



Frontline Myeloma in 2026: Quadruplets, Transplant and The First Sequencing Decision

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Content

- Risk classification
- Induction in transplant eligible multiple myeloma
- Autologous stem cell transplantation (ASCT)
- Induction in transplant ineligible multiple myeloma
- Maintenance strategies

Risk stratification

<p>ISS</p> <div><p>B2-microglobulin Albumin</p></div> <p>Stage I: Serum $\beta 2M < 3.5$ mg/L and serum albumin ≥ 3.5 g/dL</p> <p>Stage II: Not ISS stage I nor III</p> <p>Stage III: Serum $\beta 2M \geq 5.5$ mg/L</p>	<p>R-ISS</p> <div><p>ISS LDH Cytogenetic lesions t(4;14), and/or t(14;16) and/or del17p</p></div> <p>Stage I: ISS stage I, t(4;14), and/or t(14;16) and/or del17p negativity by FISH, and normal serum LDH</p> <p>Stage II: Not ISS stage I nor III</p> <p>Stage III: ISS stage III and either elevated serum LDH or t(4;14), and/or t(14;16) and/or del17p positivity by FISH</p>	<p>R2-ISS</p> <div><p>ISS LDH Del(17p), t(4;14), 1q+</p></div> <p><u>Additive score:</u> ISS II: 1 point ISS III: 1.5 points Del(17p): 1 point Elevated serum LDH: 1 point t(4;14): 1 point 1q+: 0.5 points</p> <p><u>Groups:</u> Low risk: 0 Low-intermediate: 0.5-1 Intermediate-high: 1.5-2.5 High: 3-5</p>	<p>Other risk factors</p> <ul style="list-style-type: none">Genetic lesions: deletion and mutations of TP53; deletion chromosome 1p detected by FISHExtramedullary diseaseCTCs detected in the peripheral blood by flow cytometryPlasma cell leukemia and plasma cell leukemia-like diseaseGEP: high-risk signatures
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International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma

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Loss of p53:

- del17p in $\geq 20\%$ of sorted PC
- TP53 mutation, any VAF

Biallelic del1p32

2 of the following:

- t(4;14), t(14;16), or t(14;20)
- Monoallelic del1p32
- Gain/amp 1q

β -2-microglobulin $\geq 5.5\text{mg/L}$
(ONLY IF serum creatinine
 $< 1.2\text{mg/dL}$)

Risk stratification

- Consensus Genomic Staging of high risk myeloma
- ~20% of NDMM patients have high risk myeloma

Risk stratification

- There is still variability in progression free survivals in patients assigned to particular risk groups
- In addition to static assessments prior to treatment, response to treatment measured by MRD predicts outcomes
- Functional high risk means not genetically high risk

Transplantation eligibility

- Traditionally NDMM patients are classified according to their eligibility for upfront transplantation
- Age, performance, comorbidities, frailty status and social constraints are evaluated
- Chronologic age alone or renal function do not determine transplant eligibility (improved supportive care)

Transplant eligible NDMM

NDMM treatment has evolved to quadruplet regimens incorporating anti-CD38 monoclonal antibodies to a PI, IMiD and dexamethasone backbone

Transplant eligible NDMM

Trial name	N	Median age (range)	Arms	Best MRD ⁺ rate (%)	PFS	Clinicaltrials.gov ID	Clinical cutoff
Transplant eligible ^a							
CASSIOPEIA (64)	1,085	58 (22–65)	First randomization (induction/consolidation): D-VTd vs. VTd followed by ASCT and consolidation Second randomization (maintenance): Dara vs. placebo	D-VTd → Dara vs. placebo: 60.7 vs. 52.0 ^b VTd → Dara vs. placebo 48.4 vs. 30.7 ^b	Median PFS: D-VTd → Dara vs. placebo: NR vs. 72.1 months VTd → Dara vs. placebo: NR vs. 32.7 months	NCT02541383	September 1, 2023
GRIFFIN (65)	207	60 (29–70)	Dara-RVd vs. RVd (followed by ASCT, consolidation, and Dara-R vs. R maintenance, respectively)	51.0 vs. 20.4 ^b	4-year PFS: 87.2% vs. 70.0%	NCT02874742	May 18, 2022
PERSEUS (8)	709	60 (31–70)	Dara-RVd vs. RVd (followed by ASCT, consolidation, and Dara-R vs. R maintenance, respectively)	65.1 vs. 32.2 ^b	4-year PFS: 84.3% vs. 67.7%	NCT03710603	August 1, 2023
GMMG-HD7 (96)	662	59 (range not reported)	First randomization (induction/consolidation): Isa-RVd vs. RVd followed by ASCT (single or tandem) and consolidation Second randomization (maintenance): Isa-R vs. R	66.2 vs. 47.7 ^c	3-year PFS: Isa-RVd vs. RVd: 83% vs. 75%	NCT03617731	January 31, 2024
IsKia (74)	302	61 (range not reported)	Isa-KRd vs. KRd followed by ASCT, extended consolidation, and R maintenance	67.0 vs. 48.0 ^b	Not reported	NCT04483739	May 22, 2023

Transplant eligible NDMM

- Optimal duration of induction?
At least 4 cycles
- Carfilzomib instead of bortezomib in quadruplet regimens?
Excellent MRD negativity rates esp in high risk disease
The upfront use of carfilzomib is still debated

Transplant eligible NDMM

- Should cyclophosphamide be added into induction regimens in patients with renal failure?

No improvement in renal or overall response is shown in patients with cast nephropathy

Lenalidomide is safe with appropriate dose adjustments

Autologous stem cell transplantation

- Upfront or deferred to first relapse?
- Upfront ASCT improves response depth and progression free survival following induction treatment with triplets
- Short and long term adverse effects have led some clinicians to defer ASCT to first relapse in select patients

Autologous stem cell transplantation

Melphalan is a DNA-damaging alkylating agent

High dose melphalan significantly increases mutational burden at relapse

ASCT with quadruplets → not yet long-term data from randomized trials

Autologous stem cell transplantation

Delaying ASCT may have some risks:

- Patients may become transplant ineligible later in the disease course (older, more frail)

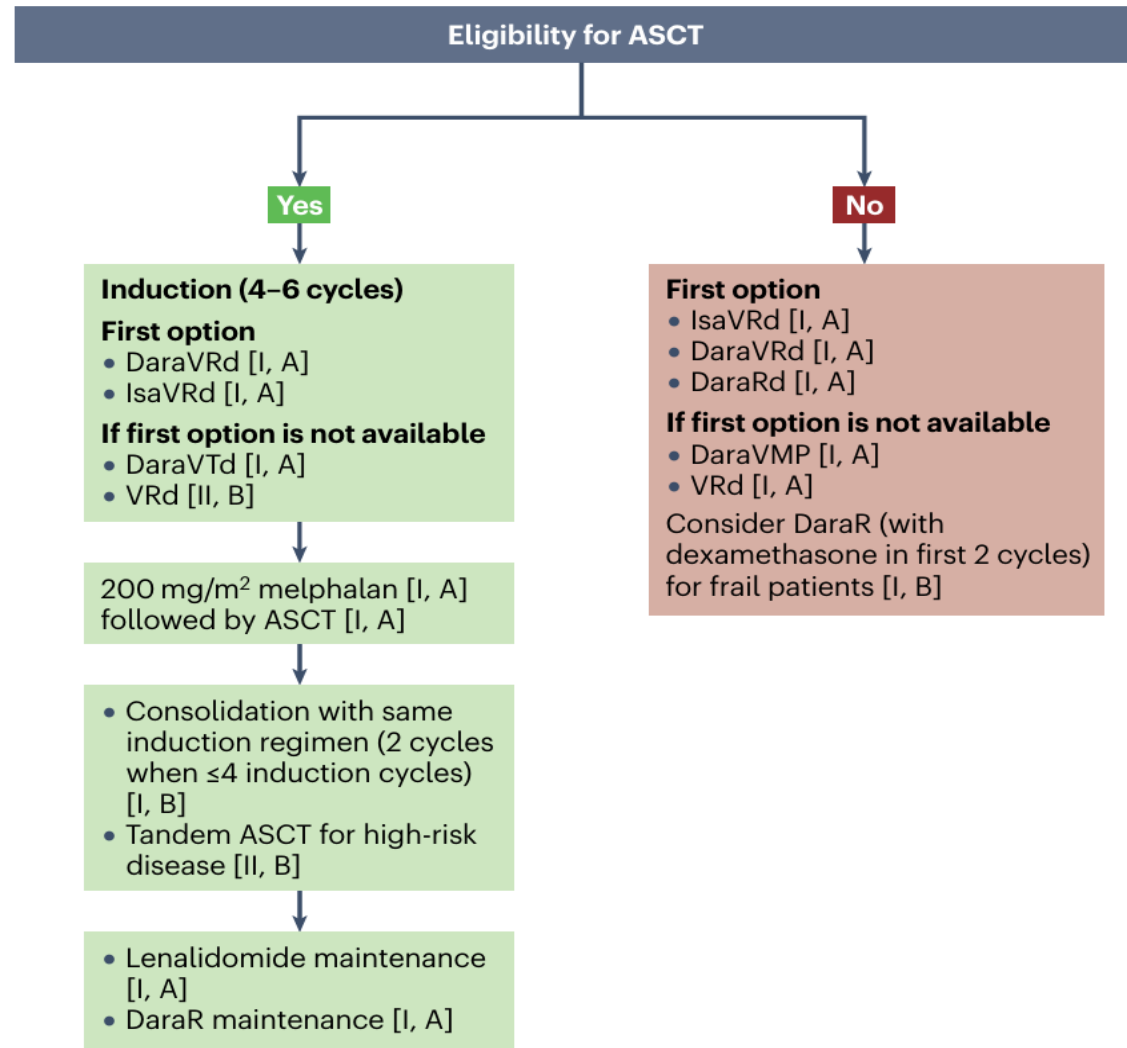
ASCT is important for patients with high risk disease biology

Significant disease-related debility at presentation can improve with therapy and patients may become transplant eligible

Taken together ASCT is still an important component of the NDMM treatment

Consolidation therapy

- There is a conditional recommendation in favor of consolidation therapy in the context of daratumumab based induction therapy
- High risk patients with MRD positivity following ASCT → transition to maintenance following consolidation can be considered
- 2 cycles



Transplant ineligible NDMM

- Identification of frailty with geriatric assessments is important in older myeloma patients
- Frequent clinical assessments and relevant dose modifications are important in this population
- The necessary aggressiveness to induce durable remissions should be balanced with minimizing the risk of treatment related toxicities

Transplant ineligible NDMM

Table 1. Frailty scores in multiple myeloma.

	IMWG frailty score	Simplified IMWG	R-MCI	UK MRP	Mayo risk score
Biological/clinical components	Age CCI	Age CCI	Age eGFR PFTs Frailty Cytogenetics	Age R-ISS CRP	Age NT-proBNP
Functionality tests	ADL IADL	ECOG	PS (Karnofsky)	PS (WHO)	PS (WHO)
Frailty groups	Fit Intermediate fit Frail	Non-frail Frail	Fit Intermediate fit Frail	Low-risk Medium-risk High-risk	I II III IV

Haziran
2024

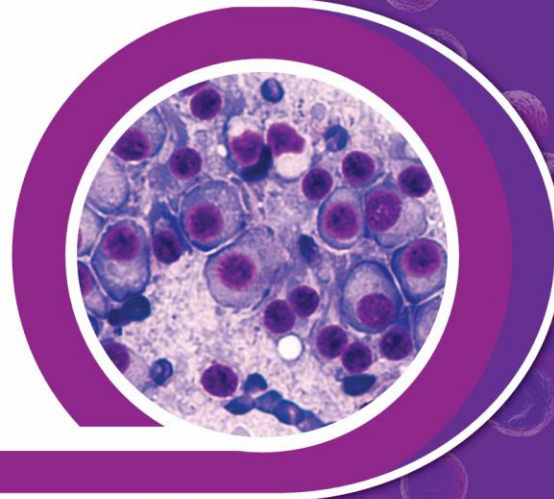


Türk Hematoloji Derneği
57. Yıl
www.thd.org.tr

Multipl Miyelom

Tanı ve Tedavi Kılavuzu
Güncelleme

Prof. Dr. Meral Beksac
Doç. Dr. Ayşe Salihoğlu
Doç. Dr. Güldane Cengiz Seval



- https://www.myelomacomorbidityindex.org/en_calc.html (R-MCI)
- <http://www.myelomafrailityscorecalculator.net>

Transplant ineligible NDMM

- A modified VRd regimen VRd lite; longer cycle length (35 days), once weekly bortezomib, lower doses of dexamethasone (20 mg)
- DRd (MAIA Trial, lenalidomide 25 mg is hardly tolerated)
- Quadruplets emerge in these patients (Isa-VRd, Dara-VRd)

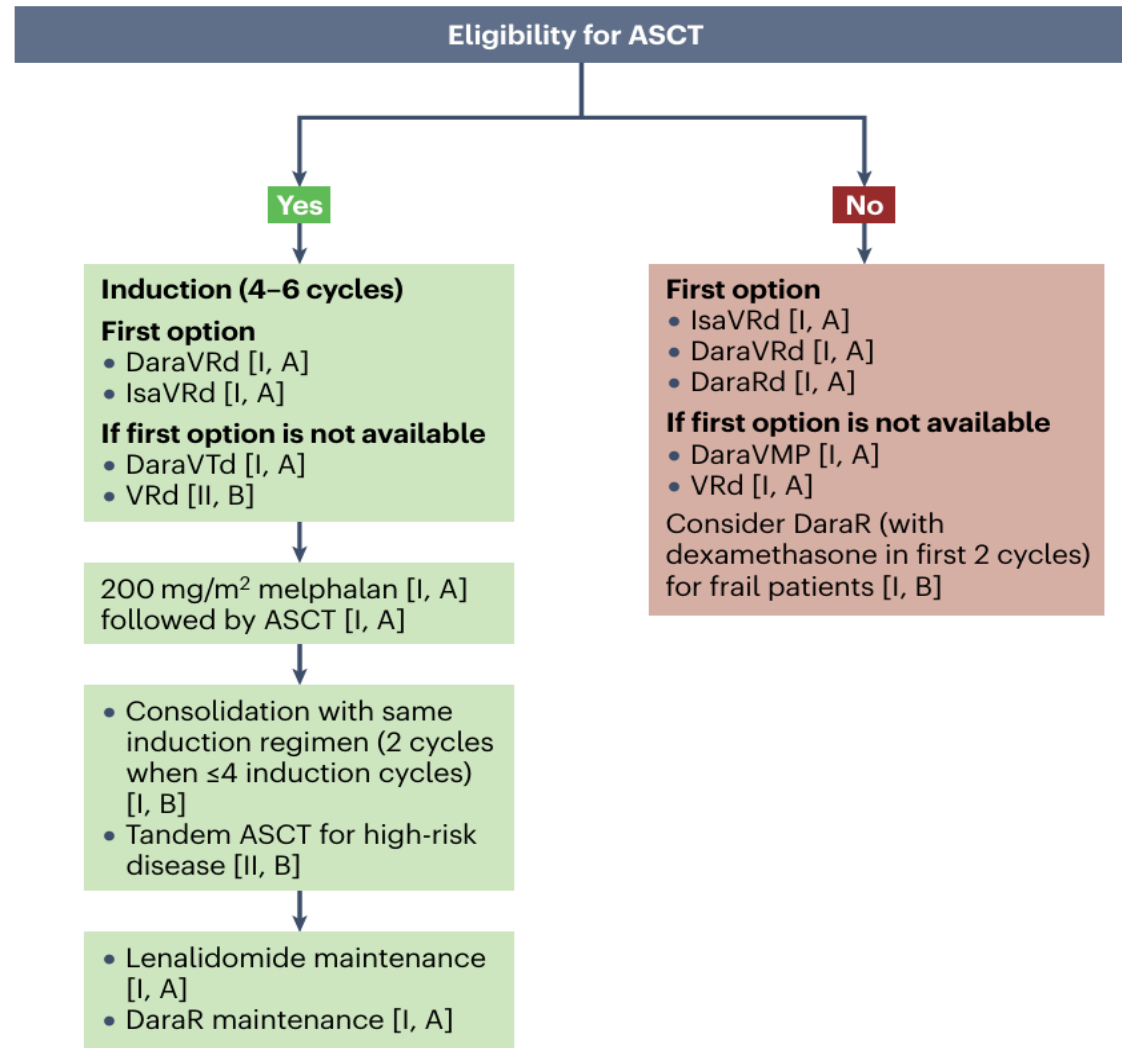
Transplant-eligible patients								
Study	N	Age (years)	Comparison	Median PFS (months)	Median OS (months)	Median TTP (months)	Median Duration of Response (months)	Median Time to Next Therapy (months)
Transplant-eligible patients								
MAIA (81)	737	73 (45–90)	D-Rd vs. Rd	32.1 vs 11.1 ^c	50.1 vs 29.6 ^c	29.6 vs 11.1 ^c	11.1 vs 11.1 ^c	11.1 vs 11.1 ^c
BENEFIT (85)	270	73 (range not reported)	Isa-RVd vs. Isa-Rd (followed by Isa-Rd maintenance)	36.0 vs. 17.0 ^b	45.2 vs. 29.6 ^b	29.6 vs. 11.1 ^b	11.1 vs. 11.1 ^b	11.1 vs. 11.1 ^b
IMROZ (83)	446	72 (55–80)	Isa-RVd vs. RVd (followed by Isa-Rd vs. Rd maintenance, respectively)	58.1 vs. 43.6 ^c	63.2 vs. 45.2 ^c	45.2 vs. 29.6 ^c	29.6 vs. 11.1 ^c	11.1 vs. 11.1 ^c
CEPHUS (84)	395	70 (31–80)	Dara-RVd vs. RVd (followed by Dara-R vs. R maintenance)	46.2 vs. 27.3 ^b	52.6 vs. 27.3 ^b	27.3 vs. 11.1 ^b	11.1 vs. 11.1 ^b	11.1 vs. 11.1 ^b
Transplant-ineligible or transplant-deferred ^a								
MAIA (81)	737	73 (45–90)	D-Rd vs. Rd	32.1 vs 11.1 ^c	50.1 vs 29.6 ^c	29.6 vs 11.1 ^c	11.1 vs 11.1 ^c	11.1 vs 11.1 ^c
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Transplant ineligible NDMM

Bortezomib is usually not given for more than 6 cycles in transplant-ineligible patients

In patients >80, starting with a triplet and then intensifying the therapy may be considered

Dexamethasone sparing strategies (only 2 cycles) should be considered in patients with high frailty scores (IFM2017-03 Trial)



Maintenance therapy

- Maintenance strategies are evolving
- Lenalidomide until progression or intolerance is well established
- Despite lenalidomide maintenance patients with high risk biology progress earlier compared with standard risk patients
- Concerns about long term lenalidomide toxicities and worsening quality of life
- Further improvements are required

Maintenance therapy

- Daratumumab is a good candidate
- Limited randomized data directly comparing daratumumab and lenalidomide
- A single center, randomized study, 74 patients enrolled, the majority treated with quadruplet induction and ASCT
- Early efficacy data suggest similar best response rates and 12 and 24 month PFS rates between dara and len arms

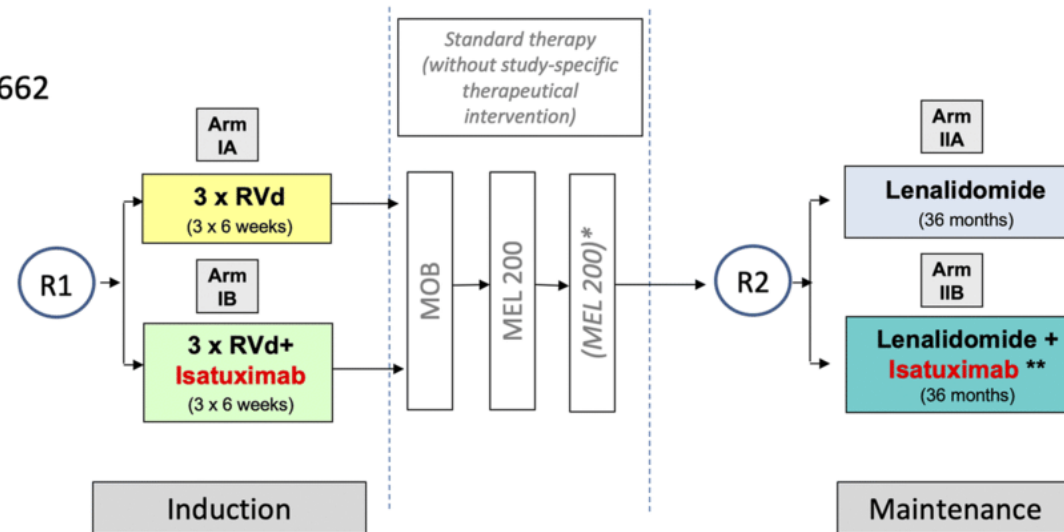
Maintenance therapy

- Can daratumumab added to lenalidomide improve maintenance?
- AURIGA Trial: the only published randomized study (dara-len vs len)
- Includes induction-daratumumab naïve patients
- Does not reflect patients treated with quadruplet induction

GMMG HD7 trial



N=662



R1 = 1st randomization (at study inclusion); R2 = 2nd randomization (prior to maintenance)

* decision for 2nd high dose therapy response-adapted (in case no CR) or for high risk patients

** Lenalidomide/Isatuximab for 36 months (thereafter, continuation of lenalidomide recommended until PD)

Maintenance therapy

- Prolonged use of bortezomib → increased risk of neuropathy
- Ixazomib maintenance compared with placebo → modest PFS increase
- Bortezomib in combination with lenalidomide had excellent outcomes in a single arm study in high risk patients
- Carfilzomib-lenalidomide maintenance better than len alone in high risk patients (3 year PFS 75% vs 65%, conversion to MRD negativity 46% vs 30%)
- In the data containing quadruplet induction regimens the value of carfilzomib added to lenalidomide is unclear

Dimopoulos MA ve ark., Lancet, 2019

Nooka AK ve ark., Leukemia, 2014

Gay F ve ark., Lancet Oncol, 2021

Maintenance therapy

- Dual maintenance strategies (carfilzomib or daratumumab plus lenalidomide) can be considered in patients with MRD positivity after ASCT and/or high risk features
- In patients who did not receive anti-CD38 in the induction and achieved \geq VGPR with positive MRD after ASCT, it is reasonable to add dara to len

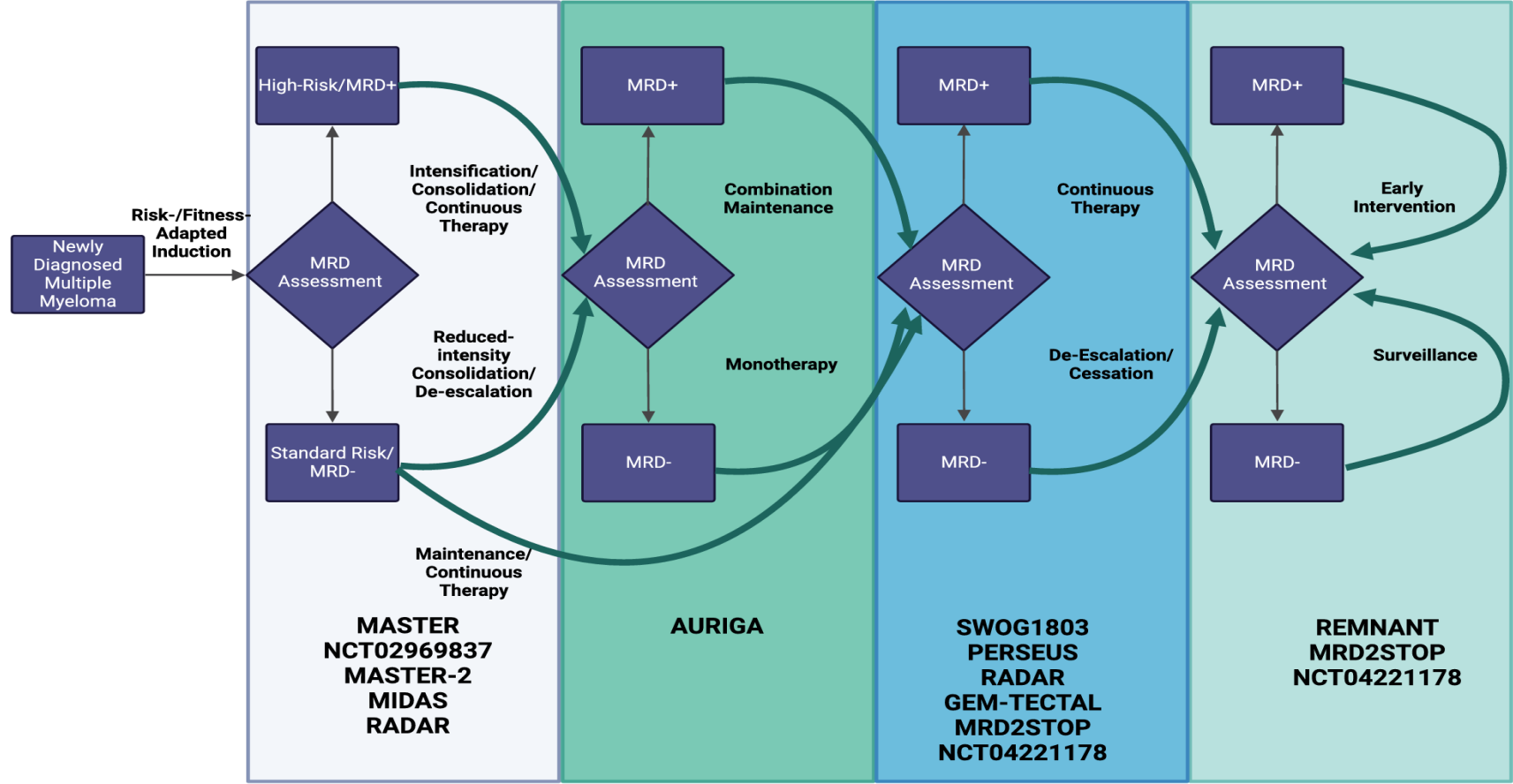
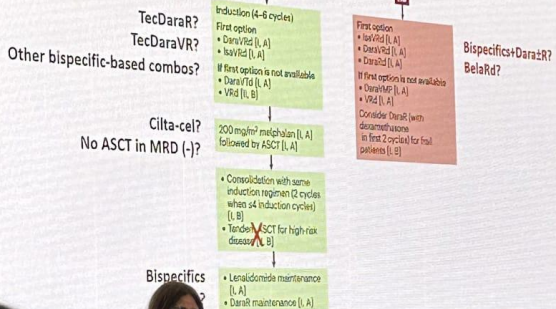


Fig. 1 Opportunities and ongoing studies for MRD-adapted therapy

In summary,

- Individualized approaches directed by risk, frailty and response are of paramount importance
- The role of ASCT in the quadruplet era is not yet clear, novel immunotherapeutic agents may become alternative consolidation strategies
- CAR T-cell and bispecific antibodies are getting their places in the frontline setting, not only in the induction but also in the maintenance

EHA/EMN 2027+ Guidelines: First-line therapy?



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present, BCMA-directed immunotherapy is investigational in NDMM, and their optimal use and patient selection remain to be defined in ongoing clinical trials.

Thank you..

