Highlights from IMS 20th meeting 2023

Dr. Roberto Mina

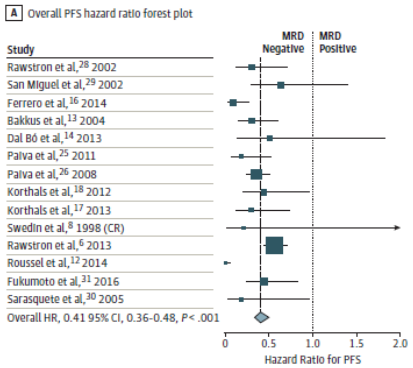
Terapie MRD-guidate: dati disponibili e possibili algoritmi terapeutici

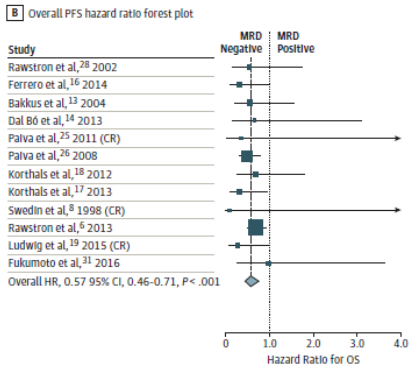
30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

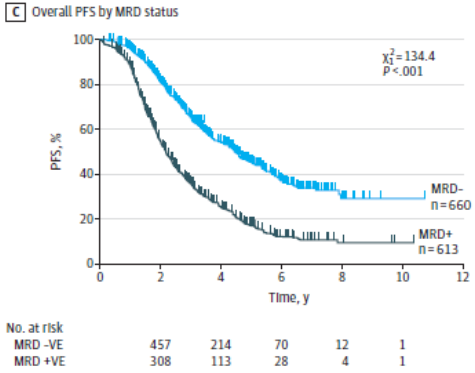
Disclosures of Roberto Mina

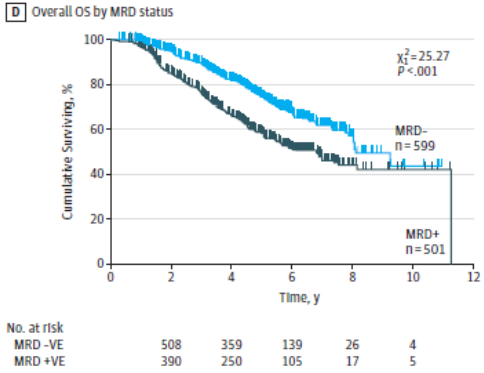
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen			x			x	x
Sanofi						x	x
BMS						x	x
GSK						x	x
Takeda						x	
Amgen						x	
Pfizer						x	
Menarini Stem-line							x

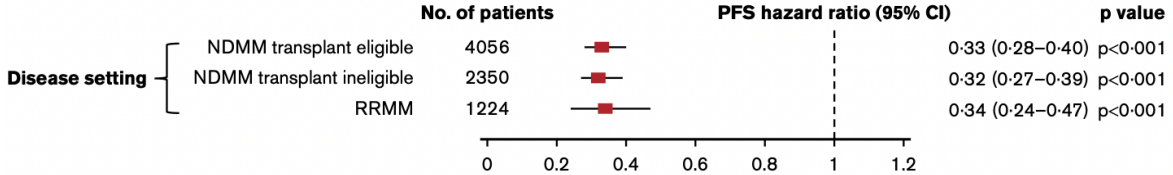
Overall effect of MRD status on PFS and OS





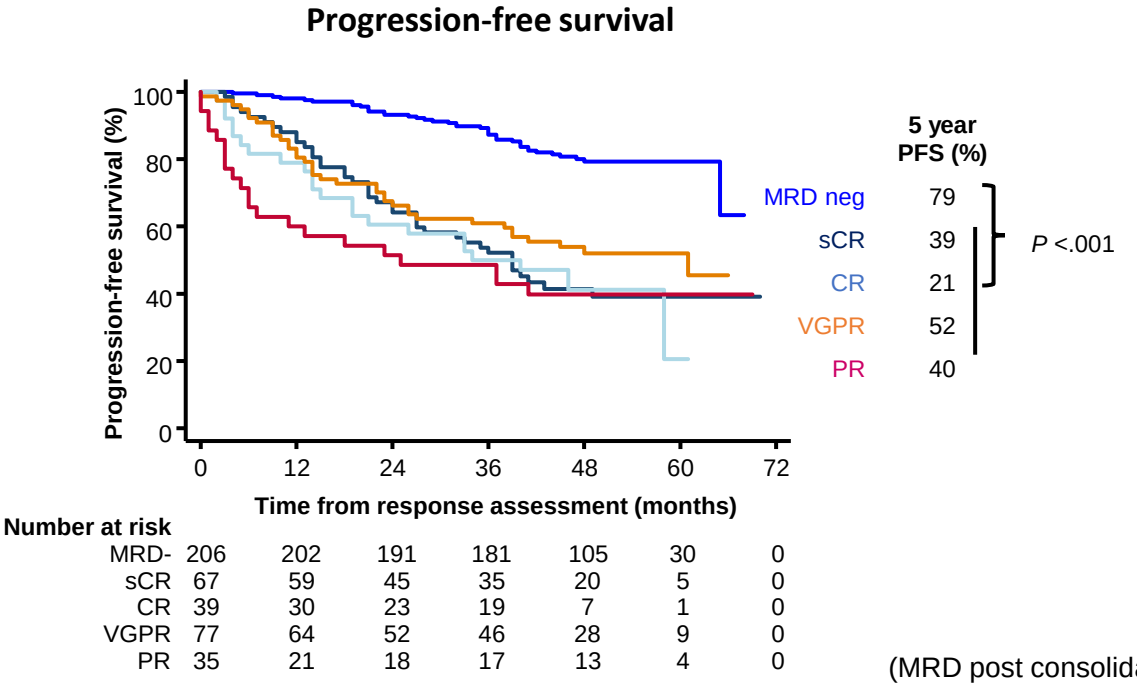






Munshi NC et al. JAMA Oncol. 2017 Jan 1;3(1):28-35; Munshi NC et al. Blood Adv (2020) 4 (23): 5988–5999.

Is the current IMWG response criteria system still relevant in the MRD era?



(MRD post consolidation, LOD 2.10^{-6})

Transplant-eligible patients treated with Bortezomib-Lenalidomide-Dexamethasone induction and consolidation

CR, complete response; IMWG, International Myeloma Working Group; LOD, limit of detection; MRD, minimal residual disease; PFS, progression-free survival; PR, partial response; sCR, stringent CR; VGPR, very good PR

Jimenez-Ubieto A et al. Blood 2021; 138(19):1901-905

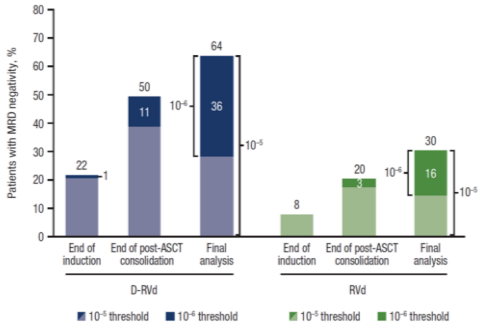
MRD as a new endpoint in clinical studies

Induction

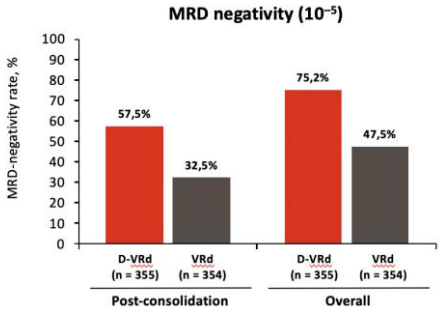
ASCT

Maintenance

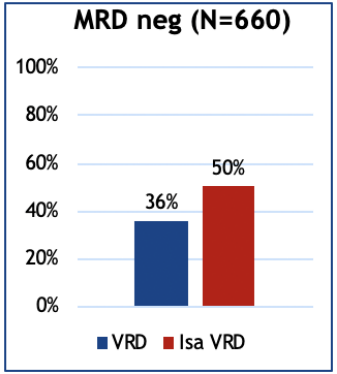
CASSIOPEIA
DVTd vs VTd



PERSEUS
DVRd vs VRd



GMMG-HD7
Isa-VRd vs VRd



Moreau et al, CASSIOPEIA trial, Lancet 2019; Sonneveld P. et al ASH2023
Goldschmidt et al., GMMG-HD7 Trial, Lancet Lancet Haematol 2022

Induction

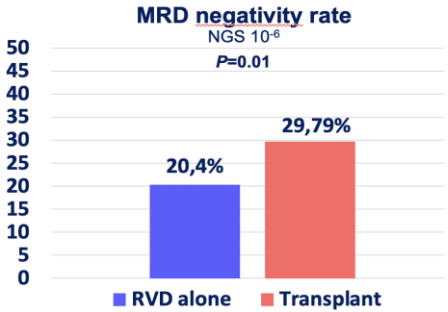
↓

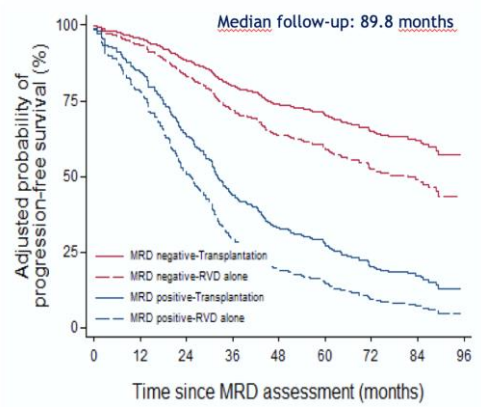
ASCT

↓

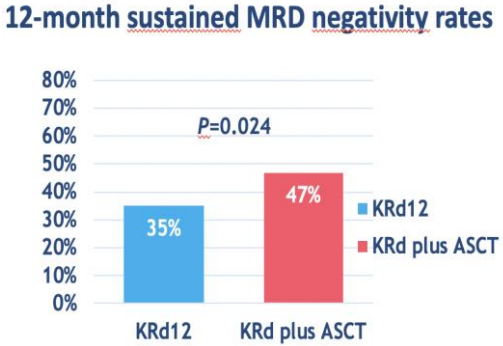
Maintenance

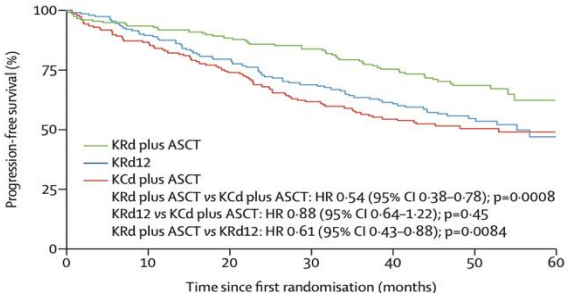
IFM2009: VRd-ASCT vs VRd





FORTE: KRd-ASCT vs KRd





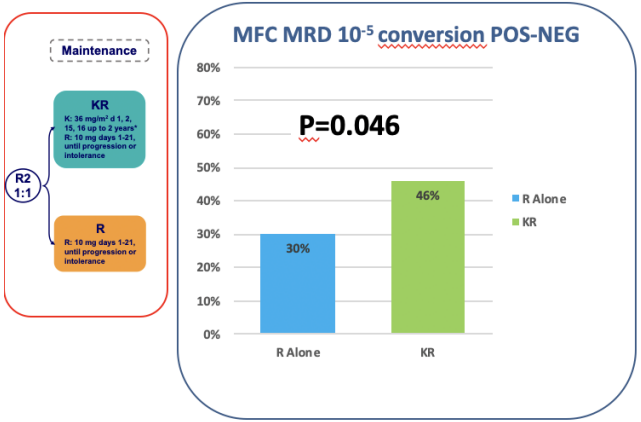
Perrot A. et al; Gay F. et al Lancet Oncol 2021

Induction

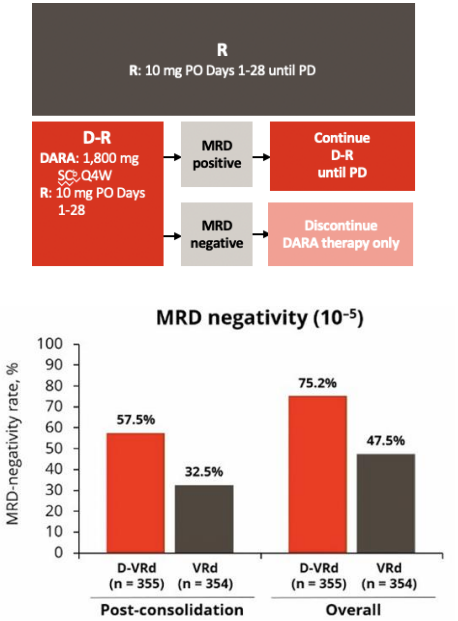
ASCT

Maintenance

FORTE: KR vs R maintenance

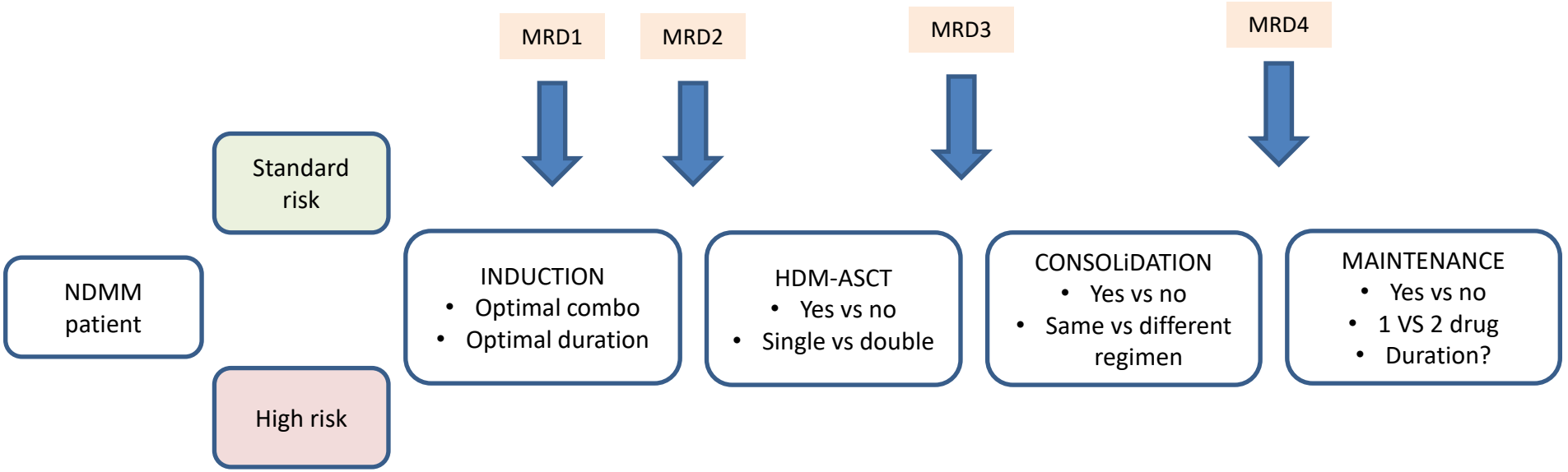


PERSEUS: DR vs R maintenance

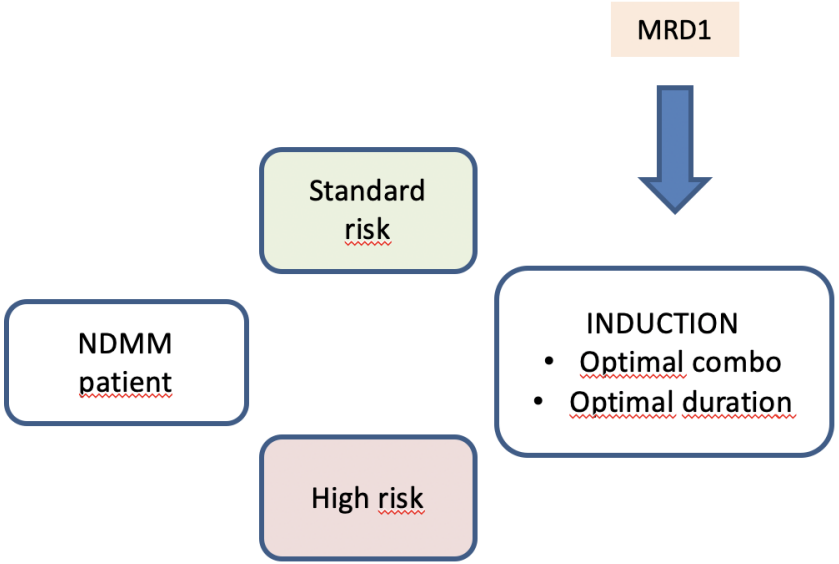


Gay F. et al Lancet Oncol et al 2021; Sonneveld P. et al NEJM 2023

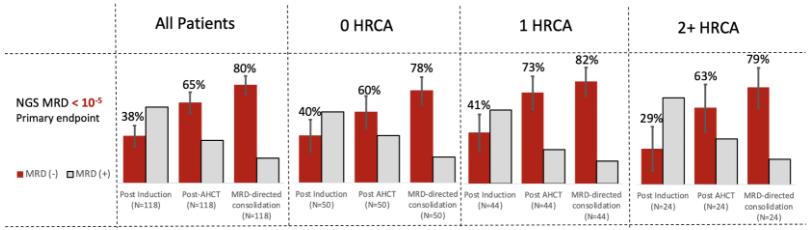
Can we use MRD to drive treatment choices?



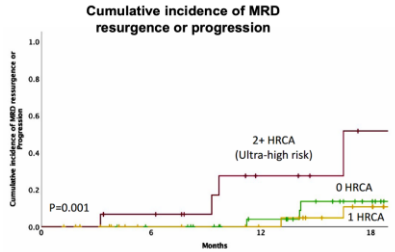
Are all MRDs created equal?



The MASTER trial



Stopping therapy in sustained MRD-negativity with Dara-KRd
MASTER MRD-SURE

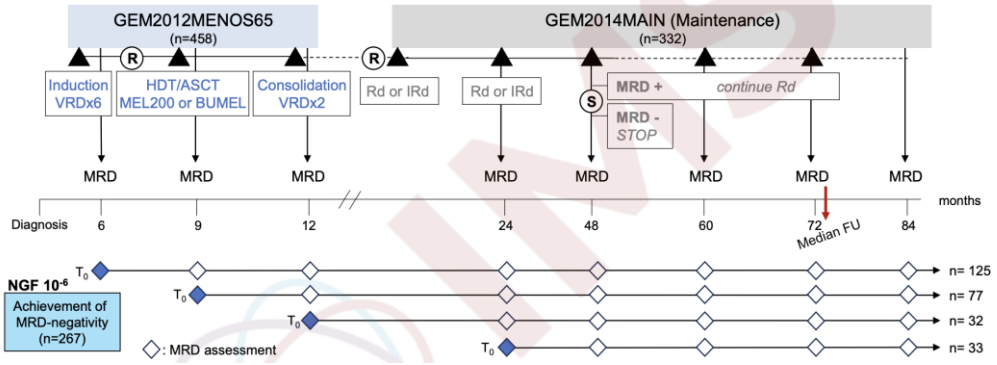


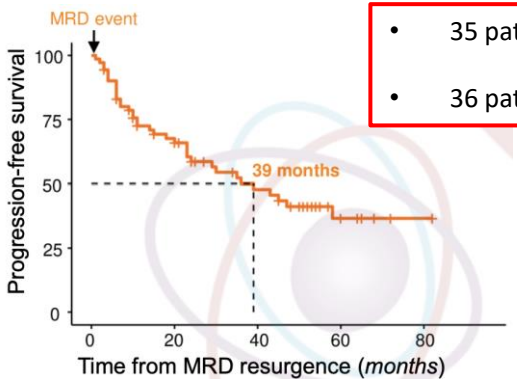
- Sustained MRD-negative similar for risk groups
  - 0 HRCA – 62%
  - 1 HRCA- 78%
  - 2+ HRCA – 63%
- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA – 4%
  - 1 HRCA- 0%
  - 2+ HRCA – 27%

high-risk cytogenetics: gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)
HRCA, high-risk cytogenetics; MRD, minimal residual disease

Costa L et al. ASH 2021; abstract 481 (oral presentation)

Predicting the risk of MRD resurgence

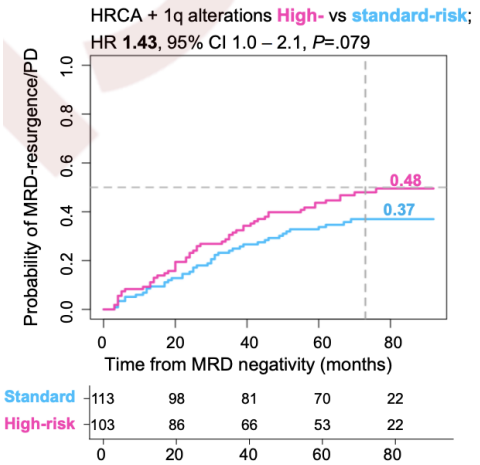


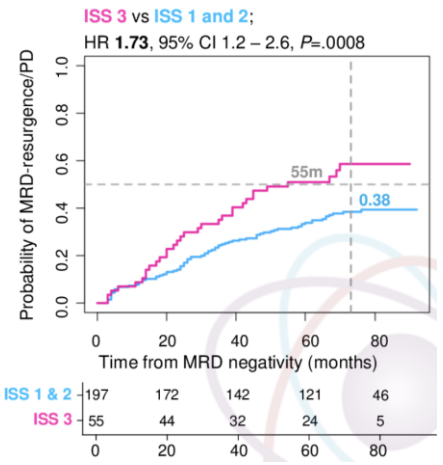


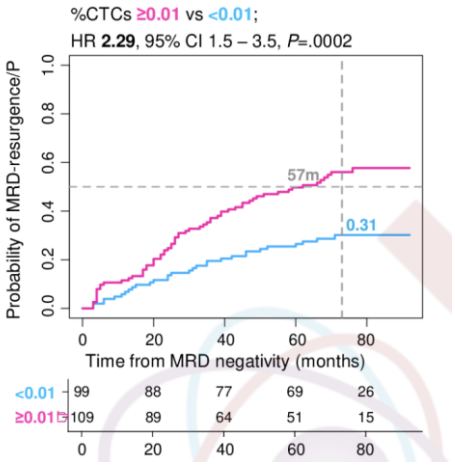
- 35 patients progression-free
- 36 patients relapsed

Guerrero C. et al IMS 23

Cytogenetics, ISS and CTC are predictors of unsustained MRD







ISS	CTCs	Achievement of MRDneg	
1 or 2	< 0.01	post-induction (≤6m)	*None*
1 or 2	< 0.01	**later (>6m)**	*One*
1 or 2	**≥ 0.01**	post-induction (≤6m)	
3	< 0.01	post-induction (≤6m)	
3	**≥ 0.01**	post-induction (≤6m)	*Two or more*
3	< 0.01	**later (>6m)**	
1 or 2	**≥ 0.01**	**later (>6m)**	
3	**≥ 0.01**	**later (>6m)**	

Risk factors:

One vs none; HR **2.24**, 95% CI 1.2–4.1, *P*=.008

Two + vs none; HR **4.39**, 95% CI 2.5–7.7, *P*<0.0001

Two + vs one; HR **1.96**, 95% CI 1.3–2.9, *P*=.001

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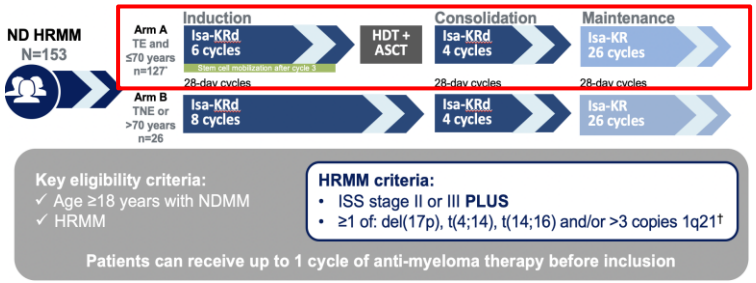
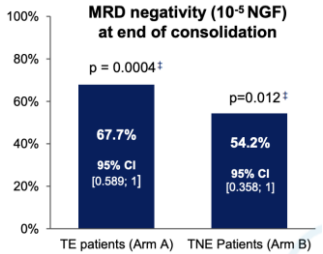
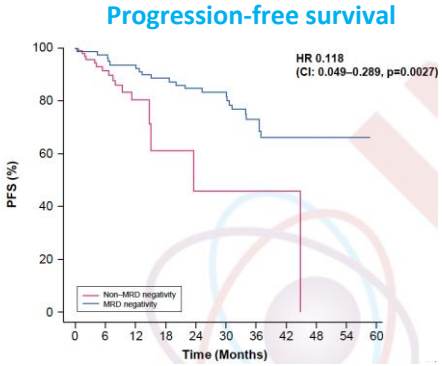
KRd plus anti-CD38 MoAb in Patients With High-Risk Newly Diagnosed MM

GMMG-CONCEPT, phase II study







Sustained MRD negativity for ≥12 months: 63% (TE) and 46% (TIE)

Leypoldt L, et al. J Clin Oncol. 2023 Sep 27:JCO2301696

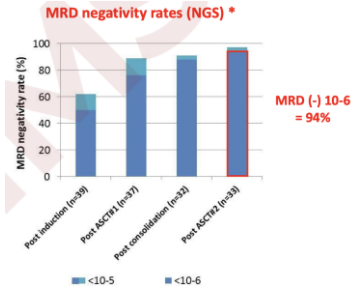
IFM 2018-04, phase II study

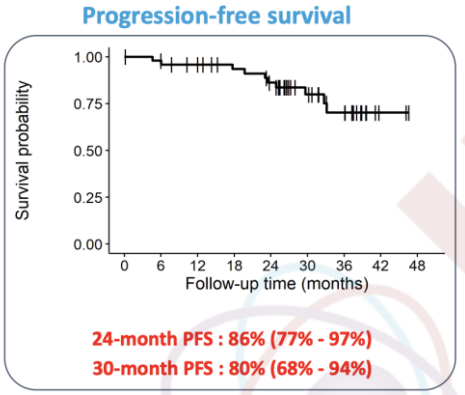
Key inclusion criteria:

- Age < 66
- **Newly diagnosed multiple myeloma**
- **Transplant-eligible**
- **High-risk FISH :** t(4;14), 17p Del, t(14;16)
- ECOG 0-2

Objectives:

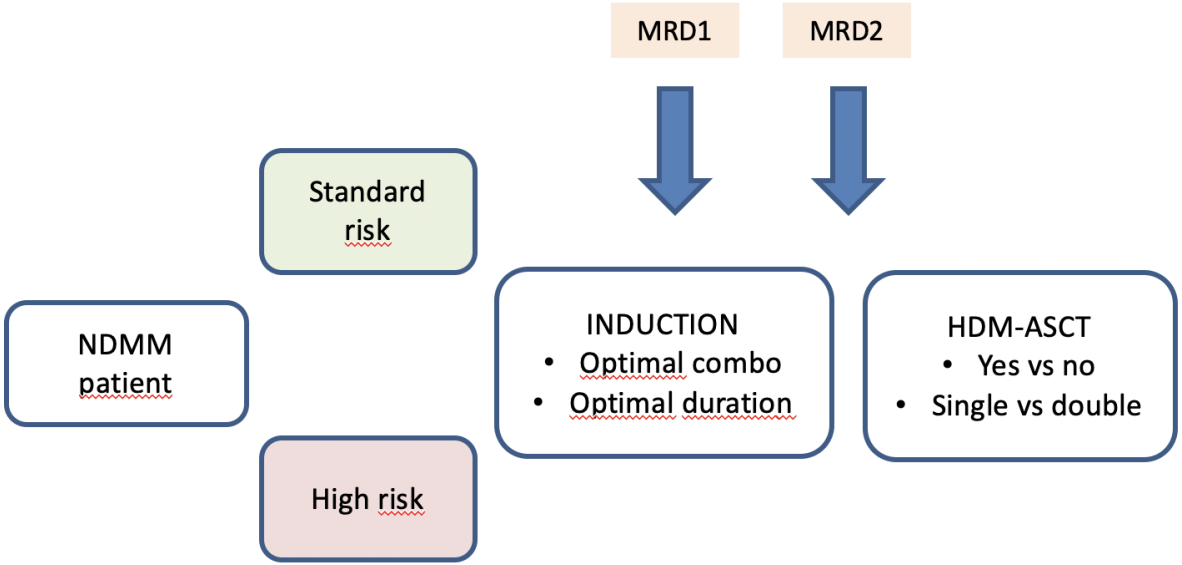
- **Primary Objective :** Feasability
  primary endpoint : >70% patients receiving 2nd transplant
- **Secondary Objectives:** Safety, ORR, PFS, OS, stem-cell collection



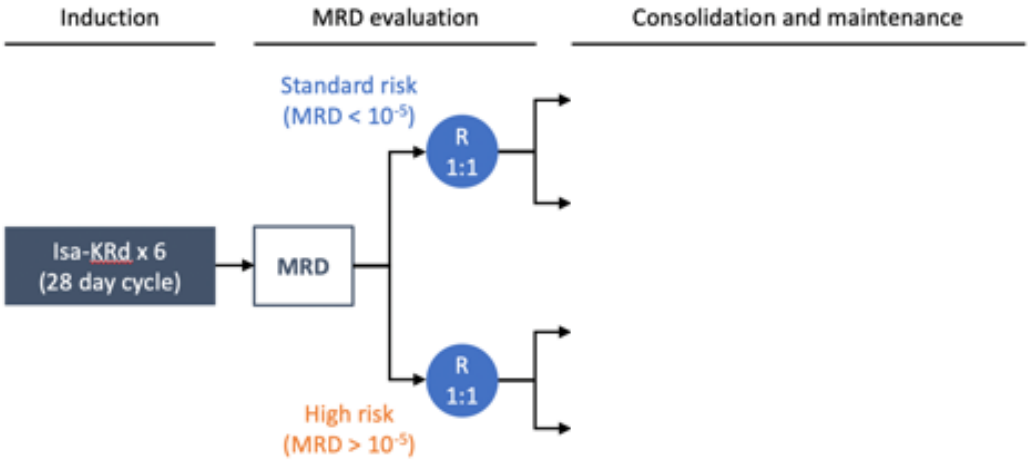


Touzeau C. et al IMS2023, oral presentation

Can we use MRD to drive treatment choices?



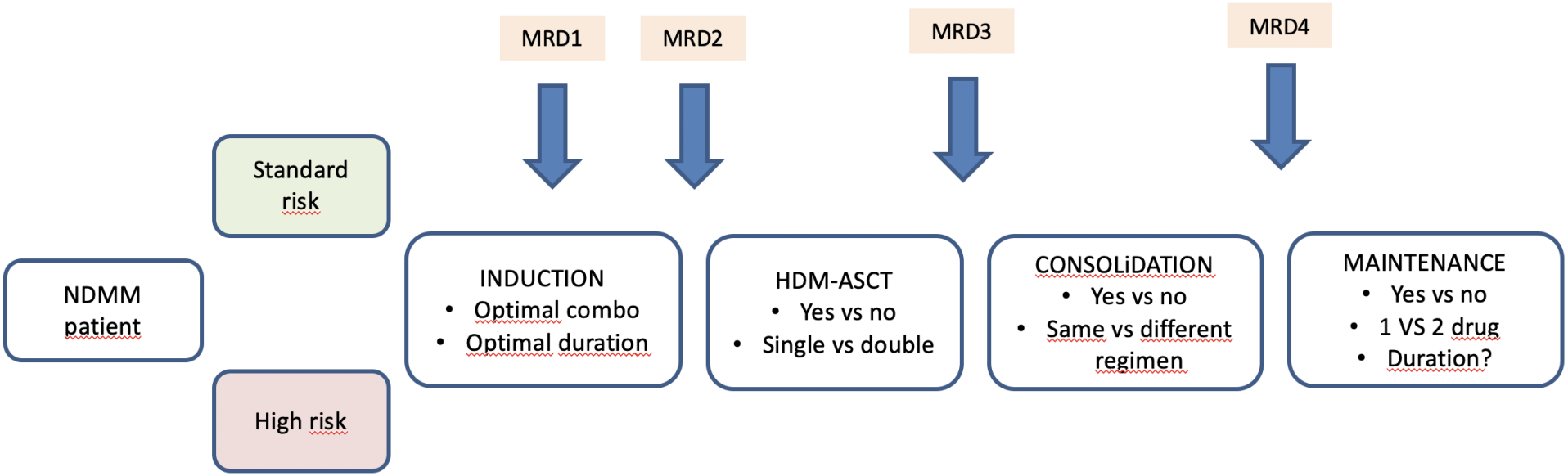
The role of Autologous transplant in standard and high risk multiple myeloma: the MIDAS[1] study



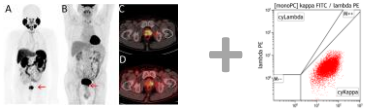
ASCT, autologous stem cell transplant; Dara, daratumumab; HDM, high-dose melphalan; Isa, isatuximab; KRd, carfilzomib, lenalidomide, dexamethasone; MRD, minimal residual disease; PD, progressive disease; R, lenalidomide; VRd, bortezomib, lenalidomide, dexamethasone

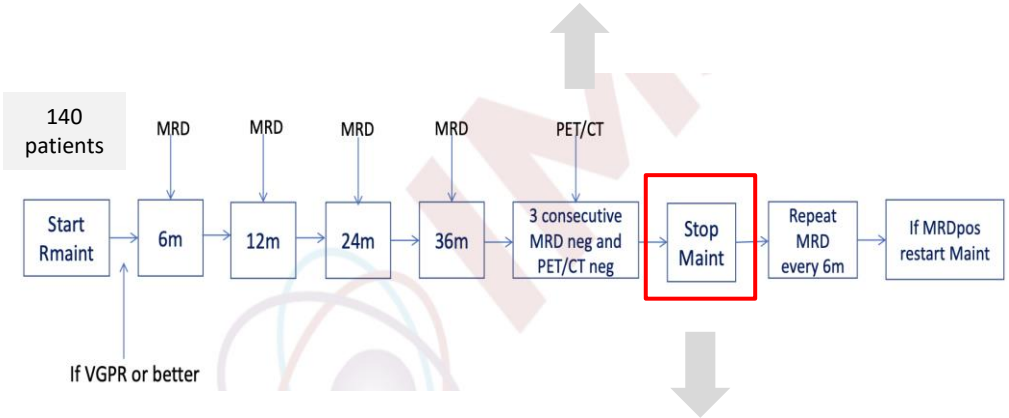
1. ClinicalTrials.gov/NCT04934475

Can we use MRD to drive treatment choices?



Can MRD status drive treatment duration?
Prospective study on maintenance discontinuation





Discontinued len after 3 years at least: 42 patients

Patients who completed 36 months of lenalidomide maintenance N=42	
Age at diagnosis (median, range)	56 (43-66)
Sex (male)	50%
MM subtype (IgG; IgA; LC)	52.4%; 26.2%; 21.4%
High risk cytogenetics	29%
ISS 3	17.1%
RISS 3	7.5%
Follow up from Maintenance start (median; range)	53 months; (38-68)
Follow up from Maintenance stop(median; range)	16 months; (1-31)

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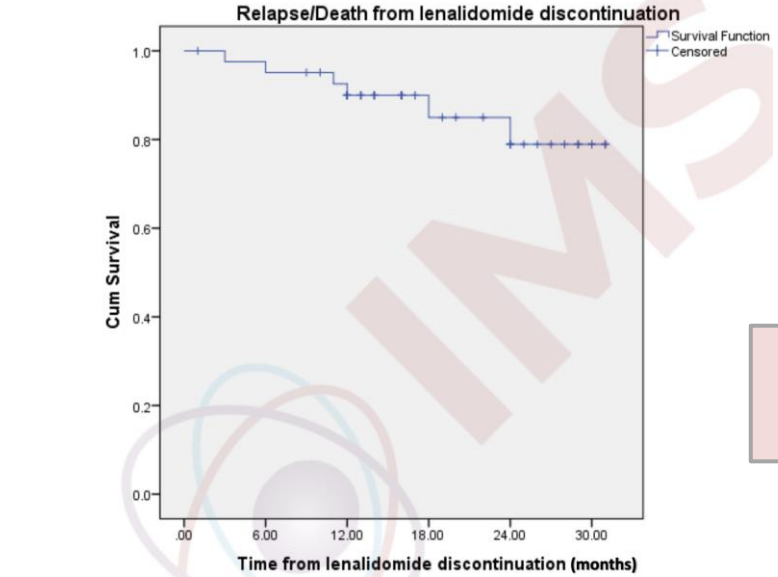
Sustained MRD negativity may be used to STOP maintenance after ASCT

Risk of relapse or death from lenalidomide discontinuation



At risk	42	41	38	18	14	4
MRD negative	42	39	36	18	13	4

42 patients with sustained MRD negativity ($10^{\wedge 6}$) discontinue lenalidomide maintenance

5 patients MRD pos → neg
1 patient → PD
1 patient → death

MRD neg after 12 months: 36/38
MRD neg after 18 months: 18/18
MRD neg after 24 months: 13/14

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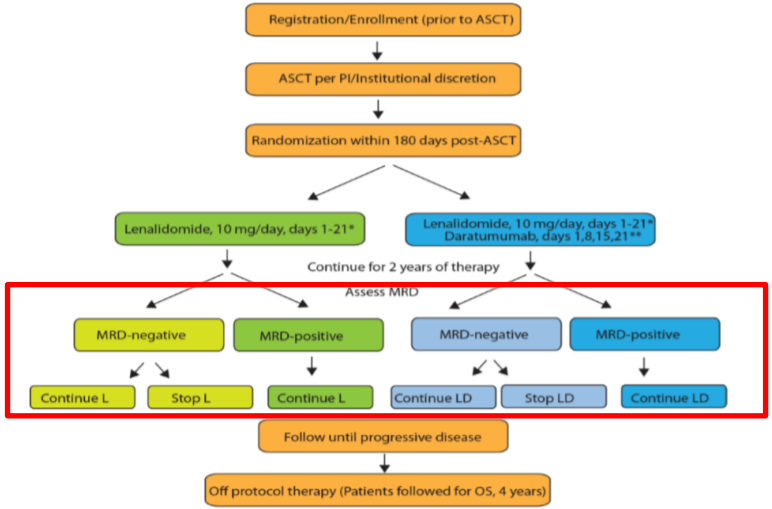
Minimal Residual Disease to Direct Therapy Duration

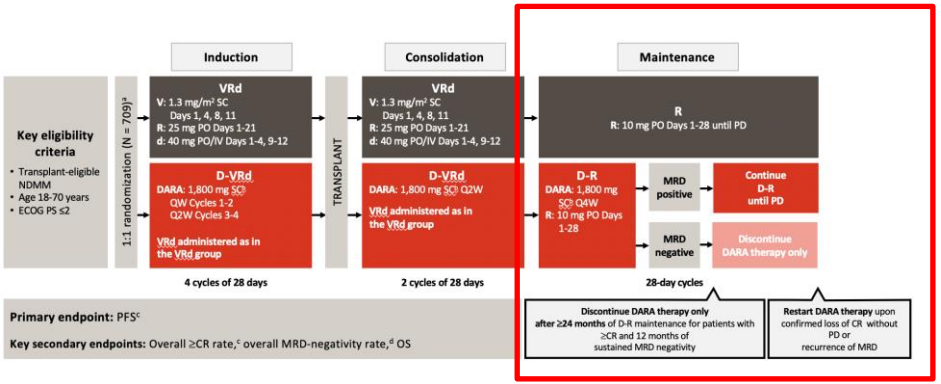
DRAMMATIC STUDY SWOG1803/BMT CTN1706

Treatment/Schema



*After 3 months, may be raised to 15 mg/day if ANC and platelet counts acceptable; non heme tox to Gr 0-1
**Dosing will be changed to monthly dosing after month 2

EMN17/PERSEUS study



64% of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity

Clinicaltrial.gov NCT04071457

Conclusions

- **MRD** status **correlates** with **PFS and OS** thus becoming a primary endpoint in an increasing number of studies.
- With current frontline treatments, 2/3 of transplant eligible and 1/3 of transplant ineligble MM patients can achieve MRD negativity (10^{-5}).

→ Can MRD be used to predict the risk of relapse and drive treatment choices?

What we know:

- High-risk patients can achieve similar rates of MRD negativity to standard risk ones with aggressive regimens
- Issue of durability: high-risk cytogenetics, CTCs and ISS3 predicts a higher risk of unsustained MRD negativity
- Sustained MRD negativity may represent a reliable tool for maintenance discontinuation

- **What we need to know**:
  - Who to test: MRD assessment: **immunofixation** positive vs negative
  - When and for how long: Optimal **time-point** for MRD assessment and definition of **sustained** MRD negativity (1, 2…5 years?)
  - Where: **peripheral blood techniques** versus bone marrow evaluation?

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