Early vs Late Transplant in Multiple Myeloma

Sahar Parkhideh

Hematologist & Oncologist

Shahid Beheshti University of Medical Sciences

Taleghani Hospital

Transplant in Myeloma: Who, When, and Why?

The MM Landscape

- MM accounts for 1-1.8% of cancers and 10-15% of hematologic malignancies.
- MM caused 22% of deaths related to hematological cancers in the US in 2022.
- Significant improvements in overall survival (OS) due to new drug classes (IMiDs, PIs, anti-CD38 mAbs).
- 5-year survival rate increased from 25% (1975-1977) to ~60% (2012-2018).
- Standard of care for transplant-eligible (TE) NDMM includes induction, HD melphalan + ASCT, consolidation, and lenalidomide maintenance.

Evolution of Transplant-Based Strategies

- HD melphalan with ASCT was established based on Phase 2/3 randomized trials in the 1990s (vs. conventional chemotherapy).
- Transplant resulted in improved EFS, PFS, and/or OS in the pre-novel agent era.
- High response rates with IMiDs, PIs, and dexamethasone led to reassessment of HD therapy.
- Four randomized clinical trials confirmed HD melphalan + ASCT as a cornerstone for TE NDMM.

ASCT vs. Quadruplet Therapy

- No study has randomly compared ASCT and quadruplet regimens containing an anti-CD38 antibody (current standard).

- The IFM 2020-02 MIDAS study is addressing this question in a subgroup of patients with good prognosis.

Melphalan 200 mg/m2: The Conditioning Standard

- IFM95-02 trial established melphalan 200 mg/m2 (Mel 200) as the standard, based on noninferior EFS and OS, along with lower toxicity.
- More intensive regimens are being studied but are limited by toxicity.
- Combining melphalan with other drugs faces challenges due to adverse effects.

Table 1. Relevant randomized clinical trials comparing transplant with standard treatment in NDMM patients aged up to 70 years

Study	Starting year	Number of randomized patients	Induction	Transplant regimen	Standard regimen	Survival benefit of transplant
IFM90[10]	1990	200	VMCP/VBAP	Mel 140/TBI-8	VMCP/VBAP	EFS + OS
MAG90[11]	1990	185	VAMP	Cc/Cy/VP/Mel 140/TBI-12	VMCP	EFS
MAG91[14]	1991	190	VAMP	Bu/Mel 140 or Mel 200	VMCP	EFS
MRC7[12]	1993	401	VAMPC	Mel 200 or Mel 140/TBI	ABCM	PFS + OS
S9321[16]	1993	516	VAD	Mel 140/TBI-12	VBMCP	None
PETHEMA[15]	1994	164	VBMCP/VBAD	Mel 200 or Mel 140/TBI-12	VBMCP/VBAD	None
M97G[13]	1997	194	VAD	Mel 100 × 2	MP	EFS + OS
IFM2009[17,18]	2010	700	VRD (× 3)	Mel 200	VRD (× 5)	PFS
DETERMINATION[19]	2010	722	VRD (× 3)	Mel 200	VRD (× 5)	PFS + EFS
EMN02/HO95[20]	2011	1197	VCD (× 3 or 4)	Mel 200 (× 1 or × 2)	VMP	PFS + PFS2 + OS
FORTE[21]	2015	474	KRD or KCD (× 4)	Mel 200	KRD (× 8)	PFS
EMN CARTITUDE6[23]	2024	750 planned	DVRD (× 4)	Mel 200	cilta-cel	?

ABCM, doxorubicin-carmustine-cyclophosphamide-melphalan; CC, lomustine; cilta-cel, ciltacabtagene-autoleucel; Cy, cyclophosphamide; DVRD, daratumumab-bortezomib-lenalidomide-dexamethasone; VAD, vincristine-doxorubicin-dexamethasone; VAMP, vincristine-doxorubicin-methylprednisolone; VAMPC, vincristine-doxorubicin-methylprednisolone-cyclophosphamide; VBAD, vincristine-carmustine-doxorubicin-dexamethasone; VBAP, vincristine-carmustine-doxorubicin-prednisone; VCD, bortezomib-cyclophosphamide-dexamethasone; VMCP, vincristine-melphalan-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-dexamethasone; VP, etoposide; VRD, bortezomib-lenalidomide-dexamethasone.

Table 2. Main randomized clinical trials assessing intensified regimens before transplant

Trial	Regimens	Efficacy	Safety
IFM phase 2 study[25]	Mel 220 + anti-IL-6 vs Mel 220	CR: 37.5% vs 11%	One toxic death Grade 4 mucositis: 62.5%
NCT00217438[26]	Mel 280 + amifostine vs Mel 200 + amifostine	ORR: 74% vs 57% ($P = .04$) mPFS: 3.5 y vs 2.7 y mOS: 6.2 y vs 5.3 y	Grade 2/3 mucositis: 33% vs 12% ($P = .004$)
German study[27]	Mel 100 × 2 + Ida 20 × 3 + Cy 60 × 2 vs Mel 100 × 2	ORR: 85% vs 83% ($P = .01$) mEFS: 20 m vs 16 m ($P = .08$) mOS: 46 m vs 66 m ($P = .02$)	TRM: 20% vs 0% Grade 3/4 mucositis: 80% vs 27% ($P < .01$)
NCT01413178[28]	Mel 70 × 2 + Bu × 4 vs Mel 200	mPFS: 64.7 m vs 43.5 m ($P = .022$) 3-y 8 OS: 91% vs 89%	Mucositis: 96% vs 49% ($P < .0001$) Febrile neutropenia: 71% vs 30% ($P < .001$)
IFM2014-02[29]	Mel 200 + ortezomib × 4 vs Mel 200	CR: 23.4% vs 20.5%	Peripheral neuropathy: 4% vs 1.2%

Bu, busulfan; Cy 60, cyclophosphamide 60 mg/kg; Ida 20, idarubicine 20 mg/m^2; mEFS, median EFS; mOS, median OS; mPFS, median PFS; Mel 280, melphalan 280 mg/m^2; ORR, overall response rate; TRM, treatment-related mortality.

ASCT and Time to Transplant

- Optimal timing of ASCT is debated: early (≤12 months) vs. delayed (>12 months).
- Retrospective analysis of 363 MM patients undergoing ASCT (2006-2019)
- Early ASCT: ≤12 months from diagnosis (n = 201)
- Delayed ASCT: >12 months from diagnosis (n = 162)
- Compared baseline characteristics, response rates, PFS, OS, and TRM.

- Clinical Lymphoma, Myeloma and Leukemia, 2022

Early ASCT Improves Outcomes

- Post-ASCT Complete Response (CR) rate higher in the early ASCT group (77.1% vs. 64.8%; $P < 0.025$)
- PFS better in the early ASCT group: 69.5 months vs. 50.0 months ($P < 0.05$)
- OS from date of transplant was better in the early ASCT group: 119 months vs 89.5 months ($P < 0.02$)

Clinical Lymphoma, Myeloma and Leukemia, 2022

A More Nuanced Approach
Personalized, Response-Driven Strategy

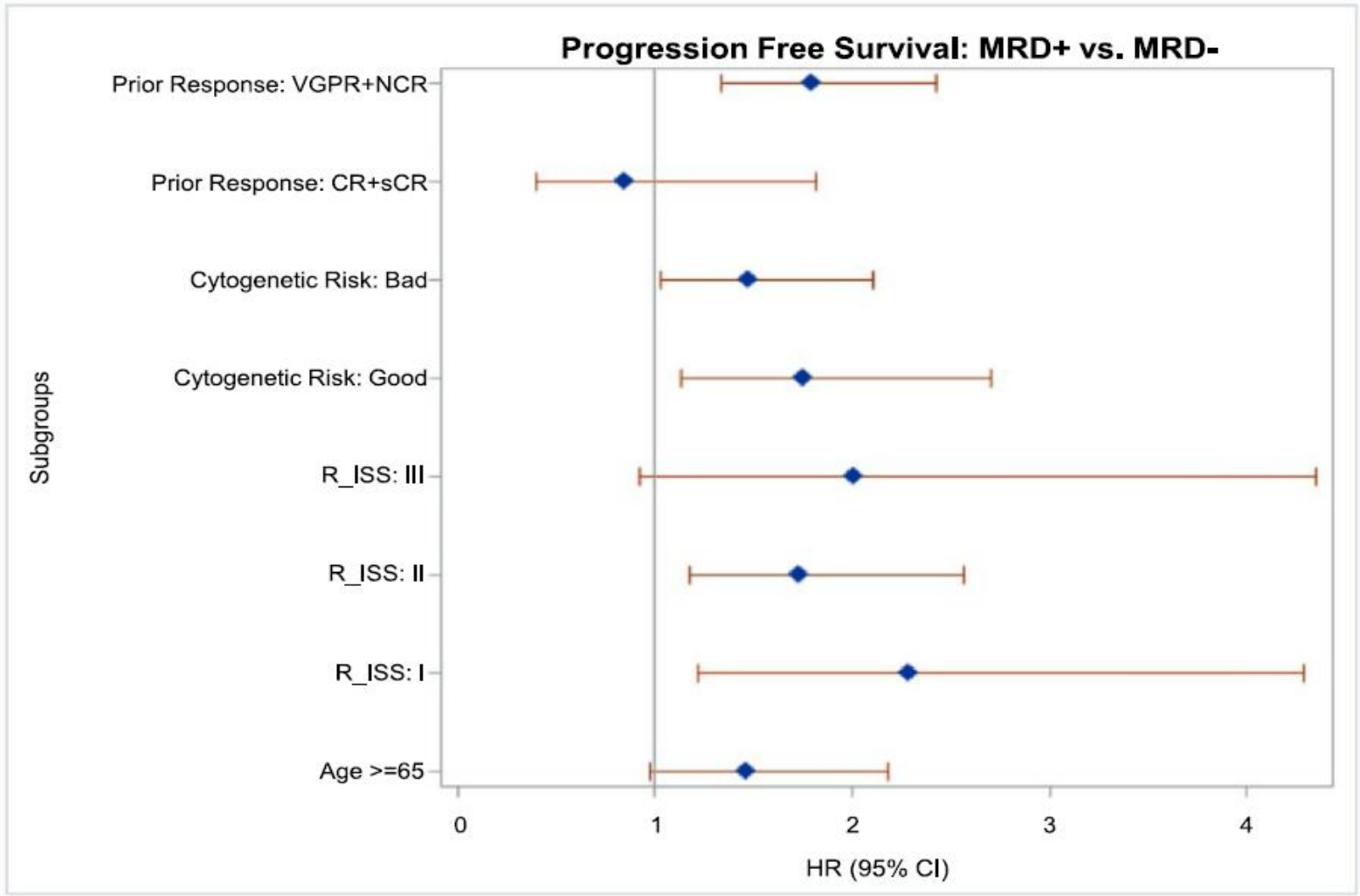
- MM treatment is being redefined; transplant is not a "one-size-fits-all" approach.
- Reasonable to collect stem cells but consider maintenance therapy without upfront ASCT in some patients.
- Monitor MRD status and consider ASCT for those who don't achieve deep responses or who relapse.
- High and Low risk is less meaningful now, give all available options up front to get deep response.

Landgren, ASH Clinical News, 2021

MRD Status as an Independent Predictor

- Pre-transplant MRDpos status was an independent predictor of shorter PFS (HR, 1.80; $p < 0.001$).
- Other factors: High-risk cytogenetics (HR, 1.86; $p < 0.001$) and post-transplant maintenance (HR, 0.49; $p < 0.001$).
- Pre-transplant MRD status predictive of PFS in most subgroups, including high-risk cytogenetics and VGPR before transplant.
- Not predictive in R-ISS stage III, ≥CR before transplant, and patients ≥65 years.

Pasvolsky et al., Cancer. 2024;130:1663–1672



Forest plot of subgroup analysis: impact of pretransplant minimal residual disease status on progression-free survival.

Pasvolsky et al., Cancer. 2024;130:1663–1672

Impact of Pre-Transplant MRD in Myeloma Patients Achieving ≥VGPR

- Retrospective, single-center study of 733 adult MM patients receiving upfront autoHCT (2015-2021).
- Patients achieved ≥VGPR after induction therapy and had pre-transplant MRD data by next-generation flow cytometry (NGF).
- Compared progression-free survival (PFS) and overall survival (OS) between MRD-negative (MRDneg) and MRD-positive (MRDpos) groups.

Pasvolsky et al., Cancer. 2024;130:1663–1672

Pre-Transplant MRD Affects Outcomes

- 425 patients were MRDneg and 308 were MRDpos at autoHCT.
- MRDpos group had more high-risk cytogenetic abnormalities and fewer achieved ≥CR before autoHCT.
- MRDpos patients had lower ≥CR rates post-transplant.

Pasvolsky et al., Cancer. 2024;130:1663–1672

PFS Significantly Shorter in MRDpos Group

- Median PFS: 48.2 months (MRDpos) vs. 80.1 months (MRDneg) ($p < 0.001$).

- No significant difference in overall survival (OS) between the groups ($p = 0.41$).

Pasvolsky et al., Cancer. 2024;130:1663–1672

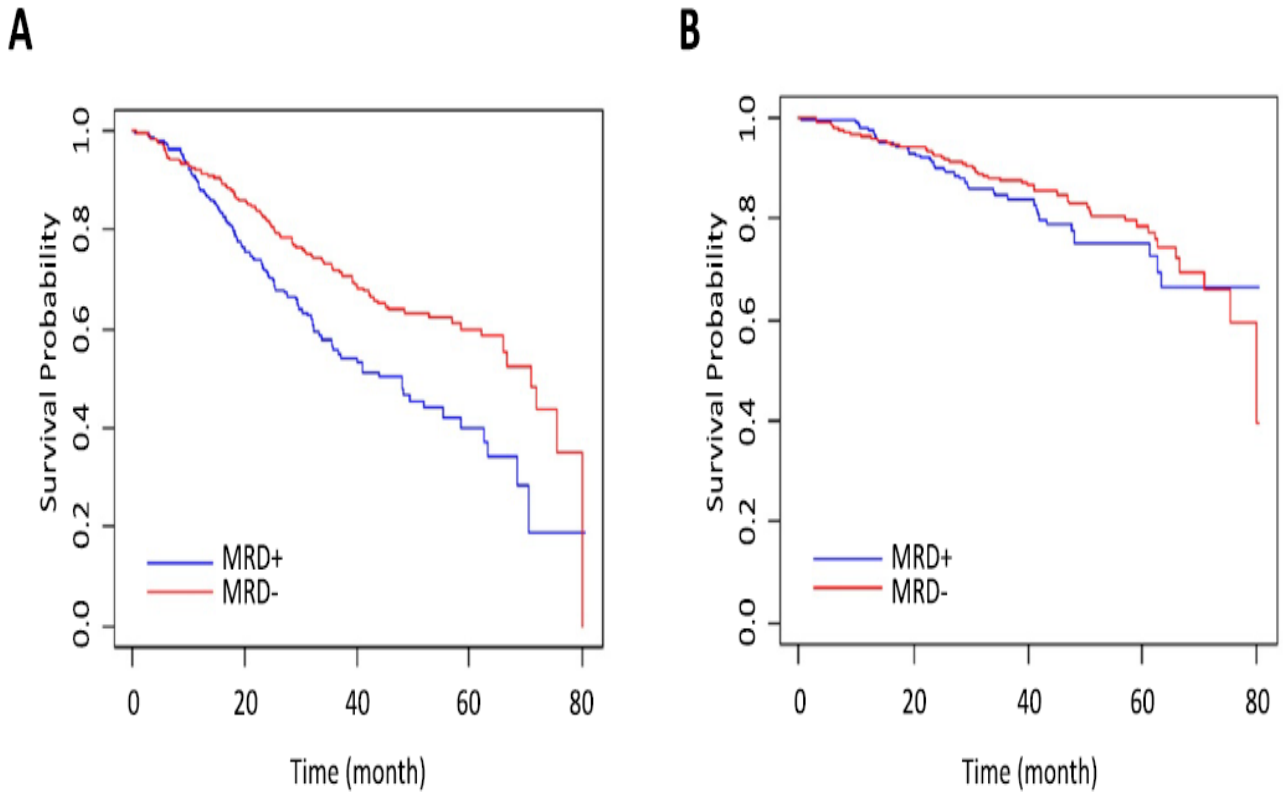


FIGURE 3 Progression-free survival (A) and overall survival (B), according to pretransplant minimal residual disease status.

Pasvolsky et al., Cancer.
2024;130:1663–1672

Single vs. Tandem Transplant

- Tandem transplant aims to deepen responses and improve survival.
- Conflicting results from trials:
  - IFM 94: Superiority of tandem over single ASCT.
  - Bologna 96: Improved PFS, no advantage in OS.
  - EMN02/HO95: Tandem transplants significantly improved 5-year PFS and OS.
  - STAMINA: No advantage for tandem transplants in PFS or OS.
- Double intensification is still commonly used for high-risk MM patients.

Table 3. Main randomized clinical trials comparing single and tandem transplant

Trial	Number of patients	Regimens	Efficacy	Benefit
IFM 94[31]	399	Mel 140/TBI vs Mel 140/TBI, then Mel 140	mEFS: 25 vs 30 mo ($P = .03$) mPFS: 29 vs 36 mo ($P < .01$) mOS: 48 vs 58 mo ($P = .01$)	EFS + PFS + OS
Bologna 96[32]	321	Mel 200 vs Mel 200, then Mel 120 + Bu 4	mEFS: 23 vs 35 mo ($P = .001$) mPFS: 24 vs 42 mo ($P < .001$) mOS: 65 vs 71 mo ($P = .09$)	EFS + PFS + OS
GMMG HD2[33]	358	Mel 200 vs Mel 200, then Mel 200	mEFS: 25 vs 28.7 mo mOS: 73 vs 75.3 mo	Not significant
EMN02/HO95[20]	1197	Mel 200 vs Mel 200, then Mel 200	5y-PFS: 44.9% vs 53.5% ($P = .036$) 5y-OS: 72.6% vs 80.3% ($P = .022$)	PFS + OS
STAMINA[34]	758	Mel 200 vs Mel 200, then VRD vs Mel 200, then Mel 200	38 mo-PFS: 58.5% vs 57.8% vs 53.9% 38 mo-OS: 81.8% vs 85.4% vs 83.7%	Not significant

Bu 4, busulfan 4 mg/kg; Mel 140, melphalan 140 mg/m^2.

Quadruplet Regimens in Frontline Therapy

- Quadruplet regimens (anti-CD38 antibody, bortezomib, IMiD, dexamethasone) have revolutionized frontline treatment.
- CASSIOPEA: DaraVTD improved stringent CR and PFS.
- GRIFFIN and PERSEUS: DaraVRD superior to VRD.
- Integration of second-generation PIs (carfilzomib) are also being examined.
- HD melphalan and transplant improve response and MRD negativity rates.

Table 4. MRD-negativity rates after induction and after consolidation with quadruplets in TE NDMM patients

	Type of quadruplet	Number of patients/ specific population	Induction details	Postinduction MRD-negativity rate	Number of ASCTs	Consolidation details	Post consolidation/premaintenance MRD-negativity rate	Outcomes
CASSIOPEIA[37]	DaraVTD	543	4 (4-week) cycles	35% (10^{-5})	1	2 (4-week) cycles	64% (10^{-5})	mPFS 83.7m
GRIFFIN[38,39]	DaraVRD	104	4 (3-week) cycles	22% (10^{-5}) 1% (10^{-6})	1	2 (3-week) cycles	50% (10^{-5}) 11% (10^{-6})	4-y PFS 70%
PERSEUS[39]	DaraVRD	355	4 (4-week) cycles	NA	1	2 (4-week) cycles	57% (10^{-5}) 34% (10^{-6})	4-y PFS 84%
GMMG-HD7[40]	IsaVRD	331	3 (6-week) cycles	50% (10^{-5})	1	No consolidation	72% (10^{-5})	NA
IFM2018-01[41]	DaraIxaRD	45 (SR)	6 (3-week) cycles	28% (10^{-5}) 6% (10^{-6})	1	4 (4-week) cycles	51% (10^{-5}) 40% (10^{-6})	2-y PFS 93%
IFM2018-04[42]	DaraKRD	50 (HR)	6 (4-week) cycles	53% (10^{-5})* 43% (10^{-6})*	2	4 (4-week) cycles	97% (10^{-5})* 94% (10^{-6})*	2.5-y PFS 80%
GMMG-CONCEPT[43]	IsaKRD	99 (HR)	6 (4-week) cycles	NA	2	4 (4-week) cycles	68% (10^{-5})	3-y PFS 69%
EMN24 IsKia[44]	IsaKRD	151	4 (4-week) cycles	45% (10^{-5}) 27% (10^{-6})	1	4 (4-week) cycles	77% (10^{-5}) 67% (10^{-6})	NA
MASTER[45]	DaraKRD	123	4 (4-week) cycles	37% (10^{-5}) 23% (10^{-6})	1	MRD adapted	NA	NA
IFM2020-02[46]	IsaKRD	791	6 (4-week) cycles	63% (10^{-5}) 47% (10^{-6})	0, 1, or 2	MRD adapted	NA	NA

* Exceptions to MRD reported in intention-to-treat population (per protocol).

HR, (cytogenetics) high-risk; NA, not available; SR, (cytogenetics) standard risk.

Who Needs Transplant Today?

- Most recent treatment guidelines recommend considering ASCT for all eligible NDMM patients.
- Studies are awaited for those that achieved MRD negativity after **DaraKRD** or **IsaKRD** induction to see if we can de-escalate therapy.
- **ASCT** remains a **standard of care** for transplant-eligible NDMM, particularly given its role in improving response rates and PFS.
- Future research should focus on personalized approaches based on MRD status and risk stratification.
- Need for robust data on the de-escalation of therapy for patients who achieved MRD negativity.

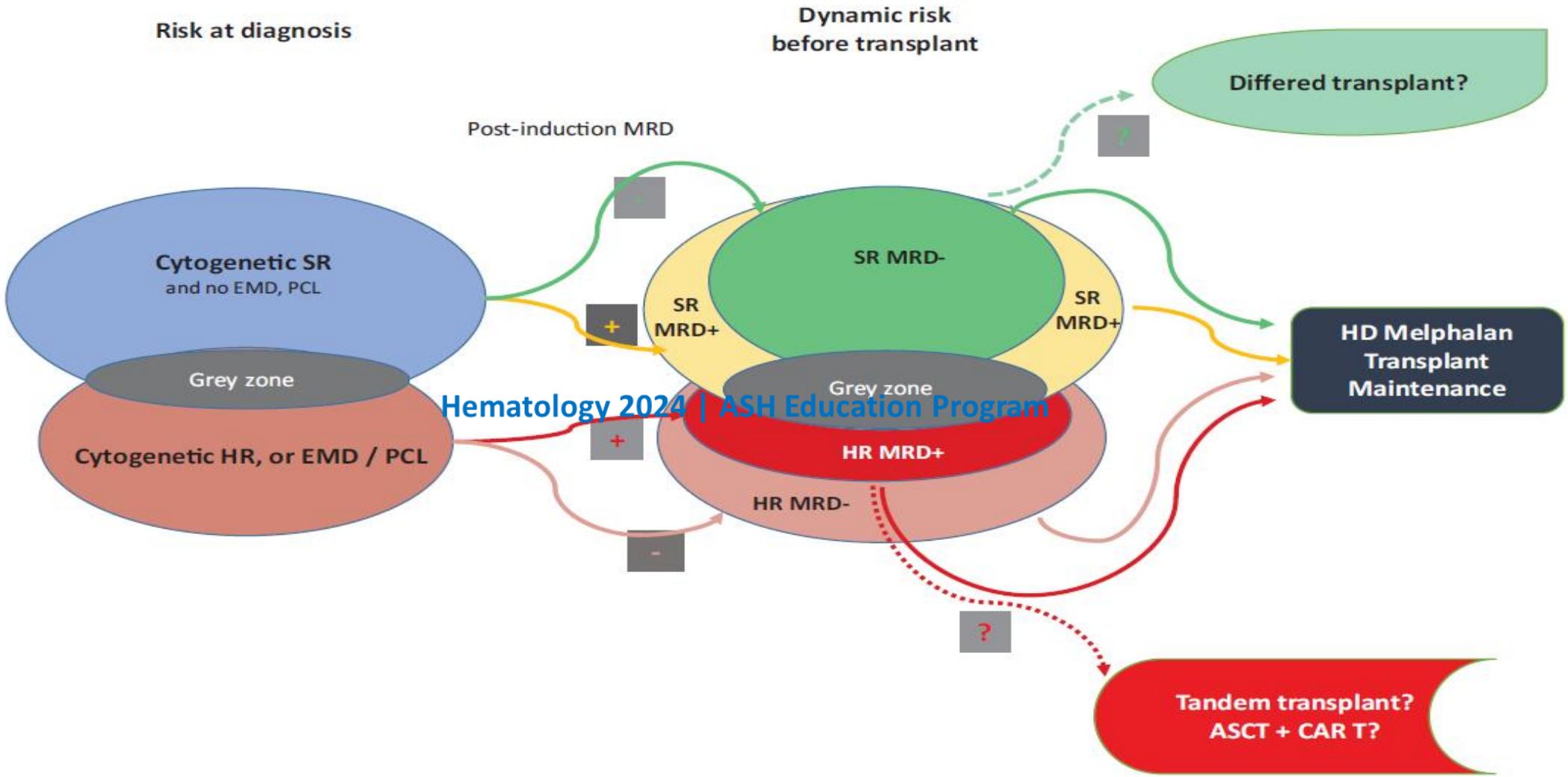


Figure 1. Multiparametric and dynamic criteria to consider the best choice of treatment for TE patients with NDMM. ASCT, autologous stem cell transplantaon; CAR T, chimeric antigen receptor; EMD, extramedullary disease; HD, high dose; HR, high risk; MRD, minimal residual disease; PCL, plasma cell leukemia; SR, standard risk.

Maintenance Treatment

Maintenance Therapy Post-ASCT in NDMM: An EBMT Review

- Despite treatment advances, most MM patients relapse.
- Maintenance prolongs/deepens responses post-ASCT.
- Lenalidomide is the primary approved agent in Europe/USA.
- Ongoing evaluation of combination/novel agents, duration, and MRD-guided strategies.

Br J Haematol. 2024

Lenalidomide: Proven Benefits

- Phase 3 studies show improved PFS, some also show improved OS.
- CALGB 100104: Lenalidomide vs. Placebo: Improved TTP and OS.
- Meta-analysis: Significant PFS and OS benefit with lenalidomide post-ASCT, especially in those with ≥VGPR or lenalidomide-based induction.
- UK Myeloma XI: Improved PFS and OS with lenalidomide maintenance post-ASCT.

- Br J Haematol. 2024

Duration of Lenalidomide: Fixed vs. Response-Adapted

- GMMG-MM5: Lenalidomide 2-year fixed duration (LEN-2Y) vs. response-adapted based on CR achievement (LEN-CR): Improved OS with LEN-2Y.

- DETERMINATION: Lenalidomide until progression: PFS benefit compared to RVd alone.

- Br J Haematol. 2024

Thalidomide: Limited Use

- MRC IX: Improved PFS with thalidomide vs. observation, but no OS benefit.
- HOVON50: Longer event-free survival with thalidomide, but significant toxicity.
- May be used in resource-constrained settings.

- Br J Haematol. 2024

Pomalidomide: Salvage Option

- EMN011/HOVON114: Pomalidomide-based re-induction and maintenance show feasibility after lenalidomide failure.

- Phase 3 studies needed to compare efficacy and tolerability to lenalidomide.

- Br J Haematol. 2024

Novel Agents and Combinations

- Review goes on to cover promising results with new treatments.
- Studies are evaluating proteasome inhibitors, monoclonal antibodies, and novel agents.
- Combinations like KRd, Dara+R, and Isa+R are being investigated in maintenance.

- Br J Haematol. 2024

Proteasome Inhibitor Maintenance in Myeloma: A Meta-Analysis

- Proteasome inhibitors (PIs) like ixazomib, bortezomib, and carfilzomib are used in maintenance.

- 8 studies included in the meta-analysis.

- Goldscmidt 2017, Dimopoulos 2018, Dimopoulos 2020, Gregersen 2021, Yong 2021, Rosinol 2012, Rosinol 2017, Sonneveld 2012

- *Heliyon 10 (2024)*

PFS and OS

- Proteasome inhibitors prolonged PFS and OS compared to placebo.
- Bortezomib has certain advantages in prolonging PFS, followed by ixazomib and carfilzomib in terms of efficacy.
- Bortezomib may be superior to carfilzomib in extending OS.

Heliyon 10 (2024)

Maintenance in High-Risk Disease

- Outcomes remain poor for high-risk patients, standard lenalidomide maintenance may not be sufficient.

- Intensified regimens are being evaluated.

- Br J Haematol. 2024

Optimizing Maintenance Therapy in Myeloma

- Lenalidomide (R) maintenance is standard of care post-autologous stem cell transplant (ASCT) for newly diagnosed multiple myeloma (NDMM).
- Most patients relapse, highlighting the need for improved maintenance strategies.
- Daratumumab (D) is a CD38-targeted antibody with proven efficacy in MM.

Blood, 16 JANUARY 2025

Daratumumab in Maintenance

- CASSIOPEIA: Daratumumab maintenance increased MRD-negative rates. Higher proportion of patients with sustained MRD negativity.

- GRIFFIN: Daratumumab + VRd resulted in higher MRD negativity rates at each phase and sustained negativity. Conversion from MRD+ to MRD- was higher with daratumumab.

- FORTE: Carfilzomib/Lenalidomide maintenance led to higher rates of converting patients to MRD negativity.

Leukemia & Lymphoma, Jan 2025

Daratumumab Maintenance in Myeloma: A CASSIOPEIA Update

- The CASSIOPEIA Study
- Two-part, randomized, open-label, phase 3 study.
- Part 1: Dara-VTd vs VTd induction before ASCT.
- Part 2: Daratumumab maintenance vs. observation after ASCT.

• thelancet.com/oncology Vol 25 August 2024

Part 2: Daratumumab Maintenance: Sustained Benefit

- Daratumumab maintenance significantly prolonged **progression-free survival (PFS)** compared to observation.
- HR 0.53 (95% CI 0.42–0.68; **p<0.0001**)

- Long-Term Follow-Up: **Overall Survival (OS)**

  significantly longer overall survival (OS).

  HR 0.55 (95% CI 0.42–0.73; **p<0.0001**)

- **Depth of Response and MRD Negativity:** Higher proportion of patients with MRD negativity (10^-6) in the Dara-VTd + daratumumab maintenance group (58.1% vs 48.9%,OR 1·56 [95% CI 1·04–2·34]; **p=0·031**)
- Dara maintenance also converted MRD status to negative versus observation in VTd induction patients.

• thelancet.com/oncology Vol 25 August 2024

Unresolved Questions

- Is daratumumab maintenance more effective than lenalidomide, the current standard of care?
- How do monoclonal antibodies impact the increased risk of disease progression in high-risk patients?
- Ongoing trials: **AURIGA** (NCT03901963), **DRAMMATIC** (NCT04071457), **RADAR** (ISCRTN46841867)

AURIGA Study: Daratumumab + Lenalidomide (D-R) Maintenance Post-Transplant for NDMM

- Phase 3, randomized, open-label study.
- 200 NDMM patients with ≥VGPR, MRD-positive (10^-5), and anti-CD38 naïve post-ASCT.
- Randomized 1:1 to Daratumumab + Lenalidomide (D-R) vs. Lenalidomide (R) alone.
- D-R: Daratumumab 1800mg SC (QW cycles 1-2, Q2W cycles 3-6, Q4W cycle 7 onwards) + Lenalidomide 10mg daily (increase to 15mg if tolerated)
- Treatment duration: Up to 36 cycles.
- Primary endpoint: MRD-negative conversion rate (10^-5) at 12 months.

- Blood, 16 JANUARY 2025

D-R Significantly Improves MRD Conversion

- Significantly higher MRD-negative (10^-5) conversion rate with D-R vs. R at 12 months (50.5% vs 18.8%; OR, 4.51; P < .0001).

- Higher MRD-negative (10^-6) conversion rate with D-R (23.2% vs 5.0%; OR, 5.97; P = .0002).

- Higher overall MRD-negative (10^-5) conversion rate throughout the study with D-R (60.6% vs 27.7%; OR, 4.12; P < .0001).

- **Blood, 16 JANUARY 2025**

D-R Improves Progression-Free Survival

- PFS favored D-R vs. R (HR, 0.53; 95% CI, 0.29-0.97).

- Estimated 30-month PFS rates: 82.7% for D-R vs. 66.4% for R.

- **Blood, 16 JANUARY 2025**

Daratumumab-Lenalidomide: A Promising Maintenance Strategy

- D-R maintenance significantly improves MRD-negative conversion rate and PFS compared to R alone in NDMM patients who are MRD-positive post-transplant.
- D-R maintenance could be a valuable option for improving outcomes in these patients.

- **Blood, 16 JANUARY 2025**

Future Directions

- Personalized maintenance strategies based on risk stratification and MRD status.
- Optimization of combination regimens and novel agents.
- Studies determining the role of drug holidays, maintenance in extramedullary disease, and the management of frail patients with MM.

- Br J Haematol. 2024

Discontinuing Maintenance in Myeloma

- **MRD2STOP Trial**
- Evaluating MRD-Guided Discontinuation
- To evaluate the outcomes of patients with MM who discontinued maintenance therapy after achieving sustained multimodal MRD negativity.
- To assess if MRD < 10^-7 is a superior cessation threshold compared to MRD < 10^-6.

Blood Cancer Journal (2024)

❑ 3-Year Cumulative Incidence of Disease Resurgence

- For baseline MRD < 10^-7: 20%
- For baseline MRD ≥ 10^-7: 75%
- Hazard Ratio (HR) 7.8, p = 0.001
- Estimated 3-Year PFS (49% vs 92%)

❑Patients with baseline MRD ≥ 10-7 had inferior PFS compared to MRD < 10^-7 (HR 10.1, p = 0.03).

❑No clinically meaningful change after treatment discontinuation.

Blood Cancer Journal (2024)

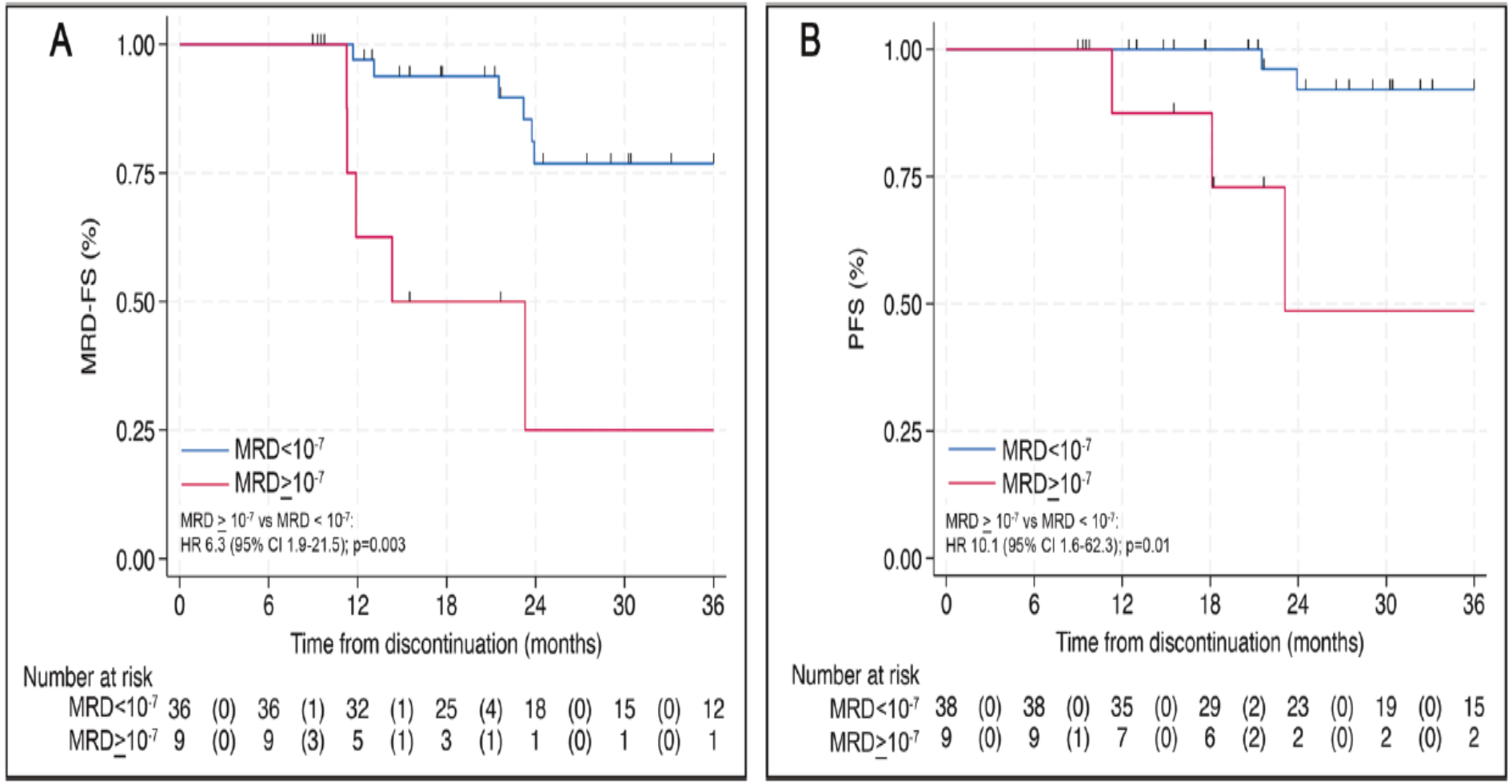


Fig. 3 Outcomes By MRD 10-7 Status. A MRD-free survival (MRD-FS) and **B** progression-free survival (PFS) stratified by MRD 10^{-7} status at baseline. MRD-FS refers to patients free of MRD 10^{-6} resurgence, progression, or death.

Key to Maintenance Cessation

- Maintenance discontinuation in patients with MM and MRD < 10^-6 led to low rates of disease resurgence.

- MRD < 10^-7 may be a superior cessation threshold.

The Role of Autologous Stem Cell Transplantation in the Era of Immunotherapy

- ASCT remains a cornerstone of NDMM therapy for eligible patients.
- Immunotherapies (CAR-T cells, bispecific antibodies) are transforming the RRMM landscape.
- This review focuses on integrating immunotherapy into ASCT-based strategies for NDMM.

Cells

2024

Bispecific Antibodies

- BsAbs redirect T-cells to target MM cells.
- Talquetamab, teclistamab, elranatamab, and cevostamab are examples.
- High ORRs in RRMM. Trials in earlier lines of therapy are ongoing.

- Cells 2024

CAR T-Cells: A Paradigm Shift in Myeloma

- CAR T-cells engineered to target B cell maturation antigen (BCMA), or other MM antigens.

- Impressive responses in RRMM, especially in patients with limited treatment options.

- Trials exploring CAR T-cell therapy in NDMM (e.g., CARTITUDE-4, showing potential in transplant-ineligible patients).

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The Future: ASCT and Immunotherapy Synergies

- ASCT remains a valuable tool, but its role may evolve with increasing use of immunotherapies.
- MRD-guided approaches will be crucial in tailoring treatment strategies.
- Novel agents such as bispecific antibodies and CAR T-cell therapy are shifting the paradigm to new remission rates and OS.

- Cells 2024

MRD Detection Techniques

MRD Detection: Laboratory Techniques

- ❑ Bone Marrow Testing:
  - Flow Cytometry: Identifies clonal plasma cells, fast turnaround, widely available, requires fresh sample.
  - Next-Generation Sequencing (NGS): Utilizes DNA, can provide deeper assessment, requires baseline sample.
  - NGS sensitivity > Flow Cytometry (10^-6 vs 10^-5), but some labs achieve similar sensitivity with flow.
- ❑ Peripheral Blood Mass Spectrometry (MS):
  - Detects monoclonal proteins secreted by clonal plasma cells, less invasive.
  - Increased accuracy and sensitivity, viable alternative.
  - Studies (STAMINA, GMMG-MM5, IFM 2009, ATLAS) show promise for MS in predicting outcomes and correlating with BM-MRD.
- ❑ Other Methods: Circulating tumor DNA and RNA seq (not readily available).
- Important Note: Optimal timing of MRD testing, or whether to test only patients in CR, are areas of contention.

Leukemia & Lymphoma, Jan 2025

MRD Detection: Imaging Techniques

- FDG PET/CT and Whole Body MRI can be used for response assessment and MRD detection.
- PET/CT appears complementary to bone marrow MRD assessment.
- Useful in patients with focal or extramedullary disease.

Leukemia & Lymphoma, Jan 2025

MRD Negativity: Strong Prognostic Indicator

- Meta-analysis (14 studies, 1273 patients): MRD-negative status after treatment for NDMM associated with long-term survival and improved PFS.

- Meta-analysis (8098 patients): MRD negativity associated with significantly better survival outcomes regardless of disease status, sensitivity, risk, or method.

- Pooled analysis (POLLUX, CASTOR, ALCYONE, MAIA): MRD negativity (NGS, 10^-5) associated with improved PFS irrespective of therapy or setting.

Leukemia & Lymphoma, Jan 2025

Sustained MRD Negativity: Deeper Responses

- Serial assessments for MRD allow for better disease evaluation.
- Sustained MRD negativity has been associated with improved outcomes in MAIA and ALCYONE (NDMM) and POLLUX and CASTOR (RRMM).
- Post-transplant, deeper responses can be observed over time, with tandem transplant, consolidation, and maintenance.

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Maintenance Strategy Based on MRD

- Post ASCT, the landscape is changing
- Pre-maintenance: MRD positive versus MRD negative.
- MRD negative: maintenance aims to sustain response
- MRD positive: Maintenance aims to convert response

Leukemia & Lymphoma, Jan 2025

Evaluating PRD as a Prognostic Tool

- To investigate the prognostic value of PRD assessment using Next-Generation Flow (NGF) and Mass Spectrometry (MS) in transplant-eligible MM patients.
- Analysis of 138 transplant-eligible MM patients enrolled in the GEM2012MENOS65/GEM2014MAIN clinical trials.
- PRD was assessed using NGF and MS after 24 cycles of maintenance therapy or observation.
- Correlated PRD results with progression-free survival (PFS) and overall survival (OS).

J Clin Oncol 43:125-132

PRD by NGF: A Strong Prognostic Indicator

- Positive PRD by NGF was associated with a significantly increased risk of progression and/or death (13-fold).
- Patients with positive PRD had shorter median PFS (2.5 months) and OS (47 months).
- In multivariate analysis, PRD by NGF was an independent prognostic factor for PFS, along with MRD in BM.

J Clin Oncol 43:125-132

Relationship Between PRD and MRD

- PRD detection using NGF showed a high positive predictive value (100%) for MRD status in BM.
- The combined evaluation of PRD using NGF and MS identified subgroups with different survival outcomes.
- Patients with undetectable PRD by both NGF and MS had excellent 2-year PFS (97%) and OS (100%).

J Clin Oncol 43:125-132

The Future of MM Monitoring

- Sensitive methods for monitoring PRD represent the next frontier in response assessment in MM.

- PRD assessment using NGF and MS is prognostic and may help reduce the frequency of BM aspirates in approximately 10% of transplant-eligible patients with MM under maintenance or observation.

J Clin Oncol 43:125-132

A New Korean Study on Maintenance Treatment

Real-World Outcomes of Maintenance Therapy Post-ASCT in NDMM

A Korean Multicenter Analysis

- Data from 15 Korean medical centers.
- Patients: NDMM treated with ASCT after VTD (bortezomib, thalidomide, dexamethasone) frontline therapy (until Oct 2020).
- Follow-up: Until August 2023.
- Excluded: Tandem ASCT.
- Retrospective data collection

- Kang *et al. BMC Cancer (2025)*

Treatment Details

Maintenance:

- Thalidomide: 50-200 mg daily (up to 1 year).
- Bortezomib: 1.3 mg/m2 SC/IV (q2 weeks up to 2 years).
- Lenalidomide/Ixazomib: Based on institutional approval.
- No insurance coverage for maintenance during the study period, so patient decision dependent on cost tolerance.

- Kang *et al. BMC Cancer (2025)*

Results: Maintenance Therapy Details

- Thalidomide: n=104, Median duration 10.9 months.
- Lenalidomide: n=33, Median duration 21.7 months.
- Bortezomib/Ixazomib: n=16, Median duration 28.6 months.
- Low use of steroids in combination.
- Common doses: Thalidomide 50mg, Lenalidomide 10mg, Bortezomib 1.6mg/m2

- Kang *et al. BMC Cancer (2025)*

Maintenance Agent Specific PFS

- Median PFS: No Maintenance = 26.4 months, Maintenance = 44.1 months
- Multivariate analysis: Use of maintenance was significantly associated with better PFS.
- Bortezomib/ixazomib was associated with better PFS over other maintenance options (Thalidomide and lenalidomide).
- Longer duration of any therapy was associated with improved PFS.

- Kang *et al. BMC Cancer (2025)*

Overall Survival (OS) & Secondary Malignancies

- No statistically significant difference in OS by use or type of maintenance.
- No clear increase in secondary malignancy rates with maintenance.

Kang *et al. BMC Cancer (2025)*

A Japanese Study with Novel Agents

- **A Japanese Phase II Study, Cancer Science (2024)**

- Autologous HSCT with VRD Induction, KRD Consolidation, and Len Maintenance in NDMM

- VRD induction (4 cycles) --> ASCT --> KRD consolidation (4 cycles) --> Lenalidomide maintenance until progression.

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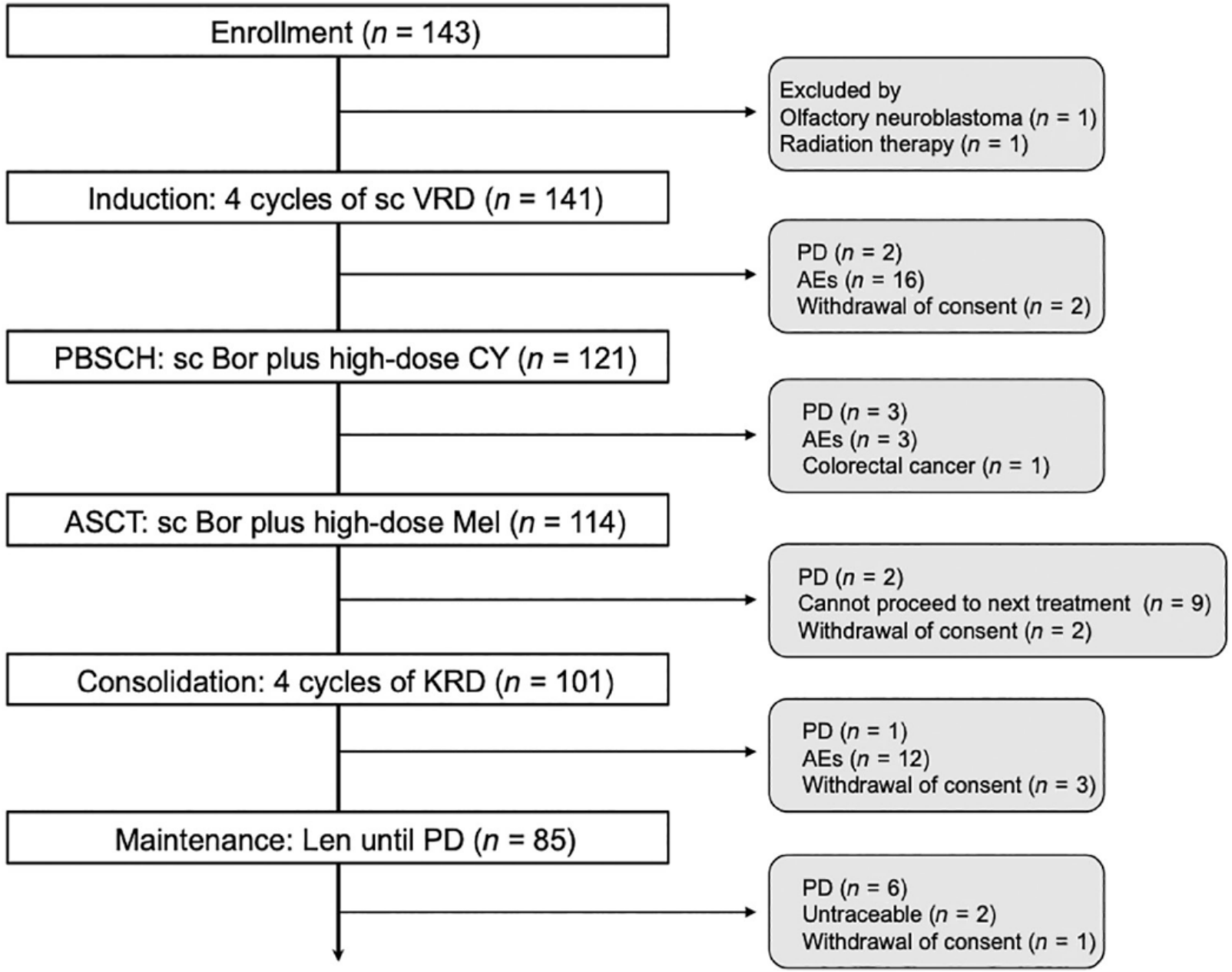

FIGURE 1 Trial design. AEs, adverse events; ASCT, autologous stem cell transplantation; Bor, bortezomib; CY, cyclophosphamide; KRD, carfilzomib, lenalidomide, dexamethasone; Len, lenalidomide; Mel, melphalan; PBSCH, peripheral blood stem cell harvest; PD, progressive disease; sc, subcutaneous; VRD bortezomib, lenalidomide, dexamethasone.

FIGURE 2 Response rates after each treatment phase (intent-to-treat population, $n = 141$). ASCT, autologous stem cell transplantation; CR, complete response; NA, not assessed; PBSCH, peripheral blood stem cell harvest; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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❑Response Rate:

- Post-Induction VGPR or better: 19.9%
- Post-ASCT VGPR or better: 39.7%
- Post-Consolidation VGPR or better: 58.9%
- After 1 year of maintenance VGPR or better: 62.4%

❑Excellent Survival Outcomes

- 3-year PFS: 83.5%
- 3-year OS: 92.5%

- Median follow-up: 38 months

❑ Safety Profile

- Grade ≥3 AEs occurred in ~30% of patients.
- No treatment-related mortality.

❑High-Risk Cytogenetics

- Patients with high-risk cytogenetics had a trend toward lower 3-year PFS (77.8% vs. 89.4%, p = 0.051).
- Ultra-high-risk cytogenetics (≥2 high-risk) had worse 3-year PFS (61.2%).

Cancer

***Science.* 2024**


Thank
you!