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PEER-REVIEWED CONFERENCE REPORT

Promising Frontline Triplet Regimen for AML

A triplet combination of 5-azacitidine, venetoclax, and magrolimab displayed promising response rates in newly diagnosed older, unfit, or *TP53*-mutated patients with acute myeloid leukaemia.

read more on PAGE 5

Trials On Second-Line CAR T for Lymphoma

While the ZUMA-7 trial showed clear clinical benefit of CAR T-cell therapy after first relapse in diffuse large B-cell lymphoma, BELINDA did not. What can we learn?

read more on PAGE 14

Fitusiran Meets Primary Endpoint in ATLAS-A/B Trial

Fitusiran prophylactic therapy improved quality of life and reduced the annual bleeding rate in patients with severe haemophilia A or B without inhibitors in a phase 3 trial.

read more on PAGE 20

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Contents

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Letter from the Editor

Prof. Gert Ossenkoppele

Dear colleagues,

It is with great pleasure to introduce this peer-reviewed ASH 2021 Medicom Conference Report. Although it was organised as a hybrid meeting, most of you stayed home and followed the conference virtual. I wonder whether this will be the future of major congresses. As always, the ASH annual meeting is a great event to which everyone is looking forward. Also, this years meeting turned out to represent a wonderful programme. From this years' ASH we selected a number of interesting abstracts that will most likely change your daily practice now or in the near future. The abstracts are summarised in a way that the information is easy to digest in a rather short time.

The rapidly evolving field of immunotherapy including bispecific antibody and CAR T-cell treatment applied in a variety of haematological malignancies was also this year of major importance. Gene therapy is now rapidly moving from bench to bedside, resulting in new treatments for haemoglobinopathies and haemophilia. Treatment of AML, a disease in which no new developments emerged for a long time, is rapidly changing with the development of new effective targeted treatments and successful maintenance treatment. But also in the other malignant and non-malignant haematological diseases, new drugs are rapidly developed and approved by the regulatory authorities. Measurable residual disease becomes an important surrogate endpoint for outcome in many hematological malignancies.

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

Gert Ossenkoppele

Biography

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

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

Acute Lymphoblastic Leukaemia

New Interfant protocol includes blinatumomab for KMT2A-r ALL

Blinatumomab added to the Interfant-06 backbone protocol was well tolerated and displayed promising efficacy data in infants with newly diagnosed *KMT2A*-rearranged acute lymphoblastic leukaemia (ALL). Therefore, the new Interfant21 protocol will add blinatumomab to the treatment regimen of these patients [1].

Dr Inge van der Sluis (Princess Máxima Center for Pediatric Oncology, the Netherlands) explained that infants (<1 year) with ALL have a worse prognosis than older children. This is especially true in patients with *KMT2A*-rearrangement, which is present in 75% of the infants with ALL. Intensifying chemotherapy did not change health outcomes in these patients. Therefore, novel effective therapies are needed for this population.

Blinatumomab is a bispecific T-cell engager that has demonstrated to be safe and efficacious in adults and older children with ALL [2,3]. The current prospective, open-label, non-randomised, multicentre pilot study included 30 patients with newly diagnosed *KMT2A*-rearranged ALL to be treated with blinatumomab (4-week continuous infusion of 15 µg/m^2/day) after induction therapy as described in the Interfant-06 backbone protocol. The primary endpoint was the incidence of clinically relevant toxicities.

All patients received 4 weeks of blinatumomab, demonstrating feasibility of the agent. During blinatumomab therapy, 10 serious adverse events (SAEs) were reported, including 4 infections, 4 cases of fever, 1 case of vomiting, and 1 hypertensive crisis. No neurological SAEs or SUSARS were reported.

Measurable residual disease (MRD) negativity was reported in 27% and 53% of the patients at initiation and after completion of blinatumomab therapy, respectively. Patients receiving blinatumomab had numerically higher MRD negativity rates (79%) than historical controls (63%) at the start of the 5th treatment period of the Interfant-06 backbone protocol. Assessing patients with MRD negative or positive-non-quantifiable status after blinatumomab therapy did show a significant advantage of blinatumomab (100%) over the historical controls (82%; P=0.02) at the start of the 5th treatment period.

After a median follow-up of 16.3 months, the 1-year event-free survival (EFS) in patients receiving blinatumomab was 90.0% and the 1-year overall survival (OS) rate was 93.1%. In contrast, historical controls displayed a 1-year EFS rate of 54.8% and a 1-year OS rate of 69.8%. Notably, in the historical controls, most relapses occurred during the first year of therapy. Therefore, it is expected that long-term follow-up data will not significantly change EFS and OS rates in the current study population.

1. Van der Sluis I, et al. A Phase 2 Study to Test the Feasibility, Safety and Efficacy of the Addition of Blinatumomab to the Interfant06 Backbone in Infants with Newly Diagnosed KMT2A-Rearranged Acute Lymphoblastic Leukemia. A Collaborative Study of the Interfant Network. Abstract 361, ASH 2021 Annual Meeting, 11–14 December.
2. Gökbuget N, et al. Blood. 2018;131(14):1522–1531.
3. Locatelli F, et al. JAMA. 2021;325(9):843–854.

Persistent disparities in ALL health outcomes

Significant disparities in health outcomes were observed across race, ethnicity, and socioeconomic status (SES) in patients with acute lymphoblastic leukaemia (ALL). Differences in leukaemia biology or disease prognosticators do not account for the full magnitude of these disparities. The Children's Oncology Group (COG) ALL committee is aiming to unravel the underlying mechanisms and to design interventions targeting the reported disparities [1].

Dr Sumit Gupta (University of Toronto, Canada) and colleagues investigated 24,979 patients with ALL, ranging from 0–31 years of age, who were enrolled in COG frontline ALL trials between 2004 and 2019, to study health outcomes across race, ethnicity, SES, and disease prognosticators. SES was inferred by insurance status. The main outcomes were event-free survival (EFS) and overall survival (OS). Change in estimate approach was used to evaluate the relative contribution of race, ethnicity, SES, and disease prognosticators.

The 5-year EFS rates among White (87.4%) and Asian patients (88.1%) was higher than the 5-year EFS rates among Hispanic (82.8%) and Black patients (81.9%). Furthermore,

the EFS rate was higher in patients with non-US insurance (89.0%) or private insurance (86.3%) compared with patients who received federal support for healthcare costs via US Medicaid (83.2%).

In addition, change in estimate analysis revealed that the reported disparities could not be fully explained by disease prognosticators or leukaemia biology. In Hispanic patients, the hazard ratio for EFS changed from 1.37 to 1.11 when adjusting for SES and disease prognosticators, demonstrating a significant influence of these factors. In Black patients, the hazard ratio changed from 1.45 to 1.32 after adjustment, leaving a significant proportion of the increased risk in this subgroup unexplained by adjustment. Dr Gupta added that the observed disparities in OS were wider, indicating that access to relapse care may be insufficient in various subgroups. Notably, additional analysis showed that the results were significant in patients with B-lineage disease phenotype (P<0.001) but not in patients with T-lineage disease phenotype (P=0.47).

Dr Gupta argued that future studies should investigate access to care, quality of care, and institutional racism to explain the reported disparities.

1. Gupta S, et al. Racial, Ethnic, and Socioeconomic Factors Result in Disparities in Outcome Among Children with Acute Lymphoblastic Leukemia Not Fully Attenuated By Disease Prognosticators: A Children's Oncology Group (COG) Study. Abstract 211, ASH 2021 Annual Meeting, 11–14 December.

EWALL-INO: Inotuzumab ozogamicin promising as first-line therapy for BCP-ALL

Fractionated inotuzumab ozogamicin plus low-intensity chemotherapy was well tolerated and demonstrated high activity as first-line therapy in older patients with CD22-positive, Philadelphia Chromosome-negative (Ph-neg) B-cell precursor acute lymphoblastic leukaemia (BCP-ALL). This was the main primary result of the prospective, multicentre, phase 2 EWALL-INO trial [1].

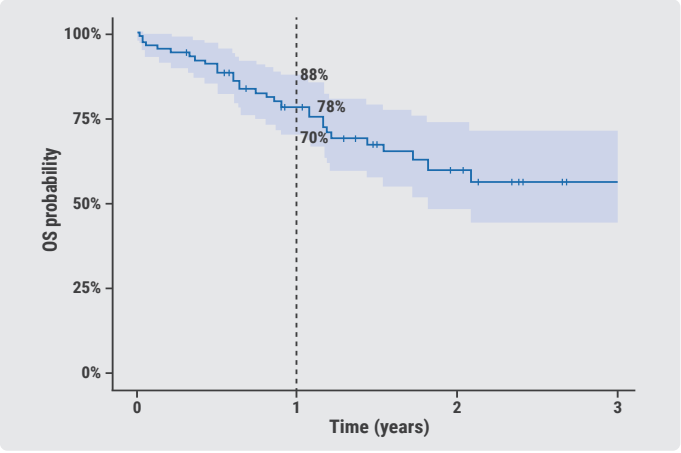
"The 2-year overall survival rate of BCP-ALL in older patients is approximately 30%," according to Prof. Patrice Chevallier (Nantes University Hospital, France). "Since BCP-ALL is the most common ALL in older patients, there is a high need for effective therapies. The high expression rate of CD22 in patients with BCP-ALL (>90%) justifies the investigation of inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, in this population." The current phase 2 EWALL-INO trial (NCT03249870) included 90 patients (age ≥55 years) with CD22-positive, Ph-neg BCP-ALL to assess inotuzumab ozogamicin via 2 inductions:

- Induction 1: 0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on day 8 and 15.
- Induction 2: 0.5 mg/m^2 on day 1 and 8.

The induction periods were followed by 6 cycles of low-intensity chemotherapy and 18 months of POMP maintenance therapy. The primary endpoint was 1-year overall survival (OS).

The complete response rate was 86.7% after induction 1 and 88.8% after induction 2. In addition, 73% of the patients displayed measurable residual disease (MRD) negativity after induction 2. The 1-year OS rate was 78% (see Figure) and the 1-year relapse-free survival rate was 76%. Patients with *KMT2A*-rearrangement displayed worse OS and relapse rates than other oncogenetic subgroups.

Figure: 1-year OS rate in EWALL-INO [1]



The safety profile of inotuzumab ozogamicin was favourable. Liver toxicity grade 3-4 was reported in 8.8% of the patients and sinusoidal obstruction syndrome was observed in 3.3% of the patients. In total, 3 deaths occurred during induction therapy, and 29 patients died during the follow-up. The deaths during follow-up were attributable to relapse (n=16) or adverse events (n=13).

In conclusion, a reduced dose regimen of inotuzumab ozogamicin plus low-intensity chemotherapy was tolerable and efficacious in older patients with CD22-positive, Ph-neg BCP-ALL.

1. Chevallier P, et al. Fractionated Inotuzumab Ozogamicin Combined with Low-Intensity Chemotherapy Provides Very Good Outcome in Older Patients with Newly Diagnosed CD22+ Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia: First Results from the EWALL-INO Study. Abstract 511, ASH 2021 Annual Meeting, 11–14 December.

UKALL 2003: Therapy de-escalation safe in low-risk MRD patients with ALL

Therapy de-escalation in patients with acute lymphoblastic leukaemia (ALL) and a low-risk measurable residual disease (MRD) profile is safe, 10-year follow-up results of the UKALL 2003 trial showed. Patients with a high-risk MRD profile continued to benefit from augmented therapy compared with standard therapy, especially high-risk genetic subgroups and patients with B-cell precursor (BCP) disease [1].

The UKALL 2003 trial (NCT00222612) was designed to evaluate the effects of de-escalation of therapy in patients with ALL and a low-risk MRD profile, and treatment intensification in patients with ALL and a high-risk MRD profile. Participants in the low-risk MRD group were randomised to 1 (n=261) or 2 (n=260) delayed intensifications (DIs) of therapy. High-risk patients were randomised to standard therapy (n=266) or augmented therapy (n=267). Dr Sujith Samarasinghe (Great Ormond Street Hospital, UK) presented the 10-year follow-up results.

In the low-risk group, participants in the 1 DI arm displayed a higher relapse rate than those in the 2 DIs arm (8.3% vs 3.6%; P=0.04). However, overall survival (OS) rates were not significantly different between the 2 arms (97.1% vs 97.6%; P=0.5). According to Dr Samarasinghe, the increased rate of treatment-related deaths in the 2 DIs arm resulted in comparable OS rates for both low-risk groups.

The relapse rate in the high-risk standard therapy arm was 14.2%, versus 9.2% in the high-risk augmented therapy arm (P=0.07). The OS rates were not significantly different after 10 years (87.9% vs 90.7%; P=0.3). Among patients with BCP-ALL, augmented therapy did result in a significant reduced risk of relapse (HR 0.54; P=0.03). Similarly, patients with high-risk cytogenetics displayed that relapse risk was significantly lower if they were treated with augmented therapy (22.1%) compared with those receiving standard therapy (52.4%; P=0.016).

Dr Samarasinghe concluded that the long-term follow-up data of UKALL 2003 showed that modest therapy de-escalation is safe in patients with low-risk MRD profiles and that augmented therapy continued to display a favourable trend in patients with high-risk MRD profiles.

1. Samarasinghe S, et al. Ten Year Outcomes of UKALL 2003: A Randomised Clinical Trial of Adjusting Treatment Intensity Based on Minimal Residual Disease. Abstract 364, ASH 2021 Annual Meeting, 11–14 December.

Acute Myeloid Leukaemia

Encouraging results of novel triplet combination for AML

A regimen of cladribine plus low-dose cytarabine plus venetoclax alternated with 5-azacytidine plus venetoclax showed encouraging efficacy in patients with newly diagnosed acute myeloid leukaemia (AML). Moreover, the displayed efficacy was consistent across European LeukemiaNet (ELN) risk groups and patients ≥70 years of age. The results of this phase 2 trial need to be confirmed in larger trials but are really very promising [1].

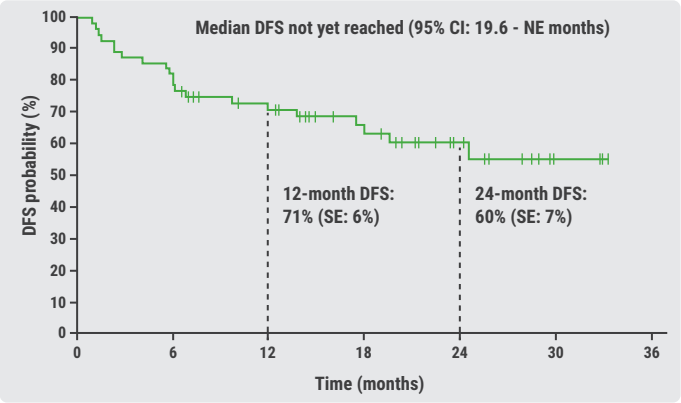
Dr Patrick Reville (MD Anderson Cancer Center, TX, USA) and colleagues included patients with newly diagnosed AML of ≥60 years of age to evaluate a regimen of cladribine plus low-dose cytarabine plus venetoclax, alternating with 5-azacytidine plus venetoclax.

Participants (n=60) followed 1 or 2 cycles (28 days per cycle) of induction therapy (cladribine, 5 mg/m^2, once daily on day 1 to 5; cytarabine, 20 mg, twice daily on day 1 to 10; venetoclax, 100 mg, 200 mg, or 400 mg [dose depending on the use of CYP3A4 inhibitors], for 21 days). Subsequently, they received 2 cycles of 5-azacytidine (75 mg/m^2) on days 1 to 7 and venetoclax on the first 7 to 14 days, depending on measurable residual disease and tolerability. Hereafter, 2 cycles of maintenance cladribine, low-dose cytarabine, and venetoclax were alternated with 2 cycles of 5-azacytidine plus venetoclax, up to 18 cycles. The primary outcome was a composite complete response (CR/CRi) rate.

In total, 93% of the patients achieved the composite CR rate, with 80% of the patients reaching CR and 13% of the patients achieving CRi. Early mortality rates were low, with 1 deceased patient after

4 weeks and 4 mortalities after 8 weeks. The observed response rate was consistent across subgroups: ELN Adverse (96%), Adverse/Complex Cytogenetics (89%), *FLT3*-mutated (88%), *MLL*-rearranged (75%), and secondary AML (93%). The disease-free survival (DFS) rate was 60% after 24 months; median DFS was not yet reached (see Figure). Similarly, median event-free survival and median overall survival were not yet reached after 24 months, with rates of 56% and 64%, respectively.

Figure: 24-month disease-free survival [1]



DFS, disease-free survival; NE, not estimable; SE, standard error.

The rate of serious adverse events was low. Febrile neutropenia (55%) and pneumonia (23%) were the most common grade 3 events. Tumour lysis syndrome was observed in 1 patient.

1. Reville PK, et al. Phase II Study of Venetoclax Added to Cladribine (CLAD) and Low Dose AraC (LDAC) Alternating with 5-Azacytidine (AZA) in Older and Unfit Patients with Newly Diagnosed Acute Myeloid Leukemia (AML). Abstract 367, ASH 2021 Annual Meeting, 11–14 December.

AMLSG 16-10: Long-term benefits of midostaurin for *FLT3-ITD*-mutated AML

The final results of the phase 2 AMLSG 16-10 trial showed that younger and older patients with *FLT3-ITD*-mutated acute myeloid leukaemia (AML) benefitted from the addition of midostaurin to intensive chemotherapy. Furthermore, the occurrence of *NPM1* mutations was a favourable prognostic factor. Older age, higher white blood cell (WBC) count, and higher *FLT3-ITD* allelic ratios increased the risk of unfavourable health outcomes [1].

Midostaurin is a first-generation, type I kinase inhibitor targeting *FLT3-ITD* and *FLT3-TKD* mutations [2]. The single-arm, phase 2 AMLSG 16-10 trial (NCT01477606) included patients with newly diagnosed, *FLT3-ITD*-mutated AML up to 70 years of age (n=440) to investigate midostaurin plus induction chemotherapy, followed by allogeneic haematopoietic cell transplantation (HCT) and 1-year midostaurin maintenance therapy. A cohort of historical AMLSG trial participants (n=415) was used as control group. Dr Hartmut Döhner (Universitätsklinikum Ulm, Germany) mentioned that patients in the historical cohort had received their treatment approximately a decade earlier than patients in the AMLSG 16-10 trial. The primary endpoint was event-free survival. The key secondary endpoint was overall survival (OS).

The response rate to induction therapy was higher in the midostaurin cohort (CR/CRi 74.9%) than in the control cohort (64.6%). Moreover, the proportion of patients undergoing HCT in CR/CRi was higher in patients receiving midostaurin (45.2%) compared with control subjects (22.6%). The 5-year event-free survival and OS rates were significantly improved in the AMLSG 16-10 trial compared with the historical cohort. Patients <60 years of age treated with midostaurin had a 5-year OS rate of 49% versus 33% in controls. Patients between 61 and 70 years of age receiving midostaurin therapy showed a 5-year OS rate of 33%. Patients in the control group in this age category demonstrated an OS rate of 8% after 5 years.

Furthermore, *NPM1* mutations had a favourable impact on event-free survival (HR 0.48; P<0.001), whereas older age (HR 1.17), higher WBC count (HR 1.21), and high *FLT3-ITD* allelic ratios (HR 1.19; P=0.072) were associated with an unfavourable effect on event-free survival. The therapy effect of midostaurin remained significant when allogeneic HCT was considered as a time-dependent variable.

Midostaurin was generally well tolerated. Respiratory, metabolic, and vascular adverse events were more frequently reported in older patients. However, Dr Döhner argued that underlying comorbidities may be the explanation for this outcome.

1. Döhner H, et al. Midostaurin Plus Intensive Chemotherapy for Younger and Older Patients with Acute Myeloid Leukemia and FLT3 Internal Tandem Duplications. Abstract 692, ASH 2021 Annual Meeting, 11–14 December.
2. Weisberg E, et al. Cancer Cell. 2002;1(5):433–443.

Comparable effectiveness of CPX-351 and venetoclax plus HMA in older AML patients

Liposomal daunorubicin/cytarabine (CPX-351) therapy did not result in different overall survival (OS) outcomes or response rates than venetoclax plus hypomethylating agent (HMA) therapy in patients with acute myeloid leukaemia (AML) between 60 and 75 years of age in this retrospective, real-world study. Subgroup analyses displayed an advantage in OS for *TP53*-positive patients who were treated with CPX-351 [1].

Both CPX-351 and venetoclax plus an HMA combination therapy have demonstrated to improve OS in older patients with AML [2,3]. Dr Justin Grenet (Weill Cornell Medical Center, NY, USA) and colleagues conducted a real-world, multicentre, retrospective chart review to compare the effectiveness of CPX-351 (n=211) versus venetoclax plus HMA (n=226). Primary outcomes were response rate, OS, and relapse-free survival. Dr Grenet explained that CPX-351 therapy is usually prescribed to younger patients who are deemed fit enough to withstand intensive chemotherapy, whereas venetoclax plus HMA is mostly prescribed in older, frailer patients. The research team was mostly interested to compare treatment results in patients between 60 and 75 years of age, the age category that shows the highest treatment overlap.

In patients between 60 and 75 years of age, there was no significant difference regarding OS between the 2 treatment regimens (logrank-P=0.3375), despite the higher rates of haematopoietic stem cell transplantations (HSCT) in the CPX-351 arm compared with the venetoclax plus HMA arm (47.7% vs 19.0%; P<0.001). Moreover, response rates did not favour one treatment over the other in this age category (59.2% vs 54.0%, respectively; P=0.41). Subgroup analyses displayed an advantage of CPX-351 therapy in patients between 60 and 75 years who were *TP53*-positive (HR 0.66; P=0.013). Strata differentiating for prior myeloid malignancy, prior HMA use, or European LeukemiaNet (ELN) risk classification did not show superiority of one treatment regimen over the other.

Dr Grenet argued that the treatment regimens display comparable effectiveness in patients with AML between 60 and 75 years. Currently, the team is investigating comorbidities and pre-induction and post-induction fitness scores in the study population to further analyse which treatment regimen provides the most benefits for each subgroup of patients.

1. Grenet J, et al. Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and HMA+Venetoclax As Frontline Therapy in Acute Myeloid Leukemia. Abstract 32, ASH 2021 Annual Meeting, 11–14 December.
2. Lancet JE, et al. J Clin Oncol. 2018;36(26):2684–2692.
3. DiNardo CD, et al. N Engl J Med 2020;383:617–629.

Heavily pre-treated *FLT3*-mutated AML population may benefit from novel triplet regimen

A combination treatment of quizartinib plus venetoclax plus decitabine was highly active in patients with relapsed/refractory *FLT3-ITD*-mutated acute myeloid leukaemia (AML). Patients with *RAS/MAPK* and *FLT3-F691L* mutations displayed more often treatment resistance. The safety profile of this combination did not show unexpected issues [1].

FLT3 mutations in AML are associated with an increased risk of relapse and a reduced overall survival. Although FLT3 inhibitors plus intensive chemotherapy may improve outcomes in younger patients, older or unfit patients continue to display poor outcomes. Dr Musa Yilmaz (MD Anderson Cancer Center, TX, USA) and colleagues designed a trial to investigate a triplet combination regimen of quizartinib, decitabine, and venetoclax in relapsed/refractory *FLT3*-mutated patients with AML (n=23) or newly diagnosed *FLT3*-mutated patients who were unfit for intensive chemotherapy (n=5). During 28-day cycles, patients received decitabine (20 mg/m^2, once daily on day 1 to 5 [consolidation] or day 10 [induction]), venetoclax (400 mg, once daily on day 1 to 14/21), and quizartinib (30–40 mg, once daily on day 1 to 14/28).

In the relapsed/refractory cohort, a complete response (CR) composite rate of 78% was established: 13%, 22%, and 43% of the patients showed CR, CR with incomplete haematologic recovery (CRi), or morphological leukaemia-free state (MLFS), respectively. The 60-day mortality rate was 5%. In addition, 34% of the patients was bridged to allogeneic bone marrow transplant.

In the frontline cohort, the CR composite rate was 100%: 40% displayed CR and 60% displayed CRi. The 60-day mortality rate was 0%, and 60% underwent a bone marrow transplant. Subgroup analysis showed consistent efficacy of the triplet regimen among patients with prior HMA plus venetoclax therapy or patients who received prior gilteritinib treatment. Patients with a *RAS/MAPK* mutation were associated with lower response rates (40%) compared with *RAS/MAPK*-negative patients (94%).

The most common non-haematologic any-grade adverse events were electrolyte disturbances, diarrhoea, and kidney or liver function abnormalities. Pneumonia (42%), febrile neutropenia (30%), and other infections (33%) were the most common grade 3 or higher adverse events. The median time to absolute neutrophil count recovery was 51 days but could be reduced to 40 days if quizartinib administration was interrupted on day 28. Grade 2 or higher corrected QT interval by Fredericia (QTcF) events were not observed.

1. Yilmaz M, et al. Quizartinib (Quiz) with Decitabine (DAC) and Venetoclax (VEN) Is Highly Active in Patients (pts) with FLT3-ITD Mutated Acute Myeloid Leukemia (AML) – RAS/MAPK Mutations Continue to Drive Primary and Secondary Resistance. Abstract 370, ASH 2021 Annual Meeting, 11–14 December.

Promising frontline triplet regimen for *TP53*-mutated AML

A triplet combination of 5-azacitidine, venetoclax, and magrolimab displayed promising response rates in newly diagnosed older, unfit, or *TP53*-mutated patients with acute myeloid leukaemia (AML). Moreover, the phase 1b/2 study showed a favourable safety profile of this regimen. Phase 3 trials investigating this triplet combination are ongoing [1].

"Older or unfit patients with AML treated with 5-azacitidine plus venetoclax show overall survival (OS) rates of 40% after 2 years," said Dr Naval Daver (MD Anderson Cancer Center, TX, USA). "Moreover, patients with *TP53*-mutated AML treated with hypomethylating agents (HMA) plus venetoclax as first-line therapy display median OS rates of only 5–7 months. Therefore, there is an obvious unmet need in these patients," Dr Daver argued. The current phase 1/2 trial included 48 patients divided over 3 cohorts:

- Cohort 1: frontline therapy for older (≥75 years), unfit, or *TP53*-mutated patients;
- Cohort 2: relapsed/refractory venetoclax-naïve patients;
- Cohort 3: relapsed/refractory patients with prior venetoclax therapy.

Patients received cycles (21 days per cycle) of 5-azacitidine (75 mg/m^2, once daily, day 1 to 7), venetoclax (400 mg, once daily, day 1 to 21/28), and magrolimab (ramped up to 30 mg/kg, at day 1 and day 11).

The overall response rate in older, unfit, or *TP53*-mutated patients (n=14) was 86%, with a complete response (CR) rate of 64%. In patients with *TP53* wildtype (n=11) the overall response rate was 100%, with a CR of 64%. Furthermore, *TP53* variant allele frequency (VAF) levels were significantly decreased in *TP53*-mutated patients who displayed a CR. This indicates biologic activity at the TP53 level. Among venetoclax-naïve patients and patients with prior venetoclax therapy, the CR rates were 38% and 0%, respectively. Notably, absolute neutrophil count and platelet recovery were robust after 28 days, which is an encouraging result in triplet therapy for AML.

According to Dr Daver, the safety profile of the current triplet regimen was similar to the safety of an HMA plus venetoclax regimen, with febrile neutropenia and lung infections as the most common serious adverse events (SAEs). In addition, increased bilirubin levels were reported. Dr Daver argued that this adverse event may be related to extravascular haemolysis, which can be observed with magrolimab. Anaemia due to haemolysis in the magrolimab arm was manageable with close monitoring and did not lead to SAEs or treatment interruption or discontinuation. No immune-related adverse events were reported.

Thus, the triplet combination of azacitidine, venetoclax, and magrolimab showed promising results as frontline therapy for newly diagnosed older, unfit, and *TP53*- mutated patients with AML in this phase 2 study. Larger trials are currently running to validate the efficacy and safety of this novel regimen.

1. Daver NG, et al. Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML. Abstract 371, ASH 2021 Annual Meeting, 11–14 December.

Benefits of eprenetapopt plus azacytidine for *TP53*-mutant MDS and oligoblastic AML

The combination therapy of eprenetapopt plus azacytidine showed favourable efficacy and safety in patients with *TP53*-mutant myelodysplastic syndrome (MDS) and oligoblastic acute myeloid leukaemia (AML). The high-risk subpopulation of patients with biallelic *TP53* mutations or complex karyotype at baseline had higher complete response rates than patients who do not display these features [1].

Dr David Sallman (H. Lee Moffitt Cancer Center, FL, USA) explained that the impact of *TP53* mutations in MDS is large. "*TP53* mutations occur in up to 20% of the patients with MDS and AML, resulting in inferior overall survival (OS) outcomes. The current therapies for this population are insufficient." The combination regimen of eprenetapopt, a first-in-class p53 reactivator, plus azacytidine was evaluated in 2 phase 2 trials (NCT03072043, NCT03588078) with a combined cohort size of 100 patients with *TP53*-mutant MDS or oligoblastic AML. The primary endpoint was complete response (CR) rate.

The overall response rate was 69% and the CR rate was 43%. The median time to CR or partial response (PR) was 3.1 months. In addition, 40% of the patients achieved *TP53* clearance (variant allele frequency [VAF] <5%), as assessed by next-generation sequencing (NGS) analysis. Furthermore, after 28 months of follow-up, *TP53*-negative patients displayed a median OS of 15.8 months, compared with 10.1 months in *TP53*-positive patients (P=0.0019). *TP53* clearance was strongly correlated with CR rates, especially in patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT). After 28

months of follow-up, median OS was not reached in patients who achieved *TP53* clearance and received allogeneic HSCT, whereas patients who did not achieve *TP53* clearance but underwent allogeneic HSCT had a median OS of 9.1 months. This result indicates that *TP53* clearance (confirmed by NGS testing) is an important biomarker of allogeneic HSCT outcomes in patients with mutant *TP53*.

Notably, patients who had only confirmed *TP53* mutations at baseline had higher CR rates (52%) than patients who also showed non-*TP53* mutations (30%). Moreover, patients with biallelic *TP53* mutations or complex karyotype at baseline had higher CR rates (49%) than other patients (8%).

The combination regimen of eprenetapopt and azacytidine was generally safe and well tolerated. The most common non-haematologic adverse events were nausea/vomiting (58%), ataxia (26%), and dizziness (23%), mostly grade 1 or 2 events. Febrile neutropenia was the most serious adverse event, occurring in 37% of the patients. However, the 30-day and 60-day mortality rates were low, with 1% and 7%, respectively.

1. Sallman DA, et al. Long Term Follow-up and Combined Phase 2 Results of Eprenetapopt (APR-246) and Azacitidine (AZA) in Patients with TP53 mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML). Abstract 246, ASH 2021 Annual Meeting, 11–14 December.

Improved risk stratification in MDS via gene-based scoring system

The newly developed molecular international prognosis scoring system for myelodysplastic syndromes (IPSS-M) delivers personalised, reproducible, and interpretable risk scores to stratify patients with MDS across 6 risk categories. The IPSS-M showed improved risk discrimination compared with the IPSS-R model and clear prognostic separation across risk categories [1].

"The current risk stratification methods for patients with MDS does not include gene mutations," explained Dr Elsa Bernard (Memorial Sloan Kettering Cancer Center, NY, USA). "The IPSS-M was developed to improve risk stratification in MDS by considering clinical, cytogenetic, and genetic parameters."

The research team collected samples of 3,675 participants with blast percentages <20% and white blood cell count <13x10^9/L, representative of all IPSS-R risk categories. Subsequently, the associations between genetic mutations and leukaemia-free survival, overall survival, and acute myeloid leukaemia (AML) transformation were assessed, demonstrating that 14, 16, and 15 gene mutations were linked to worse outcomes on the 3 endpoints, respectively. *TP53* multi-hit, *MLL* partial tandem duplication, and *FLT3* mutations showed the strongest associations with adverse outcomes. *SF3B1* mutations were related to favourable outcomes, excluding *SF3B1* mutations with specific concomitant other mutations.

The model used the weighted sum of 16 main effect genes and a genetic variable from 15 residual genes, the IPSS-R cytogenetic categories, and continuous clinical parameters (i.e. marrow blasts, platelets, haemoglobin) to calculate an individual risk score on a continuous scale. Furthermore, 6 risk categories, demonstrating prognostic separation across the relevant endpoints, were created.

The IPSS-M score outperformed the IPSS-R score regarding risk assessment: a 5-point increase in concordance index from IPSS-R to IPSS-M was reported for each endpoint. In total, 46% of the patients were re-stratified, and 7% of the patients were re-stratified by at least 2 strata. Furthermore, the new model was applicable across various settings, including low-blast-count AML and therapy-related MDS.

In conclusion, the IPSS-M model improved risk stratification in patients with MDS by assessing 31 gene mutations next to conventional parameters, delivering a highly personalised risk score.

1. Bernard E, et al. Molecular International Prognosis Scoring System for Myelodysplastic Syndromes. Abstract 61, ASH 2021 Annual Meeting, 11–14 December.

Chronic Leukaemia

CAPTIVATE: Ibrutinib plus venetoclax shows ongoing efficacy in CLL

The first-line, chemotherapy-free regimen of ibrutinib plus venetoclax showed ongoing efficacy after 2 years of follow-up in patients with chronic lymphocytic leukaemia (CLL). Patients with confirmed undetected measurable residual disease (uMRD) did not display MRD relapses, death, or progressive disease during the follow-up phase of the phase 2 CAPTIVATE trial. These results suggest that treatment-free remission may be achieved with a first-line, fixed-duration ibrutinib plus venetoclax regimen in patients with CLL [1].

The international, multicentre, phase 2 CAPTIVATE trial (NCT02910583) investigated an ibrutinib plus venetoclax regimen in patients with CLL (n=323), divided into a fixed-duration cohort and an MRD cohort. Patients received 3 cycles of oral ibrutinib (420 mg, daily), followed by 12 cycles of ibrutinib plus oral venetoclax (ramp-up to 400 mg daily). Dr Paolo Ghia (Università Vita-Salute San Raffaele, Italy) presented the 2-year follow-up results of the MRD cohort.

During cycle 16, patients with confirmed uMRD were randomised 1:1 to placebo (n=43) or ibrutinib monotherapy (n=43). Patients who did not achieve uMRD were randomised 1:1 to ibrutinib monotherapy (n=31) or ibrutinib plus venetoclax therapy (n=32). Notably, a high proportion of patients had high-risk features, such as unmutated immunoglobulin heavy-chain variable region gene (*IGHV*) (60%). The median post-randomisation follow-up was 24 months. Median treatment duration was 37 months in all patients.

No new disease-free survival (DFS) events had occurred since the primary analysis in patients with confirmed uMRD. The DFS rates remained at 95% and 100% for placebo and ibrutinib receivers, respectively. In addition, the overall study period displayed modest improvements in complete response (CR) rates for patients with confirmed uMRD compared with the pre-randomisation period (placebo 9%; ibrutinib 5%). Patients without confirmed uMRD showed larger improvements in CR rates, with ibrutinib receivers displaying a 22% improvement and ibrutinib plus venetoclax receivers demonstrating a 28% improvement. Furthermore, preliminary data suggested that patients who experience a progressive event may be re-treated with ibrutinib monotherapy. No new safety issues of the ibrutinib plus venetoclax regimen were observed.

1. Ghia P, et al. First-Line Treatment with Ibrutinib (Ibr) Plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study. Abstract 68, ASH 2021 Annual Meeting, 11–14 December.

SEQUOIA: Zanubrutinib meets primary endpoint for treatment-naïve CLL/SLL

Zanubrutinib outperformed bendamustine plus rituximab in patients with treatment-naïve chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). The effect was consistent across high-risk subgroups, such as patients with unmutated *IGHV* or del(11q). The results of this phase 3 trial showed that zanubrutinib, a chemotherapy-free therapy, is an effective frontline therapy for patients with CLL/SLL [1].

Zanubrutinub is a second-generation Bruton's tyrosine kinase (BTK) inhibitor that has demonstrated favourable efficacy and safety in patients with Waldenström macroglobulinaemia and relapsed refractory CLL/SLL [2,3]. Cohort 1 of the current open-label, phase 3 SEQUOIA trial (NCT03336333) randomised 479 patients with treatment-naïve CLL/SLL without del(17p) who were unfit for intensive chemotherapy 1:1 to zanubrutinib (160 mg, twice daily) or a regimen of bendamustine plus rituximab. The primary endpoint was progression-free survival (PFS) at 24 months. Prof. Constantine Tam (Peter MacCallum Cancer Centre, Australia) presented the primary results.

At 24 months, PFS rates favoured zanubrutinib (85.5%) over standard-of-care therapy (69.5%), with a corresponding hazard ratio of 0.42 (P<0.0001). This result was consistent across key subgroups, including high-risk subgroups, such as patients with unmutated *IGHV* (HR 0.24) or del(q11) (HR 0.21). The safety analysis did not reveal surprising safety issues. Zanubrutinib was associated with fewer grade 3 adverse events (AEs) than standard-of-care (52.5% vs 79.7%). Moreover, treatment with zanubrutinib led to fewer AE-related dose reductions (7.5%) or discontinuations (8.3%) than the standard-of-regimen (37.4%; 13.7%).

Prof. Tam added that the results in cohort 2 of the SEQUOIA trial, those with del(17p), displayed similar results for patients who are treated with zanubrutinib. The PFS in this population is 88.9% at 24 months.

In conclusion, zanubrutinib showed encouraging efficacy and safety results as a first-line therapy for patients with treatment-naïve CLL/SLL, with consistency across relevant subgroups.

1. Tam CS, et al. SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab (BR) in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL). Abstract 396, ASH 2021 Annual Meeting, 11–14 December.
2. Tam CS, et al. Blood. 2020;136(18):2038–2050.
3. Hillmen P, et al. LB1900, EHA 2021 Congress, 9–17 June.

Investigational therapies superior to standard-of-care in double-exposed CLL

Patients with chronic lymphocytic leukaemia (CLL) with prior exposure to both a covalent Bruton's tyrosine kinase (BTK) inhibitor and venetoclax demonstrated better responses to non-covalent BTK inhibitors, allogeneic stem cell transplantation (SCT), or CAR T-cell therapy than to PI3K inhibitors or chemo+/-immunotherapy (CIT). These results cast doubt on the use of PI3K inhibitors or CIT in double-exposed patients with CLL [1].

A subset of patients with CLL treated with both a covalent BTK inhibitor and venetoclax will still develop progressive disease. Dr Meghan Thompson (Memorial Sloan Cancer Center, NY, USA) explained that data is limited regarding therapy efficacy in these double-exposed patients. Therefore, practice patterns vary.

The current international, retrospective, multicentre study compared the efficacy of in USA available approved options (i.e. CIT or PI3K inhibitors) with investigational options (i.e. non-covalent BTK inhibitors, CAR T-cell therapy, or allogeneic SCT) in double-exposed patients with CLL (n=125). The primary endpoint was the investigator-assessed overall response rate.

The overall response rate was 85.7%, 76.5%, and 75.0% in patients treated with CAR T-cell therapy (n=7), allogeneic SCT (n=17), or non-covalent BTK inhibitors (n=43), respectively. In contrast, patients who received PI3K inhibitors (n=24) or CIT (n=23) achieved response rates of 40.9% and 31.8%, respectively. In addition, the median progression-free survival (PFS) was 3 months and 5 months in patients treated with CIT or PI3K inhibitors, whereas patients treated with allogeneic SCT achieved a median PFS of 11 months. The subset of patients that received non-covalent BTK inhibitors had not yet reached median PFS (see Table).

Table: Therapy responses [1]

Subsequent therapy	CAR-T	AlloSCT	ncBTKi	PI3Ki	CIT
Patients treated (n)	9	17	45	24	23
ORR	85.7%	76.5%	75.0%	40.9%	31.8%
Median PFS (months)	4	11	Not reached	5	3
Median follow-up (months)	3	6.5	9	4	2

AlloSCT, allogeneic stem cell transplantation; CAR T, chimeric antigen receptor T-cell therapy; CIT, chemo+/-immunotherapy; ncBTKi, non-covalent Bruton's tyrosine kinase inhibitor; ORR, overall response rate; PI3Ki, PI3K inhibitor.

The results showed that CIT or PI3K inhibitors yield poor outcomes compared with non-covalent BTK inhibitors, allogeneic SCT, or CAR T-cell therapy. Dr Thompson argued that the results suggest that the use of CIT and PI3K inhibitors is questionable in double-exposed patients with CLL and that treatment with allogeneic SCT or non-covalent BTK inhibitors should be considered in these patients. The administration of CAR T-cell therapy in this population should be further explored, according to Dr Thompson.

1. Thompson MC, et al. Addressing a New Challenge in Chronic Lymphocytic Leukemia: Outcomes of Therapies after Exposure to Both a Covalent Bruton's Tyrosine Kinase Inhibitor and Venetoclax. Abstract 2628, ASH 2021 Annual Meeting, 11–14 December.

Multiple Myeloma

GRIFFIN: Sustained responses of daratumumab plus RVd in MM

Patients with transplant-eligible, newly diagnosed multiple myeloma (MM) continued to benefit from daratumumab plus lenalidomide, bortezomib, and dexamethasone (RVd) after 24 months of maintenance therapy. New data from the phase 2 GRIFFIN trial showed sustained, deep responses in the study population [1].

In the phase 2 GRIFFIN trial (NCT02874742), patients with newly diagnosed MM, eligible for high-dose therapy and autologous haematopoietic cell transplantation (HCT) were randomised 1:1 to receive daratumumab plus RVd (n=104) or RVd alone (n=103). Patients were subjected to 4 cycles of high-dose daratumumab plus RVd or RVd alone, followed by autologous HCT and 2 consolidation cycles of daratumumab plus RVd or RVd alone. Subsequently, the patients received maintenance therapy of lenalidomide plus daratumumab or lenalidomide alone for 24 months. Dr Jacob Laubach (Dana-Farber Cancer Institute, MA, USA) presented the results after completion of maintenance therapy.

The primary analysis showed that patients receiving the daratumumab combination regimen had a numerically higher stringent complete response (sCR) rate after completion of consolidation therapy than patients who received RVd alone (42.4% vs 32.0%; P=0.068). After 24 months of maintenance therapy, the rate of sCR was 66.0% and 47.4% in patients receiving daratumumab plus RVd and RVd alone, respectively (P=0.0096). In addition, patients receiving the daratumumab combination regimen displayed a higher MRD-negativity rate than patients receiving RVd alone (64.4% vs 30.1%; P<0.0001). Median progression-free survival (PFS) was not reached after 38.6 months of follow-up, with a PFS rate of 88.9% in the daratumumab plus RVd arm and a PFS rate of 81.2% in the RVd alone arm. The safety analysis did not reveal new issues.

Dr Laubach argued that these updated results indicate that daratumumab plus RVd induction therapy followed by daratumumab consolidation and maintenance therapy is a promising regimen for patients with transplant-eligible, newly diagnosed MM.

1. Laubach JP, et al. Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients (Pts) with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin after 24 Months of Maintenance. Abstract 79, ASH 2021 Annual Meeting, 11–14 December.

MajesTEC-1: Teclistamab efficacious in heavily pre-treated MM

Teclistamab was safe and efficacious in patients with relapsed/refractory multiple myeloma (MM). The results of the phase 1/2 MajesTEC-1 trial showed durable and deepening responses in a triple-class exposed population. A phase 3 study, MajesTEC-3, is currently ongoing to further assess teclistamab in patients with MM [1].

Teclistamab is an off-the-shelf, T cell-directing antibody binding to CD3 on T cells and BCMA on plasma cells. The open-label, multicentre, phase 1/2 MajesTEC-1 trial (NCT04557098) included patients with relapsed/refractory MM who received at least 3 prior lines of therapy and were triple-class exposed (n=165). The patients were treated with 1.5 mg/kg teclistamab, subcutaneously administered once weekly. The primary endpoint was the overall response rate. Prof. Philippe Moreau (University Hospital of Nantes, France) presented the latest update of this trial.

At a median follow-up of 7.8 months, the overall response rate was 62.0%. In addition, 58% of the patients achieved a very good partial response or better, and 29% of the patients reached a complete response or better. The median time to first response was 1.2 months and the median time to best response was approximately 3 months. The results were consistent across subgroups, including older patients, patients with high-risk cytogenetics, and triple-class refractory patients. The 9-month event-free survival rate for responders was 85.9%. Prof. Moreau added that the responses were durable and tended to deepen over time.

Teclistamab was generally well tolerated, with no patients requiring dose reduction. The most common haematologic adverse events were neutropenia (65.5%), anaemia (49.7%), thrombocytopenia (38.2%), and lymphopenia (33.9%). Cytokine-release syndrome occurred in 71.5% of the patients; only 1 grade 3 case was reported, but this case resolved without treatment discontinuation. The grade 3 or 4 infection rate was 35.2%, which is not unexpected in this heavily pre-treated population. ICANS events were uncommon, all mild or moderate, and resolved without treatment discontinuation.

Prof. Moreau concluded that teclistamab showed an unprecedented response rate for a non-cellular therapy in triple-class-exposed patients with relapsed/refractory MM. The durable and deepening responses are encouraging. Multiple trials are currently running to further evaluate this novel agent.

1. Moreau P, et al. Updated Results from MajesTEC-1: Phase 1/2 Study of Teclistamab, a B-Cell Maturation Antigen x CD3 Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma. Abstract 896, ASH 2021 Annual Meeting, 11–14 December.

iStopMM: Smouldering MM highly prevalent in general population

A large, population-based study showed that smouldering multiple myeloma (MM) is highly prevalent in individuals 40 years or older. Approximately 1 out of 3 patients with

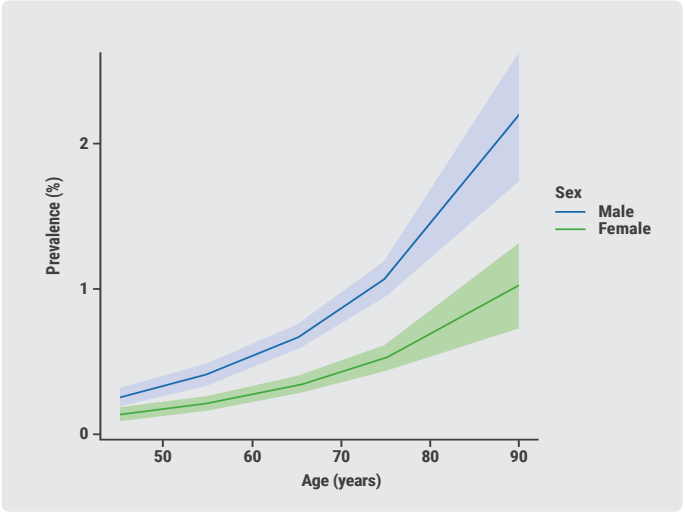
smouldering MM may progress towards MM. These results display a need to improve treatment policies and risk stratification in patients with smouldering MM [1].

Smouldering MM is an asymptomatic, preliminary condition of MM. Screening for smouldering MM is currently not recommended. Therefore, few patients with MM are diagnosed at the smouldering stage of the disease. Yet, evidence indicates that treatment initiation at the smouldering stage of MM may be beneficial for health outcomes [2,3].

Dr Sigrún Thorsteinsdóttir (University of Iceland, Iceland) and colleagues aimed to map the epidemiological and clinical characteristics of smouldering MM. The large, population-based iStopMM study (NCT03327597) screened 75,422 individuals for M-protein and abnormal free light chain ratio. In total, 3,725 participants displayed abnormal screening results and were randomised to 1 of 3 study arms: no further workup, guideline-recommended follow-up, or intensive follow-up.

Bone marrow sampling was performed in 1,503 participants, resulting in 180 diagnoses of smouldering MM (median age 70 years; 39% women). The most prevalent isotypes were IgG (57%), IgA (24%), and light chain (14%). The plasma cell burden was mostly low, with 73% of the participants showing plasma cell concentrations of 11–20%. The prevalence of smouldering MM in the total population was estimated at 0.53% in individuals 40 years or older, with increasing prevalence in older individuals (see Figure). The Mayo clinic 2018 risk stratification model for MM was used to classify participants into high risk (10%), intermediate risk (26%), or low risk (64%) of progression to MM.

Figure: Prevalence of smouldering MM according to age [1]



Dr Thorsteinsdóttir argued that treatment initiation at the smouldering MM stage may be included in the guidelines shortly. The high prevalence of smouldering MM in the general population showed the importance of better screening and risk management for this condition.

1. Thorsteinsdóttir S, et al. Prevalence of Smoldering Multiple Myeloma: Results from the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) Study. Abstract 151, ASH 2021 Annual Meeting, 11–14 December.
2. Mateos MV, et al. N Engl J Med 2013;369(5):438–447.
3. Lonial S, et al. J Clin Oncol. 2020;38(11):1126–1137.

Mechanisms of D-KRd treatment failure in MM identified

Genome-based mechanisms and bone marrow micro-environmental factors that drive treatment resistance in patients with multiple myeloma (MM) treated with daratumumab plus carfilzomib, lenalidomide, and dexamethasone (KRd) have been identified. These findings improve the understanding of treatment failure in this population, potentially adding to the development of improved therapies in the future [1].

Although treatment regimens including anti-CD38 antibodies have resulted in improved health outcomes for patients with MM, treatment resistance remains a substantial issue. The investigation of treatment failure in patients with MM can be done via single-cell microenvironmental analysis and genome-wide tumour genetics analysis.

Dr Eileen Boyle (NYU Langone Health, NY, USA) and her research team collected malignant plasma cells from bone marrow in patients with newly diagnosed MM treated with daratumumab plus KRd (n=46) or KRd alone (n=14) to perform whole-genome sequencing and single-cell RNA sequencing. MRD negativity, sustained MRD negativity, and progression of MRD negativity were the clinical endpoints.

After a median follow-up of 29 months, it was demonstrated that deletion of 13q, biallelic loss of *CYLD*, deletion of *XBP1*, deletion of 20q13.12, and 8q gains were linked to MRD positivity. Moreover, deletion of *RPL5*, *IKFZ3* structural variants, and multiple chromothripsis events were associated with disease progression. Furthermore, trisomy 21 was related to improved disease outcomes. These findings reveal novel genomic drivers associated with daratumumab plus KRd treatment failure in patients with MM.

The authors also reported that deletions of *XBP1* and 20q13.12 were associated with the loss of memory B cells, naïve B cells,

and dendritic cells in the bone marrow microenvironment. In addition, low levels of plasmacytoid dendritic cells at baseline were linked to worse disease outcomes. Also, gains in 6p24 were related to a decreased number of CD8 effectors 1 and 2. These results indicate that specific genomic lesions lead to particular changes in the bone marrow microenvironment.

Finally, a significant difference between MRD-positive and MRD-negative patients was observed regarding the depletion of natural killer cells, and naïve and memory B cells throughout the therapy. Moreover, MRD-negative patients had more CD14-positive monocytes at baseline and after induction therapy. These findings indicate that inflammatory response genes, such as IL-1B, are upregulated in MRD-positive patients and that IL-2, IL-6, and IFNα responses and adipocyte differentiation are linked to (sustained) MRD negativity.

1. Boyle E, et al. Genomic and Immune Signatures Predict Sustained MRD Negativity in Newly Diagnosed Multiple Myeloma Patients Treated with Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone (D-KRd). Abstract 325, ASH 2021 Annual Meeting, 11–14 December.

TRIMM-2: Favourable results of talquetamab plus daratumumab for MM

Talquetamab plus daratumumab demonstrated durable and deep responses in heavily pre-treated patients with refractory multiple myeloma (MM) in the phase 1b TRIMM-2 trial. The combination regimen was tolerable and did not show overlapping toxicity. This novel dual therapy is therefore a promising option for the treatment of patients with MM [1].

Daratumumab is a human monoclonal antibody targeting CD38, and talquetamab is a first-in-class T cell-redirecting antibody, targeting GPRC5D and CD3 receptors, explained Dr Ajai Chari (Mount Sinai School of Medicine, NY, USA). The multicentre, open-label, phase 1b TRIMM-2 trial (NCT04108195) investigated the safety and efficacy of a combination regimen of daratumumab (subcutaneous, as per label) plus talquetamab (subcutaneous, in 3 possible regimens: 400 µg/kg, every 2 weeks; 400 µg/kg, every week; or 800 µg/kg, every 2 weeks). In total, 29 heavily pre-treated patients were included in the study. A high proportion of patients received prior anti-BCMA therapy (55.2%) or were classified as anti-CD38 refractory (65.5%) or triple-class refractory (51.7%).

After a median follow-up period of 4.2 months, the overall response rate for the combination regimen of talquetamab plus daratumumab was between 77.8% and 85.7%, depending on the administered talquetamab dose. Moreover, the response to therapy was durable and deep in a significant proportion of the patients: between 11.1% and 28.6% of the patients displayed a complete response and 40.0% to 55.6% of the population demonstrated a very good partial response.

The combination regimen was tolerable and no new safety issues were reported. In addition, no overlapping toxicities were observed. Any grade neutropenia or thrombocytopenia occurred in 41.4% and 34.5% of the patients, respectively. These events resolved in most patients. One patient discontinued due to a haematologic adverse event (AE). Cytokine release syndrome (55.2%, all grade 1 or 2), dysgeusia, and skin-related disorders were the most common non-haematologic AEs. Infections were reported in 10 patients, 3 of which were classified as grade 3 or higher.

The results of this phase 1b trial indicate that the novel immunotherapy-based approach of talquetamab plus daratumumab is promising for the treatment of MM.

1. Chari A, et al. Phase 1b Results for Subcutaneous Talquetamab Plus Daratumumab in Patients with Relapsed/Refractory Multiple Myeloma. Abstract 161, ASH 2021 Annual Meeting, 11–14 December.

Lymphoma

Second-line tisa-cel similar to standard-of-care for R/R aggressive non-Hodgkin lymphoma

The chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel (tisa-cel) as second-line treatment did not improve event-free survival (EFS) of patients with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma compared with standard-of-care [1]. These results of the phase 3 BELINDA study contradicts previous CAR T-cell therapy trials that have shown improved clinical outcomes.

Tisa-cel, an autologous CAR T-cell therapy targeting CD19, is approved for patients with diffuse large B-cell lymphoma (DLBCL) after ≥2 lines of therapy [2,3]. Dr Michael Bishop (University of Chicago, IL, USA) presented the results of the BELINDA trial (NCT03570892), which enrolled 322 adults with confirmed R/R aggressive non-Hodgkin lymphoma within 12 months after first-line chemo-immunotherapy. All patients underwent leukapheresis for tisa-cel production and were randomised 1:1 to receive tisa-cel (arm A) or standard-of-care (arm B). Patients in arm A could receive bridging therapy, defined as an investigator choice of protocol-defined platinum-based chemotherapy, followed by lymphodepletion and a single tisa-cel infusion. Responders in arm B received investigator choice of platinum-based chemotherapy regimen followed by autologous haematopoietic cell transplantation in responders, and non-responders received a second platinum-based chemotherapy. The primary endpoint was EFS, defined as death at any time or progressive or stable disease at or after 12 weeks.

The median EFS was 3 months in both arms (HR 1.07; 95% CI 0.82–1.40; P=0.69). At week 12, the overall response rate (ORR) was 46% in arm A versus 43% in arm B. The complete response rate was 28% in both arms. A higher proportion of patients had progressive disease at week 6, prior to CAR T-cell infusion, in the tisa-cel arm.

"Our findings suggest the importance of preventing progressive disease prior to CAR T-cell infusion," Dr Bishop concluded. Moreover, effective bridging prior to CAR T-cell infusion and a shorter time to infusion for this chemotherapy-refractory patient population could be critical to improving outcomes.

1. Bishop MR. Tisagenlecleucel Vs Standard of Care As Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III Belinda Study. LBA-6, ASH 2021 Annual Meeting, 11–14 December.
2. Maude SL, et al. N Engl J Med 2018;378:439–448.
3. Schuster SJ, et al. N Engl J Med 2019;380:45–56.

Axi-cel improved event-free survival in R/R DLBCL

ZUMA-7 is the first randomised CAR T-cell trial in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). After a median follow-up of 24.9 months, the study met its primary endpoint of event-free survival (EFS), demonstrating a statistically significant and clinically meaningful improvement with axicabtagene ciloleucel (axi-cel) compared with second-line standard-of-care [1,2].

Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of patients with R/R DLBCL after ≥2 prior systemic therapies. Since CAR T-cell therapy may benefit patients in earlier lines of therapy, Dr Frederick Locke (Moffitt Cancer Cancer, FL, USA) and others conducted ZUMA-7 (NCT03391466), a global, randomised, open-label, phase 3 trial of axi-cel versus standard-of-care in patients with second-line R/R LBCL (n=359). Dr Locke reported the results of the primary analysis.

The primary endpoint of EFS, a composite of time to earliest date of disease progression, death from any cause, or new lymphoma therapy, was met (HR 0.40; 95% CI 0.31–0.51, P<0.0001). After a median follow-up of 24.9 months, median EFS was significantly longer with axi-cel versus standard-of-care (8.3 vs 2 months). Importantly, Kaplan-Meier estimates of the 24-months EFS rates were significantly higher with axi-cel (40.5% vs 16.3%). "This means that patients who receive either axi-cel or the standard-of-care remain in remission for 2 years after randomisation, without the need for any further therapy," Dr Locke added.

In conclusion, axi-cel showed superiority over standard-of-care with a more than 4-fold greater median EFS, a 2.5-fold greater EFS at 2 years, and EFS improvements across key subgroups. The safety profile of axi-cel was manageable and at least consistent with third-line treatment with axi-cel in patients with R/R LBCL.

1. Locke FL, et al. Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma. Abstract 2, ASH 2021 Annual Meeting, 11–14 December.
2. Locke FL, et al. N Engl J Med 2021;11 Dec. DOI: 10.1056/NEJMoa2116133.

Axi-cel more effective but tisa-cel less toxic in DLBCL

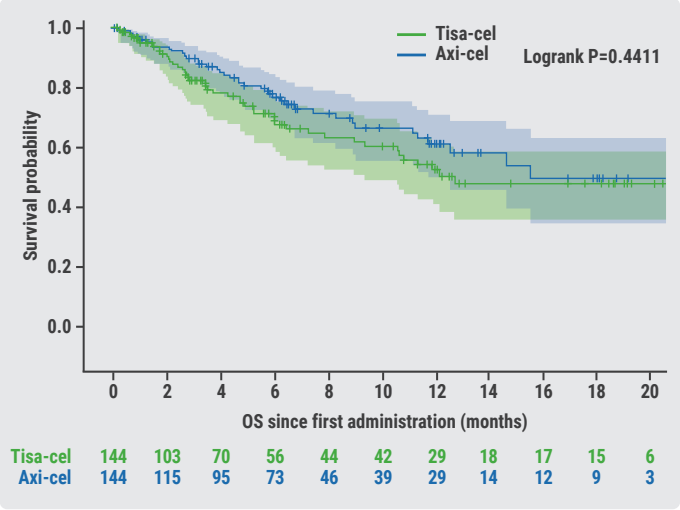
In a matched set population of patients with diffuse large B-cell lymphoma (DLBCL) who had received ≥2 lines of treatment, axicabtagene ciloleucel (axi-cel) resulted in a significantly prolonged progression-free survival (PFS) compared with tisagenlecleucel (tisa-cel). However, axi-cel was associated with significantly more frequent grade ≥3 neurotoxicity compared with tisa-cel. These results could help refine specific patient sub-populations who benefit most from each type of CAR T-cell therapy.

Axi-cel and tisa-cel are autologous anti-CD19 CAR T-cell therapies approved in the US and EU for adults with relapsed/refractory (R/R) DLBCL after ≥2 lines of systemic therapy. Dr Emmanuel Bachy (Hospices Civils de Lyon, France) and others conducted a propensity score-matched comparison of axi-cel and tisa-cel in a large cohort of R/R DLBCL patients

treated outside of clinical trials. After a 1:1 ratio propensity score-matching, therapy outcomes were compared between 144 patients treated with axi-cel and 144 patients treated with tisa-cel. The primary endpoint was overall survival (OS).

After a median follow-up of 6.6 months, OS was not significantly different between axi-cel and tisa-cel at 6 months (78% vs 70% respectively; P=0.44; see Figure). Best overall and complete response rates were significantly higher with axi-cel compared with tisa-cel (73% vs 60%; P=0.02; and 56% vs 36%; P<0.001, respectively). At 6 months, PFS was significantly longer with axi-cel than with tisa-cel (53% vs 32%; P=0.011).

Figure: Overall survival with tisa-cel versus axi-cel [1]



Axi-cel, axicabtagene ciloleucel; OS, overall survival; tisa-cel, tisagenlecleucel.

With respect to the toxicity profile, there was no significant difference in the incidence of cytokine release syndrome (CRS), but axi-cel was associated with significantly more frequent neurotoxicity (ICANS) compared with tisa-cel, namely:

- 30.6% vs 18.1% for grade 1–2 ICANS; and
- 10.4% vs 2.1% for grade ≥3 ICANS (P<0.001).

After stringent propensity score-matching on a large patient population treated with CAR T-cell therapy, axi-cel resulted in higher response rates and significantly prolonged PFS compared with tisa-cel. However, greater efficacy came at the cost of higher neurotoxicity with axi-cel.

1. Bachy E, et al. A Propensity Score-Matched Comparison of Axi-Cel and Tisa-Cel for Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Real-Life: A Lysa Study from the Descar-T Registry. Abstract 92, ASH 2021 Annual Meeting, 11–14 December.

POLARIX: Novel regimen superior to R-CHOP in DLBCL

Polatuzumab vedotin added to rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) outperformed the standard-of-care regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as initial treatment in patients with diffuse large B-cell lymphoma (DLBCL). The safety profiles of the 2 regimens were comparable [1].

Prof. Hervé Tilly (University of Rouen, France) explained that R-CHOP, the standard-of-care regimen for patients with DLBCL, is effective in 60–70% of patients with this condition. In the last 20 years, adaptations to the R-CHOP treatment regimen have not succeeded in meeting the unmet need in this population.

The current, randomised, double-blind, phase 3 POLARIX trial (NCT03274492) added polatuzumab vedotin, an antibody drug conjugate targeting CD79b, to rituximab, cyclophosphamide, doxorubicin, and prednisone. Patients with previously untreated DLBCL (n=879) were randomised 1:1 to 6 cycles of Pola-R-CHP (with 1.8 mg/kg IV polatuzumab vedotin on day 1 of a 21-day cycle) or R-CHOP. The primary endpoint was progression-free survival.

After a median follow-up of 28 months, the Pola-R-CHP regimen showed superiority over the R-CHOP regimen regarding progression-free survival (HR 0.73; P<0.02). Similarly, patients in the Pola-R-CHP arm displayed higher event-free survival rates than patients in the R-CHOP arm (HR 0.75; P=0.02). Although overall response rates did not significantly differ between treatment groups, disease-free survival rates (HR 0.70) indicated that patients who achieved a complete response in the Pola-R-CHP arm were more likely to maintain remission than patients in the R-CHOP arm who reached a complete response. The overall survival rates were 88.6% in both groups. Notably, patients treated with Pola-R-CHP received fewer subsequent therapies (22.5%) than patients treated with R-CHOP (30.3%). Exploratory subgroup analyses are ongoing to further specify the results of the POLARIX trial.

The safety profiles of the 2 regimens were comparable, with approximately 57% of the patients in both treatment groups experiencing grade 3 or 4 adverse events (AEs). Although febrile neutropenia and diarrhoea were more common in the Pola-R-CHP condition, treatment with Pola-R-CHP led to

fewer dose reductions (9.2%) than treatment with R-CHOP (13.2%). The prevalence of peripheral neuropathy was similar in both research arms.

1. Tilly H, et al. The POLARIX Study: Polatuzumab Vedotin with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma. LBA-1, ASH 2021 Annual Meeting, 11–14 December.

Novel non-invasive biomarker ctDNA shows value in CNS lymphoma

Circulating tumour DNA (ctDNA) was associated with progression-free survival (PFS) and overall survival (OS) in patients with central nervous system (CNS) lymphoma. Moreover, the ultrasensitive and robust detection of ctDNA in patients with different disease severity suggested accurate reflection of tumour burden, thereby supporting the potential of this biomarker as a decision-making tool in clinical practice [1].

Selecting patients at high risk for treatment failure is an unmet need in the management of patients with CNS lymphoma. Moreover, the invasive neurosurgical methods that are currently used for the diagnosis of this disease carry risks and require an adequate fitness level of the patient. ctDNA is a promising, non-invasive biomarker for patients with systemic lymphoma. Dr Jurik Mutter (University Medical Center Freiburg, Germany) and colleagues assessed the potential of ctDNA in CNS lymphoma through Cancer Personalised Profiling by Deep Sequencing (CAPP-Seq) and Phased Variant Enrichment and Detection Sequencing (PhasED-Seq).

In total, 794 distinct genetic regions were analysed, originating from plasma samples, tumour biopsies, and cerebrospinal fluid (CSF) specimens from 92 patients with CNS lymphoma and 44 patients with other brain cancers or inflammatory cerebral diseases. Radiological measures of tumour burden were correlated with ctDNA concentrations. Also, ctDNA concentrations were assessed for their link to clinical outcomes.

The results showed that concentrations of ctDNA were significantly correlated to MRI measures of tumour volumes ($r=0.53$; $P<0.0001$). Moreover, a positive pre-treatment ctDNA status was predictive of worse PFS (HR 4.6; $P<0.0001$) and OS (HR 6.1; $P=0.002$). Similarly, ctDNA positivity during induction therapy was related to worse PFS (HR 6.2; $P=0.0002$) and OS ($P=0.004$) outcomes. Furthermore, a novel machine learning classifier analysed 207 specimens of patients with and without CNS lymphoma. The research team observed a specificity of 100% and a sensitivity of 57% for CSF samples in diagnosing CNS lymphoma through ctDNA measures, reflecting that a substantial proportion of patients may avoid invasive diagnostic procedures.

The authors argued that ctDNA may be an important decision-making tool in the management of patients with CNS lymphoma in the future.

1. Mutter JA, et al. Profiling of Circulating Tumor DNA for Noninvasive Disease Detection, Risk Stratification, and MRD Monitoring in Patients with CNS Lymphoma. Abstract 6, ASH 2021 Annual Meeting, 11–14 December.

Myeloproliferative Neoplasms

Mechanisms behind *TP53* mutations revealed in myeloproliferative neoplasms

A single-cell, multi-omics analysis into the mechanisms behind *TP53*-mediated transformation of haematological malignancies towards acute leukaemia revealed novel aspects of the genetic, cellular, and molecular changes that occur during this transformation. Since *TP53* mutations are common, these results may have relevance for other cancer types [1].

Multi-hit *TP53* mutations are associated with treatment resistance and a worse prognosis in myeloid malignancies. Therefore, Dr Alba Rodriguez-Meira (University of Oxford, UK) and colleagues aimed to unravel the biological basis of *TP53*-mediated transformation of haematological malignancies. Since myeloproliferative neoplasms (MPN) frequently progress towards secondary acute myeloid leukaemia (AML) due to *TP53* missense mutations, the team performed single-cell, multi-omic TARGET-seq analysis of haematopoietic

stem and progenitor cells (HSPCs) (n=22,116) in 26 patients with MPN in different stages of the disease, at 40 timepoints. In addition, 9 healthy controls were included in the analysis.

The clonal evolution during the transformational process of the disease was characterised by a loss of *TP53* wildtype alleles and the evolution of *TP53* multi-hit subclones. Moreover, *TP53* multi-hit HSPCs were driven by chromosomal abnormalities. These results indicate that cytogenetic evolution, loss of *TP53* wildtype alleles, and *TP53* missense mutations are collectively responsible for leukaemic stem cell (LSC) expansion.

Three major *TP53*-mutant clusters were identified, displaying an erythroid signature, an LSC signature, and a haematopoietic stem cell (HSC) signature, respectively. Notably, the authors detected dysregulation of key stem cell regulators in the LSC cluster, from which they developed a 48-gene LSC score. A high LSC score was predictive of a worse survival probability (HR 3.13), regardless of TP53 status or disease stage, indicating a broader clinical applicability.

Furthermore, the authors identified *TP53* wildtype pre-leukaemic cells in the HSC compartment. The observed increased stemness and quiescence, abnormal inflammatory signalling, and differentiation defects of these cells, compared with MPN and control participants, suggests that cell-extrinsic haematopoietic suppression of residual *TP53* wildtype is a distinctive process in disease transformation.

Finally, the authors showed that, next to the presence of *TP53* mutations, abnormal inflammatory signalling in the genetic ancestors of *TP53* multi-hit LSCs was predictive of disease transformation: pro-inflammatory stimuli were associated with a 3-fold competitive advantage of *TP53*-mutant cells.

1. Rodriguez-Meira A, et al. Single-Cell Multi-Omics Reveals the Genetic, Cellular and Molecular Landscape of TP53 Mutated Leukemic Transformation in MPN. Abstract 3, ASH 2021 Annual Meeting, 11–14 December.

JAK2V617F variant allele frequency prognostic of venous events in polycythaemia vera

***JAK2V617F* variant allele frequency (VAF) >50% was associated with an increased risk of venous thrombosis in patients with polycythaemia vera (PV). This independent predictor distinguished between patients who were classified as low-risk patients by classical risk modelling, demonstrating that conventional risk assessment may not be sufficient to tailor treatment regarding the prevention of venous thrombosis in patients with PV [1].**

"Most patients with PV show a *JAK2* mutation in exon 14 (*JAK2V617F*), and at diagnosis, the *JAK2V617F* VAF is highly heterogeneous in these patients," said Dr Giuseppe Loscocco (University of Florence, Italy). "In addition, patients with PV have an increased risk of thrombosis." Therefore, the current study aimed to evaluate the association between *JAK2V617F* VAF at diagnosis and the rate of arterial and venous thrombosis. In total, 865 cases were analysed.

JAK2V617F VAF was significantly associated with the risk of venous thrombosis (P=0.003) but not with arterial thrombosis (P=0.8). A ROC curve analysis determined that 50% VAF was the most accurate cut-off value to predict venous thrombosis in these patients. In addition, patients with a VAF >50% demonstrated higher white blood cells count (P=0.02), higher haematocrit and haemoglobin levels (P<0.0001), and a lower platelet count (P=0.0009). Multivariable analysis confirmed that VAF >50% (HR 3.8) and previous thrombosis (HR 2.2) were independent risk factors for subsequent venous thrombosis. In contrast, diabetes (HR 2.4), hyperlipidaemia (HR 2.3), and previous arterial events (HR 2.1) were significant predictors of future arterial thrombosis.

These results indicate that the risk factors for arterial and venous events are different and that these entities require separate management strategies. Notably, patients classified as low-risk patients for future venous thrombosis events by age and history of thrombotic events could be distinguished via *JAK2V617F* VAF values for their risk of future venous events. Therefore, conventional risk stratification by age and previous venous events may not be accurate enough to separate high-risk and low-risk patients. Dr Loscocco mentioned that future investigations should elucidate whether *JAK2V617F* VAF values >50% are useful to reclassify low-risk patients to high-risk patients.

1. Loscocco GG, et al. A JAK2V617F Variant Allele Frequency Greater Than 50% Identifies Patients with Polycythemia Vera at High Risk for Venous Thrombosis. Abstract 237, ASH 2021 Annual Meeting, 11–14 December.

Immune Thrombocytopenia

Promising results of tacrolimus plus dexamethasone for ITP

In the phase 2 TARGET 020 trial, the combination regimen of low-dose tacrolimus plus high-dose dexamethasone provided benefits over high-dose dexamethasone monotherapy in patients with immune thrombocytopenia (ITP). Both the initial response rates and the sustained response rates were significantly higher in the combination therapy arm. Thus, low-dose tacrolimus plus high-dose dexamethasone could be a promising first-line treatment for patients with ITP [1].

Dr Zhuo-Yu An (Peking University People's Hospital, China) explained that approximately 30% of adult patients with ITP relapses in the first 6 months after the initiation of a first-line therapy. Therefore, first-line therapies that demonstrate long-term effectiveness are needed for patients with this condition. The prospective, multicentre, open-label, randomised, phase 2 TARGET 020 trial (NCT04747080) compared high-dose dexamethasone (40 mg, 4 consecutive days with possible repetition after 14 days) (n=56) with high-dose dexamethasone plus low-dose tacrolimus (3–5 ng/mL, 4 consecutive days with possible repetition after 14 days) (n=48). The rationale for the combination regimen was a dual-target strategy, with dexamethasone targeting abnormal B cells and antibodies to counter increased platelet destruction, and tacrolimus targeting hyperactivated T cells to reduce the impaired maturation of megakaryocytes. In this way, both increased platelet destruction and decreased platelet production may be tackled, argued Dr An. The primary outcome was sustained response at 6 months, defined as a platelet count ≥30x10^9/L (partial remission) or ≥100x10^9/L (complete remission), a 2-fold increase of baseline platelets, and no use of rescue medication at follow-up.

The initial response rate was higher in the combination regimen arm than in the monotherapy arm (77% vs 55%). In addition, patients treated with the combination therapy showed fewer relapses than patients treated with dexamethasone monotherapy (19% vs 29%). After 6 months, the sustained response rates were higher in the low-dose tacrolimus plus high-dose dexamethasone treatment group (64.6%) than in the high-dose dexamethasone monotherapy group (64.6% vs 41.1). There was no statistically significant difference in incidence of serious adverse events (SAEs) and treatment-related AEs between both treatment regimens. Treatment was well tolerated, with no patients displaying grade 3 or higher AEs.

The results demonstrate that low-dose tacrolimus plus high-dose dexamethasone could be a promising first-line treatment regimen for patients with ITP. However, larger randomised trials are needed to validate the results of the current phase 2 trial.

1. An ZY, et al. Tacrolimus Plus High-Dose Dexamethasone Versus High-Dose Dexamethasone Alone As First-Line Treatment for Adult Immune Thrombocytopenia: The Phase 2, Open Label, Randomized Trial (TARGET 020). Abstract 13, ASH 2021 Annual Meeting, 11–14 December.

Sustained remission after TPO-RA discontinuation in chronic ITP

High rates of sustained remission were achieved in patients with chronic primary immune thrombocytopenia (ITP) who discontinued thrombopoietin-receptor agonist (TPO-RA) therapy after achieving a complete response (CR). The results of the STOPAGO study support progressive dose reductions of TPO-RAs in patients who achieved a stable CR on this treatment [1].

A recent prospective study observed durable remissions in approximately 30% of the patients with ITP after TPO-RAs discontinuation [2]. However, the study population included patients with newly diagnosed ITP, in whom spontaneous remission may occur. Therefore, Prof. Matthieu Mahevas (Hôpital Henri-Mondor, France) and colleagues conducted the prospective, multicentre, interventional STOPAGO study (NCT03119974) to assess the proportion of patients with chronic or persistent ITP that display sustained remission after TPO-RA therapy discontinuation. Participants (n=49) received TPO-RA therapy (eltrombopag, n=40; romiplostim, n=9) for at least 3 months. Subsequently, a tapering protocol of 25 mg per 2 weeks or 1 µg/kg per week was initiated, until TPO-RAs were discontinued completely at week 10. The primary endpoint was the overall response at 24 weeks after treatment discontinuation.

At 24 weeks, the primary endpoint was reached for 56.2% of the participants. CR was achieved in 55.0% of the responders or 31.3% of the intention-to-treat population. After 52 weeks, the overall response rate of treatment discontinuation was 52.1%, with 56% of the responders achieving a CR. At week 24, bleeding events were reported in 61.9% of the patients who relapsed. However, no severe bleedings were reported. Notably, the median time of relapse after the initiation of the tapering protocol was 8 weeks. Few relapses occurred after these first 2 months.

Prof. Mahevas argued that the sustained remission rate among patients with chronic ITP who achieved a stable CR on TPO-RAs was unexpectedly high. He also emphasised that no severe bleedings occurred in the study population. Further studies should investigate the underlying mechanism of sustained remission to select eligible patients for a TPO-RA discontinuation strategy.

1. Mahevas M, et al. Rate of Prolonged Response after Stopping Thrombopoietin-Receptor Agonists Treatment in Primary Immune Thrombocytopenia (ITP): Results from a Nationwide Prospective Multicenter Interventional Study (STOPAGO). Abstract 583, ASH 2021 Annual Meeting, 11–14 December.
2. Lucchini E, et al. British Journal of Haematology. 2021;193(2):386–396.

Haemophilia

Fitusiran meets primary endpoint in ATLAS-A/B trial

Fitusiran prophylactic therapy reduced the annual bleeding rate in patients with severe haemophilia A or B without inhibitors in a phase 3 trial. An increase in quality of life was associated with fitusiran therapy. Moreover, fitusiran offers a reduced treatment burden compared with factor replacement therapy [1].

"Approximately 70% of patients with haemophilia do not have access to factor replacement therapy," said Dr Alok Srivastava (Christian Medical College Vellore, India). "In addition, this treatment needs to be administered intravenously, multiple times per week, placing a heavy treatment burden on our patients. New therapeutic options are needed to reduce bleeding and treatment burden, and increase the quality of life for patients with haemophilia."

The phase 3 ATLAS-A/B trial (NCT03417245) included 120 patients with severe haemophilia A or B without inhibitors. Patients were randomised 2:1 to receive fitusiran, a small interference RNA agent targeting antithrombin (80 mg, subcutaneous, once monthly), or on-demand factor concentrates. The primary endpoint was the annual bleeding rate after 9 months.

The median annual bleeding rate was 0.0 in the fitusiran arm versus 21.8 in the on-demand arm (P<0.0001). For patients with haemophilia A or B treated with fitusiran, median annual bleeding rates were 0.0 and 2.7, respectively. In addition, 50.6% of the patients in the fitusiran arm did not display any treated bleedings during the study.

The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) showed a reduction of 9.68 in total score and 23.07 in physical health score for patients treated with fitusiran, representing a clinically meaningful improvement in quality of life.

The safety analysis did not reveal unexpected safety issues. Treatment-emergent adverse events (AEs) were reported in 78.5% of the fitusiran receivers and in 45.0% of the patients in the on-demand arm. Most treatment-emergent AEs were mild, moderate, and reversible. In the fitusiran arm, 6.3% of the patients experienced a serious treatment-emergent AE, compared with 12.5% of the patients in the on-demand arm. The most prevalent treatment-emergent AE of special interest was an increased level of alanine aminotransferase, which was reported in 15.2% of the fitusiran receivers. No thrombotic events were observed.

Dr Srivastava concluded that fitusiran is an effective prophylactic therapy for patients with haemophilia A or B without inhibitors. The reduced dose frequency and subcutaneous administration of fitusiran resulted in a decreased treatment burden compared with patients who are treated with factor replacement therapy.

1. Srivastava A, et al. Fitusiran, an Investigational siRNA Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: First Results from a Phase 3 Study to Evaluate Efficacy and Safety in People with Hemophilia a or B without Inhibitors (ATLAS-A/B). LBA-3, ASH 2021 Annual Meeting, 11–14 December.

rFVIIIFc establishes rapid tolerisation in haemophilia A with inhibitors

Recombinant factor VIII Fc protein (rFVIIIFc) therapy realised immune tolerance in approximately 2 out of 3 patients with severe haemophilia A and high-titre inhibitors who underwent immune tolerance induction (ITI) therapy for the first time. In addition, the agent displayed a swift time to tolerisation and no relapses occurred. These results add to the optimisation of ITI therapy with the purpose of eradicating inhibitors in these patients [1].

The international immune tolerance study (NCT00212472) showed that 40% of patients with severe haemophilia with inhibitors in the intent-to-treat population achieved immune tolerance, in a median time of approximately 22 months after rFVIIIFc treatment initiation. However, recent retrospective evidence suggested a higher success rate and rapid tolerisation in patients who underwent ITI therapy for the first time [2].

The current, global, prospective, verITI-8 study (NCT03093480) included 16 patients with severe haemophilia with inhibitors to administer first-time ITI therapy. The patients received rFVIIIFc therapy (200 IU/kg/day) for up to 48 weeks. If tolerisation was achieved within this timeframe, the patients entered a 16-week tapering period and a 32-week follow-up period. The primary endpoint was time to tolerisation. Treatment success was defined as negative Bethesda titres plus normal recovery (incremental recovery ≥66%) on 2 consecutive visits and rFVIIIFc half-life ≥7 hours. Dr Lynn Malec (Versiti Blood Research Institute, WI, USA) presented the final results.

Tolerisation was achieved in 63% of the patients in a median time of 11.7 weeks. In addition, the median time to the first negative inhibitor titre was 7.4 weeks, and the median time to normal recovery was 6.8 weeks (see Table). No relapses were observed in the patients who achieved tolerisation. Bypassing agents aPCC and rFVIIa were consumed by 25% and 31.3% of the patients during the ITI period, respectively. The median annual bleeding rates were 3.8 during the ITI period and 0.0 during the tapering and follow-up periods.

Table: Time to treatment success criteria [1]

Time to endpoint	n (%)	Median weeks from start of ITI
Negative inhibitor titer	12 (75)	7.4 (2.2–17.8)
IR ≥66%	11 (69)	6.8 (5.4–22.4)
$t_{1/2}$ ≥7h	10 (63)	11.7 (9.8–26.5)

IR, incremental recovery; ITI, immune tolerance induction.

In total, 9 patients experienced at least 1 serious treatment-emergent adverse event (AE). However, none of these events was considered to be related to treatment. The serious treatment-emergent AEs included vascular device infections, contusions, and haemarthrosis. Importantly, no thrombotic events were reported.

1. Malec L, et al. Efficacy of rFVIIIFc for First-Time Immune Tolerance Induction (ITI) Therapy: Final Results from the Global, Prospective VerITI-8 Study. LBA-5, ASH 2021 Annual Meeting, 11–14 December.
2. Carcao M, et al. Haemophilia. 2021;27(1):19–25.

ATLAS-INH: Impressive results of fitusiran for haemophilia with inhibitors

Treatment with fitusiran prophylaxis led to a lower rate of bleeding events and an improved health-related quality of life in patients with haemophilia A or B with inhibitors. The observed safety profile of fitusiran in the phase 3 ATLAS-INH trial was favourable and consistent with previous phase 1 and 2 studies in patients with severe haemophilia [1].

"Patients with severe haemophilia can develop inhibitors against factor VIII or IX, preventing factor replacement therapy from working," said Dr Guy Young (University of Southern California, CA, USA). "A quarter of patients develops these inhibitors, leading to a worse prognosis. Novel agents are needed to protect these patients from bleeding events and arthropathy, and improve their quality of life. In addition, the current IV therapies need to be administered multiple times per week, resulting in venous access issues and poor adherence." Fitusiran is an investigational, subcutaneous, small interference RNA therapeutic targeting antithrombin. In the phase 3 ATLAS-INH trial (NCT03417102), patients with haemophilia A or B with inhibitors were randomised 2:1 to fitusiran therapy (80 mg, subcutaneous, once monthly; n=38) or on-demand bypassing agents (BPA; n=19). The primary endpoint was the annual bleeding rate after 9 months.

The median annual bleeding rate for patients in the fitusiran arm was 0.0, compared with 16.8 in the BPA on-demand arm. In addition, 65.8% of the patients treated with fitusiran displayed no bleeding events during the study. In the BPA on-demand group, only 5% of the patients had no bleeding events. The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) demonstrated a meaningful improvement in total score in patients treated with fitusiran (mean change -15.27), whereas patients in the BPA on-demand group did not show improvement in quality of life (mean change -0.42).

The safety analysis did not reveal new risks associated with fitusiran therapy. There were 11 patients with observed treatment-emergent adverse events (AEs) of special interest in the fitusiran group and 0 in the BPA on-demand group. The treatment-emergent AEs of special interest included 11 cases of mildly to moderately increased transaminases and 2 thromboembolic events. One patient in the fitusiran arm discontinued the study.

In conclusion, fitusiran was safe and efficacious in patients with severe haemophilia with inhibitors, demonstrating strongly reduced bleeding rates and improved quality of life scores in these patients.

1. Young G, et al. Efficacy and Safety of Fitusiran Prophylaxis, an siRNA Therapeutic, in a Multicenter Phase 3 Study (ATLAS-INH) in People with Hemophilia A or B, with Inhibitors (PwHI). Abstract 4, ASH 2021 Annual Meeting, 11–14 December.

Clonal Haematopoiesis

Reduced risk of Alzheimer's disease in CHIP carriers

Clonal haematopoiesis of indeterminate potential (CHIP) was associated with decreased risk of Alzheimer's disease (AD) and AD neuropathological changes. Mutated haematopoietic stem cells were detected in the brains of CHIP carriers. These mutated cells supplemented the microglial pool in ageing individuals, potentially reducing the risk of AD via improved amyloid and tau clearance [1].

"CHIP has been associated with haematologic malignancies, atherosclerosis, and increased mortality," explained Dr Hind Bouzid (Stanford University, CA, USA). The current study investigated the relation between CHIP and neurodegenerative disease via a longitudinal cohort study, a case-control study, a mendelian randomisation, and a brain pathology assessment.

The longitudinal cohort study included 3,180 patients, including 258 patients with confirmed AD, and assessed the relation between AD and CHIP. The analysis demonstrated that CHIP carriers had a reduced risk of AD compared with non-carriers (sub-distribution HR 0.62; P=0.021).

This association was subsequently assessed in a case-control study, including 1,104 patients with confirmed AD and 1,446 control participants. CHIP carriers were linked to a reduced risk of AD (OR 0.66; P<0.001), confirming the results of the longitudinal cohort study.

Next, a Mendelian randomisation was performed to evaluate the relation between the genetic causality of CHIP and the risk of AD. Three independent loci for risk of CHIP from a prior CHIP genetic association study (GAS) were used as variables for CHIP exposure [2]. This analysis found that an increased genetic risk of developing CHIP was linked to a reduced risk of AD (OR 0.92; P=0.006). Notably, the association of CHIP and a reduced risk of AD was observed in individuals with *APOE* ε3 or ε4 alleles but not in individuals with *APOE* ε2 alleles.

Hereafter, Dr Bouzid conducted a brain pathology study to assess whether CHIP influenced AD pathologic features. It was found that CHIP carriers displayed lower levels of amyloid and tau pathology, assessed via CERAD scores (OR 0.50; P=0.003) and Braak scores (OR 0.56; P=0.015), respectively.

Dr Bouzid also found that mutant haematopoietic stem cells infiltrate the brain of CHIP carriers and resemble microglial tissue. Furthermore, these mutant cells replaced endogenous microglia in the ageing brain, suggesting a support function of CHIP in the failing microglial system of older individuals.

1. Bouzid H. Clonal Hematopoiesis is Associated with Reduced Risk of Alzheimer's Disease. Abstract 5, ASH 2021 Annual Meeting, 11–14 December.
2. Bick AG, et al. Nature. 2020;586:763-768.

Lifelong patterns of clonal haematopoiesis revealed

A study into the natural history of clonal haematopoiesis revealed that different gene mutations drive different patterns of lifelong clonal behaviour, with *DNMT3A*, *TET2*, and spliced mutant clones being the most common drivers. Moreover, the share of oligoclonal clones increases with age. The current characterisation

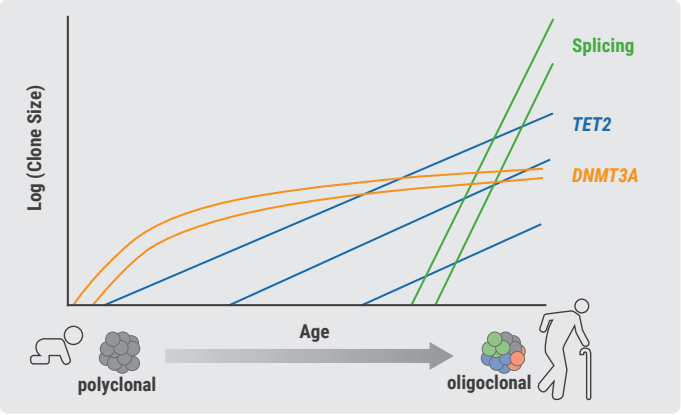
of lifelong natural clonal haematopoiesis offers insights into the interaction between somatic mutations, ageing, and clonal selection [1].

"In normal haematopoiesis, stem cells are homogenous, whereas in clonal haematopoiesis stem cells are genetically diverse due to acquired somatic mutations," Dr Margarete Fabre (University of Cambridge, UK) explained. "We conducted a study to unravel the transition from normal to clonal haematopoiesis and map the dynamics of clonal haematopoiesis."

Dr Fabre and colleagues assessed 13 years of blood samples, collected from an elderly population (n=385; mean age at baseline 69.3 years). Deep targeted sequencing was used to detect mutant clones. The results displayed that the mean clone size and number of mutations increased with age, with constant growth rates in >90% of the detected clones. *DNMT3A*, *TET2*, and spliced mutant clones were the most common drivers of these mutations. Non-genetic factors accounted for approximately 5% of the clonal growth, proportionally impacting slow driver genes more substantially. Furthermore, mutations associated with faster clonal growth were also associated with an increased risk of acute myeloid leukaemia, independent of clone size.

Next, retrograde extrapolation was performed to assess clonal expansion longitudinally. The results showed that some genetic mutations drive fast clonal expansions early in life and then slow down, such as *DNMT3A* mutations, whereas other drivers initiate expansion at an older age at a fast growth rate, such as splicing mutations. Still other mutations occur at all ages and demonstrate relatively stable growth, such as *TET2*-mutant clones (see Figure).

Figure: Different patterns of lifelong clonal behaviour [1]



Whole-genome sequencing of 1,731 single cell-derived colonies confirmed the inferences that were made from the longitudinal data. However, reconstruction of haematopoietic phylogenies showed that many clones lacked recognisable drivers and that these driverless expansions displayed similar growth rates.

In conclusion, the current findings improve the understanding of lifelong clonal behaviour by showing that clonal haematopoiesis is driven by different gene mutations that demonstrate separate patterns of longitudinal clonal behaviour.

1. Fabre M, et al. The Longitudinal Dynamics and Natural History of Clonal Hematopoiesis. LBA-2, ASH 2021 Annual Meeting, 11–14 December.