Is there a role for MRD testing in the UK?

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Overview

- Case study
- MRD testing FAQ
- MRD landmarks
- MRD testing in UK practice – current and future

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Straw poll: I would do MRD test in MM patient if.....

- Iam able to change treatment based on the results
- I know my patient is functionally cured
- Iam able to prognosticate treatment outcomes in the medium term 2-3 years
- Iam able to access these tests routinely in clinical practice

Speaker's views

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Case study of a patient with Newly diagnosed transplant eligible MM

- 62-year-old lady, lives between UK and Italy
- PS 0, Board-level executive of a large corporation
- PMH: IBD, DVT
- Presented with bone pain and fatigue

- Date diagnosed: February 2017
- IgG k MM
- Hb 92 g/l
- L4 fracture
- Hyperdiploidy on MM FISH
- Normal renal function, calcium
- ISS-2

DVT, deep-vein thrombosis; FISH, fluorescence in situ hybridisation; Hb, haemoglobin; IBD, irritable bowel disease; IgG, immunoglobulin; ISS, International staging system; MM, multiple myeloma; PMH, past medical history; PS, performance status

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Case study 1: treatment

- **FEB 2017** — Front-line treatment: VRD x 4 to VGPR. Blepharitis needing doxycycline, Grade-1 peripheral neuropathy, IBD worse
- **JUNE 2017** — PBSCH and autologous stem cell transplant with HDT melphalan
- **NOV 2017** — Bone marrow confirmed CR : PET/CT negative
- **DEC 2017** — VRD consolidation x 2, IBD symptoms worse, Started Lenalidomide maintenance therapy
- **JAN 2019** — Calf-vein DVT treated, patient considering cessation of lenalidomide maintenance therapy

ASCT, autologous stem cell transplant; CT, computed tomography; HDT, high-dose therapy; IBD, irritable bowel disease; PBSCH, peripheral blood stem cell harvest; PET, positron-emission tomography; VGPR, very good partial response; VRD, bortezomib, lenalidomide, dexamethasone

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Treatment choices

1. Use MRD to guide treatment decision

2. Low-dose lenalidomide maintenance

3. Alternative drugs for maintenance

4. Treatment-free monitoring

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MRD FAQ's

Questions	Answers
Should MRD be the new CR	Potentially, as new definitions of CR-MRD positive and CR- MRD negative are emerging
Is MRD testing for prognostication?	Yes MRD negativity consistently improves clinical outcomes
What is the right threshold for MRD testing	IMWG guidance 10^{-5}
What MRD test should I use	Not specified by IMWG
When should I test for MRD	Suspected CR and yearly provided remains in CR biochemically
Is one time MRD testing enough for my patients?	Helpful to prognosticate
Does early MRD negativity equate to improved clinical outcomes?	Need more data
Does sustained MRD negativity mean cure?	Need more data
Can I use MRD tests results to make clinical decisions?	RADAR, MIDAS, PERSEUS, MASTER

Speaker's views

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MRD landmarks

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MRD Measurement Techniques to Achieve International Myeloma Working Group (IMWG) Criterion of ≤10^{-5}

Current clinical practice guidelines include IMWG criteria for MRD[1,2]

For patients achieving CR, each treatment stage (induction, intensified therapy/ASCT, consolidation, and maintenance) should be followed by MRD assessment to assess response, according to IMWG criteria

Recommended MRD assessment methods, with a minimum sensitivity of 1 in 10^{-5} nucleated cells[2]

- NGS
- Flow cytometry*/NGF

- The IMWG defines MRD as the persistence or re-emergence of tumour cells down to **1 in at least 10^5 normal cells (MRD at ≤10^{-5})[2]**
- ASO RQ-PCR, NGS, MFC* and NGF achieve this sensitivity[3]
- Each method has advantages and limitations[3]
- Only NGS and NGF achieve high sensitivity of 10^{-6}
- ASO RQ-PCR is well-standardised but has low applicability, while **NGS produces the highest sensitivity and applicability**[3]

*Conventional MFC has sensitivity of 10^{-4}, whereas improved color combinations now achieve sensitivity of up to 10^{-5}.

ASCT: autologous stem cell transplant; ASO RQ-PCR: allele-specific oligonucleotide real-time quantitative polymerase chain reaction; CR: complete response; MFC: multiparameter flow cytometry; NGF: next-generation flow; NGS: next-generation sequencing.

1. Moreau P, *et al*. Ann Oncol. 2017;28:iv52–iv61;
2. Kumar SK, *et al*. Lancet Oncol. 2016;17:pp.e328–e346;
3. Bai Y, *et al.* Br J Haematol. 2018;181:11–26.

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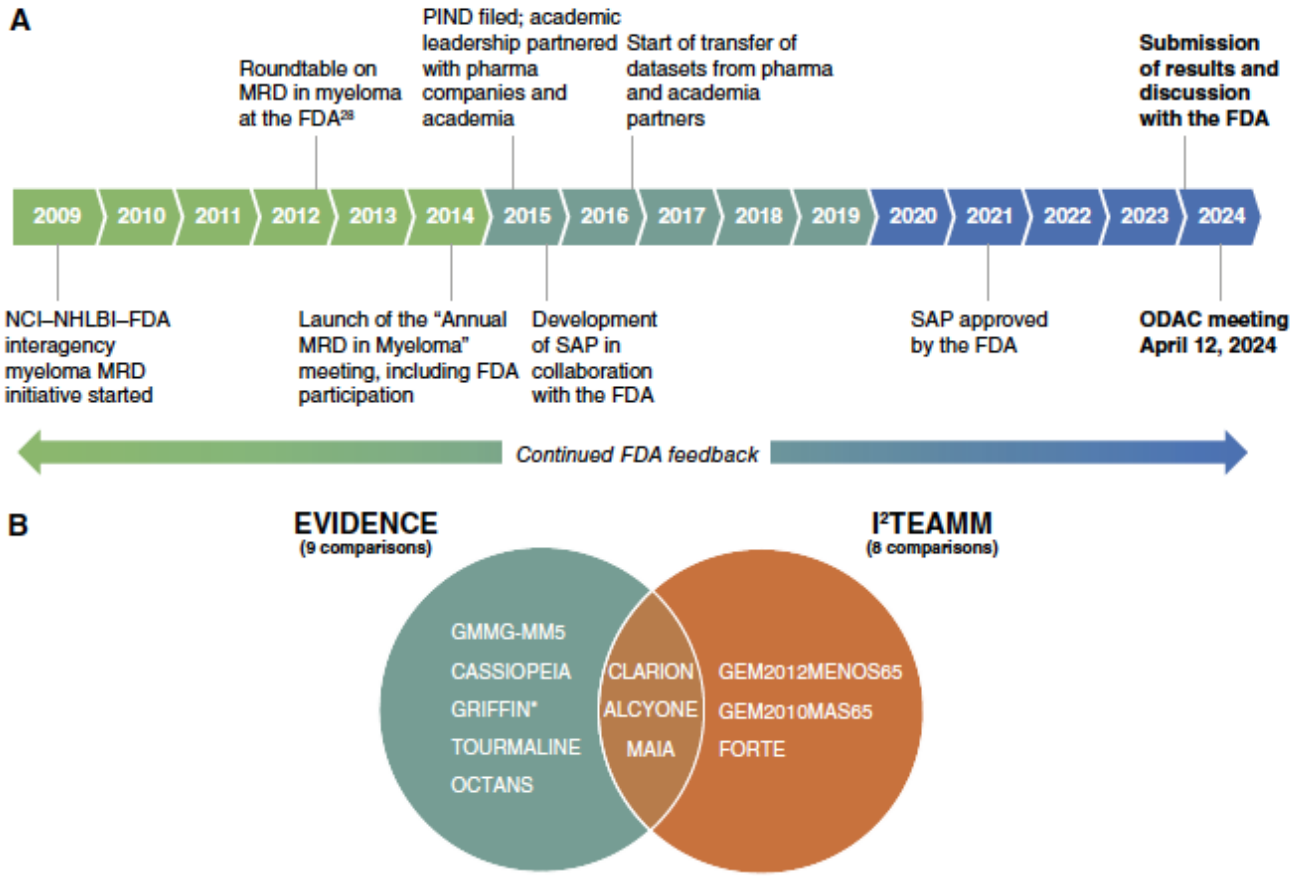

Figure 2. **A,** Timeline of FDA initiative and EVIDENCE meta-analysis on MRD in myeloma. **B,** Studies analyzed in the EVIDENCE meta-analysis and I²TEAMM study in NDMM. Registry identifiers of each trial are as follows: ALCYONE (NCT02195479), CASSIOPEIA (NCT02541383), CLARION (NCT01818752), FORTE (NCT02203643), GEM2010MAS65 (NCT01237249), GEM2012MENOS65 (NCT01916252), GMMG-MM5 (EudraCT number 2010-019173-16), GRIFFIN (NCT02874742), MAIA (NCT02252172), OCTANS (NCT03217812), and TOURMALINE (NCT01564537). *Included in 9-month MRD-negative CR analysis for I²TEAMM and sensitivity analysis in EVIDENCE. NHLBI, National Heart, Lung, and Blood Institute; PIND, pre-IND.

Strategic implications of quadruplet regimens: MRD-adapted therapy

High rates of MRD negativity, with or without ASCT

Study	Induction/ Consolidation	ASCT	MRD-neg	PFS	OS
GRIFFIN[1]	RVd x 6*	Yes	30%	4-yr 70.0%	4-yr 92.2%
GMMG-HD7[2]	RVd x 3§	No	35.6%	NR	NR
CEPHEUS[3]	RVd x 8 + Rd	No	39.4%	52.6 mos	NR
IMROZ[4]	RVd x 8 + Rd	No	43.6%	5-yr 45.2%	5-yr 66.3%
PERSEUS[5]	RVd x 6	Yes	47.5%	4-yr 67.7%	NR
GMMG-HD7[6]	RVd x 3§	Yes	47.7%	NR	NR
FORTE[7]	KRd x 12‡	No	56%	4-yr 56%	4-yr 85%
FORTE[7]	KRd x 8‡	Yes	62%	4-yr 69%	4-yr 86%
ISKIA[8]	KRd x 8	Yes	67%	1-yr 95%	NR

Study	Induction/ Consolidation	ASCT	MRD-neg	PFS	OS
GMMG-HD7[2]	Isa-RVd x 3§	No	50.1%	NR	NR
IMROZ[4]	Isa-RVd x 8 + Isa-Rd	No	58.1%	5-yr 63.2%	5-yr 72.3%
CEPHEUS[3]	Dara-RVd x 8 + Dara-Rd	No	60.9%	54-mo 68.1%	NR
GRIFFIN[1]	Dara-RVd x 6*	Yes	64%	4-yr 87.2%	4-yr 92.7%
GMMG-HD7[6]	Isa-RVd x 3§	Yes	66.2%	NR	NR
MANHATTAN[9]	Dara-KRd x 8‡	No	71%	1-yr 98%	1-yr 100%
PERSEUS[5]	Dara-RVd x 6	Yes	75.2%	4-yr 84.3%	NR
ISKIA[8]	Isa-KRd x 8	Yes	77%	1-yr 95%	NR
GEM2017FIT[10]	Dara-KRd	No	79%	NR	NR

High rates of MRD-negative responses and very promising outcomes → **Either in conjunction with ASCT or as ASCT-sparing approaches** → **Tolerable mAb-based quadruplet regimens followed by immune therapy-based maintenance** → **MRD-negative rates higher with mAb-based quadruplet regimens, PFS appears longer**

1. Voorhees PM, et al. Lancet Haematol 2023;10(10):e825–37. 2. Goldschmidt H, et al. Lancet Haematol 2022;9(11):e810–21.
3. Usmani SZ, et al. IMS Annual Meeting, 2024, abstract #OA-63. 4. Facon T, et al. N Engl J Med 2024;doi: 10.1056/NEJMoa2400712.
5. Sonneveld P, et al. N Engl J Med 2024;390(4):301–13. 6. Raab MS, et al. HemaSphere 2024;8(S1):218–220.
7. Gay F, et al. Lancet Oncol 2021;22(12):1705–20. 8. Gay F, et al. Blood 2023;142(suppl 1):abstract 4.
9. Landgren O, et al. JAMA Oncol 2021;7(6):862–8. 10. Mateos M-V, et al. Blood 2023;142(suppl 1):abstract 209.

*3-week cycles.
†Preliminary data in 198 patients from start of R maintenance.
‡4-week cycles. §6-week cycles.
NR, not reported.

Role of MRD in UK practice

- Prognostication
- Duration of therapy
- Deferring ASCT

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Implications to current practice

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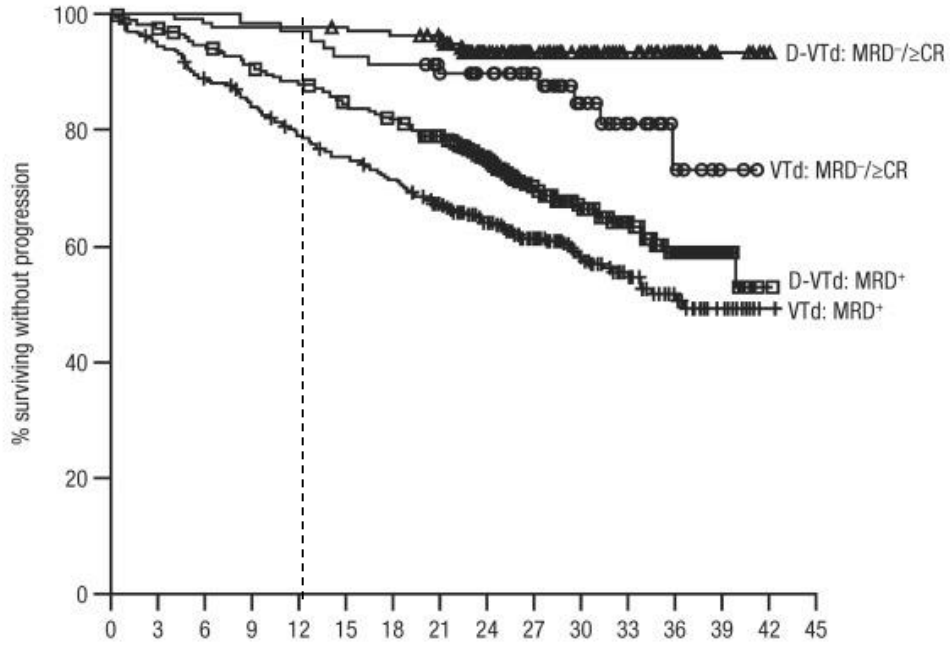
Opportunity to limit duration of therapy

Figure: Landmark PFS analysis of pts progression-free at 1 year post-induction for pts who achieved 1 year sustained MRD negativity and pts who did not by treatment group



No. at risk																
VTd: MRD⁺	380	359	336	315	294	279	264	239	185	137	99	64	43	19	1	0
VTd: MRD⁻/≥CR	70	70	70	69	68	65	64	60	53	45	27	18	9	2	0	0
D-VTd: MRD⁺	337	329	316	305	293	277	269	251	194	148	101	68	42	15	1	0
D-VTd: MRD⁻/≥CR	147	147	145	144	144	143	141	135	107	79	60	42	26	5	1	0

PFS, progression-free survival; pts, patients; MRD, minimal residual disease; D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ≥CR, complete response or better.

Avet Loiseau et al Blood, Volume 138, Supplement 1, 2021, Page 82,

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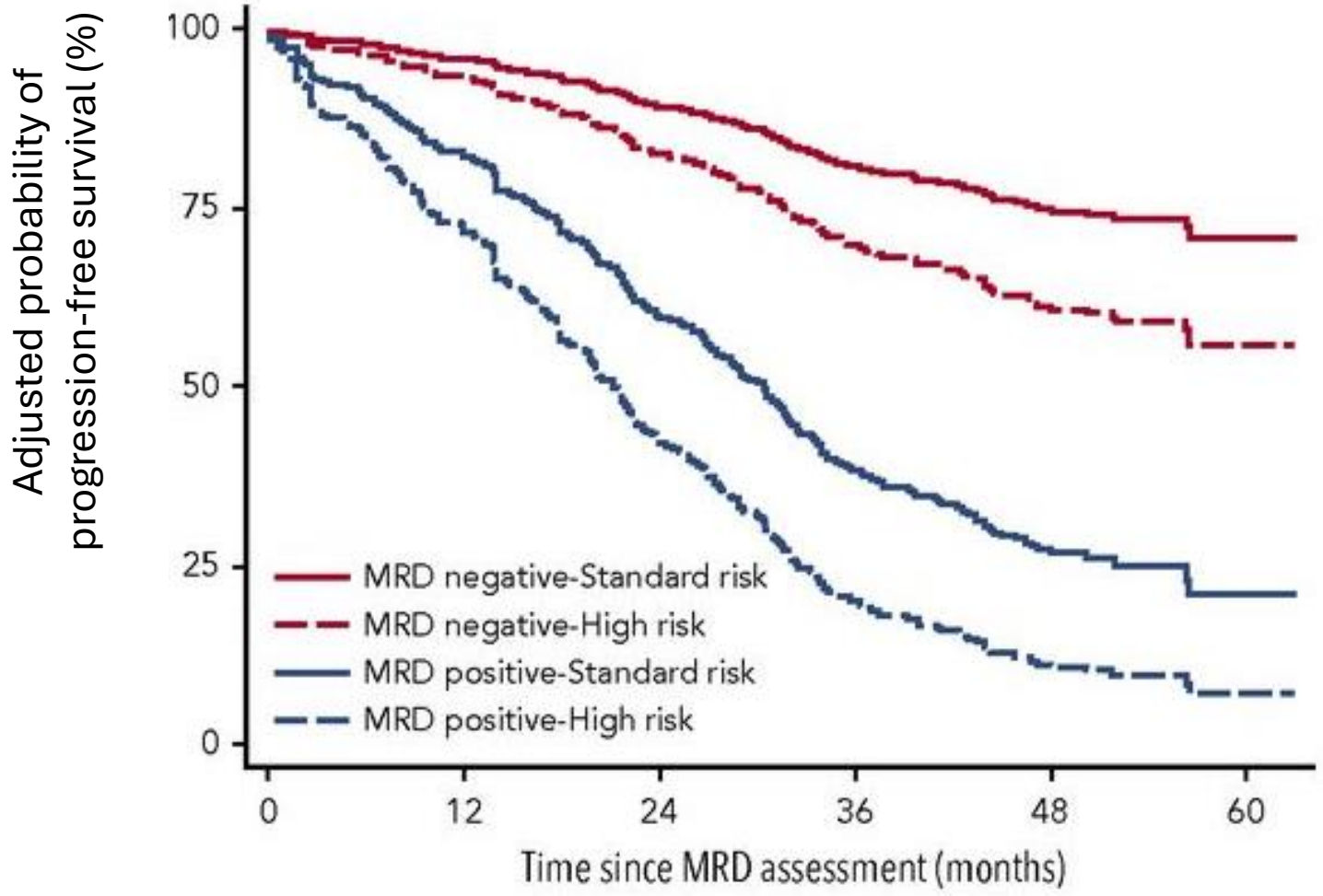
IFM 2009 : Limited duration Lenalidomide maintenance MRD Negativity Improves Outcomes with MM



Perrot A, *et al*. Blood. 2018;132:2456–64

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Isa-based quadruplets also demonstrating benefit in non-ASCT setting

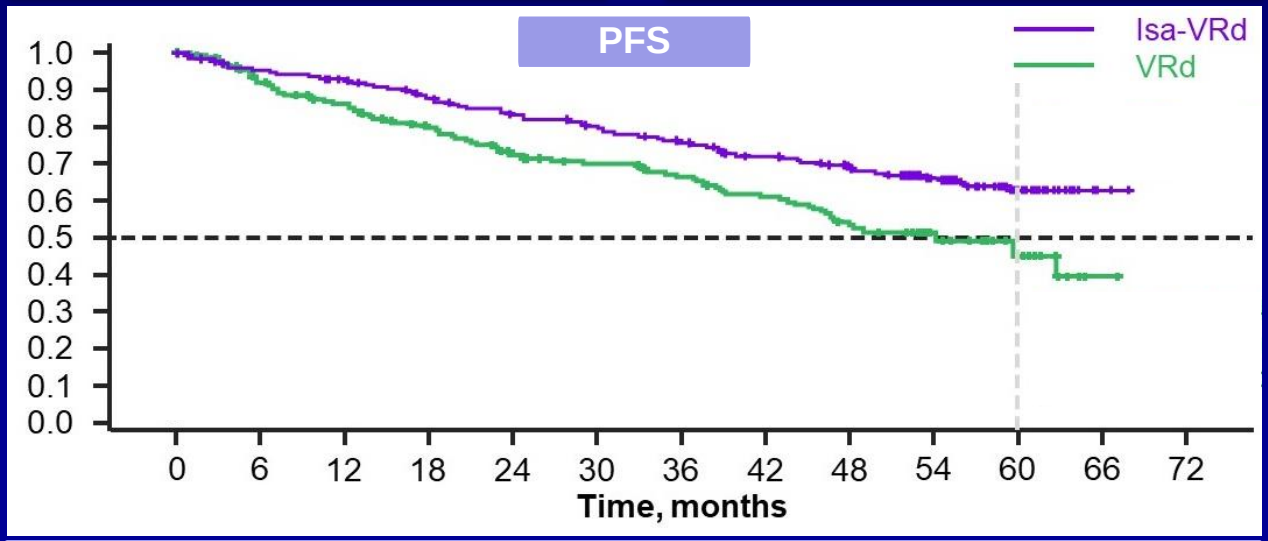
IMROZ: Isa-RVd vs RVd in transplant-ineligible NDMM patients

IMROZ study design (NCT03319667)

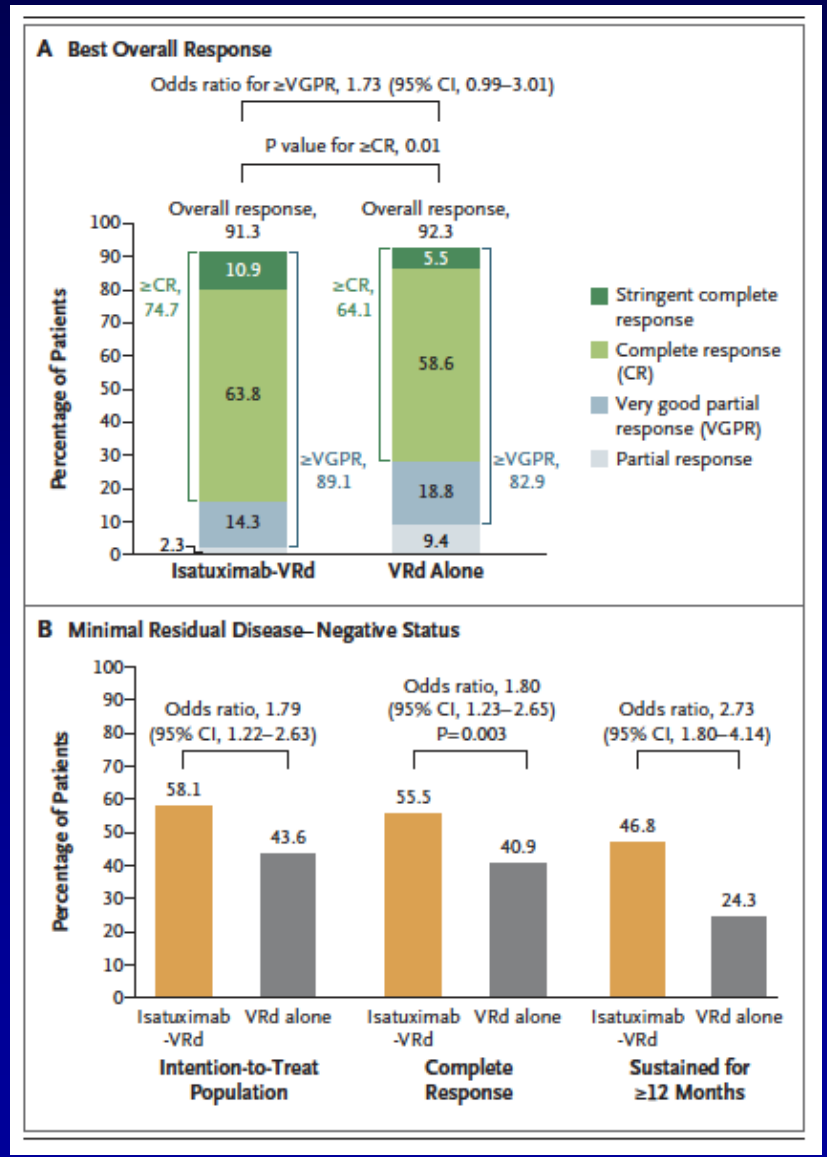
- 3:2 randomization to Isa-RVd vs RVd
- Induction: 4 x 6-week cycles of Isa-RVd/RVd
- Maintenance: 4-week cycles of Isa-Rd/Rd until PD/toxicity
- Primary endpoint: PFS

446 NDMM patients randomized, Isa-RVd vs RVd 265 vs 181

- Median age 72 vs 72 years, 26.0% vs 31.5% aged ≥75 years
- 6.8% vs 3.3% EMD
- 10.9% vs 11.6% R-ISS stage III
- 15.1% vs 18.8% high-risk cytogenetics
- 35.8% vs 38.7% 1q21+



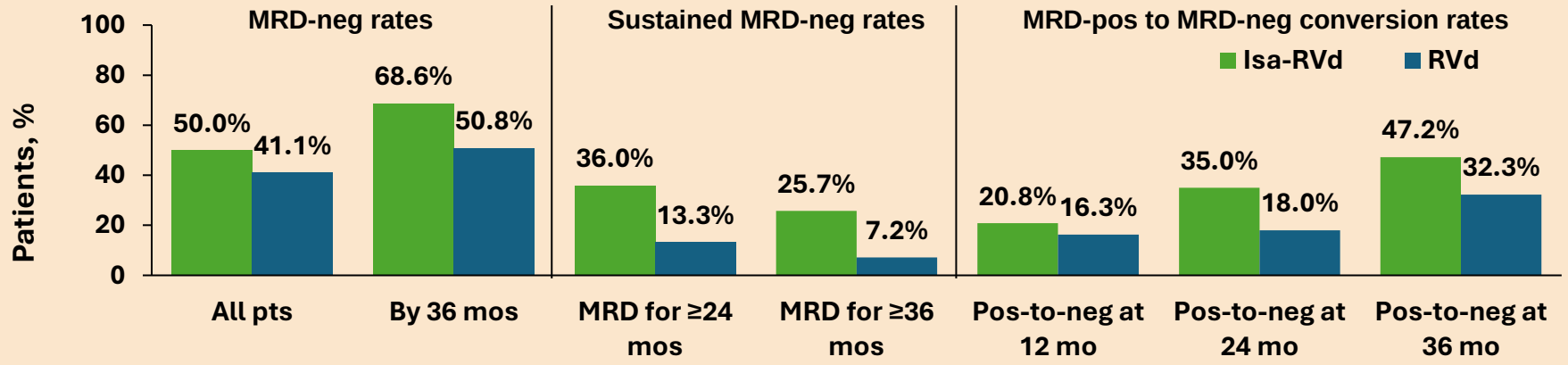
- Median follow-up 59.7 months
- 5-year PFS 63.2% vs 45.2%, HR 0.60
- Consistent benefit across subgroups, HR in high-risk cytogenetics 0.97



1. Facon T, et al. N Engl J Med 2024;391(17):1597–609.

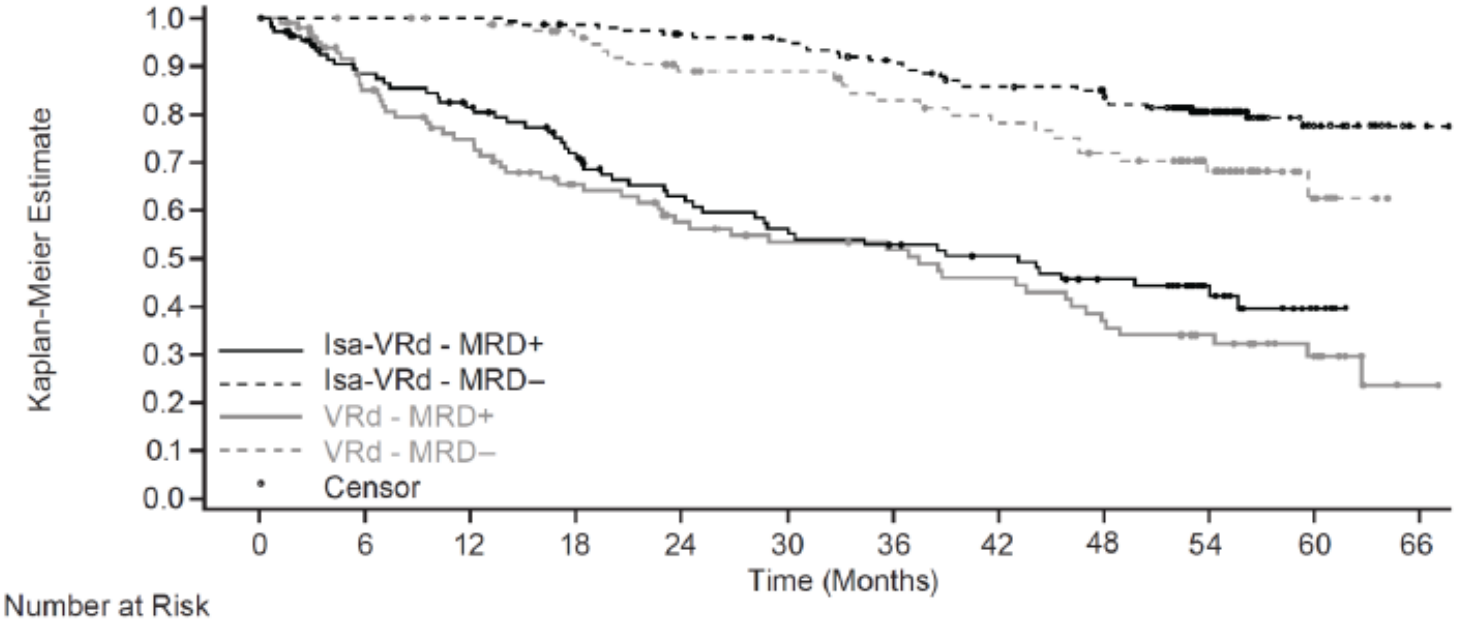
Updated analysis of MRD-neg (10^{-5}) rates

MRD dynamics based on 1610 MRD assessments over 5 years



Orlowski RZ, et al. Blood 2024;144(Supplement 1):770 (oral presentation).

PFS based on MRD status



Number at Risk												
Isa-VRd - MRD+	111	89	80	67	56	50	46	42	35	21	6	0
Isa-VRd - MRD–	154	154	154	150	145	140	131	122	118	83	37	2
VRd - MRD+	102	77	65	51	42	37	35	31	25	19	11	2
VRd - MRD–	79	78	76	70	62	59	54	50	45	32	9	0

Shown are the results of Kaplan–Meier estimates of PFS based on disease assessment by the IRC by MRD status among patients in the ITT population.

1. Facon T, et al. N Engl J Med 2024;391(17):1597–609.

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Implications to future practice

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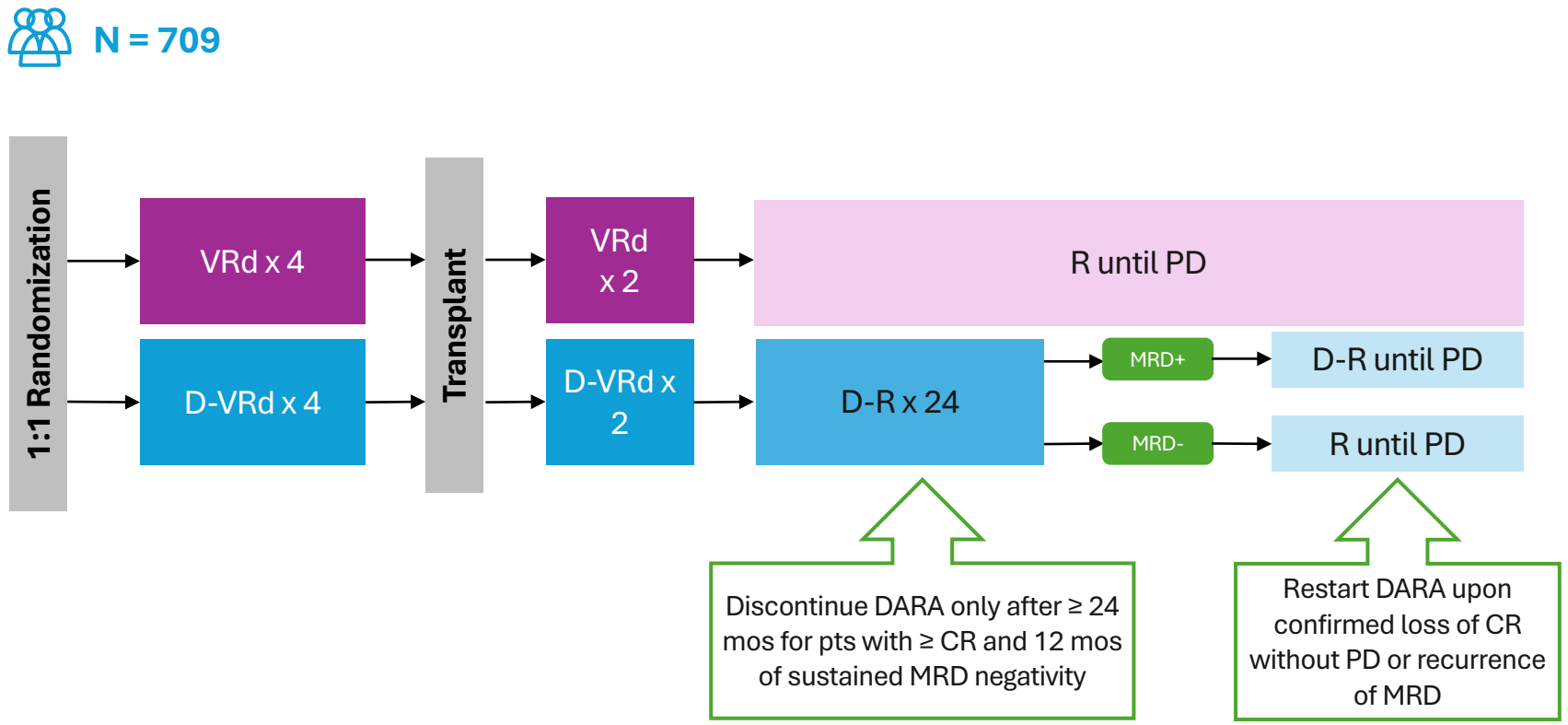
PERSEUS: Study Design – Opportunity to modify maintenance therapy

Study Design:

MRD Aims

1. **1°**: PFS
2. **2°:** Overall MRD-negativity rate at 10^{-5} in patients with ≥ CR
3. **Exploratory**: MRD-negativity rate at 10^{-6}



Sonneveld P, et al. ASH 2023; abstract LBA-1.

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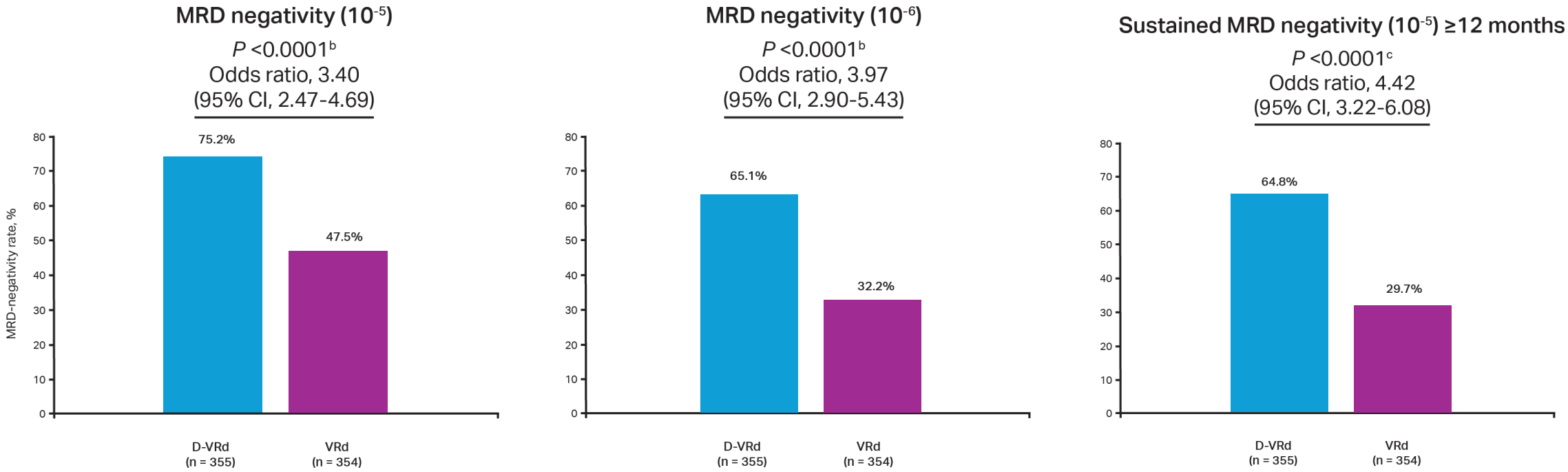
PERSEUS: Overall and Sustained MRD-negativity Rates

- **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



Sonneveld P, et al. ASH 2023; abstract LBA-1.

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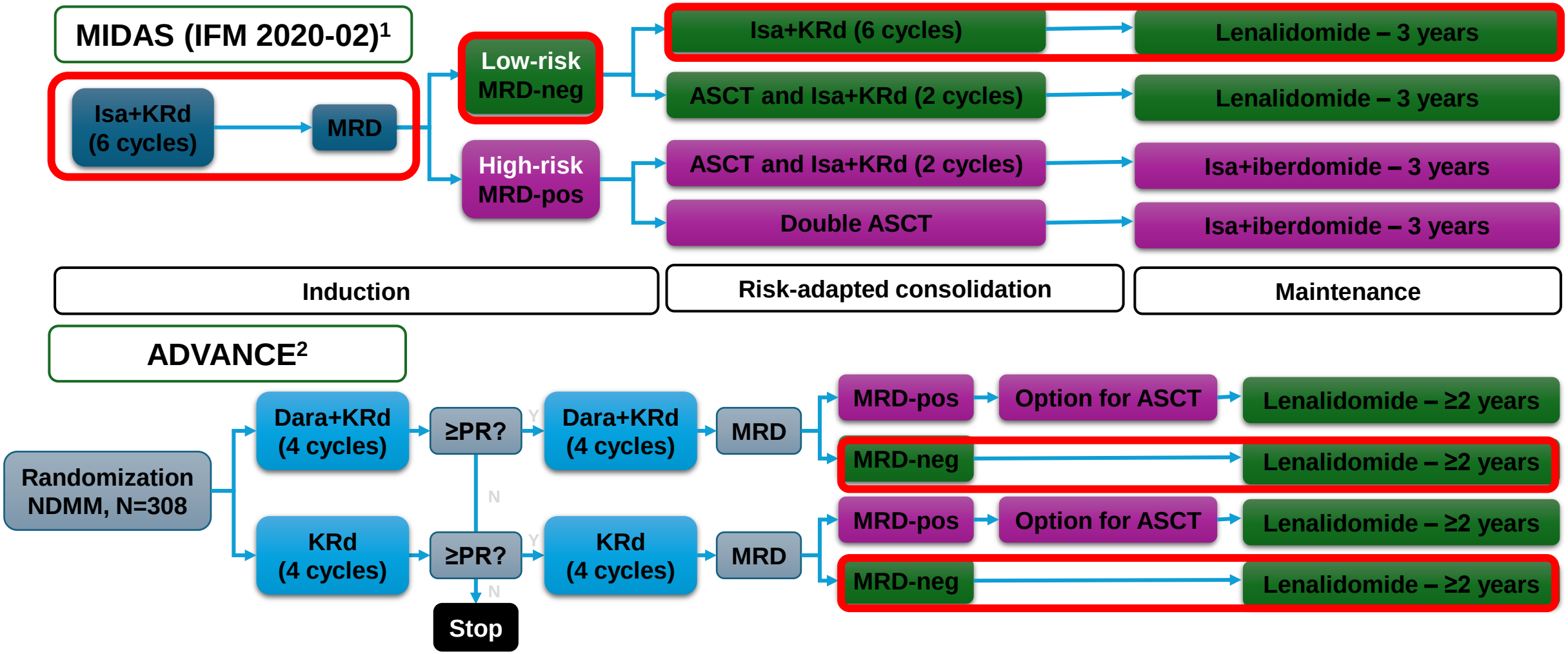
MRD-adapted therapeutic approaches with CD38 mAb-based quadruplets – MIDAS (IFM 2020-02) / ADVANCE (University of Miami) – Deferred ASCT



1. Perrot A, et al. COMy 2021. https://clinicaltrials.gov/ct2/show/NCT04934475.

2. Landgren O, et al. Blood 2023;142(suppl 1):abstract 3392.

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Isa-KRd induction in NDMM

MIDAS phase 3 trial: MRD-adapted therapy after Isa-KRd

- N=791 transplant-ineligible NDMM patients
- MRD-neg rate: 63% (10^{-5}), 47% (10^{-6})

Perrot A, et al. Blood 2025;doi:10.1182/blood.2024026230.

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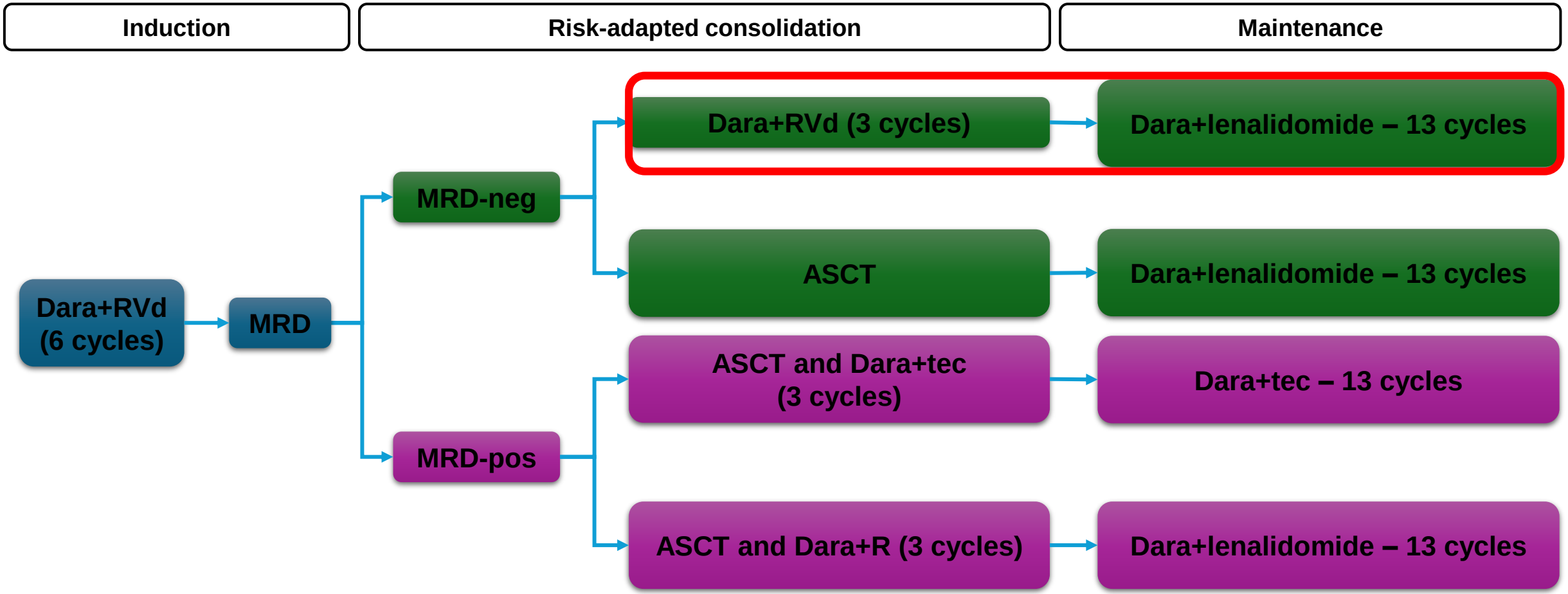
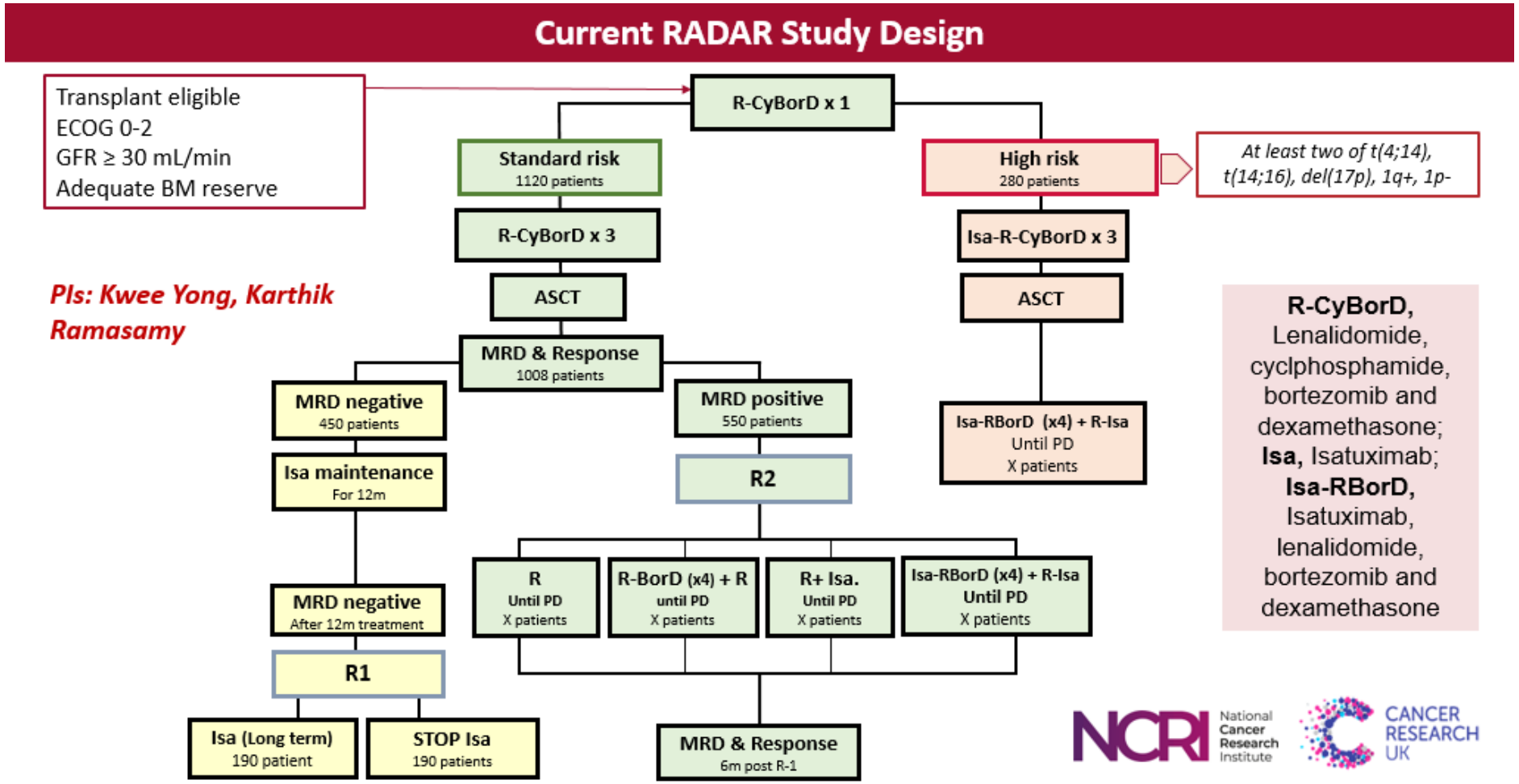
MRD-adapted therapeutic approaches – MASTER-2 (University of Alabama at Birmingham)



Dhakal B, et al. Blood 2024;144(Supplement 1):2000.1.
https://www.clinicaltrials.gov/ct2/show/NCT05231629

RADAR trial: Opportunity to prospectively confirm MRD response driven therapy



Royle KL BMJ Open. 2022 Nov 17;12(11):e063037. doi: 10.1136/bmjopen-2022-063037.

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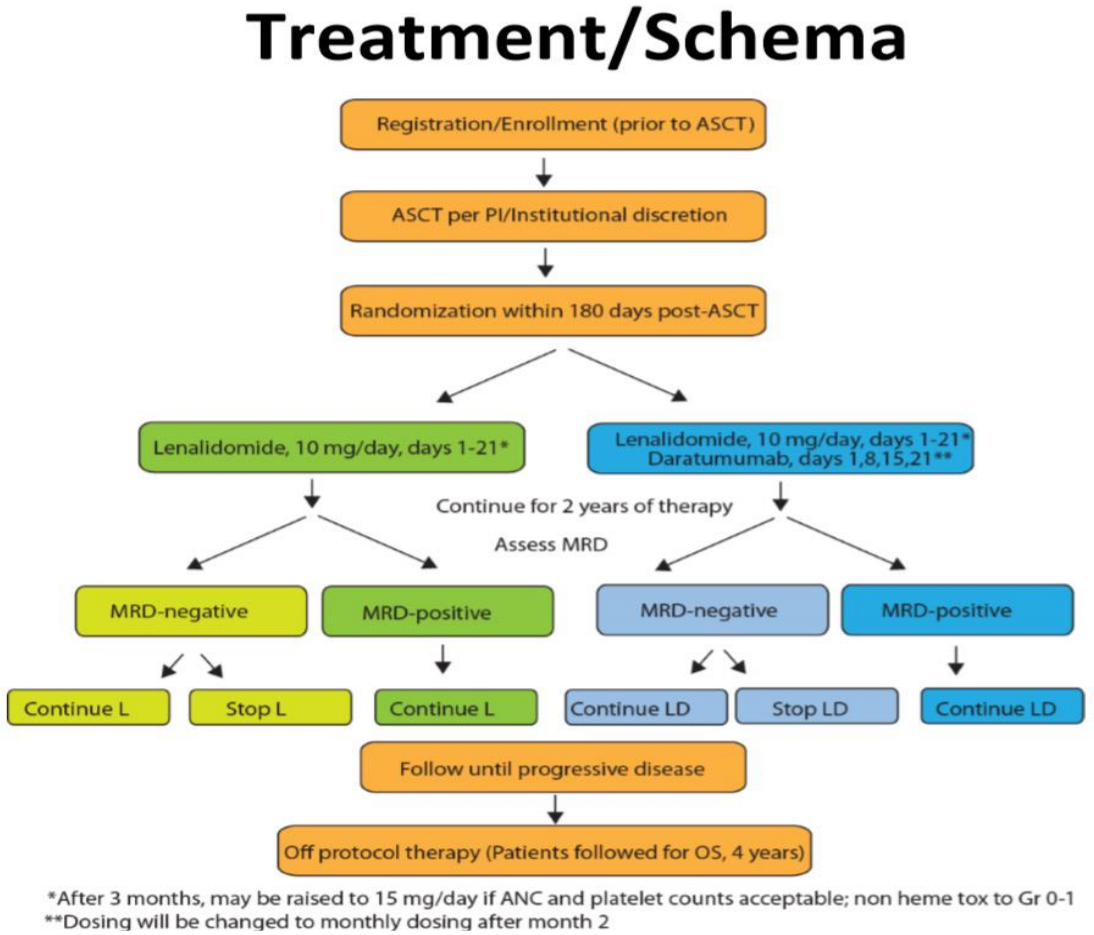
MRD Directed maintenance study

DRAMMATIC STUDY SWOG1803/BMT CTN 1706: Using Minimal Residual Disease to Direct Therapy Duration



1. https://clinicaltrials.gov/ct2/show/NCT04071457;
2. Krishnan A, et al. Blood 2020;136:21–2;
3. Krishnan A, et al. ASH 2020;136: Presentation 1515

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Treatment choices

1. Use MRD to guide treatment decision

2. Low-dose lenalidomide maintenance

3. Alternative drugs for maintenance

4. Treatment-free monitoring

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Panel discussion

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