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# memo – in Haematology SPECIAL ISSUE

Congress Report ASH 2025

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## A GLOBAL CONGRESS DIGEST ON THE LATEST ADVANCEMENTS IN MALIGNANT HEMATOLOGY

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## Preface

Out of the 8,200 abstracts accepted for the ASH 2025 annual congress, we highlight several key abstracts that discuss targeted treatment strategies for lymphoid and myeloid malignancies, especially the high-impact ones showcased in the late-breaking abstract and plenary sessions.

There were significant advancements in multiple myeloma, centered on novel immunotherapy combinations, earlier use of bispecific antibodies and in vivo CAR T-cell therapy. Key abstracts included the phase III MajesTEC-3 trial evaluating the combination of the bispecific antibody Teclistamab with daratumumab and the inMMyCAR trial, which

tested a novel approach that offers an alternative to traditional ex vivo CAR T-cell therapy. In addition, the long-term data from DREAMM-7 and DREAMM-8 highlight sustained benefits of Belantamab-Mafodotin in the treatment of relapsed or refractory multiple myeloma.

Additionally, at ASH 2025, several practice-changing data from CLL/SLL studies were presented, including the CLL17 trial, which demonstrated the effectiveness of time-limited venetoclax-based combinations compared with continuous BTKi therapy. Updates included new information on the novel non-covalent BTK inhibitor pirtobrutinib and second-generation BCL2 inhib-

itors such as sonrotoclax. Early-phase data on BTK degraders were also presented, offering potential insights that could inform future clinical practice and research in the treatment of B-cell malignancies.

Finally, the last section of the report emphasizes key highlights from the ASH 2025 congress, especially the PARADIGM trial, suggesting a possible shift in AML treatment approaches. The abstract discusses the combination of azacitidine and venetoclax as an alternative to the traditional intensive chemotherapy (7+3) for fit, newly diagnosed patients with AML. ■

## Deepening and extending response to treatment in Multiple Myeloma

### Follow-up on long-term responders in the DREAMM-7 trial

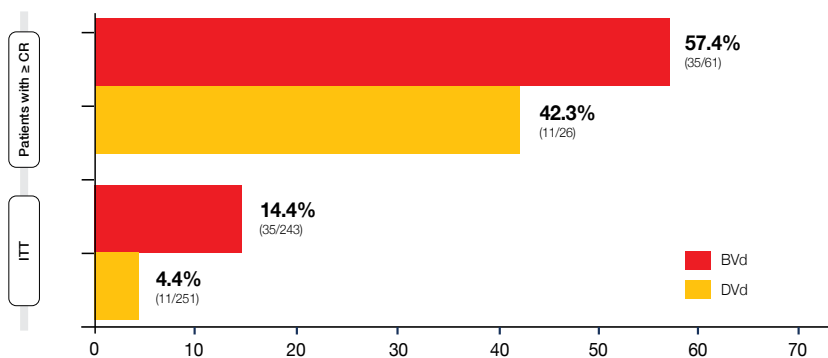
The open-label, randomized phase III trial DREAMM-7 compared the safety and efficacy of two combination treatments, BVd (Belantamab-Mafodotin, Bortezomib, dexamethasone) and DVd (Daratumumab + Vd) in patients with refractory and relapsing Multiple Myeloma (R/R MM) who have received  $\geq 1$  line of treatment (LOT). Belantamab-Mafodotin is a novel antibody-drug conjugate (ADC) targeting the B-cell matu-

ration antigen (BCMA) in myeloma cells. Patients in the BVd group experienced deeper responses and higher rates of minimal residual disease negativity (MRD-) compared to those in the DVd group. Total MRD rates were 25% vs. 10%, while MRD6 rates (1 cancer cell among 106 cells in peripheral leukocytes) were 16% vs. 4% [1].

At ASH 2025, Hungria et al. and Mateos et al. presented new data, following up on long-term responders and patients who achieved MRD- in the DREAMM-7 trial. Patients who responded for at least 36 months were

considered long-term responders (LTR). In the BVd arm, 72% of patients achieved at least a complete response (CR) compared to 57% in the DVd arm. Response durability was strongly associated with the depth of response. In the BVd vs. DVd treatment arms, 75% vs. 70% of LTRs who achieved  $\geq$  CR and 73% vs. 58% of LTRs who achieved  $\geq$  very good partial response (VGPR) also reached MRD- status [2]. MRD- was achieved faster (11.14 vs. 17.02 months) and sustained significantly longer with BVd vs. DVd, reaching 12-month-rates of 57.4% vs. 42.3% in patients with  $\geq$  CR and 14.4% vs. 4.4% overall. Among MRD- patients, the BVd arm had a higher proportion of patients with unfavorable prognostic markers, with 40% vs. 27% having high-risk cytogenetics and 37% vs. 9% having had  $\geq 2$  LOT. This suggests BVd can induce deep responses in high-risk patients more effectively than DVd [3].

The safety profiles in the MRD- and long-term responder groups were consistent with the primary analysis and similar between treatment arms, thus confirming the established efficacy of the BVd regimen in patients with R/R MM [2,3].



**Figure 1:** Rate of patients achieving MRD negativity with BVd and DVd in DREAMM-7. ITT, intention-to-treat.

### Long-term follow-up in DREAMM-8

DREAMM-8 is a phase III, open-label, randomized clinical trial that evaluated the safety and efficacy of the BpD (Belantamab-Mafodotin, Pomalidomide and dexamethasone) vs. the Pvd (Pomalidomide, Bortezomib and dexamethasone) treatment regimen in patients with R/R MM after ≥1 line of treatment. At a median follow-up of 21.8 months, BpD demonstrated superior efficacy over Pvd in terms of progression-free survival (PFS) (12-month PFS rate: 71% vs. 51%) [4].

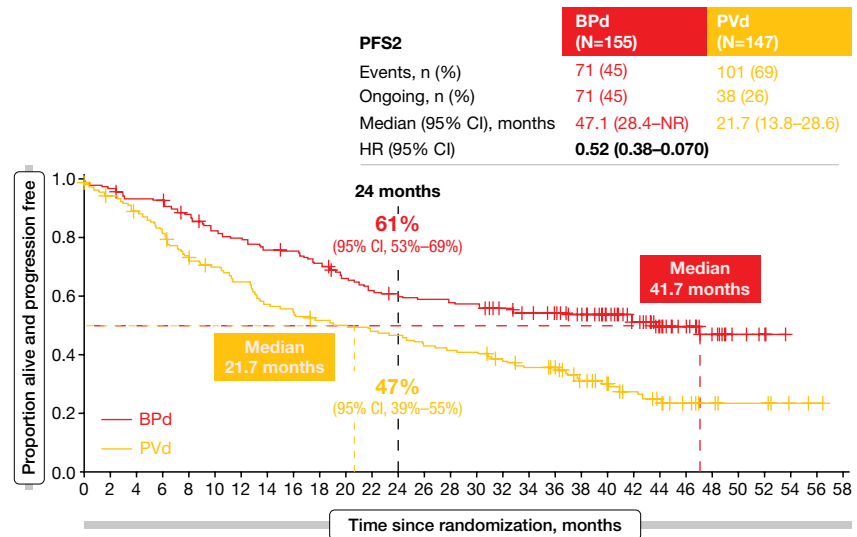
A presentation by Trudel et al. showed long-term follow-up data (median: 35.8 months) from DREAMM-8, including efficacy and safety findings. Deep responses to treatment occurred more frequently with BpD vs. Pvd (VGPR: 63% vs. 39%; CR: 43% vs. 17%) and more patients achieved MRD- (28% vs. 6%; 64% vs. 36% in patients who achieved CR). CR-based MRD- was sustained for ≥12 months in 15% vs. 3% of the intention-to-treat populations. This resulted in a markedly longer median progression-free survival (mPFS; 32.6 months vs. 12.5 months), which persisted into the subsequent antimyeloma therapy (mPFS2: 47.1 months vs. 21.7 months).

The updated safety data was consistent with the primary analysis, confirming the previously established manageable safety profile [4].

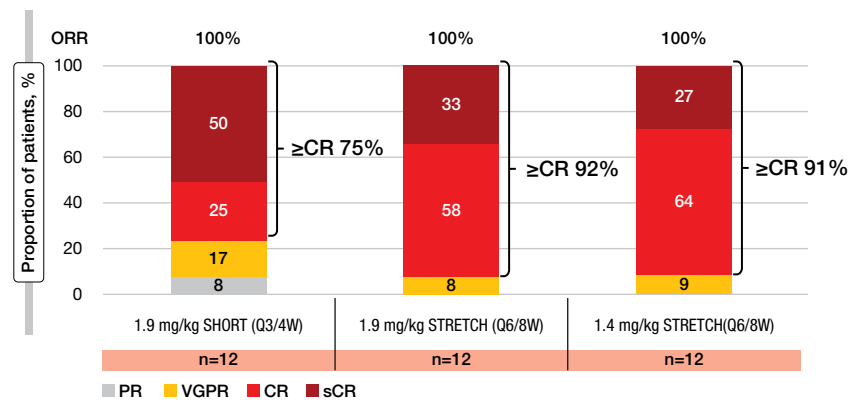
### Treatment efficacy and Ocular Events in DREAMM-9

The phase I, randomized clinical trial DREAMM-9 is a dose-finding and schedule-evaluation study investigating Belantamab-Mafodotin + VRd (BVRd) in patients with transplant-ineligible, newly diagnosed MM (TI NDMM). Data from three cohorts with dosage regimens of 1.9 mg/kg three times in a four-week cycle (Q3/4W), 1.9 mg/kg Q6/Q8W, and 1.4 mg/kg Q6/8W were presented at the ASH 2025 congress. In the respective cohorts, rates of ≥ CR were at 75%, 92% and 91%, indicating poorer response at the most intensive dosing regimen; rates of stringent CR, however, were 50%, 33% and 27%, and MRD negativity occurred in 100%, 67% and 45% of participants with ≥ CR, respectively [5].

Intensity of treatment correlated with the occurrence of adverse events (AEs), e.g., Grade (Gr) 3/4 events related to Be-



**Figure 2:** Progression-free survival with BpD vs. Pvd after subsequent antimyeloma therapy (PFS2) in DREAMM-8. CI, confidence interval; HR, hazard ratio; NR, not reached.



**Figure 3:** Response rates in three DREAMM-9 cohorts. (s)CR, (stringent) complete response; ORR, objective response rate; Qx/Wy; x times in a y week cycle; (VG)PR, (very good) partial response.

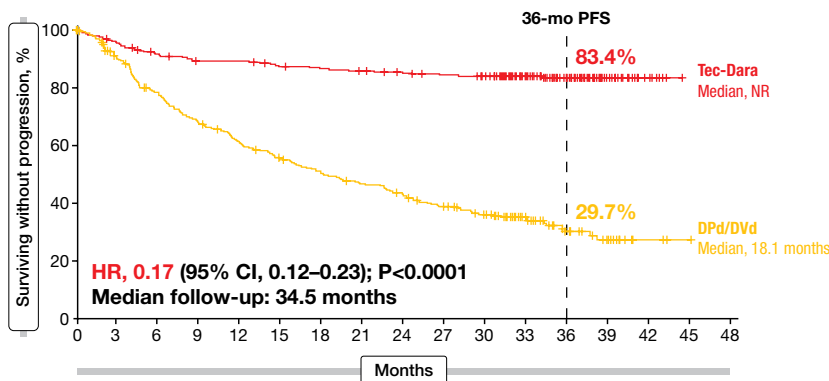
lantamab-Mafodotin (67% vs. 25% vs. 33%). This, however, did not apply to the rate at which at least one treatment drug was discontinued (50% vs. 42% vs. 50%). Interestingly, ocular examination findings (OEFs) Gr ≥ 2, especially bilateral decrease in best corrected visual acuity (BCVA) to 20/50, did not occur at increased rates with higher treatment intensity (50% vs. 50% vs. 50%). Ocular events were managed by dose delays and schedule extensions and resolved for the most part (resolution of first decrease in BCVA to 20/50 or worse: 100% vs. 100% vs. 67%) [5].

To conclude, these data indicate that the BVRd treatment regimen was highly efficacious for patients with NDMM, resulting in high MRD- rates that were strong predictors of long-term response. The authors concluded that strategies for mitigating ocular events remained a priority.

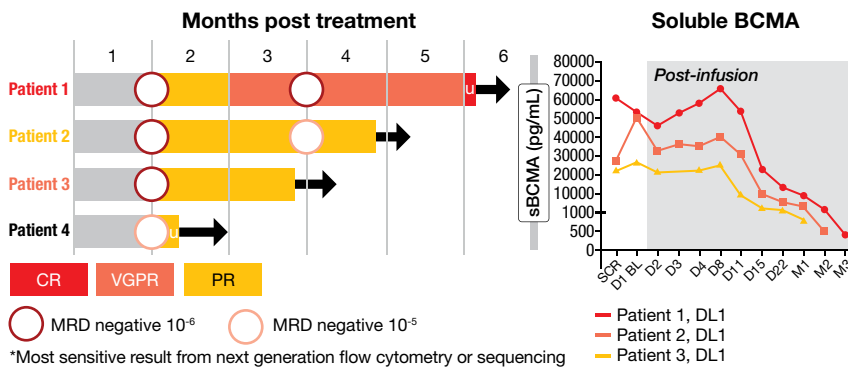
### Teclistamab + Daratumumab superior to DVd/DPd combinations: MajesTEC-3

MajesTEC-3 is a phase III, randomized clinical trial, comparing Teclistamab + Daratumumab (Tec + Dara) to Dara + Dexamethasone and Bortezomib (DVd) or Pomalidomide (DPd) by investigator's choice in patients with R/R MM who had 1-3 LOT. Tec is a bispecific antibody targeting the B-cell maturation antigen (BCMA) and CD3, while Dara is an anti-CD38 monoclonal antibody.

At the primary analysis presented by Mateos et al., MajesTEC-3 met its primary PFS endpoint, achieving a 36-month rate of 83.4% vs. 29.7% in the DVd/DPd treatment arm. This advantage was seen in all analyzed patient subgroups, including patients ≥ 75 years, with prior anti-CD38 exposure, high-



**Figure 4:** Progression-free survival in the Tec-Dara vs. DPd/DVd treatment arms. MajesTEC-3 clinical trial. CI, confidence interval; HR, hazard ratio; NR, not reached.



**Figure 5:** Ongoing responses in the four initial patients treated with KLN-1010 in the inMMycAR trial. CR, complete response; DL, dose level; MRD, minimal residual disease; (VG)PR, (very good) partial response; sBCMA, soluble B-cell maturation antigen.

grade disease and high-risk cytogenetics. Importantly, the curve reached a plateau after 6-12 months. Tec-Dara led to CR in 81.8% vs. 32.1% of patients, and 58% vs. 17.1% achieved MRD- status. This translated into a substantial overall survival (OS) benefit, with 83.3% vs. 65% of patients still alive after 36 months [6].

The most common adverse events were neutropenia (any Gr: 78.4%; Gr 3/4: 75.6%) and cytokine release syndrome (CRS; any Gr: 60.1%; Gr 3/4: 0%). Three patients (1.1%) experienced immune ef-

factor cell-associated neurotoxicity (ICANS), one of which had Gr 4 ICANS, which led to discontinuation of Teclistamab. All CRS and ICANS events have been resolved. Rates of treatment discontinuation (4.6% vs. 5.5%) and fatal treatment-emergent adverse events (TEAEs; 7.1% vs. 5.9%) were comparable between treatment arms. Most TEAE-related deaths in the Tec-Dara group were associated with infection (4.6% total).

The authors conclude that the plateauing PFS curve suggests Tec-Dara has

the potential to be a functional cure, with its CRS profile enabling its adoption as a new standard of care (SOC) for the second line (2L) and following lines [6].

### In-patient CAR-T cell generation leads to MRD-outcome: inMMycAR study

A new in vivo gene therapy, KLN-1010, generates anti-BCMA CAR-T cells in patients. Harrison et al. reported preliminary findings from the first-in-human, phase I, inMMycAR trial in patients with R/R MM. KLN-1010 is based on lentiviral particles, eliminating the need for ex vivo cultivation and lymphodepletion before administration, thereby simplifying logistics and reducing time and financial burden [7].

KLN-1010 demonstrated greater anti-myeloma activity vs. ex vivo generated CAR-T cell products in mice and high specificity for T-cells in animal models. The inMMycAR trial is a dose-escalation and expansion trial with three dose levels and ~20 study participants. The initial four patients showed CAR-T cell expansion and persistence for at least one month and memory T-cell formation. All patients achieved MRD- status one month after treatment and showed continuously decreasing levels of serum free light chain, monoclonal protein spike and soluble BCMA.

Among this small number of patients, no events of ICANS, delayed neurotoxicity, or CRS Gr ≥ 3 were recorded. The authors report a favorable safety profile compared to ex vivo CAR-T cell products.

In conclusion, KLN-1010 has the potential to become the first available off-the-shelf CAR-T cell therapy if the safety findings from this phase I trial are confirmed, and responses are durable in continued follow-up and later phase trials. ■

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## New BTK modalities in B-cell malignancies

### Fixed-duration versus continuous targeted treatment for previously untreated CLL

Results from the CLL17 trial (NCT04608318) presented by Othman Al-Sawaf [8].

Targeted agents such as Bruton tyrosine kinase inhibitor (BTKi; e.g., ibrutinib) and B-cell lymphoma-2 inhibitors (BCL2i) have emerged for the treatment of Chronic Lymphocytic Leukemia (CLL). One of the approved first-line treatments for patients with CLL is the time-limited combination of venetoclax,

a first-generation BCL2i, with the anti-CD20 antibody obinutuzumab.

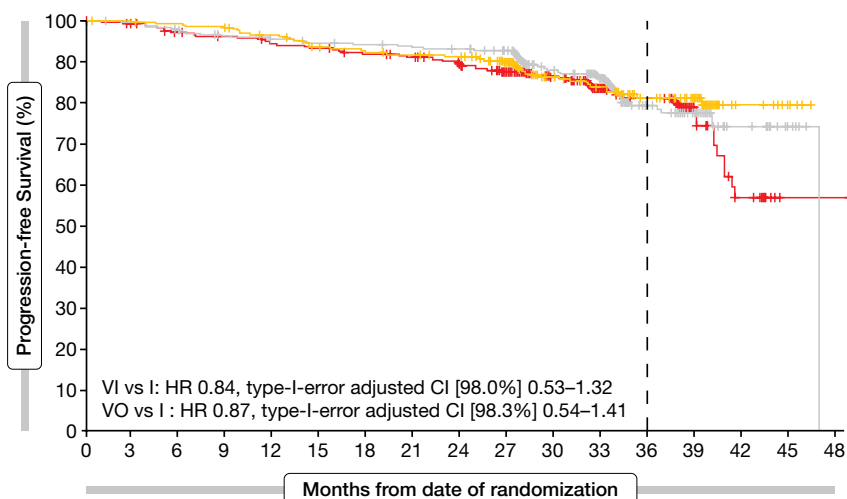
Currently, treatment paradigms can be classified into two categories: continuous BTKi or fixed-duration regimens combining BCL2i with a CD20 antibody or BCL2i with BTKi. These two paradigms were compared with chemo-immunotherapy; however, a direct comparison between them is lacking.

In this prospective, randomized, investigator-initiated, phase III trial, Al-Sawaf et al. tested which of these targeted agents and regimens had the longest PFS and how they compared under randomized testing. For this pur-

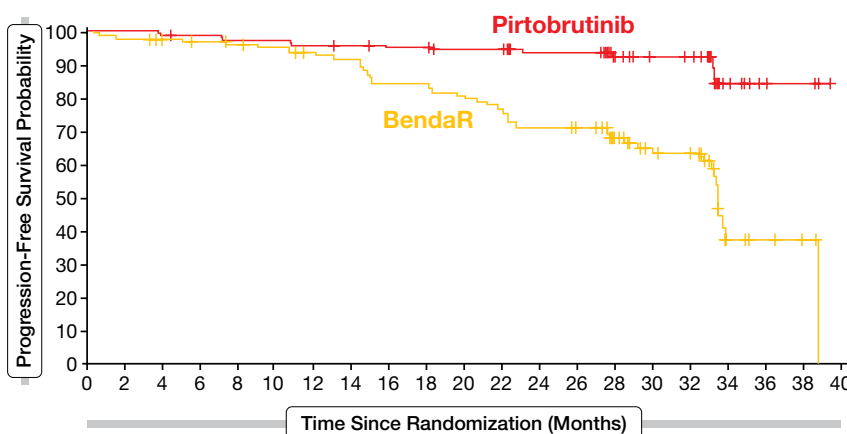
pose, they designed the trial comparing continuous ibrutinib (I) monotherapy to fixed-duration venetoclax plus obinutuzumab (VO) and fixed-duration venetoclax plus ibrutinib (VI) for CLL. The hypothesis was to test the noninferiority of VO vs. I and of VI vs. I, with PFS as the primary endpoint.

Patients were randomized to receive, I) ibrutinib continuously until intolerance or progression (n = 301), or II) fixed-duration venetoclax plus obinutuzumab for 6 cycles (28 days each) followed by 6 additional cycles of venetoclax monotherapy (n = 303), or III) fixed-duration venetoclax plus ibrutinib (VI, n = 305), initiated with a 3-cycle ibrutinib lead-in, followed by 12 cycles of VI.

The results revealed that 3-year PFS was 81.0% for I, 79.4% for VI and 81.1% for VO. In conclusion, venetoclax plus obinutuzumab and venetoclax plus ibrutinib were non-inferior in investigator-assessed PFS compared with continuous ibrutinib and can be considered as the preferred treatment option for patients with previously untreated CLL. Considerations for treatment, such as the ongoing follow-up and infection control, should be taken into account, and it should be noted that PFS may not be the only clinically relevant endpoint for CLL.



**Figure 6:** Progression-free survival (%) results for ibrutinib (I), venetoclax plus obinutuzumab (VO), and venetoclax plus ibrutinib (VI) groups from the CLL17 trial [9]. CI, confidence interval; HR, hazard ratio.



**Figure 7:** Progression-free survival for pirtobrutinib and bendamustine plus rituximab in the BRUIN CLL-313 study.

### Pirtobrutinib vs. bendamustine plus rituximab (BR) in patients with CLL/SLL

First results from the BRUIN CLL-313 (NCT05254743) trial examining a non-covalent BTKi in untreated patients presented by Wojciech Jurczak (2025) [10].

Pirtobrutinib is a highly selective, non-covalent (nc) BTKi. While covalent BTKi have significantly improved PFS for untreated patients with CLL, there are no phase III data assessing an ncBTKi.

In this global, open-label, randomized phase III study, the efficacy and safety of pirtobrutinib were evaluated. Pirtobrutinib was compared vs. benda-

mustine plus rituximab (BendaR), which is a common frontline chemoimmunotherapy for patients with previously untreated CLL or small lymphocytic lymphoma (SLL) lacking a 17p deletion/TP53 mutation.

A total of 282 patients were randomized 1:1 to receive continuous pirtobrutinib monotherapy (200 mg once daily) or 6 cycles of BendaR. The trial's primary endpoint was PFS assessed by an independent review committee (IRC). A stratified log-rank test was employed to compare PFS using a two-sided alpha threshold of 0.05.

The results demonstrated that pirtobrutinib significantly improved PFS compared with BendaR at a median follow-up of 28.1 months (HR: 0.199; 95% CI: 0.107-0.367;  $p < 0.0001$ ).

Furthermore, in this trial, pirtobrutinib was well tolerated, consistent with its known safety profile, with low rates of discontinuation and atrial fibrillation/flutter. Overall, pirtobrutinib demonstrated statistically significant superiority over BendaR in IRC-assessed PFS in treatment-naïve CLL/SLL. It should be noted that, at the time of publication [11], this was the third positive phase III study of pirtobrutinib in patients with CLL/SLL, and future research is needed to examine outcomes of covalent BTKi after ncBTKi to address sequencing questions.

### Sustained efficacy of zanubrutinib vs. bendamustine + rituximab in TN SLL/CLL

**6-year follow-up in the Phase III SEQUOIA study (NCT03336333) presented by Constantine Tam (2025) [12].**

SEQUOIA is a global phase III, open-label, randomized study that investigated zanubrutinib, a next-generation covalent BTKi with potentially improved selectivity as compared to ibrutinib. The study included patients with treatment-naïve (TN) CLL/SLL with or without the del(17p) mutation. In this poster session at the ASH 2025 congress, updated efficacy results from the SEQUOIA study, with a median long-term follow-up of approximately 6 years, were presented.

The primary goal was to compare the efficacy of zanubrutinib vs. chemoimmunotherapy with bendamustine and rituximab.

Participants were randomized 1:1 to receive zanubrutinib (Arm A,  $n = 241$ ) or bendamustine plus rituximab (Arm B,  $n = 238$ ). Neither Arm A nor Arm B patients had del(17p). Zanubrutinib was administered at a dose of 160 mg twice daily (BID) until unacceptable toxicity or end of the study. Bendamustine plus rituximab was administered for a maximum of 6 cycles.

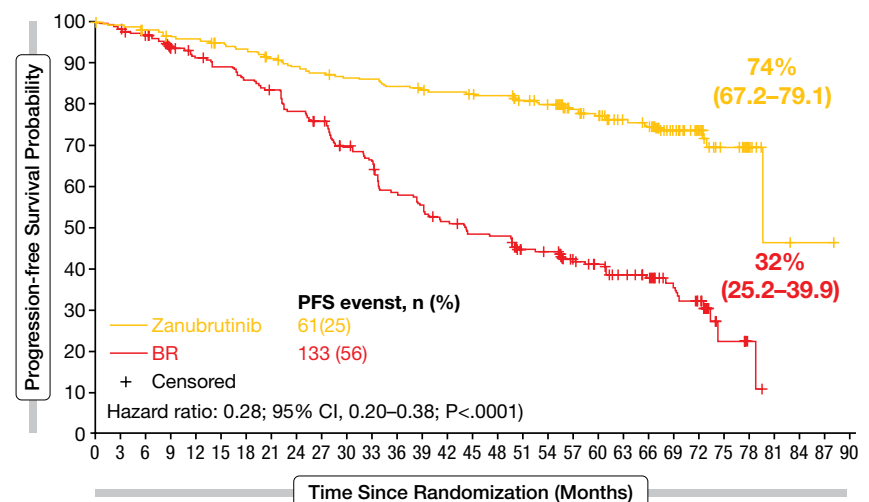
Participants in Arm C ( $n = 111$ ) had del(17p), and all patients in Arm C received zanubrutinib without randomization. As a side note, Arm C might represent the largest collection of patients with del(17p) receiving frontline treatment.

Additionally, the PFS rate in Arm C when adjusted for COVID-19 was 65% (95% CI, 54.3-73.5). At 72 months, 83% of patients in Arm C (95% CI, 73.6-88.6)

### Symptom-Based Progression-Free Survival (S-PFS) as a Patient-Centric Endpoint in CLL/ SLL

*In this talk during the ASH 2025 congress, the symptom-based PFS results for the ALPINE trial were presented by Jennifer Brown (2025) [13].*

Advances in BTKi have improved the treatment landscape for CLL/SLL. Given this, there is a need for patient-focused approaches and outcome measures to complement traditional endpoints, such as PFS. In this patient-reported outcome (PRO)- focused presentation, the association between longitudinal deterioration in disease-specific symptoms and time to disease progression (defined as PFS events) was evaluated.



**Figure 8:** Progression-free survival for zanubrutinib (Arm A) and bendamustine plus rituximab (BR; Arm B). The graph represents results in patients without the del(17p) mutation. CI, confidence interval.

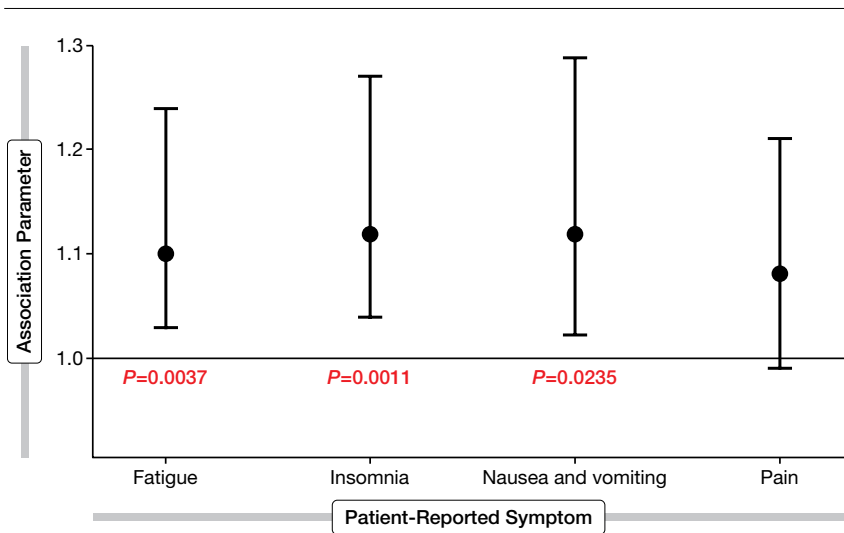
had not yet initiated subsequent treatment. Thus, in patients with del(17p), zanubrutinib may improve the historically poor prognosis.

The safety profile of zanubrutinib was consistent with prior studies, and fewer patients treated with zanubrutinib ( $n = 27$ ) required subsequent treatment as compared to patients treated with bendamustine plus rituximab ( $n = 84$ , including 67 who crossed over).

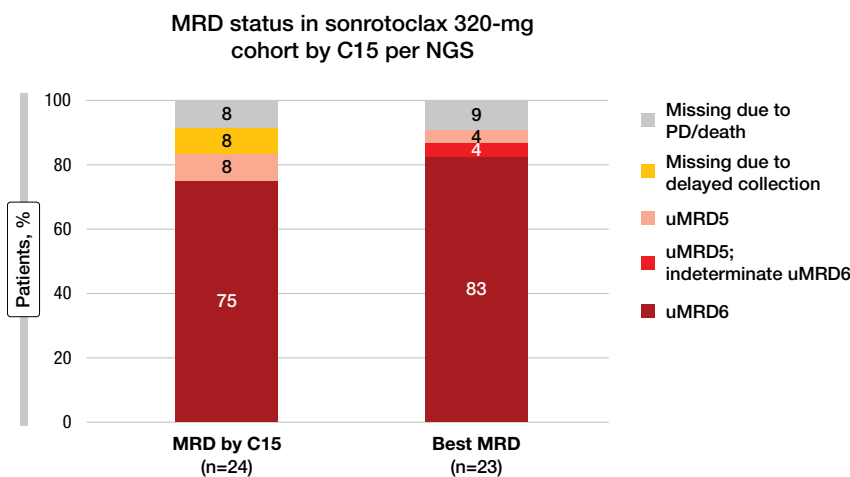
In conclusion, at a 6-year long-term follow-up, zanubrutinib continues to demonstrate robust efficacy and sustained superiority over bendamustine plus rituximab, including among patients with del(17p) mutations.

For context, the ALPINE trial included patients with relapsed/refractory (R/R) CLL/SLL with  $\geq 1$  prior treatment ( $N = 652$ ) who were randomized in a 1:1 stratified fashion in two groups: zanubrutinib 160 mg BID or ibrutinib 420 mg once daily. Treatment was continued until disease progression or unacceptable toxicity. As evidenced by prior research, improved PFS in patients with R/R CLL treated with zanubrutinib compared with ibrutinib has been observed.

For the purpose of assessing the association between PROs and PFS events, the EORTC-QLQ-C30 questionnaire was used as a PRO instrument. Deterioration was classified as  $\geq 10$ -point worsening



**Figure 9:** Association parameter indicating an increase in hazard of disease progression when a PRO worsening event for CLL-related symptom domains is observed; calculated with the joint model framework.



**Figure 10:** MRD status in sonrotoclax 320 mg cohort at the end of treatment cycle 15 per NGS. C, Cycle; (u)MRD, (undetectable) minimal residual disease; PD, progressive disease.

from baseline, and CLL-related outcomes (fatigue, nausea/vomiting, insomnia, and pain) were considered.

A joint model framework combining mixed-effects logistic regression (to estimate the probability of longitudinal symptom deterioration) and Cox proportional hazards regression (to estimate time to investigator-assessed PFS) served as the basis for statistical analysis. The hazard ratio (HR) of >1 indicated an increase in hazard of disease progression when a PRO worsening event is observed. In other words, HR >1 would indicate if symptom worsening predicts the risk of earlier disease progression.

These findings support an association between worsening patient-reported symptoms (particularly in-

creased fatigue, insomnia, and nausea/vomiting) and disease progression. In conclusion, future studies could develop symptom-based PFS to demonstrate treatment effectiveness.

### Sonrotoclax combination with obinutuzumab continued to demonstrate safety and efficacy in TN CLL

The time-limited combination of venetoclax and obinutuzumab (Ven + Obi) as a first-line therapy for patients with CLL has resulted in a high rate of undetectable MRD and extended PFS, but its use may be constrained by toxicity [14]. Sonrotoclax (BGB-11417), a next-generation BCL2i, is a more selective and pharma-

cologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation [15]. Marc Hoffmann shared the initial results from a cohort of the Phase I/Ib BGB-1147-101 study evaluating sonrotoclax (Sonro) + Obi in TN CLL patients, which used MRD status to guide treatment discontinuation [16].

The conventional dosing of Obi (6 cycles, 1000 mg) was followed. Obi monotherapy was initiated one cycle before the start of Sonro. Sonro was administered orally QD, with ramp-up to target doses of 160 or 320 mg until PD, unacceptable toxicity, or uMRD4 (<1 CLL cell per 10,000 leukocytes [ $<0.01\%$ ]) in peripheral blood by next-generation sequencing (NGS) after 15 treatment cycles. Only data for Sonro 320 mg + Obi were discussed, as data for Sonro 160 mg + Obi were still immature and were presented only for reference.

Patients enrolled in the study had a median age of 62 years, with 65% male. Approximately 10% had del(17p) or TP53 mutations, and approximately 60% had unmutated IGHV status.

The drug combination was generally well tolerated, with most TEAEs being low-grade. The most common Gr  $\geq 3$  TEAEs were neutropenia and thrombocytopenia; neutropenia was not linked to serious infections, and thrombocytopenia did not cause major bleeding. There were no TEAE-related deaths, and no treatment discontinuations related to Sonro. Two cases of laboratory tumor lysis syndrome were observed during the Obi ramp-up, but none occurred during the Sonro ramp-up.

An ORR of 94% and a CR/CRi rate of 40% were observed. During the median study follow-up of 12.3 months, there were two episodes of Richter's transformation in the Sonro 320 mg cohort, both of which occurred early in cycle 2 and cycle 6. The estimated 18-month PFS rate was 94.3% (95% CI: 83.5%-98.1%).

All patients who reached cycle 15 with an NGS sample analyzed achieved at least uMRD5 and discontinued therapy as defined per protocol. Approximately 90% of patients achieved uMRD6, and all patients remained in remission, with a median time off treatment of 7.2 months (range: 1.7-14.4 months).

In conclusion, the combination of Sonro + Obi was well tolerated and showed potent activity in patients with

TN CLL. A registrational phase III study (CELESTIAL-RRCLL, BGB-11417-303) assessing this combination is currently recruiting patients with relapsed/refractory CLL.

**Sonrotoclax is effective in heavily pretreated patients with MCL**

Sonrotoclax is a 2nd generation BCL2i with higher affinity and better selectivity for its target compared to venetoclax. The BGB-11417-201 phase I/II dose escalation trial investigates the safety and efficacy of sonrotoclax (160 mg QD -> 320 mg QD) in patients with mantle cell lymphoma (MCL) who relapsed after ≥1 line of CD20-based therapy and ≥1 line of BTK inhibition but no previous BCL2i exposure.

Of 125 patients enrolled in the trial, 115 received sonrotoclax 320 mg QD. No dose-limiting toxicities (DLTs) were observed. 42 patients (36.5%) experienced TEAEs, mostly infections. In 31 patients (27%), TEAEs led to treatment modifications, including 31 temporary interruptions and one dose reduction. The most common Gr ≥3 TEAEs (≥5%) were neutropenia (19.1%), thrombocytopenia (9.6%), anemia (7.8%), infections (16.5%) and tumor lysis syndrome (TLS) (7.0%).

The objective response rate (ORR; PR + CR) at the recommended phase 2 dose (RP2D) of 320 mg QD was 52.4%, and the CR rate was 15.5% at a median follow-up of 14.2 months. All subgroups with ≥5 patients showed an ORR benefit relative to the 30% historical control. Patients who responded to treatment remained in response for a median of 15.8 months, yielding an mPFS of 6.5 months. Median OS was not reached [17].

In summary, sonrotoclax demonstrated significant efficacy with good tolerability in a heavily pretreated patient population.

**Resistance to BTKi spurs evaluation of early-phase BTK degraders**

Patients with CLL/SLL experience disease progression with BTKi, often due to resistance mutations in BTK [18]. BTK degraders are a new class of drugs that specifically block B-cell receptor signaling by promoting proteasome-mediated degradation of both wild-type BTK and

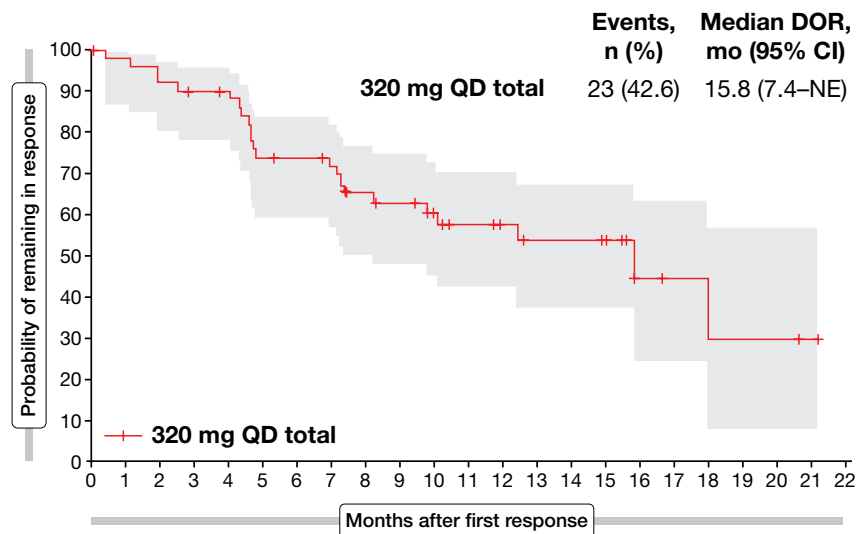


Figure 11: Probability of remaining in response for patients with partial and complete responses in the BGB-11417-201 clinical trial. CI, confidence interval; DOR, duration of response; NE, not evaluable; QD, once daily.

BTK-resistant mutations. Initial data from two new BTK degraders currently being tested in phase I/II trials in relapsed/refractory CLL/SLL were presented at ASH 2025 [19,20].

Inhye Ahn presented results from the CLL/SLL cohort of the CaDanCe-101 (BGB-16673-101) study, an open-label, dose escalation/expansion study evaluating monotherapy with BGB-16673 in patients with B-cell malignancies [19].

Eligible patients must have confirmed R/R CLL/SLL with ≥2 prior therapies, including a covalent BTK inhibitor (cBTKi), if approved for their disease. In total, 68 CLL/SLL patients were treated

with the drug at a dose between 50 and 600 mg once daily orally. Patients were heavily pre-treated, with a median of 4 prior lines of therapy (range, 2-10), and almost 90% discontinued prior BTKi due to disease progression. After a median treatment duration of 13.6 months, TEAEs occurred in 95.6% of patients, most commonly fatigue (36.8%) and contusion (bruising; 30.9%). Grade ≥3 TEAEs occurred in 61.8% of patients, primarily neutropenia (25%) and pneumonia (12%). Three patients discontinued treatment due to treatment-related TEAEs, and no treatment-related deaths were reported.

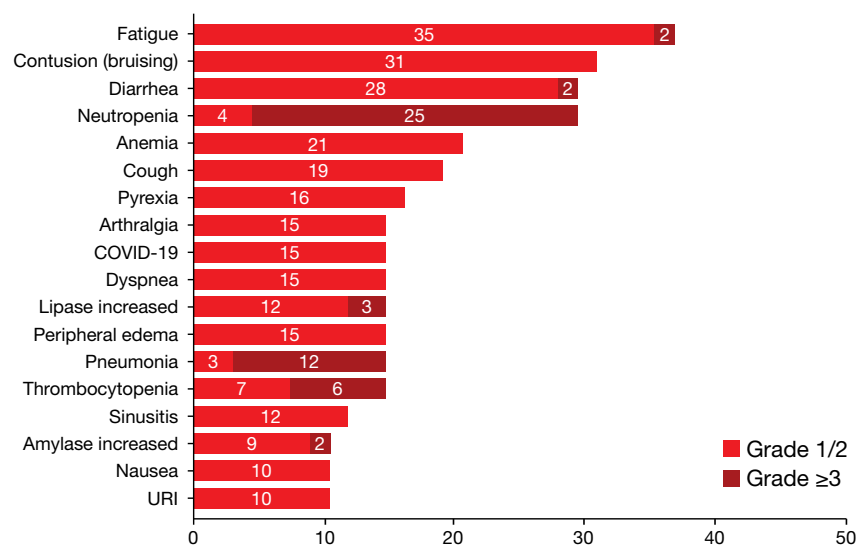
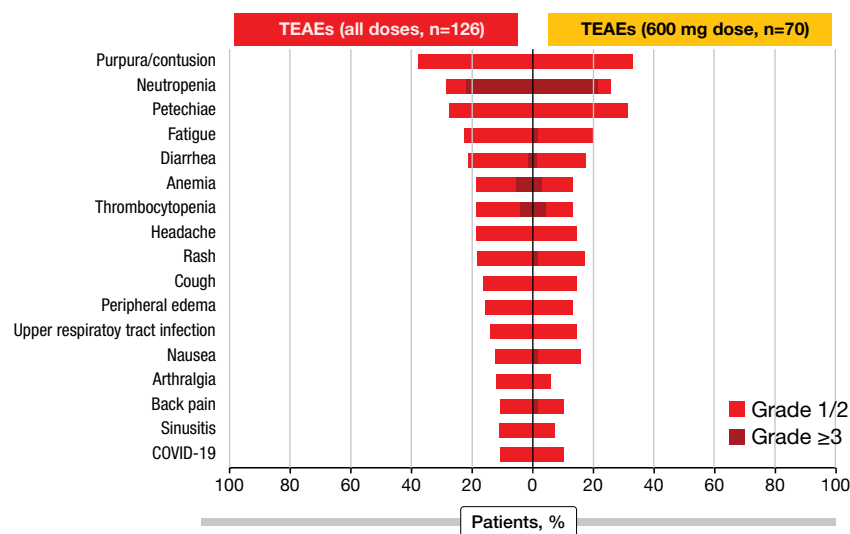


Figure 12: Summary of all grade TEAEs in ≥10% of all patients from CaDanCe-101. TEAE, treatment-emergent adverse event.



**Figure 13:** TEAEs in  $\geq 10\%$  in Phase 1a/b NX-5948-301 comparing 600 mg group vs all patients. TEAE, treatment-emergent adverse event.

The ORR was 85.3%, with most patients achieving PR (72.1%) or partial response with lymphocytosis (PR-L; 10.3%). The intermediate dose of 200 mg showed the highest ORR (94.4%). Significant antitumor activity was observed, regardless of BTK mutation status and the number of prior lines of therapy. ORR was 75% in patients with triple exposure to covalent BTK, non-covalent BTK, and BCL2 inhibitors. After a median study follow-up of 19.8 months, the 18-month PFS rate of 65.9% indicating

sustained disease control. Based on these results, the 200 mg dose was selected as the recommended dose for the expansion study. BGB-16673 is currently being evaluated in ongoing phase II and phase III studies in R/R CLL.

Zulfa Omer presented updated findings from the first-in-human trial (NX-5948-301) of a novel BTK degrader, bexobrutideg, in patients with relapsed/refractory B-cell malignancies [20]. The phase Ia/Ib study included 126 heavily pretreated CLL/SLL patients treated

with a range of bexobrutideg doses (50–600 mg). After a median follow-up of 19 months (phase Ia, 9.8 months in phase Ib), bexobrutideg was well tolerated with no dose-limiting toxicities. The most common adverse events were purpura/contusion, neutropenia (grade  $\geq 3$ : 23.7%), fatigue, and diarrhea.

The ORR was 83% (CR-rate of 4.3%), with rapid responses (median 1.9 months) and sustained remissions (median PFS: 22.1 months) across all doses, including those in difficult-to-treat subgroups with baseline BTK mutations, high-risk molecular features and central nervous system involvement. In the Phase Ib randomized cohort of the trial (200 mg vs. 600 mg), higher ORR and superior PFS were observed at the 600 mg bexobrutideg dose, supporting its selection as the recommended phase 2 dose. Bexobrutideg will be evaluated in the ongoing pivotal phase II DAYBreak CLL-201 and planned phase III DAYBreak CLL-306 trials.

These early findings from two new BTK degraders showed a manageable safety profile and rapid, profound remissions in heavily pretreated CLL groups, particularly those resistant to BCL2i or covalent/non-covalent BTKi, offering hope for new treatment options for CLL/SLL patients. ■

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## A PARADIGM shift in newly diagnosed fit AML

### Aza-Ven outperforms standard care for AML patients eligible for intensive chemotherapy

Standard initial treatment for acute myeloid leukemia (AML) patients varies based on age and fitness. Typically, **younger and fit patients**, under 65 years old, receive intensive induction chemotherapy (IC), commonly known as the “7+3” regimen, which consists of cytarabine and an anthracycline, followed by consolidation therapy, allogeneic stem-cell transplantation (HCT), or a combination of both [21]. In contrast, the standard for **older or unfit patients** has shifted toward lower-intensity but effective combinations of the BCL2 inhibitor venetoclax paired with the hypomethylating agent azacitidine (Aza-Ven), based on the VIALE-A phase III data [22]. Results from the PARADIGM study presented at ASH 2025 challenged the current standard by testing whether Aza-Ven is superior to IC in fit patients [23].

The investigator-initiated, open-label, multicenter, phase II randomized trial enrolled previously untreated adult AML patients eligible for IC and randomized them 1:1 to receive Aza-Ven or IC (7+3 regimen or liposomal daunorubicin and cytarabine [CPX351]). Patients with t(15;17), acute promyelocytic leukemia, core binding factor alterations, FLT3 mutations, NPM1 mutations (if aged <60 years), BCR::ABL1 fusion or mixed phenotype AML were excluded from the study. Patients were allowed to proceed to HCT on both treatment arms following a response. The primary endpoint was event-free survival (EFS), with key secondary endpoints being response rates, overall survival (OS), toxicity, hospitalization metrics, and quality of life (QoL).

In total, 172 patients were enrolled (86 per treatment arm), with a median age of 64 years and 67% male. The major-

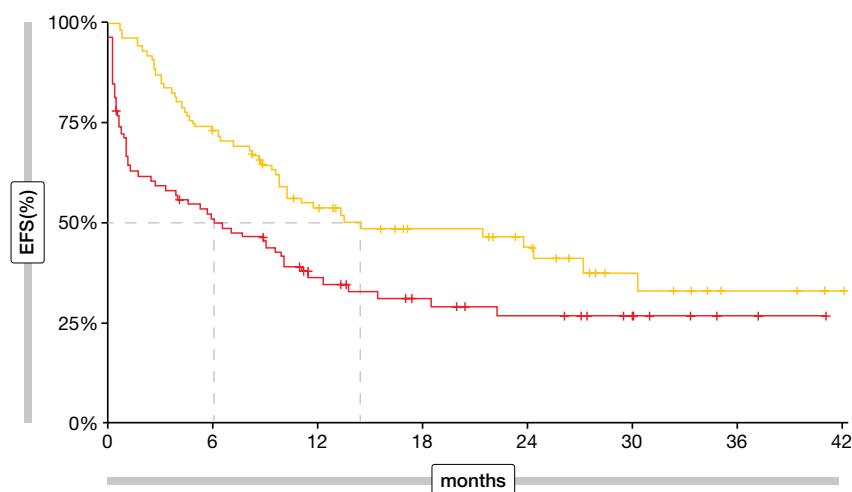


Figure 14: Primary endpoint of event-free survival (EFS) for Aza-Ven (yellow) vs. IC (red)

ity of patients (72%) were in the adverse risk category (ELN 2022), and the distributions of risk category and mutation did not differ across arms. At a median follow-up of 21.9 months, the trial’s primary endpoint was met, showing that Aza-Ven extended the median EFS to 14.6 months compared with 6.15 months with IC ( $p = 0.0021$ ). The 1-year EFS was 53.4% with Aza-Ven vs. 36.0% with IC.

Overall response rates were markedly different (88% for Aza-Ven vs. 62% for IC;  $p < 0.0001$ ), as were composite remission rates (78% for Aza-Ven vs. 54% for IC;  $p = 0.0006$ ). While complete remission rates were similar (56% vs. 49%;  $p = 0.2227$ ), more patients treated with Aza-Ven proceeded to HCT (61% vs. 40%;  $p = 0.009$ ), suggesting that Aza-Ven not only induces remissions but also preserves fitness for transplantation. Even after adjustment for HCT, the effect of Aza-Ven on EFS still remained protective (HR 0.67;  $p = 0.0302$ ).

The secondary endpoint of OS was not statistically significant with a median OS of 21.5 months vs. 18.6 months with Aza-Ven vs. IC ( $p = 0.1873$ ). The authors ar-

gued that, as many patients who start IC subsequently receive hypomethylating agent plus Ven, OS is a challenging endpoint to pursue and interpret in a setting where placebo control is not feasible.

The toxicity data and patient-reported outcomes also favored the Aza-Ven arm, with numerically fewer infections and bleeding events, significantly improved QoL and symptom burden during initial therapy, and less time in the hospital and the ICU. The ICU admission rates in the first 30 days and the 60-day mortality on the Aza-Ven arm were both 0% vs. 9.6% and 4.7% in the IC arm, respectively.

In conclusion, the phase II PARADIGM study met its primary endpoint, demonstrating significantly improved EFS with Aza-Ven vs. IC in functionally fit patients with newly diagnosed AML. Furthermore, PROs indicated that Aza-Ven improved QoL and was associated with reduced healthcare utilization. Together, these findings support the use of Aza-Ven in functionally fit patients with intermediate or adverse-risk, FLT3-wildtype AML. ■

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