# ASH 2023 MRD highlights

Adaptive Biotechnologies

## Multiple myeloma

New data in multiple myeloma (MM) advanced both treatment approaches and diagnostic utility, with studies like IsKia and PERSEUS showing that upfront quadruple therapies (Isa-KRd, D-VRd) lead to better outcomes, especially in high-risk patients by achieving deeper MRD negativity. Additionally, new findings suggested the utility of peripheral blood MRD testing as a feasible and early indicator of treatment response, enhancing disease monitoring and decision-making.

## Non-Hodgkin's lymphoma

A central theme of this year's conference was the rapidly growing interest in MRD analysis in NHL. The VIPOR and BOVen trials were key examples, demonstrating the prognostic value of MRD testing in relapsed/refractory DLBCL and the utility of MRD-guided treatment duration in MCL, respectively. The findings from these studies support the integration of MRD analysis into clinical practice, pointing towards a more precise and personalized approach to NHL treatment.

## Chronic lymphocytic leukemia

New data presented in CLL, including the FLAIR study, demonstrated the value of MRD-guided treatment, showing that adopting Ibrutinib-Venetoclax therapy duration based on MRD status can improve survival outcomes. The CLL13 trial further highlighted the significance of achieving MRD <10$^{-4}$ across various treatment options, underscoring the importance of monitoring deep responses in the context of novel combination therapies.

## IsKia: Upfront quads and MRD as a primary endpoint

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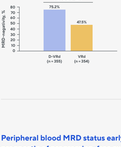
| Title | Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone vs. Carfilzomib-Lenalidomide-Dexamethasone as Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients |
| Plenary | Francesca Gay, et al., Sunday, 12/10/2023, 2-4 p.m. |
| Disease state | Multiple myeloma |
| Research phase | Phase 3 |
| Primary objective | Assess the efficacy and safety of isatuximab-carfilzomib-lenalidomide-dexamethasone (Isa-KRd) vs. KRd alone as pre-ASCT induction and post-ASCT consolidation |




HRCA high-risk cytogenetic abnormalities

### Key results

- Post-consolidation MRD negativity was significantly higher for Isa-KRd arm at both MRD sensitivity thresholds, though the relative difference in response was more pronounced at 10$^{-6}$.
- Isa-KRd increased rates of MRD negativity (10$^{-5}$ and 10$^{-6}$) after each treatment phase and across all patient subgroups relative to KRd.
- Subgroup analysis of cytogenetic risk demonstrated that MRD at a threshold of 10$^{-5}$ provided greater discrimination for the superiority of Isa-KRd in patients with 2+ HRCA relative to a threshold of 10$^{-6}$.

### Potential impact

- First readout of a phase 3 study in multiple myeloma that incorporates MRD as a primary endpoint.
- Assessment of MRD at 10$^{-6}$ being more informative of treatment response, particularly in higher risk patients, strengthens rationale for examination of this threshold in future studies.

## PERSEUS: Upfront quads and MRD as a secondary endpoint

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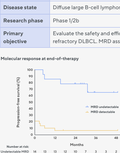
| Title | LBA-1 Phase 3 Randomized Study of Daratumumab (DARA) + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus Vrd Alone in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Who Are Eligible for Autologous Stem Cell Transplantation (ASCT): Primary Results of the Perseus Trial |
| Late breaking oral | Pieter Sonneveld, et al., Tuesday, 12/12/2023, 9-10:30 a.m. |
| Disease state | Multiple myeloma |
| Research phase | Phase 3 |
| Primary objective | Evaluate the efficacy and safety of D-VRd induction/consolidation with dara-R maintenance compared to VRd induction/consolidation with R maintenance in transplant eligible newly diagnosed multiple myeloma patients. |




### Key results

- While overall MRD negativity rate at 10$^{-5}$ was significantly higher in D-VRd arm vs. VRd arm (secondary endpoint), the difference between treatment groups was more pronounced at 10$^{-6}$.
- Sustained MRD negativity rate of 64.8% at 10$^{-5}$.
- Maintenance was MRD-adapted: 207 of 322 patients on dara-R maintenance discontinued dara based on sustained MRD negativity for 12 months while in complete response. Outcomes have not yet been reported.

### Potential impact

- These data likely signal the completion of a shift in standard of care for implementation of a CD38-containing quad regimens as frontline treatment in newly diagnosed multiple myeloma patients.
- The more pronounced differences between patient subsets at 10$^{-6}$ compared to 10$^{-5}$ add to a growing dataset highlighting the utility of deeper thresholds of analysis and the necessity of using an assay which can reliably reach these levels of assessment.

## Peripheral blood MRD status early in treatment of multiple myeloma is prognostic of progression-free survival and overall survival

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| Title | Early Peripheral Blood Minimal Residual Disease Status By NGS in Patients with Newly Diagnosed Multiple Myeloma on a Phase 2 Trial Receiving Elotuzumab, Carfilzomib, Lenalidomide, and Dexamethasone (Elo-KRd) |
| Poster | 4747. Benjamin A. Derman, et al., Monday, 11/11/2023, 6-8 p.m. |
| Disease state | Multiple myeloma |
| Research phase | Phase 2 |
| Primary objective | Evaluate the concordance and prognostic significance of early MRD status by next generation sequencing (NGS) in both the bone marrow and peripheral blood |


PB peripheral blood

### Key results

- At this early timepoint, there was no progression-free survival difference when patients were stratified by clinical response alone (i.e., complete response vs. non-complete response).
- Consistent with previous findings, disease burden was found to be higher in bone marrow than in the peripheral blood compartment (1.38 logs).
- Despite the difference between compartments, clonoSEQ MRD positivity from peripheral blood cycle 4 was associated with inferior progression-free survival and overall survival.

### Potential impact

- Authors suggest peripheral blood MRD early in therapy may be an indicator of early response and can be informative if bone marrow testing is not available.

## VIPOR: ctDNA assessed via clonoSEQ at end of treatment in relapse/refractory DLBCL is predictive of outcomes

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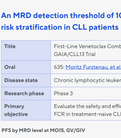
| Title | Phase Ib/II Study of Multi-Targeted Therapy with Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (VIPOR) in Relapsed/Refractory Diffuse Large B-Cell Lymphoma |
| Oral | 434. Christopher Melani, et al., Sunday, 12/10/2023, 9:45 a.m. |
| Disease state | Diffuse large B-cell lymphoma (DLBCL) |
| Research phase | Phase 1/2b |
| Primary objective | Evaluate the safety and efficacy of the VIPOR regimen in 50 patients with relapsed/refractory DLBCL. MRD assessed via ctDNA using clonoSEQ |




EOT: end of treatment

### Key results

- At end of treatment, ctDNA was undetectable in 14 of 42 evaluable patients.
- Fourteen of 15 patients (93%) in complete response at end of treatment had undetectable ctDNA. Nine patients remain ctDNA negative at 2-years from enrollment.
- Patients with undetectable ctDNA at cycle 2 and end of treatment had significantly longer progression-free survival relative to patients with detectable ctDNA.

### Potential impact

- Although this study used the previous version of Adaptive's ctDNA assay, these data strengthen the case for the utility of NGS MRD testing in the relapsed/refractory setting for patients with DLBCL.

## MRD status used to determine duration of the BOVen regimen in high-risk mantle cell lymphoma

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| Title | A Multicenter, Phase 2 Trial with Zanubrutinib, Obinutuzumab and Venetoclax (BOVen) in Patients with Treatment-naive, TP53-mutant Mantle Cell Lymphoma |
| Oral | 738. Anita Kumar, et al., Monday, 12/11/2023, 11:45 a.m. |
| Disease state | Mantle cell lymphoma (MCL) |
| Research phase | Phase 2 |
| Primary objective | Evaluate the safety and efficacy of the BOVen regimen in 25 patients with untreated mantle cell lymphoma with a TP53 mutation |




uMRD: detectable MRD, EOT: end of treatment, FU: follow up, sMRD: undetectable MRD

### Key results

- MRD-guided strategy: Patients in complete response and peripheral blood MRD-negative at week 24 stopped treatment.
- 95% of patients (18/19) had undetectable MRD by clonoSEQ (10$^{-5}$) at cycle 13.
- Sensitivity matters: None of the patients that achieved undetectable MRD at 10$^{-5}$ and stopped therapy required retreatment. Both patients that stopped therapy with undetectable MRD at 10$^{-4}$ required retreatment.

### Potential impact

- Demonstrates the feasibility of MRD testing in peripheral blood to guide therapy duration in MCL.
- Add to a growing evidence base that MRD sensitivity (10$^{-4}$ vs. 10$^{-5}$) has uniquely high prognostic value for this disease state.

## Growing support for fixed duration, MRD-guided approaches in chronic lymphocytic leukemia

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| Title | Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study |
| Oral | 631. Peter Hillmen, et al., Sunday, 12/10/2023, 4:30 p.m. |
| Disease state | Chronic lymphocytic leukemia (CLL) |
| Research phase | Phase 3 |
| Primary objective | Compare the safety and efficacy of MRD-guided ibrutinib-venetoclax to FCR |




FCR: fludarabine-cyclophosphamide-rituximab; I: ibrutinib; sMRD: undetectable MRD; V: venetoclax

### Key results

- MRD performed via flow cytometry at a threshold of 10$^{-4}$.
- Unique MRD-guided strategy: Total duration of I-V was double the time after MRD negative (i.e., MRD negative at 2-years; 4 years therapy).
- Survival results indicated that I-V therapy is optimized with an MRD-adapted approach.

### Potential impact

- May be representative of growing shift toward acceptance of MRD-guided, fixed duration approaches in CLL; "I+V with duration guided by MRD is a new gold standard for CLL treatment."
- In a separate oral presentation, the authors suggest that "for MRD-guided treatment in the future, bone marrow assessment may be replaced with peripheral blood monitoring if the uMRDS threshold is applied."

## An MRD detection threshold of 10$^{-6}$ improves risk stratification in CLL patients

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| Title | First-Line Venetoclax Combinations in CLL: 4-Year Follow-up From the Phase 3 GAIA/CLL13 Trial |
| Oral | 635. Moritz Furstenau, et al., Sunday, 12/10/2023, 5:30 p.m. |
| Disease state | Chronic lymphocytic leukemia (CLL) |
| Research phase | Phase 3 |
| Primary objective | Evaluate the safety and efficacy of three fixed-duration venetoclax regimens relative to FCR in treatment-naive CLL patients |




CR: complete response, EOT: end of treatment, FCR: fludarabine-cyclophosphamide-rituximab, PFS: progression-free survival, PR: partial response, pts: patients, uMRD: undetectable MRD

### Key results

- NGS MRD performed via EuroClonality-NGS group.
- Despite differences in uMRD6 rates, MRD -10$^{-4}$ was prognostic relative to lower thresholds across all treatment arms.
- Among uMRD6 patients, PFS was similar for patients assessed as CR or PR at 3 months post-EOT.

### Potential impact

- Demonstrates prognostic value of MRD assessed at 10$^{-4}$ relative to lower sensitivity thresholds.
- Suggests that traditional response criteria are not sufficient to differentiate among patients that have achieved MRD <10$^{-4}$.