currently enrolled in the BELLINI clinical trial who are receiving clinical benefit may continue the treatment after reconsenting.

"Novel therapies targeting disease biology are key to continuing the survival gains achieved in multiple myeloma," lead study author Dr Shaji Kumar (Mayo Clinic, USA) said in his presentation. "The decrease in overall survival in the experimental arm was a surprise; it appears to be related to infection in patients with worse overall survival."

Venetoclax targets BCL-2, a protein that prevents apoptosis in cancer cells, and had previously demonstrated activity in this patient population. BELLINI enrolled patients with relapsed/refractory multiple myeloma who had received 1 to 3 prior therapies and were either sensitive or naïve to proteasome inhibitors. Patients were randomised 2:1 to receive venetoclax at 800 mg daily or placebo plus bortezomib at 1.3 mg/m2 on days 1, 4, 8, 11 and dexamethasone at 20 mg on days 1, 2, 8, 9, 15, 16, 22, 23 of 28-day cycles for 8 cycles. The primary endpoint was PFS by an independent review committee.

As of the data cut-off on 26 November 2018, 194 patients were randomised to the venetoclax arm and 97 to the placebo arm. The median age was 66 years (range 36-87), 53% had International Staging System (ISS) II/III disease, and 54% of patients had received 2 or 3 prior lines of therapy. Prior treatments included proteasome inhibitors in most patients (70%), and immunotherapy in 68%; 41% of patients had received both. Most patients (59%) underwent prior stem cell transplant. High-risk cytogenetics were reported in 18% of patients, and 13% had translocation t(11;14). Immunohistochemistry testing revealed that 79% of patients were BCL-2 high.

An overall survival analysis in key subgroups indicated that low BCL-2 expression, high-risk cytogenetics, or ISS III disease were associated with both decreased PFS and overall survival in the venetoclax arm. However, patients with translocation t(11;14) derived more benefit from venetoclax and the median PFS was not reached, compared with 9.5 months in those who received placebo (HR 0.11; 95% CI 0.022-0.560; P=0.002). Also, the overall survival in this subgroup was not reached in either arm (HR 0.343; P=0.363).

Regarding safety, the most common adverse events of any grade with the venetoclax combination vs the placebo arm were diarrhoea (58% vs 48%, respectively), constipation (34% vs 31%), and nausea (36% vs 22%). The most common haematological adverse events in the respective arms were thrombocytopenia (39% vs 52%), neutropenia (32% vs 10%), and anaemia (25% vs 25%).

Dr Kumar said, "Five deaths occurred in the context of concomitant infection and disease progression and most of the deaths occurred within the first 6 months of treatment."

1. Kumar S, et al. Abstract LB2601, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Benign Haematology

New sickle cell drug voxelotor boosts levels of haemoglobin

Results from the randomised, placebo-controlled, phase 3 Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) trial of voxelotor in adults and adolescents with sickle cell disease showed promising effects on anaemia and haemolysis in roughly 60% of patients included [1]. As well as being presented at the EHA meeting, the data were simultaneously published in the New England Journal of Medicine [2].

Dr Jo Howard (King's College London, United Kingdom) presented new data from the late-stage HOPE trial, which showed that voxelotor, a new treatment for sickle cell disease (SCD), significantly improves anaemia and haemolysis, and provides strong evidence that voxelotor has the potential to be a disease-modifying treatment that could prevent chronic organ damage. SCD is a genetic blood disorder that affects millions worldwide and can cause recurrent pain episodes and chronic anaemia, leading to damaged organs, stroke, and premature death. Voxelotor reversely binds to haemoglobin, stabilising the oxygenated state. This increases haemoglobin oxygen affinity which prevents polymerisation of (otherwise deoxygenated) sickle haemoglobin, ultimately reversing the sickling of previously sickled red blood cells under hypoxic conditions [2].

Patients (n=274) treated with voxelotor in the HOPE study demonstrated robust improvements in anaemia as measured by an increase in haemoglobin after 24 weeks of treatment compared with placebo, and reduced the incidence of worsening anaemia during the study. In addition, voxelotor treatment reduced the amount of haemolysis. However, the researchers reported no significant difference between voxelotor and placebo in the rate of vaso-occlusive crises. The annualised incidence rate was 2.77 and 2.76 with voxelotor dosed at 1,500 mg and 900 mg, respectively, vs 3.19 with placebo. The HOPE trial met its primary endpoint, the percentage of patients with a haemoglobin response, at least at the 1,500 mg voxelotor dose.

Haemoglobin response was defined as an increase of more than 1g/dL at week 24 in the intention-to-treat analysis;

59.5% of patients in the 1,500 mg group met this benchmark vs 9.2% in the placebo arm, which was statistically significant with a P-value less than 0.001. Meanwhile, 38% of patients in the 900 mg group had a haemoglobin response. The study's authors said longer-term follow-up was needed, and added that an analysis at 72 weeks was planned, as well as an open-label extension trial of voxelotor's long-term effects.

1. Howard J, et al. Abstract S147, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Vichinsky E, et al. N Engl J Med. 2019 Jun 14.

Positive initial data evaluating the safety and efficacy of IMR-687 for treatment of sickle cell disease

Promising 13-week interim phase 2a data on IMR-687 in patients with sickle cell disease (SCD) were presented by Dr Biree Andemariam (UConn Health, USA). Treatment with IMR-687 in adult patients was generally well tolerated. The data also support the dual mechanism of action of IMR-687, with activity seen across both red and white blood cell biomarkers.

IMR-687 is an investigational, orally administered, selective phosphodiesterase 9 (PDE9) inhibitor. Dr Andemariam explains: "In the laboratory we saw that IMR-687 inhibition of PDE9 increases intracellular cGMP levels, increases foetal haemoglobin expression, reduces sickling and haemolysis of red blood cells, and does not induce neutropenia. The interim phase 2a data reflect trends that could be indicative of meaningful clinical translation of these important measures in SCD."

The phase 2a clinical trial is designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of escalating doses of IMR-687 administered once daily for 16 to 24 weeks in 2 groups of patients with SCD: those not on hydroxyurea (HU) (Population A) and those receiving a stable dose of HU according to the current standard of care (Population B). Blinded white cell markers in Population A (n=19), along with red cell markers and quality of life measures (ASCQ-Me) (n=13) were analysed. The blinded interim analysis was conducted on the monotherapy IMR-687 (Population A) subgroup. At 5 weeks, in the 100 mg dose group of Population A, there was a trend to reduced soluble P selectin (sPsel), soluble vascular cell adhesion molecule-1 (sVCAM), and myeloperoxidase (MPO) compared with placebo. At 13 weeks, the 100 mg dose group of Population A saw an increase (110%) in the percent of F cells, which are red blood cells that contain foetal haemoglobin (HbF) that often precede rises in total HbF. A corresponding decrease in absolute reticulocyte count and the percentage of reticulocytes, with a trend towards improved pain as measured by ASCQ-Me, was also observed at 13 weeks in Population A.

Blinded safety data for 27 patients demonstrated good tolerability, with no clinically significant changes in white blood cell counts and no evidence of neutropenia. There were no treatment-related serious adverse events.

1. Andemariam B, et al. Abstract S854, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Haematopoietic stem cell transplantation improves stroke risk in children with sickle cell anaemia

Matched sibling donor stem cell transplantation (MSD-HSCT) was associated with lower transcranial doppler velocities (TCDs) at 1 year compared with chronic transfusions. Furthermore, MSD-HSCT was also associated with changes in highest TCDs at 3 years, normalisation rate at 1 year, and ferritin levels at 1 and 3 years [1].

In the late-breaking plenary session, Dr Francoise Bernaudin (Intercommunal Hospital Center de Créteil, France) presented their study data showing that increased TCD in children with sickle cell anaemia (SCA) is associated with an increased risk of ischaemic stroke, stenosis, and silent cerebral infarcts. Previous studies have identified the pivotal role of chronic transfusions in reducing stroke risk, while newer studies have considered other preventive approaches such as hydroxyurea or MSD-HSCT. The DREPAGREFFE study is a nonrandomised, controlled, open-label intervention study that was conducted at 9 sites in France [2].

A total of 67 children were enrolled with 32 assigned to the transplantation group and 35 to the standard care group. Study visits were completed at baseline, 1 year, and 3 years. Primary outcome consisted of time-averaged mean of maximum velocities (TAMV) without angle correction in the 8 cerebral arteries at 1 year. A total of 29 secondary outcomes were utilised in the study that included highest TAMV at 1 and 3 years, incidence of ischaemic stroke, and survival without ischaemic stroke.

In the transplantation group, highest TCDs were significantly lower on average at 1 year (129.6 cm/s vs 170.4 cm/s; P<0.001). Similarly, highest TCDs at 3 years were lower in the transplantation group (112.4 cm/s in transplantation group vs 156.7 cm/s in standard of care; P=0.001). Normalisation at 1 year was higher in the transplantation group (80.0% in transplantation group vs 48.0% in standard of care; P<0.05). Ferritin levels were lower in the transplantation group at 1 year (905 ng/mL in transplantation group vs 2,529 ng/mL in standard of care group; P<0.05) and 3 years (382 ng/mL in transplantation group vs 2,170 ng/mL in standard of care group; P<0.05).

The post-hoc analysis strongly supported the conclusion that in children who had not experienced a stroke, stenosis of the Circle of Willis, a known predictor of stroke, was significantly reduced in children who had received a stem cell transplantation (P<0.01).

1. Bernaudin F, et al. Abstract LB2605, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Bernaudin F, et al. JAMA. 2019 Jan 22;321(3):266-276.

Early trial data shows positive results for treating anaemia in patients with end-stage renal failure

A multicentre, randomised, double-blind, placebo-controlled, multiple ascending dose, pilot phase 2a study determined that PRS-080 is safe in anaemic stage 5 chronic kidney disease patients requiring haemodialysis. A haemoglobin (Hb) response with clear segregation of Hb values between placebo and PRS-080 in the 8 mg/kg cohort during the treatment period showed early efficacy, consisting of an increase of Hb in drug-treated patients and a decline in placebo patients, potentially related to the withdrawal of iron treatment [1].

Nephrologist Prof. Lutz Renders (Klinikum Rechts der Isar, Germany) explained that patients with chronic kidney disease (CKD) commonly present with anaemia. Current treatment regimens consist of iron, erythropoietin stimulating agents (ESAs), or both, but a significant proportion of patients remain anaemic despite these therapies. Hepcidin, a liver-derived hormone, is a central regulator of iron homeostasis, frequently elevated in CKD patients and thought to represent a root cause of the hypoferremia. Therefore, hepcidin inhibition has the potential to ameliorate functional iron deficiency anaemia in CKD patients. PRS-080 is a pegylated hepcidin protein antagonist that has been shown to induce dose-dependent serum iron mobilisation and increased transferrin saturation (TSAT) in single ascending dose phase 1 clinical studies, both in healthy male volunteers and dialysis-dependent CKD patients [2].

The study authors aimed to determine the safety and tolerability of 5 repeated intravenous administrations of PRS-080 at doses of 4 and 8 mg/kg body weight compared with placebo in anaemic, haemodialysis-dependent stage 5 CKD patients, as well as to assess pharmacokinetics, pharmacodynamics, and immunogenicity. The decision to escalate the dose was based on an interim analysis of clinical and laboratory safety as well as on a comparison with pharmacokinetic data.

Twelve patients were enrolled. Using a standard 4+2 design, 4 patients in each cohort were randomised to PRS-080, and 2 patients to placebo. The study included a screening period of 4 weeks; the mean of 3 Hb values during the screening period, each obtained at least 7 days apart, was required to be ≤10.5 g/dL with a difference of ≤1.0 g/dL between the lowest and highest values. Additional inclusion criteria included ferritin > 300 ng/mL and TSAT ≤30%. The ESA dose had to remain stable for at least 4 weeks prior to screening, as well as through the treatment period, and iron therapy had to be withdrawn 1 week before randomisation. Study medication was administered by infusion over 60 minutes using an infusion pump on day 0, 7, 14, 21, and 28. Patients were observed with regard to safety up until day 112. Safety was monitored continuously by a data safety monitoring board, including prior to dose escalation.

The study results indicated no treatment-related adverse events or serious adverse events. Robust iron mobilisation with increases in both serum iron and TSAT were consistently observed following each weekly dose in both dose cohorts. Peak iron concentrations were higher in the 8 mg/kg cohort than in the 4 mg/kg cohort.

Whereas no clear difference was observed in Hb values between placebo and PRS-080 patients in the 4 mg/kg cohort over the course of treatment, evidence of a Hb response with clear separation of Hb values between placebo and PRS-080 could be shown in the 8 mg/kg cohort during the treatment period, consisting of an increase of Hb in drug-treated patients and a decline in placebo patients, potentially related to the withdrawal of iron treatment.

1. Renders L, et al. Abstract S1630, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Renders L, et al. PLoS One. 2019 Mar 27;14(3):e0212023.

Bench-to-Bedside

Transformation of foetal haematopoietic stem and progenitor cells in the background of trisomy 21

In the Presidential Symposium, Sofia Gialesaki (Hannover Medical School, Germany) presented her functional studies aimed to understand the pathophysiology behind myeloid leukaemia predisposition in trisomy 21 [1].

Children with Down syndrome (DS) are at high risk of developing myeloid leukaemia (ML-DS). Up to 30% of DS newborns develop a pre-leukaemic transient abnormal myelopoiesis (TAM), characterised by the accumulation of immature megakaryoblasts of foetal origin. TAM is characterised by *GATA1* mutations (GATA1-s) that result in a shorter protein isoform lacking the N-terminal transactivation domain. To understand how trisomy 21 cooperates with GATA1-s in TAM development, the researchers performed a CRISPR/Cas9 screen, targeting the 218 currently annotated coding genes on Hsa21 with 1,090 sgRNAs in both a ML-DS and control cell line.

RUNX1 loss resulted in depletion of ML-DS cells. Additionally, the researchers observed differential *RUNX1* isoform expression in acute megakaryoblastic leukaemia (non-DS) and ML-DS primary cells compared with normal haematopoietic stem/progenitor cells or terminally differentiated cells. In a newly established TAM/ML-DS assay, GATA1-s synergised with particular isoforms leading to a hyperproliferative phenotype *in vitro* and induction of leukaemia *in vivo*. This was further confirmed by co-immunoprecipitation assays followed by mass spectrometric analysis and DNA sequencing, showing differences in the physical interactions of GATA1/GATA1-s and RUNX1 isoforms as well as at genomic loci in TAM and ML-DS. These results highlight the importance of analysing all isoforms of a gene when studying its function in leukaemogenesis, with relevance for targeted therapies.

1. Gialesaki S, et al. Abstract S146, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Treating thalassemia twice, in mice

Dr Antonella Nai (San Raffaele Scientific Institute, Italy) and colleagues combined two experimental approaches to treat thalassemia in a mouse model [1]. They first used *TMPRSS6* gene-specific antisense oligonucleotides (ASOs) to decrease excess iron. In addition, they deleted the *TFR2* gene in the bone marrow using gene therapy.

The ASO treatment is effective in degrading this TMPRSS6 gene product, a key regulator in iron homeostasis, allowing iron levels to decrease to a healthy level. Dr Nai pointed out that loss-of-function mutations in the TMPRSS6 gene cause an inherited cause of iron-refractory iron-deficient anaemia. This increases erythropoietin sensitivity in the bone marrow cells and improves red blood cell production. This two-pronged approach significantly improved anaemia and increased red blood cell and haemoglobin concentrations in the mouse model. Dr Nai explained that the treatment holds promise for some patients but also comes at a high cost. In addition to the expenses associated with gene therapy, Dr Nai also claimed that data has shown more promise for younger patients than in older adults, being that living long-term with a genetic condition can bring about other complications. She concluded that gene therapy has great potential, and that a combination of gene and pharmaceutical therapy may be best fit for patients who do not respond to conventional management.

1. Nai A, et al. Abstract S148, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.

Haematopoietic stem cells can sense tissue damage in the gut

In the late-breaking oral session, Dr Hitoshi Takizawa (Kumamoto University, Japan) presented their study investigating how intestinal damage results in bone marrow haematopoiesis induction of haematopoietic stem cell (HSC) expansion followed by directional multipotent progenitor (MPP) migration to inflamed lymphoid tissues and generation of myeloid cells specialised for intestinal tissue repair [1].

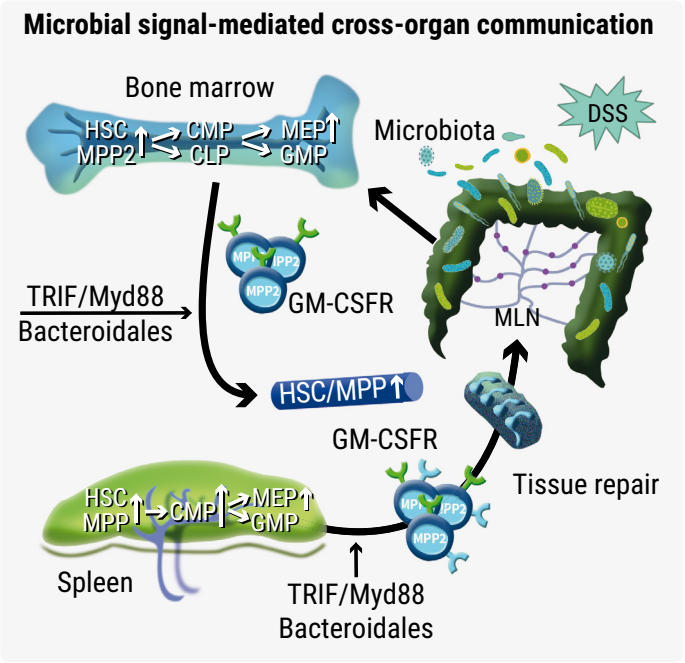
HSCs sustain lifelong haematopoiesis, while lineage-restricted progenitors actively divide and mainly contribute to daily haematopoiesis. Haematopoietic challenges such as inflammation or infection activate HSCs to self-renew. Systemic

challenge of gram-negative bacteria directly activates dormant HSCs to proliferate and impairs their competitive fitness via Toll like receptor (TLR)-4 signalling [2]. To test their hypothesis that progenitor cells (HSPCs) can sense tissue damage signals derived from distal organs such as the gut, and translate that to haematopoietic production, Dr Takizawa's team induced inflammatory bowel disease (IBD) in mice by adding dextran sodium sulfate (DSS) to their drinking water.

Inducing inflammatory bowel disease in the mice enhanced proliferation and expansion of HSPCs such as MPP and myeloid-restricted progenitors in bone marrow, while simultaneously reducing lymphoid-restricted progenitors, as measured by flow cytometry, microscopy, *in vivo* pharmacological treatment, and *in vivo* serial transplantation. Proliferating MPPs were localised adjacent to endothelial cells within the gut-associated mesenteric lymph node (MLN) but not in other lymph nodes, suggesting a specific haematopoietic response to gut inflammation, which the researchers demonstrated to be dependent on TLR signalling. Mice were then pre-treated with either a single or a mixture of antibiotics to deplete specific types of bacteria to determine what might trigger the TLR signalling. Pre-treatment with gram-positive directed antibiotics like vancomycin and ampicillin, completely abrogated haematopoietic responses to IBD, whereas neomycin and metronidazole, directed against gram-negative bacteria, enhanced haematopoietic response. Genome profiling and bacterial lysate injection identified that gram-negative bacterial species prompt MPP migration to the MLN through TLR-related signals. Following the MPP recruitment, myeloid cells including eosinophils and monocytes rapidly increased in MLN and their cell depletion by neutralising antibody worsened IBD-induced colitis.

This data suggests that in response to intestinal damage, bone marrow haematopoietic PCs sense microbiota via innate immune receptor and induce HSPC expansion followed by directional MPP migration to inflamed lymphoid tissues and generation of myeloid cells specialised for intestinal tissue repair (see Figure).

Figure: Schematic of the working hypothesis presented by Dr Takizawa et al [1]



1. Takizawa H, et al. Abstract LB2604, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.
2. Takizawa H, et al. Cell Stem Cell. 2017 Aug 3;21(2):225-240.e5

Promising news for gene therapy for sickle cell disease

An engineered lentivirus delivers functional copies of a modified form of the β-globin gene (βA-T87Q-globin gene or LentiGlobin) into a sickle cell disease (SCD) patient's own haematopoietic stem cells. Once patients have the βA-T87Q-globin gene, they can make functional red blood cells, with the goal of reducing sickled red blood cells, haemolysis, and ensuing complications [1]. In patients who were at least 6 months post-treatment with lentiviral LentiGlobin for SCD, the median level of abnormal sickle haemoglobin was reduced to ≤50% of total haemoglobin. At up to 15 months post-treatment with LentiGlobin, no serious vaso-occlusive crisis or acute chest syndrome were reported in this cohort.

In the plenary session, Dr Olivier Hermine (Necker Hospital, France) presented the ongoing, phase 1/2 HGB-206 study. Adults and children living with SCD experience unpredictable episodes of pain due to vaso-occlusion as well as other acute complications, such as acute chest syndrome, stroke, and infections, which can contribute to early mortality in these patients. LentiGlobin for SCD adds functional copies of a modified form of the β-globin gene (βA-T87Q-globin gene) into a patient's own haematopoietic stem cells. The latest data shows robust production of gene therapy-derived anti-sickling haemoglobin, HbA^{T87Q}, such that patients with 6 or more months of follow-up after treatment with LentiGlobin for SCD had median sickle haemoglobin levels reduced to 50% or less of total haemoglobin, in the absence of blood

transfusions. The potential for gene therapy with LentiGlobin to fundamentally alter the pathophysiology of SCD was also supported by the normalisation of haemolysis markers, increase in total haemoglobin, and substantial reduction in vaso-occlusive crises relative to baseline.

HGB-206 is an ongoing, phase 1-2, open-label study designed to evaluate the efficacy and safety of LentiGlobin gene therapy for SCD that includes 3 treatment cohorts: Groups A, B and C. As of March 2019, 25 patients were enrolled and a total of 13 patients had been treated with LentiGlobin in Group C, with a median post-treatment follow-up of 9 months (1.0-15.2 months). Of the 13 treated patients in Group C, 8 had at least 6 months of follow-up at the time of the data cut-off. In these patients, production of gene therapy-derived Hb^{AT87Q} ranged from 4.5-8.8 g/dL and total unsupported Hb levels ranged from 10.2-15.0 g/dL at the last study visit. The median concentration of Hb^{AT87Q} continued to increase, accounting for ≥50 percent of total Hb in patients with at least 12 months of follow up (n=4).
No acute chest syndrome or serious vaso-occlusive crisis was reported in patients in Group C at up to 15 months post-treatment with LentiGlobin.

In an exploratory analysis, key markers of haemolysis, including reticulocyte counts, lactate dehydrogenase (LDH), and total bilirubin levels, trended toward normal levels. As of the data cut-off date, with up to 15 months of follow-up, the safety data from all patients in HGB-206 are reflective of underlying SCD, the known side effects of haematopoietic stem cell collection and myeloablative conditioning. No serious adverse events were reported related to LentiGlobin for SCD. The amount of Hb^{AT87Q} and HbS protein in blood samples from 5 patients who were at least 9 months post-treatment showed that at least 70% of each patient's red blood cells expressed Hb^{AT87Q}.

1. Cavazzana M, et al. Plenary session, 24th Congress of the EHA, 13-16 June 2019, Amsterdam, the Netherlands.