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1. Pan-clonal score predicts first-line treatment response in AML

Acute myeloid leukaemia (AML) is a very heterogeneous disease with high patient-to-patient variability in treatment response. Pharmacoscopy allows *ex vivo* functional drug-response profiling of (tumour) cells and might pave the way to a tailor-made treatment.

AML is a heterogeneous disease due to a fast natural or treatment-induced clonal expansion of premature myeloid cells leading to the presence of multiple clones at the same time, each with different drug-sensitivity profiles. In addition, myeloid maturation of rare leukaemic stem cell populations can give rise to new tumour cell populations leading to relapse after an initial treatment of the patient. Hence, a successful treatment needs to eradicate all sub-populations of tumour cells present, ultimately requiring a tailored treatment regimen for every individual AML patient.

Dr Yannik Severin (ETH Zurich, Switzerland) presented a technique called pharmacoscopy, which allows *ex vivo* functional drug-response profiling of (tumour) cells [1]. In pharmacoscopy, the sensitivity of both healthy cells and tumour cells derived from the patient to 100 distinct drugs and drug combinations is analysed by automated microscopy [2].

In a prospective, non-interventional study, 180 AML patient biopsies were collected from 44 patients with newly diagnosed AML undergoing intensive induction chemotherapy. Patient-matched bone marrow and blood samples were obtained from each donor at 3 different time points across the course of their treatment (at time of diagnosis, after the first-line, and after the second-line of chemotherapy). Tumour cells were recognised by their expression of CD33, CD117, CD34, or combinations of these markers; healthy cells were recognised by CD3 expression.

A neural network automatically characterised cells into 1 of 5 distinct myeloid populations (CD34+, CD33+, CD117+/CD33+, CD117+/CD33+/CD34+, or negative for all markers) or 2 healthy T-cell subtypes (conventional, activated). Dr Severin showed that this technique is able to illustrate the highly heterogeneous blast composition across

samples. In addition, blast composition and maturity of tumour cells could predict first-line treatment (cytarabine/daunorubicin) success, with an overall predictive power of 85% accuracy and a diagnostic odds ratio of 47. For example, the expression of CD34 on leukaemic blast cells is predictive of non-response leading to an increased fraction of CD34-positive cells after the first-line of chemotherapy. Based on the *ex vivo* response to different drugs, Dr Severin calculated a pan-clonal score. This score could predict the response of all clones present in the sample to a specific drug or combination of drugs. This pan-clonal score proved to be highly predictive of response to the first-line chemotherapy in the used patient cohort. "Using the pan-clonal score, it is possible to select a (combination of) drug(s) that is most likely to kill most tumour cells, irrespective of their actual abundance," Dr Severin concluded.

1. Severin Y, et al. Intra-patient functional heterogeneity of AML determines first-line treatment response. Abstract S134. EHA2022 Hybrid Congress, 09–12 June.
2. Snijder B, et al. Lancet Haematol. 2017;4(12):e595–e606.

2. Quizartinib prolongs survival of newly diagnosed *FLT3*-ITD-mutated AML

Quizartinib improves overall survival when combined with standard induction and consolidation therapy, and as continuation therapy as a single agent for up to 3 years in patients with newly diagnosed acute myeloid leukaemia (AML) characterised by internal tandem repeats within the *FLT3* gene (*FLT3*-ITD-mutated), results from the phase 3 QuANTUM-First study demonstrated.

FLT3-ITD is among the most common driver mutations in AML (approximately 25% of all AML cases), and is associated with poor prognosis, high relapse rates, and inferior overall survival. The prognosis of *FLT3*-TKD mutations remains unclear [1,2]. The RATIFY study ([NCT00651261](#)) showed an improved overall survival in *FLT3*-mutated AML patients with midostaurin, albeit with a high rate of relapse [3]. Quizartinib is a highly potent and selective second-generation type II *FLT3* inhibitor that demonstrated a signal of clinical efficacy and a manageable safety profile in a phase 2 trial [4]. The QuANTUM-First trial ([NCT02668653](#))

aimed to determine if the addition of quizartinib to standard induction and post-remission consolidation therapy, followed by quizartinib continuation therapy for up to 3 years, improves survival compared with chemotherapy alone. Dr Harry Erba (Duke Cancer Institute, NC, USA) presented the results [5].

The study enrolled 533 patients (18–75 years old) who were randomised 1:1 to induction therapy (cytarabine/daunorubicin) plus quizartinib or induction therapy plus placebo. In the quizartinib arm, 173 patients entered the consolidation phase (HiDAC/quizartinib

and/or allogeneic HCT) and 116 patients thereafter continued with single-agent quizartinib. In the placebo arm, 175 patients entered the consolidation phase (HiDAC/placebo and/or allogeneic HCT); subsequently, 92 patients continued with placebo consolidation.

The median overall survival (primary endpoint) was 31.9 months in the quizartinib arm versus 15.1 months in the placebo arm (HR 0.776; P=0.0324). A total of 193 patients (n=102 in the quizartinib arm, n=91 in the placebo arm) received allogeneic HCT. Overall survival censored for allogeneic HCT also numerically favoured quizartinib, but did not reach significance at this time point (HR 0.752; P=0.055). Complete remission was comparable between arms, however, the duration of complete remission was 38.6 months in the quizartinib arm versus 12.4 months in the placebo arm.

The safety of quizartinib combined with intensive chemotherapy and as continuation monotherapy was generally manageable, with no new safety signals. Discontinuation due to treatment-emergent adverse events was observed in 20.4% of patients in the quizartinib arm versus 8.6% in the placebo arm.

"These data have the potential to change the standard-of-care for the treatment of adult patients with newly diagnosed *FLT3*-ITD-mutated AML," Dr Erba concluded.

1. [Levis M. Hematology Am Soc Hematol Educ Program. 2013;2013:220–226.](#)
2. [Kottaridis PD, et al. Blood. 2001;98:1752–1759.](#)
3. [Stone RM, et al. N Engl J Med. 2017;377:454–464.](#)

4. [Takahashi T, et al. Int J Hematol. 2019;110:665–674.](#)
5. Erba H, et al. Quizartinib prolonged survival vs placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients aged 18–75 years with newly diagnosed *FLT3*-ITD+ AML. Abstract S100. EHA2022 Hybrid Congress, 09–12 June.

3. No survival benefit of CPX-351 over FLAG-Ida in AML patients with adverse cytogenetics

CPX-351 does not improve response, overall survival, or event-free survival compared with FLAG-Ida in patients with acute myeloid leukaemia (AML) with adverse cytogenetics, but is associated with an improvement in duration of remission and relapse-free survival, results from the AML19 trial demonstrated.

AML patients with adverse cytogenetics have a poor prognosis; less than 10% will survive for 5 years or more following standard intensive chemotherapy [1]. Previous studies reported improved survival with FLAG-Ida (fludarabine/cytosine arabinoside, granulocyte-colony stimulating factor, and idarubicin) treatment in younger patients identified with high-risk AML following induction therapy and in patients with secondary AML [2]. On the other hand, CPX-351 (liposomal daunorubicin and cytarabine) has demonstrated an improved survival predominantly in older patients (>60 years) with secondary AML compared with standard chemotherapy [3].

To compare the efficacy of CPX-351 and FLAG-Ida, the AML19 trial ([ISRCTN78449203](#)) randomised 635 patients (mainly <60 years) with high-risk AML or myelodysplastic syndrome (>10% blasts) to CPX-351 or FLAG-Ida. Endpoints included overall and event-free survival, response, and the number of patients delivered to transplant with their

post-transplant survival. Groups of high-risk patients were randomised with the aim of proceeding to allogeneic transplant:

- Group 1 (n=195) had known adverse-risk cytogenetics; they were randomised at diagnosis between 4 courses of CPX-351 and 2 courses of FLAG-Ida followed by MACE/MidAC consolidation.
- Group 2 (n=263) were determined high-risk by validated risk score, had *FLT3*-ITD without an *NPM1* mutation, and had refractory disease; they were randomised after induction course 1.
- Group 3 (n=177) were randomised after course 2 if they had persisting minimal residual disease at the time of relapse.

Prof. Nigel Russell (Guy's and St Thomas' NHS Foundation Trust, UK) presented the results from Group 1 (n=88 FLAG-Ida, n=107 CPX-351) [4]. Overall response rate after course 2 was 75.6% and 63.8% for treatment with FLAG-Ida and CPX-351, respectively (HR 0.54; P=0.06). Complete response was observed in 51.2% in the FLAG-Ida arm versus

40.0% in the CPX-351 arm. The median duration of remission, however, numerically favoured CPX-351 (510 vs 391 days; P=0.24).

There was no significant difference in median overall survival (13.3 vs 11.4 months), median event-free survival (7.1 vs 6.0 months), and median relapse-free survival (22.1 vs 8.4 months) for CPX-351 and FLAG-Ida, respectively. Time to transplant was comparable in both arms (139 days vs 131 days), and slightly more patients receiving CPX-351 proceeded to transplant (50.5% vs 43.9%; P=0.41). Post-transplant survival was not different between treatments received.

"In this exploratory study of AML patients with adverse cytogenetics, CPX-351 did not improve response, overall survival, or event-free survival compared with FLAG-Ida, but was associated with an improvement in duration of remission and relapse-free survival," summarised Prof. Russell.

1. [Hills RK, et al. Lancet Oncol. 2014;15:986–996.](#)
2. [Burnett AK, et al. Leukemia. 2018;32:2693–2697.](#)
3. [Lancet JE, et al. J Clin Oncol. 2018;36:2684–2692.](#)
4. Russell N, et al. A randomised comparison of CPX-351 and FLAG-IDA in high risk acute myeloid leukaemia. Results from the NCRI AML 19 trial. Abstract S128. EHA2022 Hybrid Congress, 09–12 June.

4. New subtypes of oncogenic deregulation in childhood T-ALL

Large-scale whole-genome sequencing, whole-exome sequencing, and RNA-expression profiling can be used to uncover new subtypes of T-cell acute lymphoblastic leukaemia (T-ALL).

T-ALL represents approximately 15% of all newly diagnosed ALL cases in paediatric

patients. T-ALL is an aggressive malignancy showing immunophenotypic diversity,

including early T-cell precursor lymphoblastic leukaemia (ETP-ALL) and leukaemia of transformed thymocytes. About 20% of patients relapse or have refractory disease. Prognostic factors other than minimal residual disease are unclear [1]. Previous genetic

research on patients with T-ALL has identified 8 molecular subtypes with 106 putative drivers based on gene expression clustering [2]. However, this study had a limited cohort size, excluded refractory disease, and focused on alterations in coding parts of the genome. It is now known that T-ALL gene activation is also frequently achieved by alterations in non-coding parts of the genome, e.g. *MYC* activation by an alteration in a distal NOTCH1 *MYC* enhancer [3].

Identification of genomic drivers in non-coding regions requires whole-genome sequencing and could improve the subclassification of T-ALL. Therefore, Dr Petri Pöllönen (St. Jude Children's Research Hospital, TN, USA) and colleagues performed comprehensive genomic characterisation –whole-genome

sequencing, whole-exome sequencing, and RNA sequencing– of all children enrolled in the AALL0434 study ([NCT01295476](#)) (n=1,313, median age 9 years old) [4].

A total of 21 T-ALL driver variants were observed in 94% of the patients combining the different genomic characterisation results, with mutations in *TAL1* being the most abundant (25%). Of note, 60% of the patients had alterations in non-coding regions. Based on the genomic data, it was possible to identify 16 subtypes of T-ALL, thereby doubling the previous number of genetic subtypes. Combining the genetic characteristics with the clinical outcome of the patients, the researchers were able to show an improved survival of patients with a *RPL10* R98S/C mutation over patients with

RPL10 wildtype and improved survival of patients with *LMO2* wildtype over *LMO2* with intergenic deletion.

Based on these results, Dr Pöllönen concluded that "large-scale genomic profiling of all children enrolled in the AALL0434 study has enabled the comprehensive discovery of T-ALL drivers, including candidate novel enhancer hijacking events and enhancer duplications, that are likely to result in oncogene deregulation in T-ALL."

1. [Petit A, et al. Blood 2018;131:289–300.](#)
2. [Liu Y, et al. Nat Genet. 2017;49:1211–1218.](#)
3. [Herranz D, et al. Nat Med. 2014;20:1130–1137.](#)
4. Pöllönen P, et al. Comprehensive genome characterization reveals new subtypes and mechanisms of oncogene deregulation in childhood T-ALL. Abstract S102. EHA2022 Hybrid Congress, 09–12 June.

5. Triple-therapy improves PFS in fit, previously untreated CLL

Results from the phase 3 GAIA/CLL13 trial demonstrated improved progression-free survival (PFS) with triple therapy of venetoclax/obinutuzumab/ibrutinib in fit, previously untreated patients with chronic lymphocytic leukaemia (CLL).

In fit patients with advanced CLL of favourable genetic risk, chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab (BR) is still standard first-line treatment. In less fit patients, venetoclax/obinutuzumab (VG) is superior to chlorambucil/obinutuzumab concerning PFS [1]. Triple combinations including BTK inhibitors have shown promising results in phase 2 trials [2]. Data comparing VG with FCR or BR, nor data comparing VG plus ibrutinib (GIV) with FCR or BR as a first-line treatment in fit patients with CLL is currently available. Therefore, the 4-arm, phase 3 GAIA/CLL13 study ([NCT02950051](#)) evaluated the efficacy and safety of 3 time-limited, venetoclax-based, first-line regimens in comparison with chemoimmunotherapy in fit patients with CLL.

Patients (n=920) were randomised 1:1:1:1 to receive 6 cycles of FCR (for patients <65

years) or BR (>65 years), 12 cycles rituximab/venetoclax (RV), 12 cycles VG, or 12 cycles GIV. The first co-primary endpoint, a superior undetectable minimal residual disease (MRD) rate in both the VG arm and GIV arm over the FCR/BR arm at month 15, was already met in 2021 [3]. Now, Prof. Barbara Eichhorst (University Hospital Cologne, Germany) presented results on the second co-primary endpoint of the trial: interim PFS in the GIV arm versus the FCR/BR arm [4].

Results demonstrated superior PFS for GIV compared with FCR/BR (90.5% vs 75.5% at 3 years; HR 0.32; P<0.000001). Superior PFS was also seen in the VG arm versus FCR/BR (87% vs 75.5% at 3 years; HR 0.42; P<0.0001). PFS was not significantly different between the RV and FCR/BR arms (80.8% vs 75.5% at 3 years; HR 0.79; P=0.183). In all study arms, 3-year PFS rates were higher for

patients with mutated *IGHV* compared with patients with wildtype *IGHV*. With respect to time to next treatment, GIV was superior to FCR/BR: at 3 years, 98.3% of GIV patients, 94.1% of VG patients, 92.9% of RV patients, and 87.2% of FCR/BR patients were without new treatment. Overall response data are not yet mature.

"These results demonstrate that time-limited treatment with GIV or VG improves both undetectable MRD rate at 15 months and PFS compared with standard chemoimmunotherapy in fit, previously untreated patients with CLL," summarised Prof. Eichhorst.

1. [AlSawaf O, et al. Lancet Oncol. 2020;21:1188–1200.](#)
2. [Huber H, et al. Blood. 2022;139:1318–1329.](#)
3. [Eichhorst B, et al. Abstract 71. ASH 2021 Annual Meeting, Atlanta, GA, USA, 11–14 December.](#)
4. Eichhorst B, et al. Time-limited venetoclax-obinutuzumab +/- ibrutinib is superior to chemoimmunotherapy in frontline chronic lymphocytic leukemia (CLL): PFS co-primary endpoint of the randomized phase 3 GAIA/CLL13 trial. Abstract LB2365. EHA2022 Hybrid Congress, 09–12 June.

6. Axi-cel superior to standard-of-care in older patients with relapsed/refractory large B-cell lymphoma

A subgroups analysis of patients aged 65 years or older in ZUMA-7 demonstrated axicabtagene ciloleucel (axi-cel) to be superior to standard-of-care for second-line treatment, despite the greater frequency of high-risk features in the axi-cel arm.

The prognosis of patients with early relapsed or refractory large B-cell lymphoma after the receipt of first-line chemoimmunotherapy is poor. Particularly in older patients, outcomes of second-line standard-of-care treatment are inferior and often associated with poor health-related quality of life [1,2]. Recently, results from the phase 3 ZUMA-7 trial ([NCT03391466](#)) showed significant improvement in event-free survival with axi-cel compared with second-line standard-of-care in patients with relapsed/refractory large B-cell lymphoma [3]. Dr Anna Sureda (University of Barcelona, Spain) presented results on safety, efficacy, and patient-reported outcomes in a pre-planned subgroup analysis of ZUMA-7 of patients aged ≥65 years [4].

A total of 109 patients enrolled in ZUMA-7 were aged 65 years or older (median age 70 years); 51 participants were allocated to the axi-cel arm, 58 participants were allocated

to the standard-of-care arm (i.e. high-dose chemotherapy plus stem cell transplantation). Compared with standard-of-care patients, more axi-cel patients had high-risk features at baseline.

The median event-free survival (primary endpoint in ZUMA-7) was 21.5 months in the axi-cel arm and 2.5 months in the standard-of-care arm (HR 0.276; P<0.0001). Objective response rate was 88% (75% complete response) in the axi-cel arm and 52% (33% complete response) in the standard-of-care arm. The overall survival rate at 2 years was 64% in the axi-cel arm versus 51% in the standard-of-care arm. Of note, 57% of patients in the standard-of-care arm received subsequent cellular immunotherapy (of protocol).

The safety profile of axi-cel was manageable and consistent with previous studies in

refractory large B-cell lymphoma. Cytokine-release syndrome grade ≥3 was observed in 4 (8%) patients in the axi-cel arm (median duration 8 days). In the quality-of-life analysis set (axi-cel n=46; standard-of-care n=42), a clinically meaningful difference in quality-of-life scores was observed in favour of axi-cel from day 100 to 150, suggesting a faster recovery to pre-treatment quality-of-life.

"This data demonstrates that older patients with relapsed/refractory large B-cell lymphoma, who are frequently considered transplant-ineligible based on age, can safely receive second-line curative intent therapy," concluded Dr Sureda.

1. [Di M, et al. Oncologist. 2021;26:120–132.](#)
2. [Oerlemans S, et al. Ann Hematol 2014;93:1705–1715.](#)
3. [Locke FL, et al. N Engl J Med 2022;386:640–654.](#)
4. Sureda A, et al. Clinical and patient-reported outcomes in a phase 3 study of axicabtagene ciloleucel (AXI-CEL) vs standard-of-care in elderly patients with relapsed/refractory large B-cell lymphoma (ZUMA-7). Abstract S211. EHA2022 Hybrid Congress, 09–12 June.

7. Abscopal response in patients with relapsed or refractory Hodgkin lymphoma who failed on anti-PD1 treatment

Treatment with nivolumab and radiotherapy at a single lesion is well tolerated and leads to an abscopal response in the majority of relapsed/refractory Hodgkin lymphoma patients who failed on anti-PD1 treatment, preliminary results of the AERN trial showed.

Anti-PD1 blockade has proven to be highly effective and is approved for the treatment of relapsed/refractory Hodgkin lymphoma. In addition, the progression-free survival (PFS) and overall survival (OS) outcomes are superior in patients achieving a complete response to anti-PD1 therapy [1]. However, most patients eventually develop progression of disease, constituting an unmet need due to a lack of approved novel treatment options. Local radiotherapy is postulated to induce systemic anti-tumour immunity leading to a tumour response outside the

irradiated area. This so-called abscopal effect may be augmented by anti-PD1 therapy [2].

The ongoing AERN (Abscopal Effect of Radiotherapy and Nivolumab in Relapsed or Refractory Hodgkin Lymphoma) trial ([NCT03480334](#)) is a phase 2, proof-of-concept study that prospectively evaluates the efficacy and safety of nivolumab and radiotherapy in patients with relapsed/refractory Hodgkin lymphoma who failed on anti-PD1 treatment. Dr Paul Bröckelmann (University

Hospital of Cologne, Germany) presented the results of the first pre-planned interim analysis [3].

The study enrolled 29 patients (n=9 in stage I, n=20 in stage II) who showed progressive disease while on anti-PD1 treatment or stable disease for more than 6 months as best response while on active treatment. The last dose of anti-PD1 was within 4 weeks prior to enrolment. Patients had ≥2 distinct FDG-avid lesions with at least 5 cm distance between them and 1 lesion considered to be eligible for radiotherapy with 20 Gy. Radiotherapy was administered after the first dose of nivolumab. The primary endpoint is abscopal response rate at the first interim restaging after 6 infusions.

In the participants enrolled in stage I, the overall response rate at first interim restaging was 56% (all partial responses), and abscopal response rate was present in 56% (n=5) of patients. In many cases, lesions far away from the radiated area showed a response. Even a patient who was classified as progressive due to a new lesion had a substantial reduction of tumour burden in the non-radiated lesions. PFS at 1 year was 42.3%.

The treatment was well-tolerated and most adverse events were grade 1; mostly skin toxicity due to radiotherapy.

Based on these preliminary results, Dr Bröckelmann concluded that "radiation combined with anti-PD1 treatment is feasible and safe in patients with relapsed/refractory Hodgkin lymphoma who failed on anti-PD1 treatment. In addition, the results show encouraging early signals of efficacy,

in particular an abscopal response rate of 56%. This warrants further enrolment of patients in the trial."

1. [Ansell SM, et al. Abstract 074. ICML 2021, 18–22 June.](#)
2. [Ngwa W, et al. Nat Rev Cancer. 2018;18:313–322.](#)
3. Bröckelmann P, et al. Abscopal effect of radiotherapy and nivolumab in relapsed or refractory Hodgkin lymphoma: pre-planned interim analysis of the international GHSH phase II AERN trial. Abstract S203. EHA2022 Hybrid Congress, 09–12 June.

8. DA-EPOCH-R is equally effective but less toxic compared with CODOX-M/R-IVAX in high-risk Burkitt lymphoma

Results from the prematurely closed HOVON/SAKK trial demonstrated equal efficacy of DA-EPOCH-R and CODOX-M/R-IVAX regimens as first-line treatment in patients with high-risk Burkitt lymphoma. However, DA-EPOCH-R is less toxic.

Burkitt lymphoma is a rare (outside of Africa) but aggressive form of non-Hodgkin B-cell lymphoma for which the optimal first-line treatment remains to be defined. Treatment with high-dose multi-agent chemotherapy such as R-CODOX-M/R-IVAC is effective (2-year progression-free survival [PFS] of 64–71%), however at the cost of significant toxicity and long hospitalisation [1]. Treatment with lower intensity, patient dose-adjusted, and continuous DA-EPOCH-R has demonstrated favourable 2-year PFS of 85% and lower toxicity [2].

The multicentre, randomised HOVON/SAKK trial ([EudraCT2013-004394-27](#)) compared both regimens. The primary objective was to demonstrate improvement in 2-year PFS from 70% with R-CODOX-M/R-IVAC to 85% with DA-EPOCH-R. Prof. Martine Chamuleau (Amsterdam UMC, the Netherlands) presented the first results [3].

The study enrolled a total of 89 newly diagnosed patients with high-risk Burkitt lymphoma (18–75 years old). Of note, to confirm the hypothesis, 260 patients were needed, but due to a slow accrual rate and the inability of another cooperative group to participate the trial was closed prematurely. Enrolled participants were randomised to receive 2 cycles of R-CODOX-M/R-IVAX or 6 cycles of DA-EPOCH-R.

The estimated 2-year PFS after a median follow-up of 19.1 months was 76% for the R-CODOX-M/R-IVAX arm versus 70% for the DA-EPOCH-R arm (P=0.38). Estimated 2-year overall survival was comparable in both arms (76% vs 75%, respectively; P=0.85). In addition, the objective response rate (complete metabolic remission) was comparable in both arms (65% vs 66%).

Toxicity was –as expected– lower in the DA-EPOCH-R arm: 84 adverse events occurred in

30 patients versus 129 adverse events in 34 patients in the R-CODOX-M/R-IVAX arm. In addition, patients in the R-CODOX-M/R-IVAX needed significantly more transfusions (both red blood cells and platelets) and had significantly more hospitalisations compared with patients in the DA-EPOCH-R arm (P<0.01).

Prof. Chamuleau concluded that "R-CODOX-M/R-IVAX and DA-EPOCH-R were comparable effective regarding PFS, overall survival and objective response rate, in this prematurely closed trial. However, DA-EPOCH-R is associated with significantly fewer complications, transfusions, and hospitalisation nights. Based on these results, DA-EPOCH-R seems the preferred regimen for high-risk Burkitt lymphoma patients."

1. [Barnes JA, et al. Ann Oncol. 2011;22:1859–1864.](#)
2. [Roschewski M, et al. J Clin Oncol. 2020;38:2519–2529.](#)
3. Chamuleau M, et al. R-CODOX-M/R-IVAC versus dose-adjusted (DA) EPOCH-R in patients with newly diagnosed high-risk Burkitt lymphoma; first results of a multi-center randomized HOVON/SAKK trial. Abstract LB2370. EHA2022 Hybrid Congress, 09–12 June.

9. Post-transplant carfilzomib, lenalidomide, and dexamethasone outperforms post-transplant lenalidomide in multiple myeloma

First results of the phase 3 ATLAS trial showed benefit of post-transplant maintenance therapy with carfilzomib, lenalidomide, and dexamethasone over post-transplant lenalidomide maintenance therapy.

In multiple myeloma (MM), lenalidomide maintenance therapy after autologous stem cell transplant (ASCT) has been established

as a standard of care [1]. However, post-ASCT treatment for MM remains an area of active investigation. Previously, a phase 2 trial ([NCT01816971](#)) showed an improvement in the depth of response associated with long progression-free survival (PFS) after extended post-ASCT with carfilzomib, lenalidomide, and dexamethasone (KRd) after KRd induction [2]. Outcomes of the phase 2 FORTE trial ([NCT02203643](#)) further supported a benefit of extended KR maintenance [3].

In the multicentre, international, phase 3 ATLAS trial ([NCT02659293](#)), post-ASCT KRd maintenance therapy was directly compared with standard lenalidomide maintenance therapy. Dr Dominik Dytfield (Poznan University of Medical Sciences, Poland) presented the outcomes of this ongoing trial [4].

A total of 180 newly-diagnosed MM patients were enrolled. Patients received any induction therapy for up to 12 months followed

by single ASCT and achieved at least stable disease within 100 days before they were randomised 1:1 to receive either KRd or lenalidomide. KRd-treated patients with standard-risk cytogenetics who achieved minimal residual disease (MRD) negativity after 6 cycles of KRd (n=34) crossed over to lenalidomide after 8 cycles KRd; the rest continued on KRd through 36 cycles, followed by lenalidomide maintenance. The primary endpoint was PFS.

MRD-negativity (by IMWG criteria) at 6 cycles was reached by 44% of KRd-treated patients and 27% of lenalidomide-treated patients. After a median follow-up of 33.8 months, the median PFS was 59.0 months in the KRd arm versus 41.1 months in the lenalidomide arm (HR 0.56; P=0.026). The benefit of KRd over lenalidomide was observed in all subgroup analyses. Median PFS in patients with standard-risk cytogenetics (n=139) was not reached in the KRd arm versus 65.4 months in the lenalidomide arm (HR 0.44; P=0.01).

Overall survival data are still immature.

Both treatment regimens were well tolerated. Neutropenia (13% vs 7%) and infections (15% vs 6%) were more common in the KRd arm than in the lenalidomide arm.

"These results indicate superior PFS with extended post-transplant KRd maintenance therapy compared with lenalidomide therapy," Dr Dytfield concluded. "In addition, MRD-directed, risk-adapted KRd maintenance could be an alternative to lenalidomide maintenance and may represent a new standard-of-care."

1. McCarthy PL, et al. *J Clin Oncol*. 2017;35:3279–3289.
2. Jasielec JK, et al. *Blood*. 2020;136:2513–2523.
3. Gay F, et al. *Lancet Oncol*. 2021;22:1705–1720.
4. Dytfield D, et al. ATLAS: A phase 3 randomized trial of carfilzomib, lenalidomide, and dexamethasone versus lenalidomide alone after stem-cell transplant for multiple myeloma. Abstract S175. EHA2022 Hybrid Congress, 09–12 June.

10. Triplet therapy plus early ASCT improves PFS in newly diagnosed multiple myeloma versus triplet therapy alone

In the phase 3 DETERMINATION trial, the addition of early ASCT to triplet therapy of lenalidomide, bortezomib, and dexamethasone followed by lenalidomide maintenance therapy until disease progression significantly improved progression-free survival (PFS) in patients with newly diagnosed multiple myeloma (MM). However, overall survival (OS) did not improve.

The optimal use of induction therapy, allogeneic stem cell transplantation (ASCT), and maintenance therapy in transplant-eligible, newly diagnosed MM patients continues to evolve. Based on the knowledge at that time, the phase 3 DETERMINATION trial ([NCT01208662](#)) was developed in 2010 to evaluate the efficacy addition of early (first-line) ASCT to triplet therapy (lenalidomide, bortezomib, and dexamethasone [RVd]) followed by lenalidomide maintenance therapy until disease progression in patients with newly diagnosed MM.

A total of 722 patients were randomised 1:1 to RVd alone (8 cycles) followed by lenalidomide maintenance, or RVd (5 cycles) plus ASCT followed by lenalidomide maintenance. The primary endpoint of the study

was PFS, secondary endpoints were OS, response rate, duration of response, quality-of-life, and safety. Dr Paul Richardson (Dana-Farber Cancer Institute, MA, USA) presented the results of the study, which had been published days previously in the *New England Journal of Medicine* [1,2].

After a median follow-up of 76.0 months, the primary endpoint was met: median PFS in the RVd alone arm was 46.2 months versus 67.5 months in the RVd plus ASCT arm (HR 1.53; P<0.0001). However, a post-hoc sensitivity analysis showed that for median event-free survival, the difference narrowed (32.0 months vs 47.3 months; HR 1.23). OS was comparable in both treatment arms: 5-year OS was 80.7% and 79.2% in RVd plus ASCT and RVd alone, respectively. "This could be

related to subsequent therapies in patients off protocol therapy," Dr Richardson said. Best response rates did not significantly differ between the treatment arms. Best response ≥PR was reached in 97.5% and 95% in RVd plus ASCT and RVd alone, respectively; best response ≥VGPR in 82.7% and 79.6%; and best response ≥CR in 46.8% and 42% of patients. However, duration of response favoured RVd plus ASCT (median 56.4 vs 38.9 months; HR 1.45; P=0.003) for response ≥PR. Quality-of-life in the RVd plus ASCT showed a significant but transient decrease at the time of ASCT.

Dr Richardson summarised that "among adults with MM, RVd plus ASCT was associated with longer PFS than RVd alone. However, no overall survival benefit was observed."

1. Richardson PG, et al. The phase 3 DETERMINATION trial in newly diagnosed multiple myeloma: lenalidomide, bortezomib, and dexamethasone (RVd) with or without autologous stem cell transplantation (ASCT) and lenalidomide maintenance to progression. Abstract LB2366. EHA2022 Hybrid Congress, 09–12 June.
2. Richardson PG, et al. *N Engl J Med* 2022; June 5. DOI: 10.1056/NEJMoa2204925.

11. Momelotinib induces a rapid and sustained improvement in haemoglobin levels in patients with myelofibrosis

Results from the phase 3 MOMENTUM trial showed a significant improvement in symptoms, spleen size, and anaemia measures with momelotinib versus danazol.

Myelofibrosis is driven by dysregulated JAK-STAT signalling that typically manifests as bone marrow fibrosis, anaemia, splenomegaly, and debilitating symptoms [1]. JAK inhibitors can decrease many symptoms of myelofibrosis but fail to address, and may even induce or worsen, anaemia. Anaemia is the most important negative prognostic factor in myelofibrosis and therefore the most important unmet need in patients with myelofibrosis. Momelotinib is a new drug inhibiting not only JAK1 and JAK2, but also ACVR1 and thus promotes iron metabolism and erythropoiesis [2]. In previous phase 3 trials, treatment with momelotinib demonstrated benefits on symptoms, spleen, and anaemia in JAK inhibitor-naïve myelofibrosis patients [3–5].

The MOMENTUM trial ([NCT04173494](#)) was designed to further evaluate the clinical benefits of momelotinib. In this phase 3 trial, momelotinib was compared with danazol, a drug in use to ameliorate anaemia in patients with myelofibrosis as recommended by NCCN and ESMO guidelines. Prof. Srdan Verstovsek (University of Texas

MD Anderson Cancer Center, TX, USA) presented the first results [6].

A total of 195 patients with symptomatic and anaemic ($\text{Hb} < 10 \text{ g/dL}$) myelofibrosis who were previously treated with a JAK inhibitor were (after JAK inhibitor washout of ≥ 21 days) randomised 2:1 to momelotinib or danazol treatment for 24 weeks. After 24 weeks, all patients were treated with momelotinib. The primary endpoint was total symptoms score (TSS) response after 24 weeks. TSS response was defined as achieving a $\geq 50\%$ reduction in TSS over the 28 days immediately before the end of week 24, compared with baseline. Secondary endpoints were transfusion independence rate and splenic response rate at week 24.

TSS response for momelotinib at week 24 was 24.6% versus 9.2% for danazol ($P=0.0095$). Spleen response also showed momelotinib to be superior to danazol: 40% versus 6.2% of patients achieved a 25% reduction ($P<0.00001$); 23.1% versus 3.1% of patients achieved a 35% reduction ($P=0.0006$). Transfusion-independence at

week 24 was achieved by 31% of patients in the momelotinib arm versus 20% in the danazol arm, which was non-inferior according to the strict definition. However, mean haemoglobin level showed a rapid, sustained, and higher increase with momelotinib: within 4 weeks mean haemoglobin increased from 8.0 to 9.5 g/dL in the momelotinib arm versus 8.5 g/dL in the danazol arm. The most common adverse events (predominantly grade 1–2) of treatment with momelotinib were diarrhoea, nausea, and asthenia.

"All prespecified primary and secondary endpoints of MOMENTUM were met," Prof. Verstovsek concluded. "These results support future use of momelotinib as an effective treatment in myelofibrosis patients, especially in those with anaemia."

1. [Vainchenker W, et al. Blood. 2017;129:667–679.](#)
2. [Asshoff M, et al. Blood 2017;129:1823–1830.](#)
3. [Mesa R, et al. J Clin Oncol 2017;35:3844–3850.](#)
4. [Harrison CN, et al. Lancet Haematol 2018;5:e73–e81.](#)
5. [Mesa R, et al. Leuk Lymphoma. 2022;7:1–5.](#)
6. Verstovsek S, et al. MOMENTUM: phase 3 randomized study of momelotinib (MMB) versus danazol (DAN) in symptomatic and anaemic myelofibrosis (MF) patients previously treated with a JAK inhibitor. Abstract S203. EHA2022 Hybrid Congress, 09–12 June.

12. Caplacizumab is safe and effective in patients with iTPP, also in the long term

Data from the post-HERCULES trial supports the long-term safety and efficacy of caplacizumab, including its repeated use, in patients with acquired or immune-mediated thrombotic thrombocytopenic purpura (iTPP).

Acquired or immune-mediated thrombotic thrombocytopenic purpura (iTPP) is a rare thrombotic microangiopathy that is characterised by thrombocytopenia and haemolytic anaemia. Recently, the HERCULES trial ([NCT02553317](#)) showed that among patients with iTPP, treatment with caplacizumab was associated with faster normalisation of the platelet count; with a lower

incidence of a composite of iTPP-related death, recurrence of iTPP, or a thromboembolic event during the treatment period; and with a lower rate of recurrence of iTPP during the trial than placebo [1]. However, follow-up in the HERCULES trial was 28 days after the end of treatment. To evaluate the long-term safety and efficacy of caplacizumab in patients with iTPP, and safety and

efficacy of repeated use of caplacizumab for iTPP recurrence, the post-HERCULES trial ([NCT02878603](#)) was performed. Prof. Marie Scully (University College London Hospitals, UK) presented the results. [2]

Participants who completed the HERCULES trial were invited to attend twice-yearly visits, for 3 years. Participants experiencing iTPP exacerbation or relapse (recurrence) post-HERCULES could receive open-label caplacizumab with therapeutic plasma exchange (TPE) and immunosuppressive

therapy (IST). Of 104 patients who enrolled in HERCULES, 75 had been treated with caplacizumab with TPE plus IST (Capla group) and 29 had been treated with TPE plus IST only (placebo group).

Of the patients in the Capla group, 11 (15%) patients had ≥ 1 recurrence during post-HERCULES; 8 of them were re-treated with caplacizumab. In the placebo group, 8 (28%) patients had ≥ 1 recurrence post-HERCULES; 5 of whom were treated with open-label caplacizumab. All first and second recurrences treated with caplacizumab were resolved,

whereas only 4 out of 6 patients with recurrence who were not treated with caplacizumab resolved during post-HERCULES; 1 patient died from iTPP disease after recurrence, this patient did not receive caplacizumab in HERCULES or post-HERCULES.

The frequency of (serious) adverse events was generally similar between the Capla group and the placebo group during post-HERCULES, respectively, e.g. for headache (21% vs 31%), acute TTP (15% vs 28%), nasopharyngitis (8% vs 21%), and bleeding events (21% vs 31%).

Prof. Scully summarised that "these data support the long-term safety and efficacy of caplacizumab, including its repeated use for iTPP recurrence. In addition, there were no observed increases in relapse or exacerbation of iTPP in patients receiving caplacizumab versus placebo."

1. [Scully M, et al. N Engl J Med 2019;380:335–346.](#)
2. Scully M, et al. Long-term safety and efficacy of caplacizumab for acquired thrombotic thrombocytopenic purpura (aTTP): the post-HERCULES study. Abstract S294. EHA2022 Hybrid Congress, 09–12 June.

13. Transfusion-dependent β-thalassaemia patients continue to benefit from luspatercept after 3 years of treatment.

Continued treatment with luspatercept, for up to 3 years, allowed more patients to experience a reduction in red blood cell transfusion burden and an increase in time between transfusions, longer-term results from the BELIEVE trial demonstrated.

β-thalassaemia is a hereditary blood disorder characterised by impaired haemoglobin production and chronic anaemia of varying severity [1]. Patients with transfusion-dependent β-thalassaemia require lifelong regular red blood cell transfusions for survival as well as iron chelation therapy to manage iron overload [2]. However, many patients still experience multiple morbidities due to iron toxicity. There is also a need for treatments that lessen the burden of transfusions. Luspatercept is a recombinant fusion protein that enhances late-stage erythropoiesis and improves haemoglobin levels in patients with β-thalassaemia [3]. Recently, the primary analysis of the phase 3 BELIEVE trial ([NCT02604433](#)) showed an improved reduction of the need for red blood cell transfusion in patients receiving luspatercept over placebo through 24 weeks (21.3% versus 4.5%) [4]. However, long-term results of luspatercept were unknown. Prof. Maria Capellini (University of Milan, Italy) now presented long-term results of the BELIEVE study, including the effects of treatment on

the transfusion burden and liver iron concentration [5].

A total of 336 transfusion-dependent β-thalassaemia patients were enrolled and randomised 2:1 to luspatercept or placebo. After 24 weeks of treatment, the study was unblinded and patients in the placebo arm were allowed to cross over to luspatercept. Post-treatment follow-up was 192 weeks post-last dose. Data presented was from 224 participants who were allocated to luspatercept from the start of the study. Of these, 211 completed 24 weeks of treatment, 202 completed 48 weeks, 155 completed 96 weeks, 125 completed 144 weeks, and 6 participants (so far) completed 192 weeks. Discontinuation was partly due to the commercial availability of luspatercept. Data was presented from 3 different study data cuts with a median of 64 weeks, 95 weeks, and 154 weeks of treatment, respectively.

The percentage of patients with a reduction of $\geq 33\%$ transfusion burden in any rolling

12-week period increased in time, from 70.5% to 77.2%. The percentage of patients with a reduction of transfusion burden of $\geq 50\%$ also increased in time, from 40.2% to 50.0%. In addition, the median duration of the reduction of transfusion burden increased, whereas the number of units of red blood cells per transfusion decreased. The percentage of patients achieving transfusion independence increased from 10.7% to 12.1%. Finally, at week 144, a small decrease was observed in the liver iron concentration of patients treated with luspatercept.

"Continued treatment with luspatercept, up to 3 years, allowed more patients to experience a reduction in red blood cell transfusion burden and an increase in time between transfusions," summarised Dr Cappellini.

1. [Taher AT, et al. N Engl J Med 2021;384:727–743.](#)
2. [Borgna-Pignatti C, et al. Haematologica 2004;89:1187–1193.](#)
3. [Piga A, et al. Blood 2019;133:1279–1289.](#)
4. [Cappellini MD, et al. N Engl J Med 2020;382:1219–1231.](#)
5. Cappellini MD, et al. Longer-term analysis of efficacy of luspatercept versus placebo in patients with transfusion-dependent beta-thalassemia enrolled in the BELIEVE study. Abstract S270. EHA2022 Hybrid Congress, 09–12 June.

14. Single-dosed exa-cel leads to early and durable increase of foetal haemoglobin

Exa-cel, an *ex vivo* CRISPR/Cas9 gene-editing therapy, is associated with an early, consistent, and durable increase in foetal haemoglobin (Hb) and total Hb in patients with transfusion-dependent β-thalassaemia or severe sickle cell disease, results from CLIMB THAL-111 and CLIMB SCD-121 showed.

Diminished production of adult Hb is a common feature in transfusion-dependent β-thalassaemia and sickle cell disease. Elevated production of foetal Hb is associated with improved outcomes in these diseases. Naturally occurring genetic polymorphisms in *BCL11A* are associated with reduced expression of *BCL11A*, resulting in elevated production of foetal Hb and decreased severity of transfusion-dependent β-thalassaemia and sickle cell disease [1]. Exa-cel, also known as CTX001, is a cell therapy designed to reactivate foetal Hb production by *ex vivo* CRISPR/Cas9 gene-editing of *BCL11A* in autologous CD34-positive haematopoietic stem and progenitor cells (HSPCs).

The open-label, single-arm CLIMB THAL-111 trial ([NCT03655678](#)) and CLIMB SCD-121 trial ([NCT03745287](#)) evaluate the efficacy and safety of exa-cel in patients with transfusion-dependent β-thalassaemia and

severe sickle cell disease, respectively. Prof. Franco Locatelli (University of Pavia, Italy) presented the results of these trials [2].

In CLIMB THAL-111, 44 β-thalassaemia patients were infused with a single dose of exa-cel (median 7.5×10^6 cells/kg) and in CLIMB SCD-121, 31 sickle cell disease patients were infused with a single dose of exa-cel (median 4.0×10^6 cells/kg). In the CLIMB THAL-111 trial, 42 of 44 patients became transfusion-independent after exa-cel therapy. Two patients had reductions (75% and 89%, respectively) in transfusion volume. All patients in the CLIMB SCD-121 trial became free from vaso-occlusive crises after exa-cel therapy. In both trials, the production of foetal Hb increased with time. In β-thalassaemia patients, foetal Hb concentration was >9 g/dL by month 4 and thereafter further increased to 12 g/dL. In sickle cell disease patients, foetal Hb concentration was 5 g/dL by month 4 and thereafter further increased to 6 g/dL (total Hb 11 g/dL).

Proportions of edited *BCL11A* alleles in bone marrow CD34-positive HSPCs and peripheral blood mononuclear cells were stable in patients with ≥ 1 year of follow-up.

The exa-cell safety profile was consistent with that of busulfan myeloablation and autologous haematopoietic stem cell transplantation. Two patients with β-thalassaemia had exa-cel-related serious adverse events.

"This data shows that a single dose of exa-cel in patients with transfusion-dependent β-thalassaemia or sickle cell disease leads to an early increase in foetal Hb and total Hb that is durable up to 3 years," concluded Dr Locatelli. "Therefore, exa-cel has the potential to be the first CRISPR/Cas9-based therapy to provide a functional cure for patients with transfusion-dependent β-thalassaemia or severe sickle cell disease."

1. Bauer DE, et al. *Science* 2013;342:253–257.
2. Locatelli F, et al. Efficacy and safety of a single dose of CTX001 for transfusion-dependent beta-thalassemia and severe sickle cell disease. Abstract LB2367. EHA2022 Hybrid Congress, 09–12 June.

15. PI3Kδ inhibitor leniolisib improves symptoms in patients with APDS/PASLI

The PI3Kδ inhibitor leniolisib is safe, increases naïve B cells, decreases lymphadenopathy, decreases spleen size, and improves cytopenia in patients with APDS/PASLI, results from a phase 3 trial demonstrated.

APDS (activated PI3Kδ syndrome), also known as PASLI (p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency) is a rare primary immunodeficiency caused by pathogenic variants in *PIK3CD* or *PIK3R1*, leading to PI3Kδ signalling hyperactivity. Clinical characteristics of APDS are lymphoproliferation, auto-immunity, immunodeficiency, and increased risk of lymphoma. Current treatment options include stem cell

transplantation, immunoglobulin replacement therapy, and empirical treatment such as immunomodulatory, antibiotic, and anti-viral therapy for symptom relief. Leniolisib is a small-molecule inhibitor of hyperactive PI3Kδ signalling [1].

Dr Koneti Rao (National Institute of Health, MD, USA) presented results from a phase 3, placebo-controlled, randomised clinical trial ([NCT02435173](#)) that evaluated the efficacy

and safety of leniolisib in patients with APDS [2]. A total of 31 patients were randomised 2:1 to leniolisib (twice daily for 12 weeks) or placebo. Primary outcomes measures were the change from baseline in percentage of naïve B cells out of total B cells, and diameters in the index lesions (lymph nodes). Additional observations included changes in spleen size and cytopenia.

Leniolisib significantly increased the mean percentage of naïve B cells over time (from 40% at baseline to 65% at day 85), whereas no change was observed in the placebo arm ($P=0.0006$). Lymphadenopathy was

significantly reduced in the leniolisib arm. In addition, leniolisib significantly decreased splenomegaly from baseline: differences of -13.5 cm² (2D diameter) and -186.3 cm³ (3D diameter), whereas no changes were observed in the placebo arm. Cytopenia improved in 82% of patients receiving leniolisib, versus in 60% of patients receiving placebo.

Leniolisib was well tolerated, and no serious adverse events related to the study treatment were observed. However, leniolisib resulted in a transient neutropenia (nadir on day 15).

Based on these results, Dr Rao concluded that "leniolisib is safe, increases naïve B cells, decreases lymphadenopathy, decreases spleen size, and improves cytopenia."

1. [Rao VK, et al. Blood 2017;130:2307–2316.](#)
2. Rao VK, et al. Hematological outcomes from a phase 3, placebo-controlled, randomized clinical trial of PI3K delta inhibitor leniolisib in patients with activated PI3K delta syndrome (APDS/PAS-LI). Abstract LB2369. EHA2022 Hybrid Congress, 09–12 June.