Themes from ASCO and EHA 2024

Adaptive biotechnologies™

Multiple myeloma

- Upfront quadruple therapy further established as standard of care
- MRD analyses at 10^{-6} becoming routine in large multiple myeloma trials
- Broad interest in approaches to sequencing immunotherapy

Non-Hodgkin's lymphoma

- Broadening therapeutic options in follicular lymphoma
- Optimization of CAR-T therapy in relapsed/refractory disease
- Continued interest in bi-specifics

Chronic lymphocytic leukemia

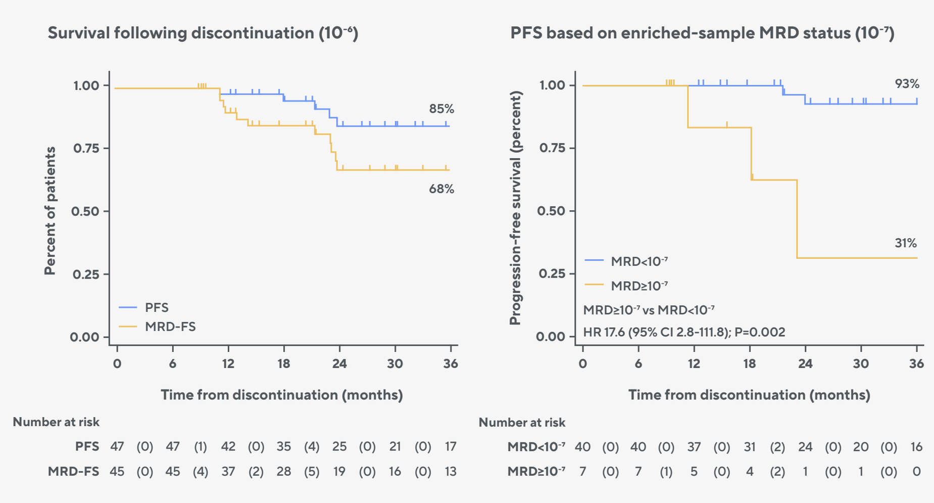
- Continued evaluation of MRD-guided therapy and targeted combination therapy

Acute lymphoblastic leukemia

- Newer CAR-T therapies and peripheral blood monitoring

MRD2STOP: MRD assessment of CD138+ enriched samples identifies patients at risk of relapse following treatment discontinuation

Title	Discontinuation of maintenance therapy in multiple myeloma guided by multimodal measurable residual disease negativity (MRD2STOP)
Oral	Benjamin Derman, et al. Monday, June 3, 2024
Disease state	Multiple myeloma
Research phase	N/A
Primary objective	Investigate MRD resurgence and survival outcomes for 47 multiple myeloma patients who discontinued maintenance therapy after multi-modal MRD negativity



Key results

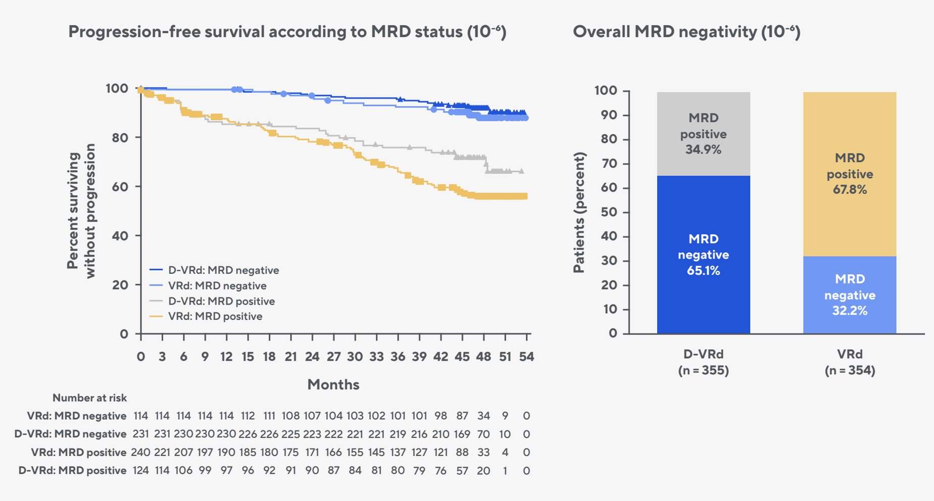
- Relatively low rates of MRD resurgence (10^{-6}) and disease progression were observed within three years of treatment discontinuation.
- Enriching samples for CD138+ cells allowed for detection of disease below a sensitivity threshold of 10^{-6}.
- Survival analyses based on an MRD threshold <10^{-6} indicate that this threshold detects patients with very low levels of disease who are at risk of future relapse.

Potential impact

- These data provide support for discontinuation of maintenance therapy as a viable option for multiple myeloma patients with persistent MRD negativity.
- Further research is needed, but enrichment strategies may one day provide an opportunity for broad-scale assessment of disease burden beyond the 10^{-6} threshold in multiple myeloma.

PERSEUS: Deepening response correlates with MRD negativity during maintenance with Dara-containing regimens

Title	Daratumumab (Dara) + bortezomib/lenalidomide/dexamethasone (VRd) in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM): Analysis of minimal residual disease (MRD) in the PERSEUS trial
Oral	Paula Rodriguez-Otero, et al. Monday, June 3, 2024
Disease state	Multiple myeloma
Research phase	Phase 3
Primary objective	Evaluate the efficacy and safety of Dara-VRd induction/consolidation with Dara-R maintenance compared to VRd induction/consolidation with R maintenance in transplant-eligible newly diagnosed multiple myeloma



Key results

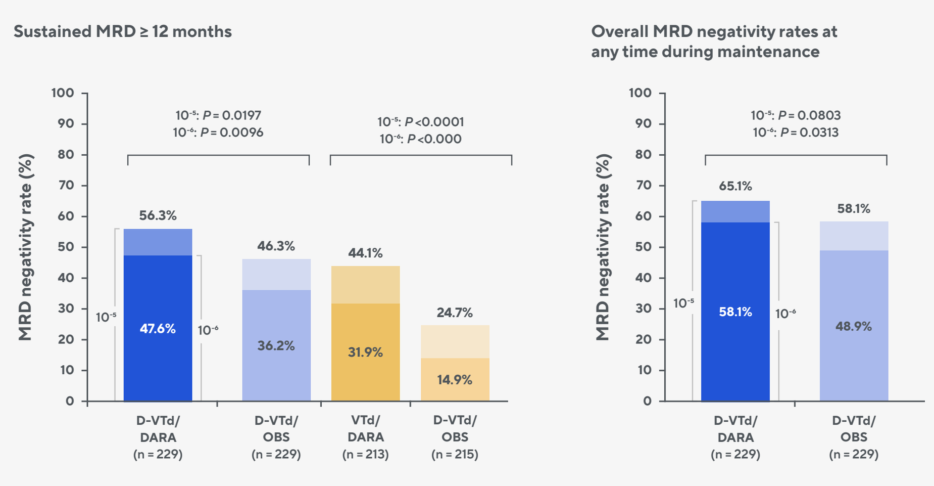
- Achievement of MRD negativity at 10^{-6} in both treatment arms translated to similar progression-free survival improvement compared to MRD positive patients.
- Overall MRD negativity rates at 10^{-5} and 10^{-6}, along with sustained MRD negativity rates at 12 and 18 months (10^{-5}), were uniformly higher among D-VRd treated patients compared to patients in the VRd arm.
- Rates of MRD negativity at 10^{-6} continued to increase through maintenance administration, with a more pronounced increase in the D-VRd arm relative to the VRd arm.

Potential impact

- The authors note that "the potential for a cure in NDMM is predicated on reaching sustained MRD negativity at 10^{-6}."
- D-VRd with D-R maintenance may emerge as a new standard of care in transplant-eligible newly diagnosed multiple myeloma.

CASSIOPEIA: MRD negativity as a prognostic indicator across multiple treatment phases

Title	Daratumumab (Dara) + Bortezomib/Thalidomide/Dexamethasone (VTd) Followed by Data Maintenance in Transplant-Eligible (TE) Newly Diagnosed Multiple Myeloma (NDMM): >6-Year Update of CASSEOPEIA
Oral	Philippe Moreau, et al. Thursday, June 13, 2024
Disease state	Multiple myeloma
Research phase	Phase 3
Primary objective	Evaluate the long-term safety and efficacy outcomes from 1,085 newly diagnosed multiple myeloma patients after a median follow-up period of greater than six years. Dara-VTd vs. VTd induction/consolidation; Dara vs. observation maintenance



Key results

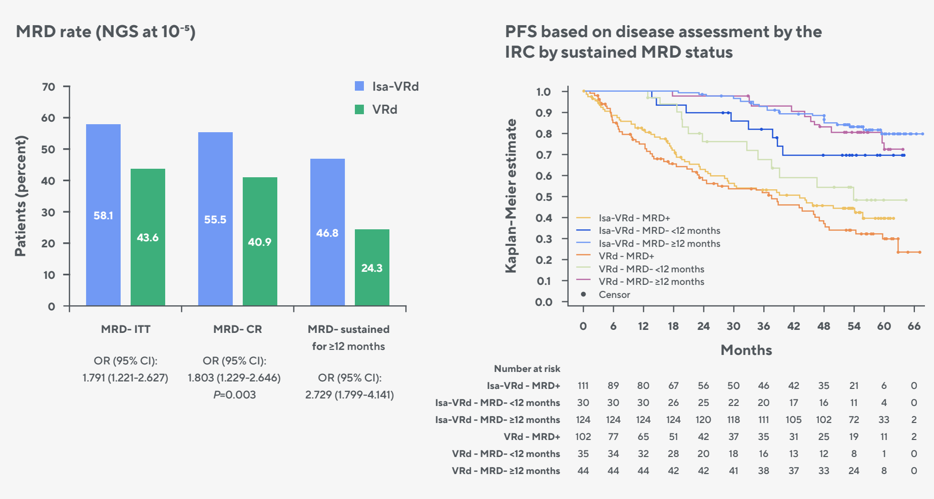
- Across treatment groups, sustained MRD negativity rates were highest for patients who received Dara during induction/consolidation and maintenance.
- For patients who received D-VTd followed by Dara or observation, the MRD negativity rates were significantly higher when assessed at 10^{-6}, but not at 10^{-5}.

Potential impact

- The response differentiation observed for MRD assessment at 10^{-6} relative to 10^{-5} further establishes the critical importance of deploying an assay that can reliably reach the deepest level of assessment.
- These results are part of a growing body of evidence showing the benefit of Dara in the maintenance setting for newly diagnosed multiple myeloma patients.

IMROZ: Elevating MRD-negative response rates with isatuximab-VRd in multiple myeloma

Title	Phase 3 study results of isatuximab, bortezomib, lenalidomide, and dexamethasone (Isa-VRd) versus VRd for transplant-ineligible patients with newly diagnosed multiple myeloma (IMROZ)
Oral	Thierry Facon, et al. Monday, June 3, 2024
Disease state	Multiple myeloma
Research phase	Phase 3
Primary objective	Evaluate the efficacy of IsaVRd vs. VRd alone in 446 patients with newly diagnosed multiple myeloma and transplant-ineligible



Key results

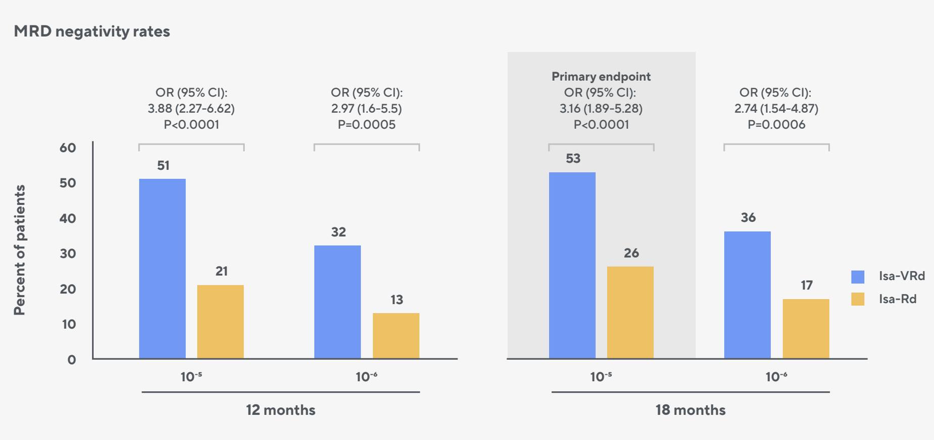
- Deeper MRD responses, and higher rates of sustained MRD negativity, were observed in the Isa-VRd arm relative to the VRd arm.
- For patients that achieved sustained MRD-negativity (10^{-5}), the progression-free survival benefit was similar regardless of treatment regimen.

Potential impact

- These data, alongside those from the BENEFIT study, support continuous post-induction treatment with anti-CD38 mAB-containing regimens for patients with transplant-ineligible newly diagnosed multiple myeloma.
- The marked difference in progression-free survival between patients with ≥12 months of MRD negativity vs. <12 months highlights the growing importance of assessing disease kinetics in this disease state.

BENEFIT: MRD provides an early and reliable read on outcomes and is being used as a primary endpoint in multiple myeloma

Title	Phase 3 randomized study of isatuximab (Isa) plus lenalidomide and dexamethasone (Rd) with bortezomib versus Isa-Rd in patients with newly diagnosed transplant-ineligible multiple myeloma (NDMM TI)
Oral	Xavier Leleu, et al. Monday, June 3, 2024
Disease state	Multiple myeloma
Research phase	Phase 3
Primary objective	Evaluate the added value of weekly bortezomib therapy to isatuximab plus lenalidomide and dexamethasone (IsaRd vs. Isa-VRd) in 270 transplant-ineligible patients with newly diagnosed multiple myeloma



Key results

- The study's primary endpoint, rate of MRD negativity at 18 months (10^{-5}) was higher in the Isa-VRd arm compared to the Isa-Rd arm (53% vs. 26%).
- MRD negativity rates assessed at 10^{-6} were also higher for patients treated with Isa-VRd compared to Isa-Rd.

Potential impact

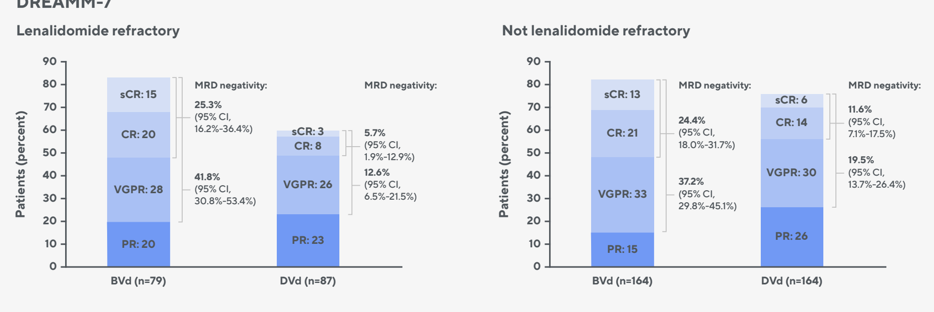
- This is the first phase 3 study to utilize MRD as a primary endpoint in transplant-ineligible newly diagnosed multiple myeloma patients.
- Data supporting the effectiveness of specific drug regimens in achieving deeper MRD levels at the 10^{-6} threshold may be useful in optimal pairing of agents, enhancing drug development strategies focused on combination therapies.

DREAMM-7 and -8: MRD negativity rates support utility of belantamab mafodotin in relapsed/refractory multiple myeloma

Title	DREAMM-7 update: subgroup analyses from a phase 3 trial of belantamab mafodotin (belamaf) + bortezomib and dexamethasone (BVd) vs. daratumumab, bortezomib, and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM)
Oral	Maria Victoria Mateos, et al. Monday, June 3, 2024
Disease state	Multiple myeloma
Research phase	Phase 3
Primary objective	Evaluate the efficacy and safety of belamaf in combination with BVd compared to DVd in 494 patients with relapsed or refractory multiple myeloma

Title	Results from the randomized phase 3 DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone (BPd) vs. pomalidomide plus bortezomib and dexamethasone (PVd) in relapsed/refractory multiple myeloma (RRMM)
Oral	Suzanne Trudel, et al. Sunday, June 2, 2024
Disease state	Multiple myeloma
Research phase	Phase 3
Primary objective	Evaluate BPd vs. PVd in 302 lenalidomide-exposed patients with relapsed or refractory myeloma

DREAMM-7



Key results

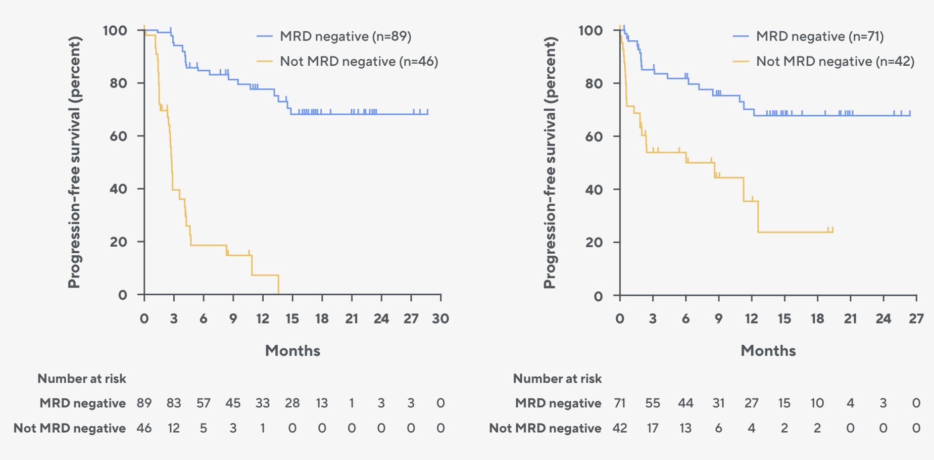
- **DREAMM-7:** Patients treated with BVd had higher MRD negativity rates (60% vs. 24%) and sustained MRD negativity rates (24% vs. 6%) compared to DVd-treated patients. MRD-related outcomes data were not described.
- **DREAMM-8:** Patients treated with BPd had higher MRD negativity rates (37% vs. 7%) and sustained MRD negativity rates (13% vs. 2%) compared to PVd-treated patients. MRD-related outcomes data were not described.

Potential impact

- These data signal the shifting treatment landscape in relapsed/refractory multiple myeloma and support the likely future utilization of belamaf-containing regimens.
- In multiple myeloma, MRD assessment by clonoSEQ continues to be the standard for differentiation of MRD response for novel agents/regimens.

EPCORE NHL-1: MRD assessment following treatment is predictive of outcomes in follicular lymphoma

Title	Epcoritamab induces deep responses in relapsed or refractory (R/R) follicular lymphoma (FL): safety and pooled efficacy data from EPCORE-NHL-1 pivotal and cycle (C) 1 optimization (Opt) FL cohorts
Oral	Umberto Vitolo, et al. Thursday, June 13, 2024
Disease state	Follicular lymphoma
Research phase	Phase 2
Primary objective	Evaluate the safety and efficacy of epcoritamab treatment in 86 patients receiving an optimized C1 dosing schedule relative to the pivotal cohort (n=128)



Key results

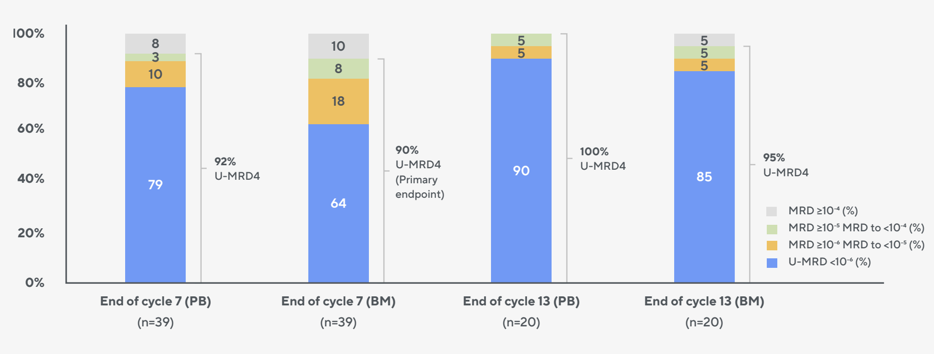
- MRD negativity at 10^{-6} from peripheral blood mononuclear cell samples was associated with improved progression-free survival (overall and at the cycle 3, day 1 landmark).
- MRD negativity rates were similar in the pivotal (dose expansion) cohort and the cycle 1 optimization cohort: 67% (61/91) and 64% (28/44), respectively.

Potential impact

- These data strengthen the growing body of data indicating that MRD negativity at 10^{-6} is prognostic for outcomes in follicular lymphoma.
- The cycle 1 optimized dosing to mitigate CRS and ICANS had similar MRD negativity rates and supports exploration of epcoritamab as an outpatient option.

The PVO regimen achieves very high rates of undetectable MRD (10^{-6}) in untreated CLL

Title	Combined pirtobrutinib, venetoclax, and obinutuzumab in first-line treatment of patients with chronic lymphocytic leukemia (CLL): A phase 2 trial
Oral	Nitin Jain, et al. Thursday, June 13, 2024
Disease state	Chronic lymphocytic leukemia
Research phase	Phase 2
Primary objective	Evaluate the safety and efficacy of triple combination therapy (pirtobrutinib, venetoclax, and obinituzumab) in 40 patients with untreated CLL



Key results

- Treatment with the PVO combination regimen resulted in high rates of MRD negativity at 10^{-6} in both peripheral blood (90%) and bone marrow (85%).
- No patient had disease progression or died within ~12 months of follow-up.

Potential impact

- Using an assay with 10^{-6} sensitivity provides meaningful insight into the full depth of response achieved with newer CLL therapies below the traditional threshold of 10^{-4}.

High concordance between peripheral blood and bone marrow MRD measurements in ALL, making peripheral blood monitoring feasible

Title	Comparison of immunoglobulin high-throughput sequencing MRD in bone marrow and peripheral blood in pediatric B-ALL: a report from the Children's Oncology Group AALL1731
Oral	Rachel Rau, et al. Monday, June 3, 2024
Disease state	Acute lymphoblastic leukemia
Research phase	N/A
Primary objective	Evaluate high-throughput sequencing (HTS) of immunoglobulin loci as a method to monitor MRD in peripheral blood by evaluating peripheral blood and bone marrow samples from 808 standard-risk patients enrolled in AALL1731

Key results

- There was a strong correlation between peripheral blood MRD and bone marrow MRD (10^{-6}) assessed at the end of induction in B-ALL patients.
- Peripheral blood MRD was detectable in most patients with bone marrow MRD, particularly for the standard-risk "high" group that had bone marrow MRD >0.01% by flow cytometry.
- The ratio of bone marrow to peripheral blood MRD was significantly higher in the standard-risk "high" group and in patients with unfavorable cytogenetic profiles.

Potential impact

- To date, this is the largest bone marrow/peripheral blood concordance dataset assessing MRD at 10^{-6}.
- These data support consideration of NGS MRD to assess peripheral blood MRD in patients with B-ALL, particularly when frequent monitoring is important.

ALL: acute lymphoblastic leukemia; B: belantamab; B-ALL: B-cell acute lymphoblastic leukemia; BPd: belantamab/mafodotin/pomalidomide/dexamethasone; BVd: bortezomib/dexamethasone; C: cycle; CAR T: chimeric antigen receptor T-cell; CLL: chronic lymphocytic leukemia; CRS: cytokine release syndrome; D: daratumumab; d: dexamethasone; Dara: daratumumab; DVd: daratumumab/bortezomib/dexamethasone; FL: follicular lymphoma; HTS: high-throughput sequencing; ICANS: immune effector cell-associated neurotoxicity syndrome; Isa: isatuximab; mAB: monoclonal antibodies; MRD: minimal residual disease; NDMM: newly diagnosed multiple myeloma; O: obinituzumab; P: pirtobrutinib; PFS: progression-free survival; PVd: pomolidomide/bortezomib/dexamethasone; PVO: pirtobrutinib/venetoclax/obinituzumab; R: lenalidomide; Rd: lenalidomide/dexamethasone; R/R: relapsed/refractory; TE: treatment-eligible; TI: treatment-ineligible; V: bortezomib; VRd: bortezomib/lenalidomide/dexamethasone; VTd: bortezomib/thalidomide/dexamethasone