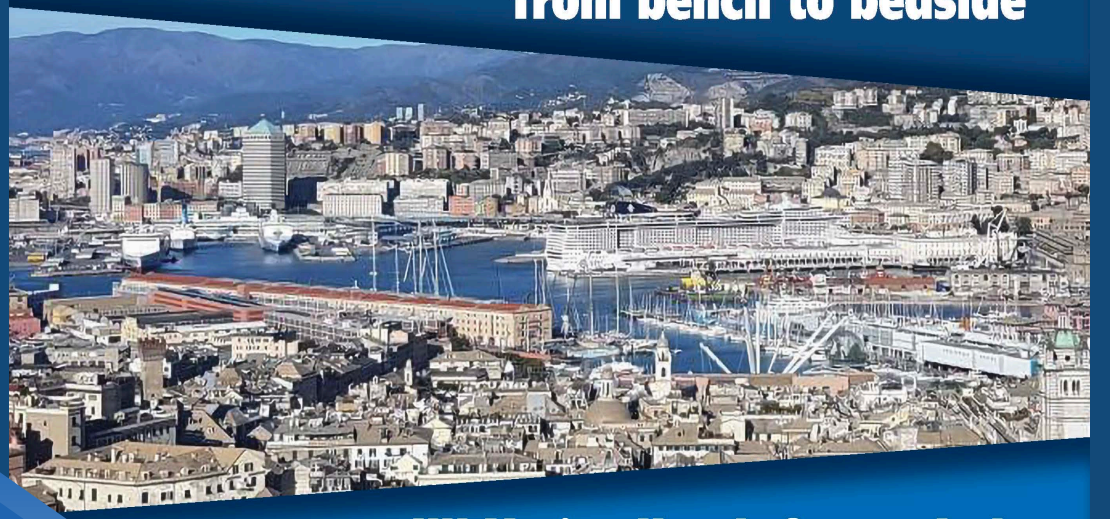
2023 Multiple Myeloma updates:
from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

Stefania Oliva, MD, PhD
AOU Città della salute e della Scienza di Torino,
Division of Hematology,
University of Torino, Italy

Disease monitoring:
How to use MRD in clinical practice

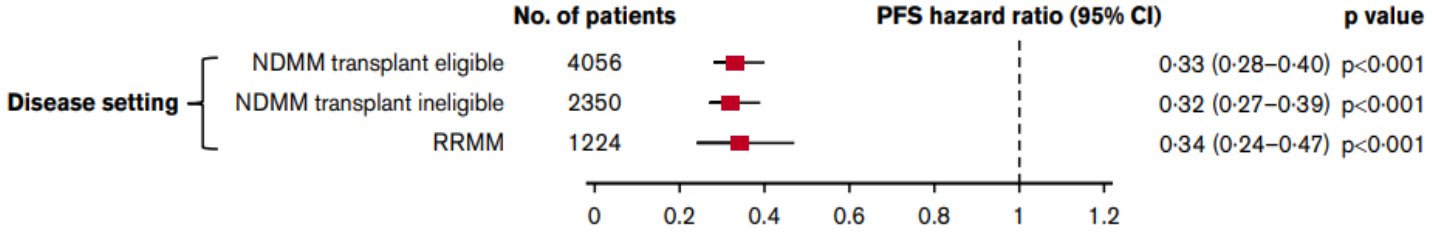
The literature evidence for the use of MRD is strong

4 metanalysis published #, *

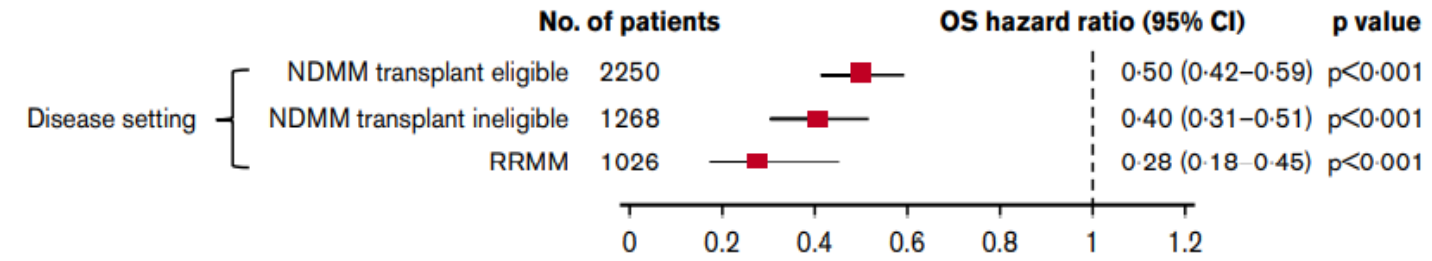
~ 100 publications supporting MRD on PFS/OS

IMWG revised response criteria including MRD in CR patients * *

PFS



OS



Landgren O et al Bone Marrow Transplant 2016; 51: 1565–1568, Munshi NC et al. JAMA Oncol. 2017 Jan 1;3(1):28-35; * Munshi NC et al. Blood Adv 2020; 4(23):5988–99; Avet-Loiseau H et al. Clinical Lymphoma, Myeloma & Leukemia, 2020. * * Kumar S, et al. Lancet Oncol 2016;17(8):e328–46.

Yes…but…what about the use in clinical practice?

Clinical case

- 53 years old Man MM patient, IgGk, ISS-2, bone lesions
- Hb level: 10.2 g/dL, normal creatinine and calcium levels
- BM: 60% monoclonal plasma cells, FISH: t(4;14) and amp1q chromosomal abnormalities
- First line treatment in Italy: Dara-VTD 4 cycles, tandem ASCT, Dara-VTD consolidation 2 cycles
- Response post Induction: VGPR
- Response post ASCT: CR with MRD persistence by NGF (LOD: 0,0021%)

Questions:

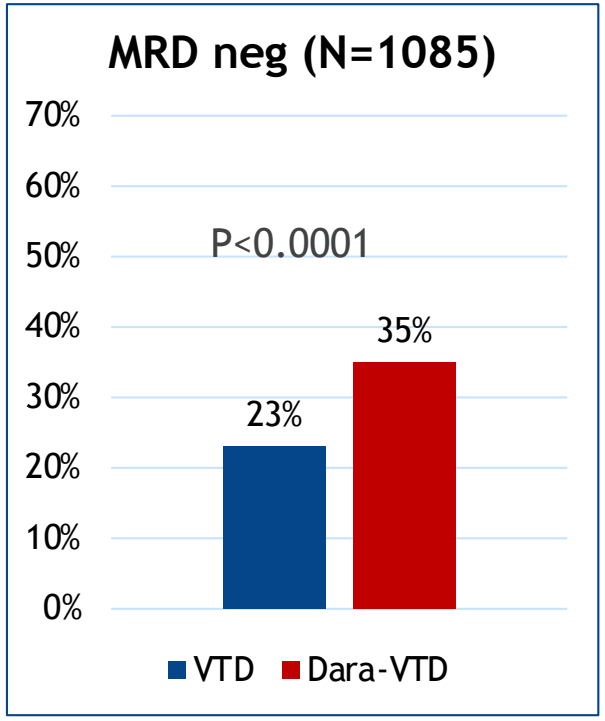
1. Is it correct to perform MRD to deeply assess response in clinical practice? When?
2. NGF or NGS?
3. PET/CT? Peripheral Blood?
4. MRD in *high risk* patients?
5. MRD to modulate/intensify treatment in *high risk*?

Is it correct to perform MRD to deeply assess response in clinical practice? MRD to identify most effective treatments up-front

Triplets vs quadruplets as induction in transplant eligible patients: the more, the deeper

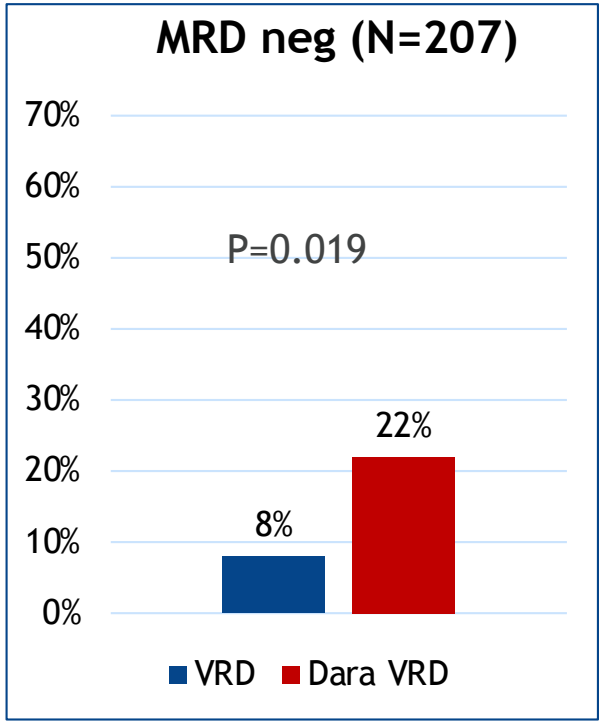
Post Induction 10^{-5} MRD negativity rates with the addition of Anti-CD38 monoclonal antibodies to standard triplets

CASSIOPEIA[1]
DVTd vs VTd (4x4w cycles)



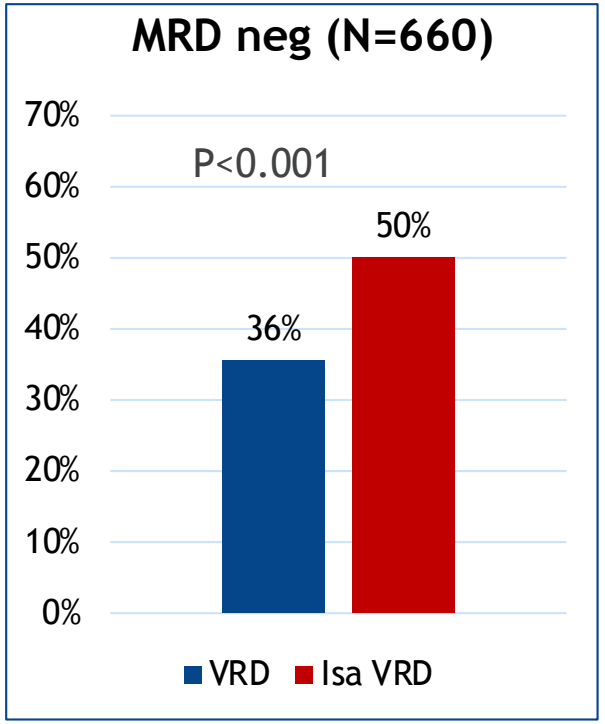
Duration of induction therapy: 112 days

GRIFFIN[2,3]
DVRd vs VRd (4x4w cycles)



Duration of induction therapy: 84 days

GMMG-HD7[4]
IsaVRd vs VRd (3x6w cycles)



Duration of induction therapy: 126 days

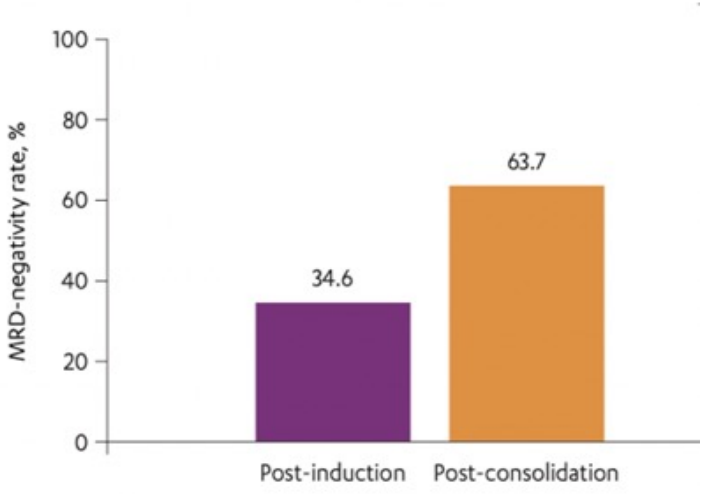
D, daratumumab; d, dexamethasone; Isa, isatuximab; MRD, minimal residual disease; R, lenalidomide; TE, transplant eligible; T, thalidomide; V, bortezomib

1. Avet Loiseau H et al. ASCO 2019;abstract 8017 (oral presentation); 2. Voorhees P et al Blood 2020;136(8):936-945; 3. Sborov WD et al. IMS 2022;abstract OAB-057;4. Goldschmidt H et al. ASH 2021; abstract 463 (oral presentation)

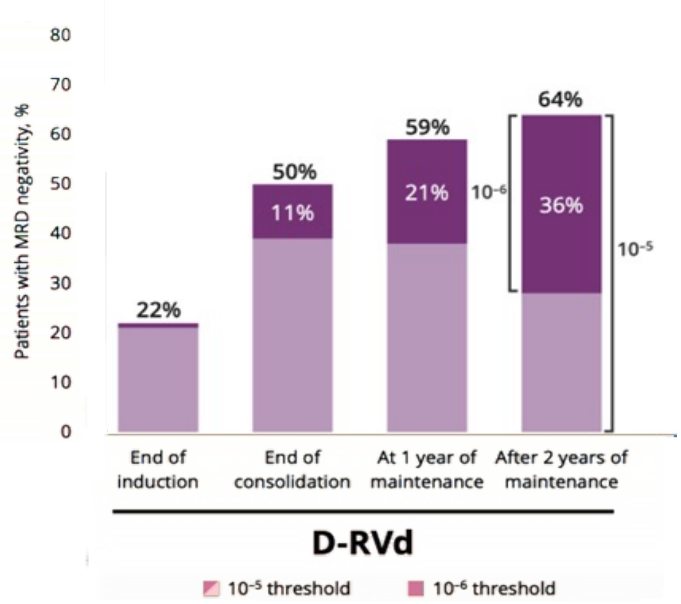
Is it correct to perform MRD to deeply assess response in clinical practice? MRD to identify most effective treatments up-front

ASCT remains a standard of care in the era of anti-CD38 monoclonal antibodies-based quadruplets

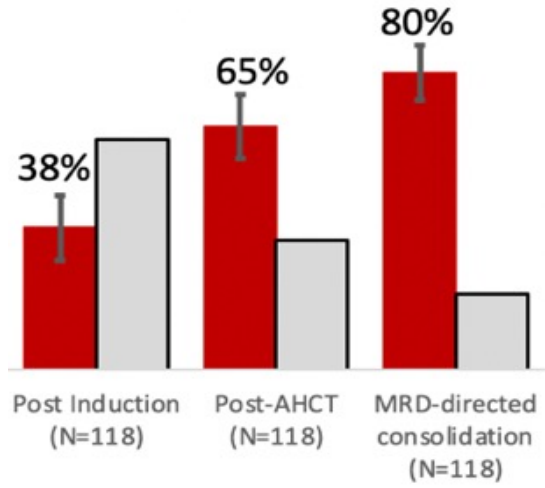
CASSIOPEA
Dara-VTd



GRIFFIN
Dara-VRd



MASTER
Dara-KRd

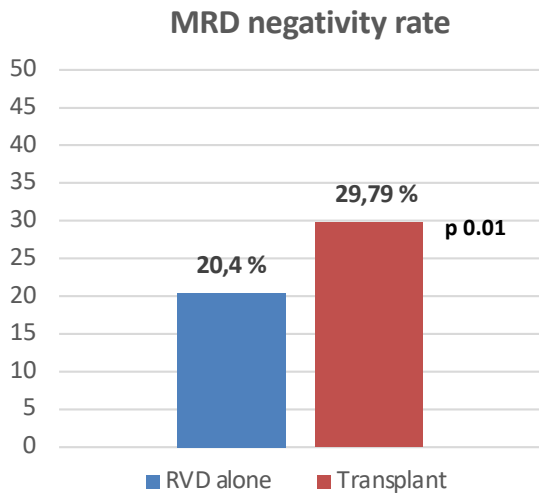


HDM, high-dose melphalan; MRD, minimal residual disease; Dara, D, daratumumab; V, bortezomib; T, thalidomide; d, dexamethasone; R, lenalidomide; K, carfilzomib

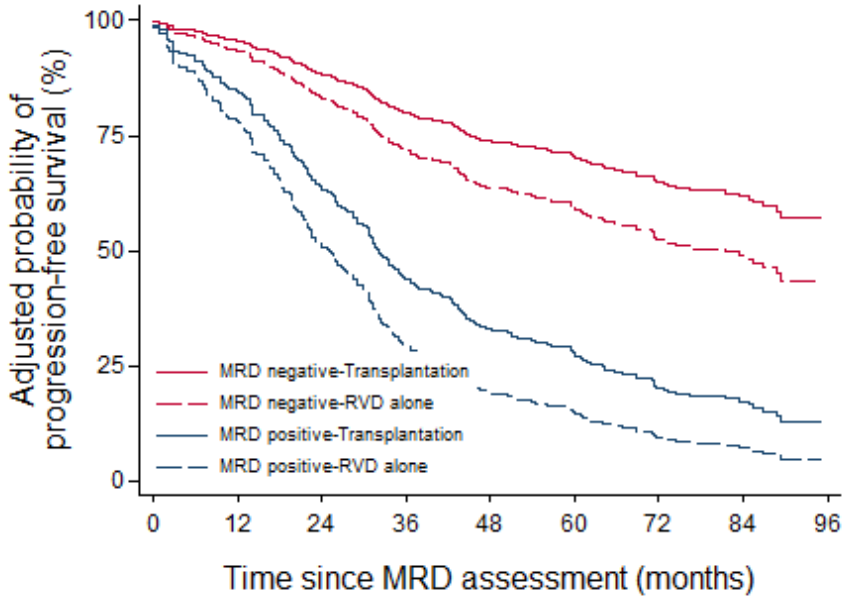
- Avet-Loiseau H et al. ASH 2021;abstract 82 (oral presentation); Laubach JP et al. ASH 2021;abstract 79 (oral presentation); Costa LJ et al. ASH 2021;abstract 481 (oral presentation)

Is it correct to perform MRD to deeply assess response in clinical practice? MRD to identify most effective treatments up-front

ASCT vs No-ASCT



Median follow up	89.8 months

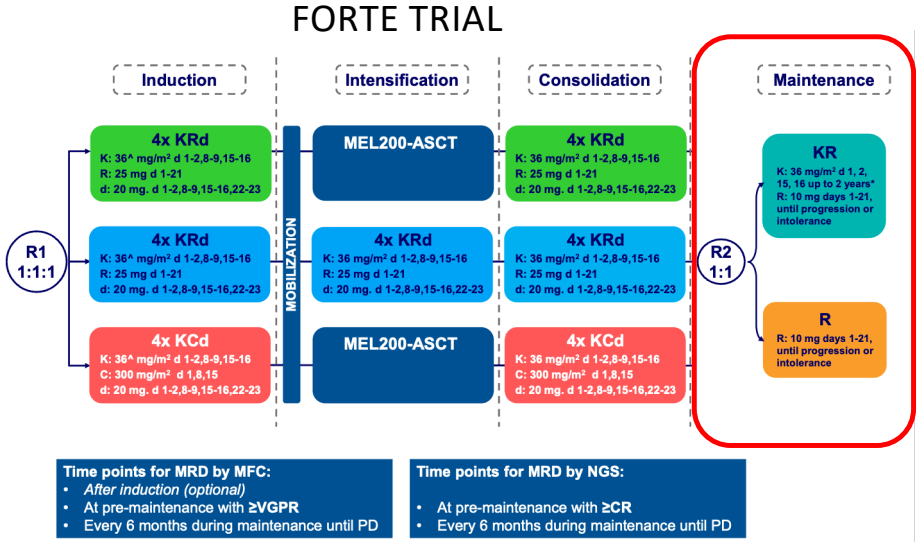


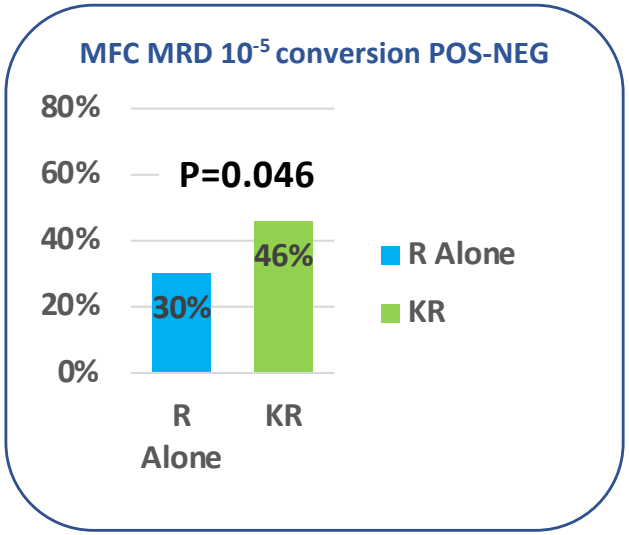
Transplant is superior to VRD alone, even in patients who achieved undetectable MRD at 10^{-6}

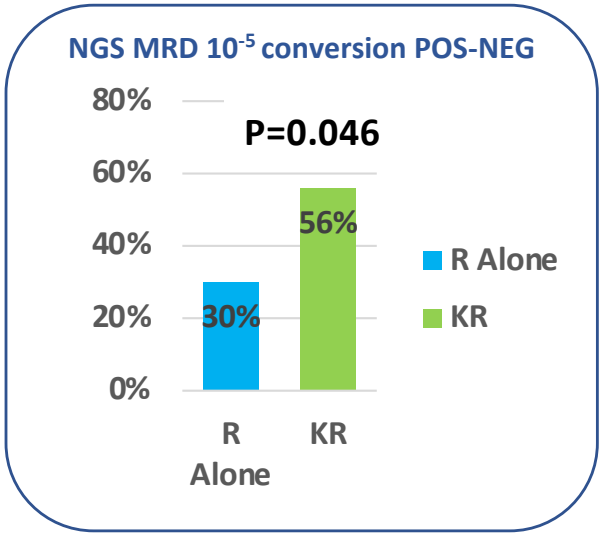
Perrot A ASH 2020

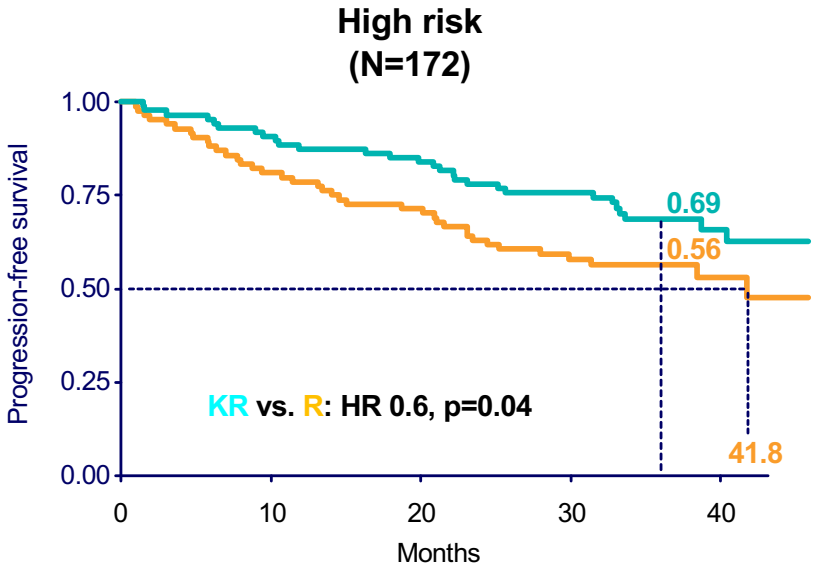
How to use MRD in clinical practice: MRD to identify most effective treatments up-front

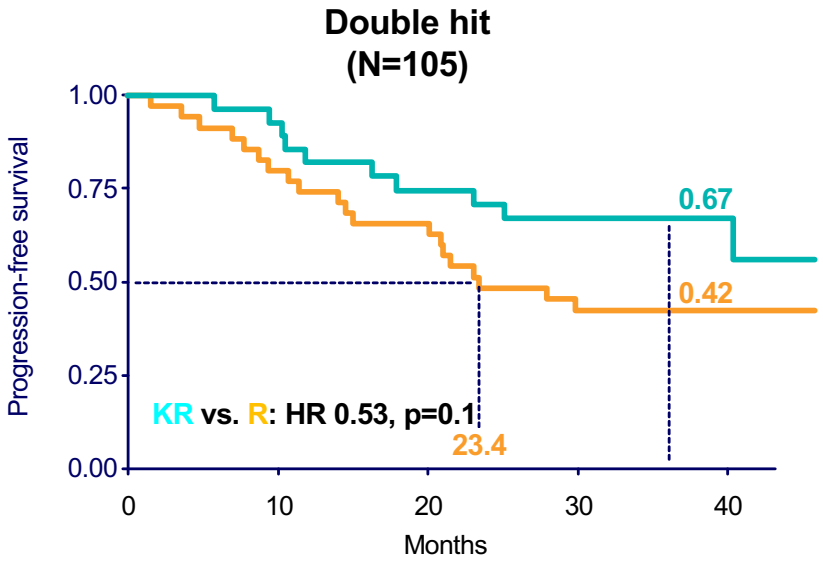
Maintenance











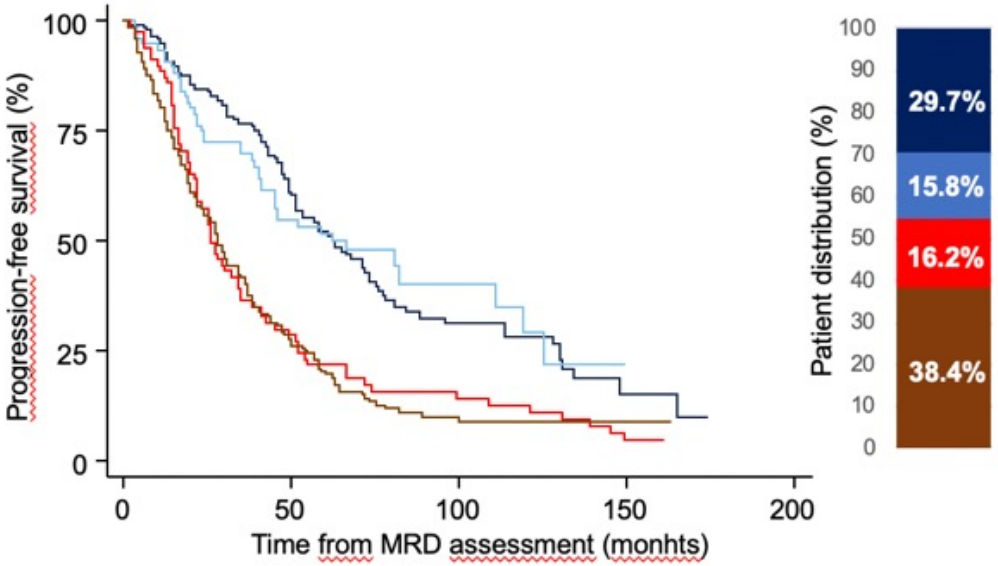
Gay F Lancet Oncol 2021, Oliva S et al eClinMedecine 2023, Mina R. et al. Lancet Oncol 2023

Whom should we test for MRD status? CR only or Ifx positive patients?

MRD^{-ve} patients display similar PFS regardless of IFx status

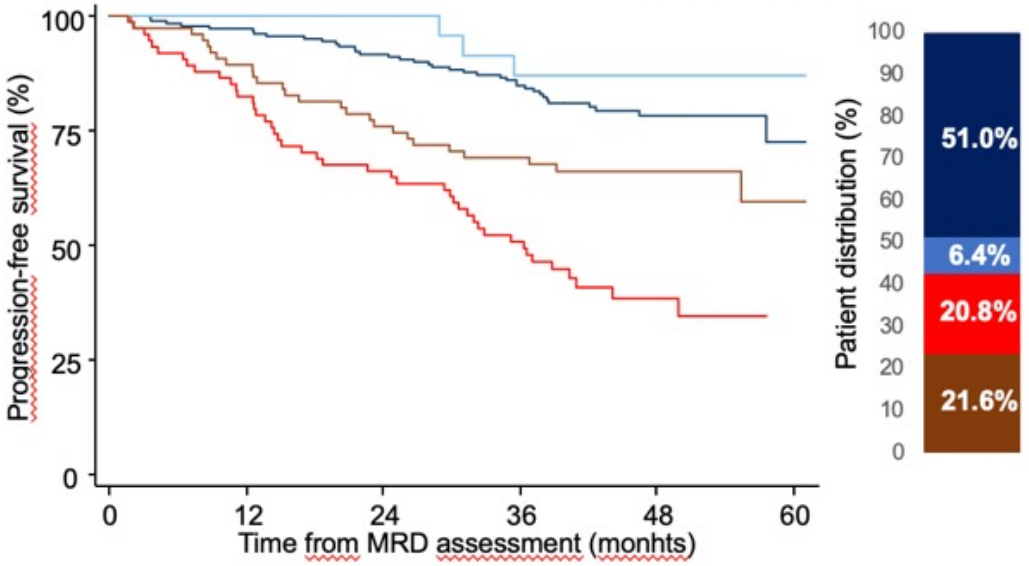
6% of patients with positive IFx were MRD^{-ve} NGF

GEM2000 & GEM2005MENOS65 (N=482): 4-color MFC/Day 100 after ASCT



	IFx+ & MRD+	IFx- & MRD+	IFx+ & MRD-	IFx- & MRD-
Median PFS (mo)	28	26	66	63
P-value	0.77		0.96	

GEM2012MENOS65 (N=356): NGF/After consolidation



	IFx+ & MRD+	IFx- & MRD+	IFx+ & MRD-	IFx- & MRD-
4-year PFS (%)	64	38	87	78.5
P-value	0.03		0.35	

Albeit the higher sensitivity of NGF and the later time point (consolidation), approximately 1/10 MRD- pts by NGF continued showing positive IFx, but their outcome was as favorable as that of MRD- cases in CR

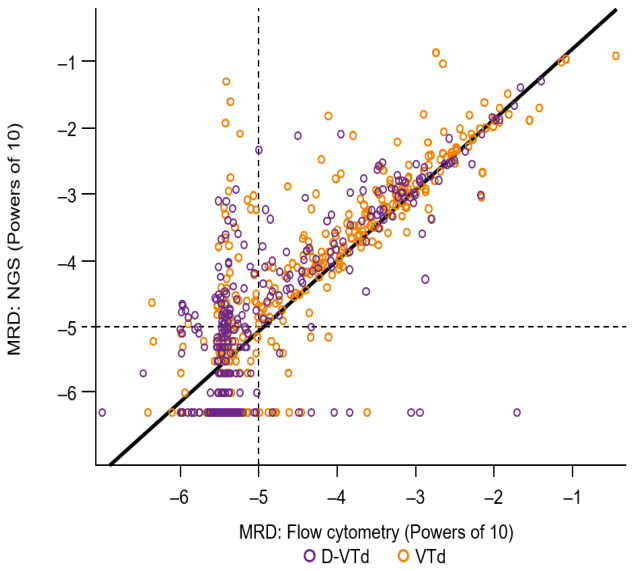
ASCT, autologous stem cell transplant; CR, complete response; Ifx, immunofixation; MFC, multiparametric flow cytometry; MRD, minimal residual disease; NGF, next-generation flow

Rodriguez-Otero P. et al ASH 2020;abstract 2288

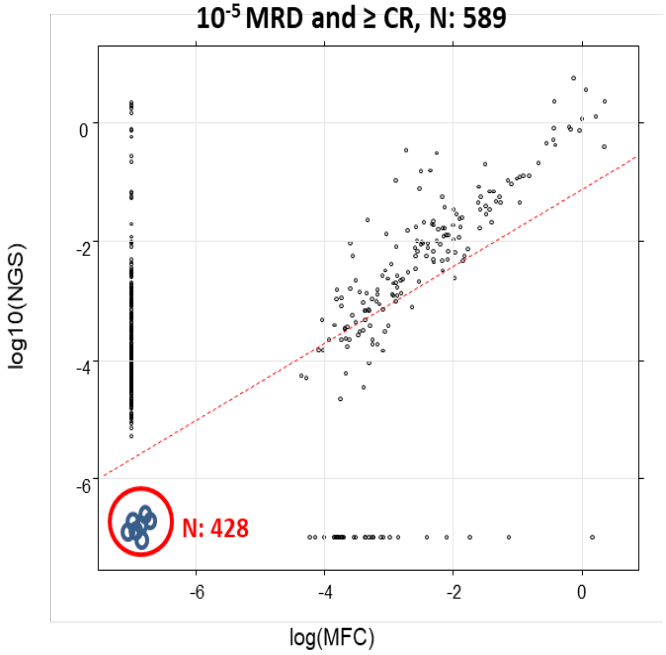
NGF or NGS?

CONCORDANCE NGF/MFC and NGS

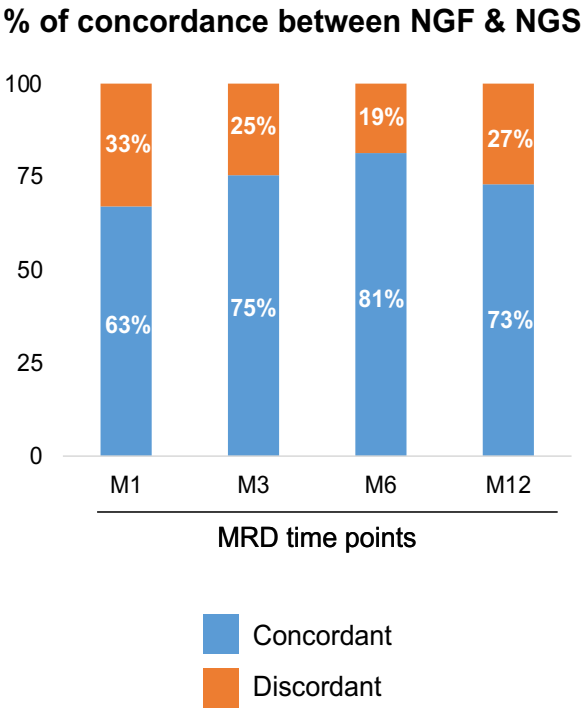
Cassiopeia trial



Forte trial



KarMMa trial (Ide-cel)



Good general agreement (> 80%) between MRD assessments was observed in the paired evaluation, with no differences between treatment arms

Avet Loiseau H et al. IMWG 2019.

Oliva S et al. Manuscript under revision.

Paiva B et al ASH 2022 (oral presentation)

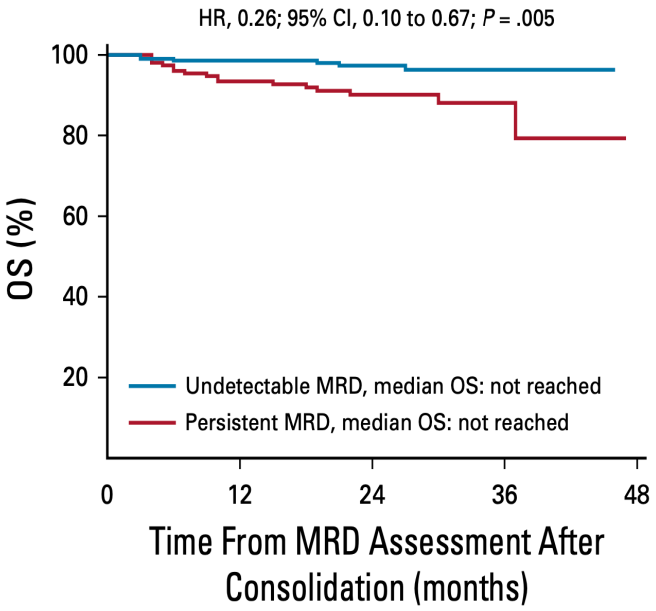
NGF or NGS?

Next generation flow (NGF) Sensibility 10^{-5}

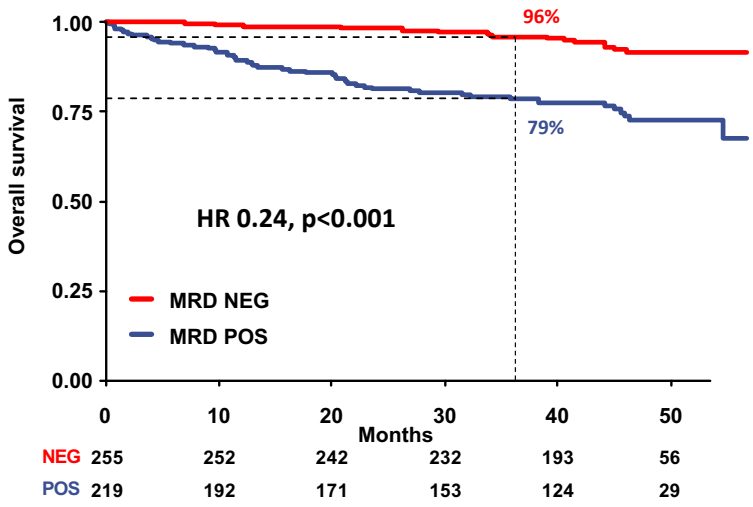
Next generation flow (NGF) Sensibility 10^{-5}

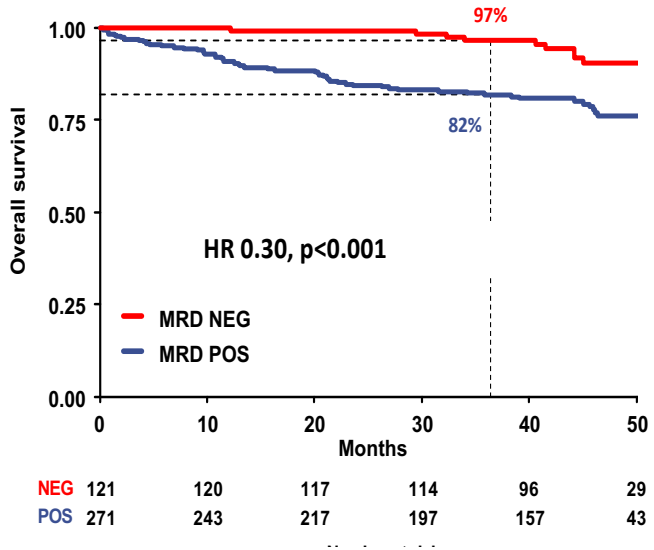
Next generation sequencing (NGS) Sensibility 10^{-5}

Pethema trial



Forte trial





Paiva B et al. J Clin Oncol 38:784-792 2019, Oliva S et al. eClinicialMedecine 2023

NGF or NGS?

PROS and CONS of NGF/MFC and NGS

Flow

PROS	CONS
• feasible in most pts	• fresh sample (<24-48h)
• does not require diagnostic sample	• PC die quickly outside BM
• widely available	• operator-dependent
• same day results	• Hemodiluition

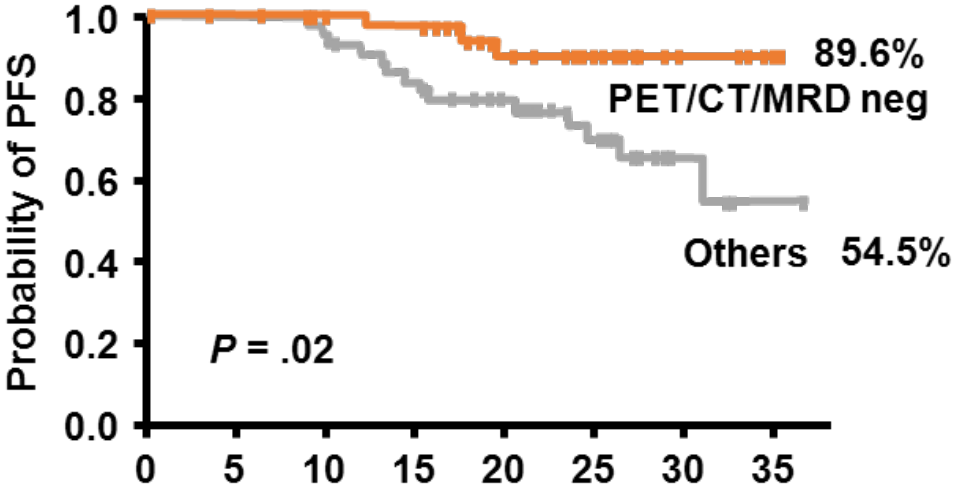
NGS

PROS	CONS
• sensitivity (up to 10^{-6})	• requires diagnostic samples
• paraffin stored samples	• Commercial service only, few academic platforms
• highly reproducible	• turnaround time, complexity with bioinformatic support
• Clonal evolution	• high cost

Stetler-Stevenson et al, Cytometry Part B 2016, Flores-Monteiro et al, Leukemia 2017, Oliva s et al Front. Oncol. 2020

What about MRD-PET/CT?
PET/CT and MRD Negativity as Predictor for PFS1-2

	PET/CT Positive	PET/CT Negative
MRD positive	**11**	**20**
MRD negative	**14**	**41**



IMPeTUs CRITERIA
(Italian Myeloma Criteria for PET USe)[3]

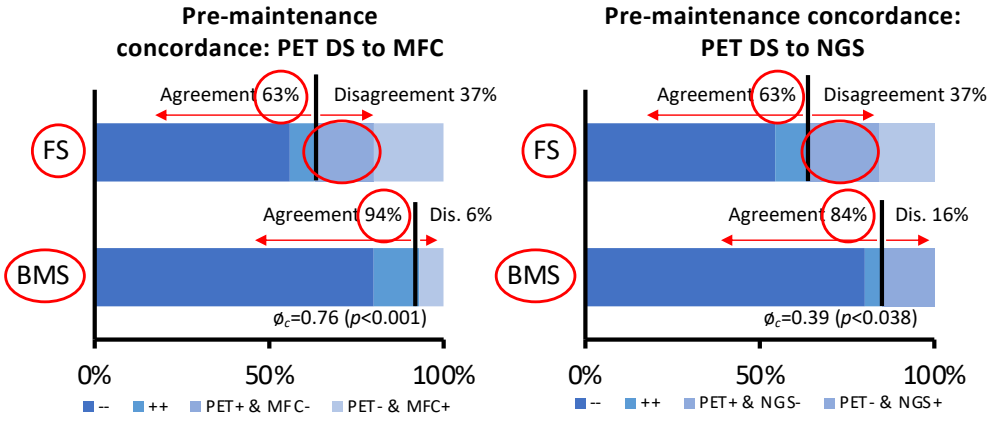
PET Response After Therapy	Response Criteria
Complete metabolic response	Uptake ≤ liver activity in BM sites and FLs previously involved (including extramedullary and paramedullary disease [DS score 1-3])
Partial metabolic response	Decrease in number and/or activity of BM/FLs present at baseline, but persistence of lesion(s) with uptake > liver activity (DS score 4 or 5)
Stable metabolic disease	No significant change in BM/FLs compared with baseline
Progressive metabolic disease	New FLs compared with baseline consistent with myeloma

Abbreviations: BM, bone marrow; DS, Deauville scale; FL, focal lesion; PET, positron emission tomography.

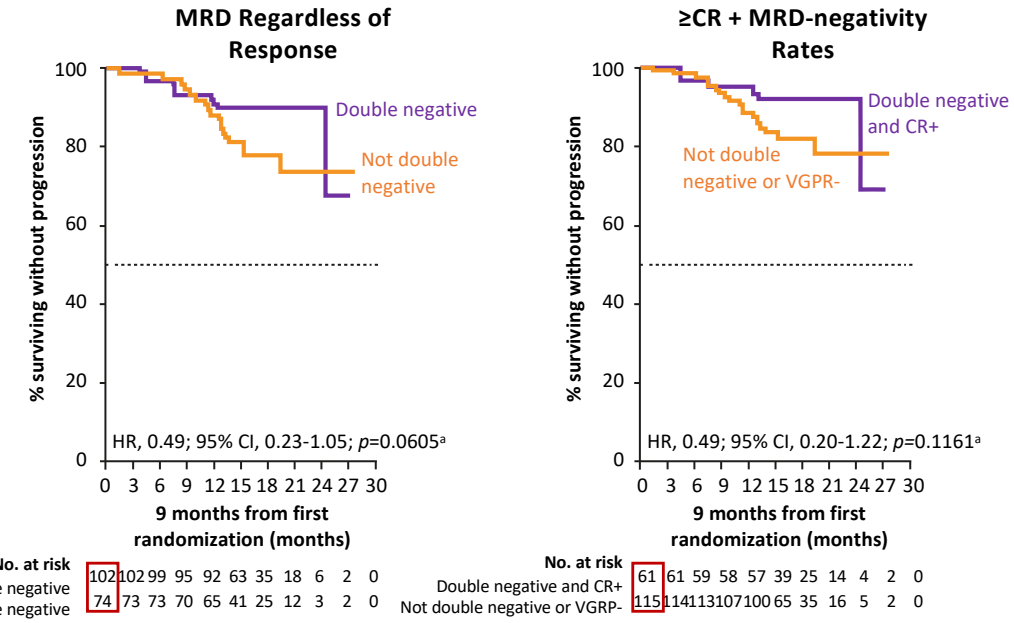
1. Avet-Loiseau et al. 2. ASH 2015; abstract 730; Moreau et al. ASH 2015; abstract 395; 3. Zamagni E et al JCO https://doi. org/10.1200/JCO.20. 00386

Bone marrow and Imaging MRD are complementary: The role of PET/CT

	PET/CT		
	Positive	Negative	Kappa coefficient (SE)
MRD			
Positive, n	7	55	0.0091
Negative, n	12	102	(0.0587)
MRD + ≥ CR, n			
Positive/VGPR or worse, n	13	97	0.0214
Negative + ≥ CR, n	6	60	(0.0368)



Landmark analysis for PFS by double-negativity rate for MRD (MFC; 10^{-5}) and PET/CT post-consolidation



Zamagni E et al. EHA 2020;abstract S207, Zamagni E et al. eClinicialMedecine 2023

BM, bone marrow; BMS, bone marrow score; CI, confidence interval; CR, complete response; CT, computed tomography; DS, Deauville score; HR, hazard ratio; MFC, multiparameter flow cytometry; MRD, minimal residual disease; NGS, next-generation sequencing; PET, positron emission tomography; PFS, progression-free survival; SE, standard error; VGPR, very good partial response

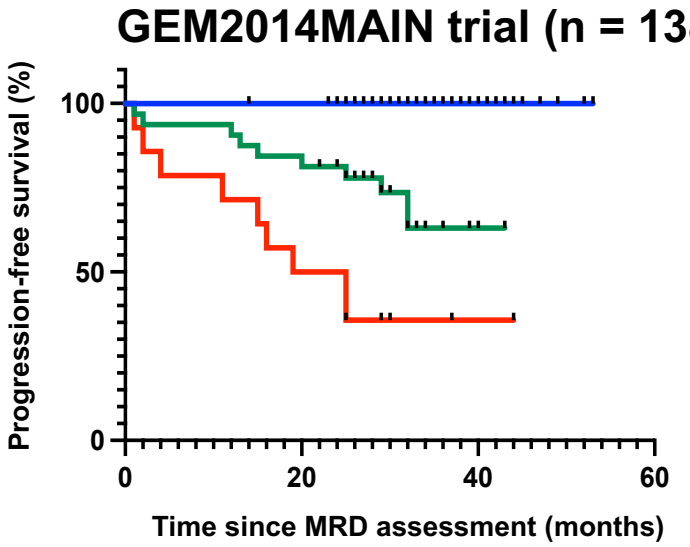
Moreau P et al. ASH 2019;abstract 692

What about the use of peripheral blood in clinical practice?

Agreement/disagreement NGF in BM vs PB

	Blood CTPC Status			*P*
BM MRD Status	**Negative**	**Positive**	**Total**	
Negative	46/137 (34%)	0/137 (0%)	46/137 (34%)	
Positive	55/137 (40%)	36/137 (26%)	91/137 (66%)	<0.0001
Total	101/137 (74%)	36/137 (26%)	137/137 (100%)	
Serum IF Status				
Negative	60/137 (44%)	15/137 (11%)	75/137 (55%)	
Positive	41/137 (30%)	21/137 (15%)	62/137 (45%)	0.08
Total	101/137 (74%)	36/137 (26%)	137/137 (100%)	
BM MRD Negative				
sIF Negative	36/46 (78%)	0/46 (0%)	36/46 (78%)	
sIF Positive	10/46 (22%)	0/46 (0%)	10/46 (22%)	-
Total	46/46 (100%)	0/46 (0%)	46/46 (100%)	
BM MRD Positive				
sIF Negative	24/91 (26%)	15/91 (17%)	39/91 (43%)	
sIF Positive	31/91 (34%)	21/91 (23%)	52/91 (57%)	1.0
Total	55/91 (60%)	36/91 (40%)	91/91 (100%)	
From sCR/CR MM Cases				
BM MRD Negative	36/71 (51%)	0/71 (0%)	36/71 (51%)	
BM MRD Positive	23/71 (32%)	12/71 (17%)	34571 (49%)	<0.0001
Total	59/71 (83%)	12/71 (17%)	71/71 (100%)	

Sanoja-Flores L et al. Blood (2019) 134 (24): 2218–2222



	MRD PB / BM	No.	Median PFS	PFS @2y	Hazard ratio
	- / -	90	NR	100%	
	- / +	33	NR	80%	*P* < .0001
	+ / +	15	22 mo	50%	

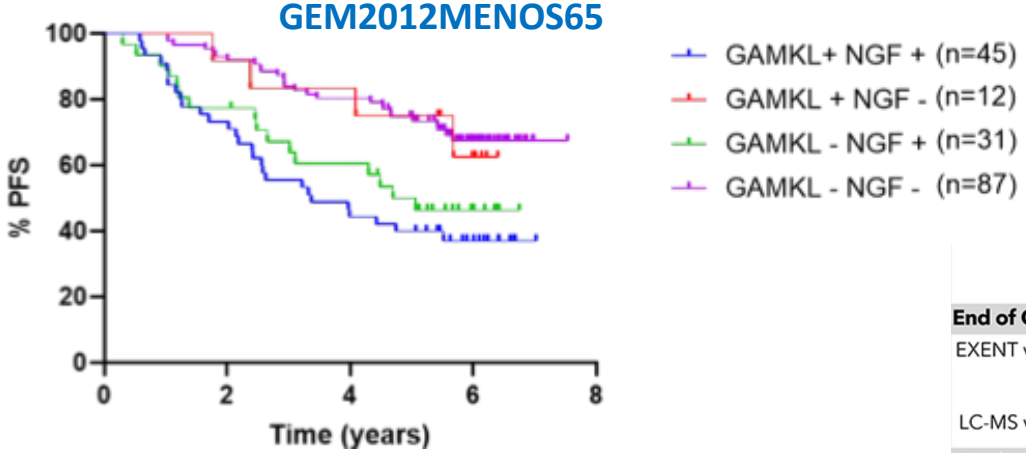
24%

Notarfranchi L, et al. Blood 2022;140 (Supplement 1): 2095–2097

What about the use of peripheral blood in clinical practice?

Application of QIP-MS & NGF for MRD evaluation

GEM2012MENOS65



Test	Fisher's exact test
P value	<0.0001

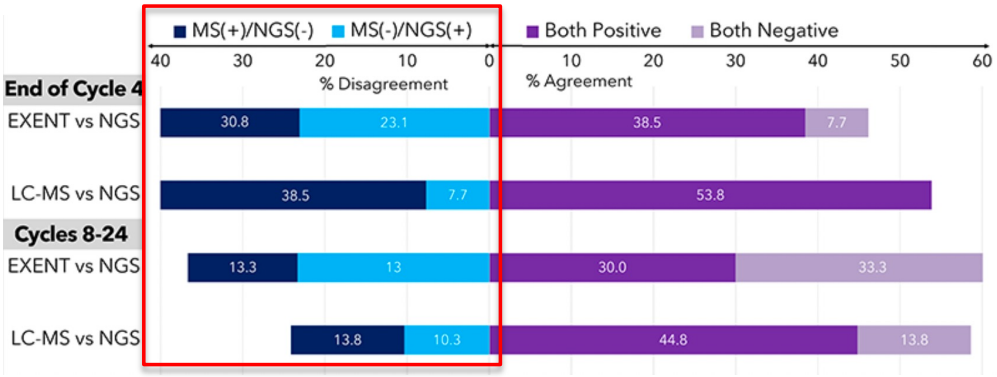
Sensitivity	0.5921	0.4798 to 0.6956
Specificity	0.8788	0.8000 to 0.9293
Positive Predictive Value	0.7895	0.6671 to 0.8753
Negative Predictive Value	0.7373	0.6513 to 0.8083

Puig N et al IMS 2022 **(oral presentation)**

Application of EXENT and LC-MS & NGS for MRD evaluation

Dara-KRD

At later timepoints, concordance 63% and 59% with EXTENT and LC-MS Median follow-up of 10 months: no progressions or deaths among discordant cases.

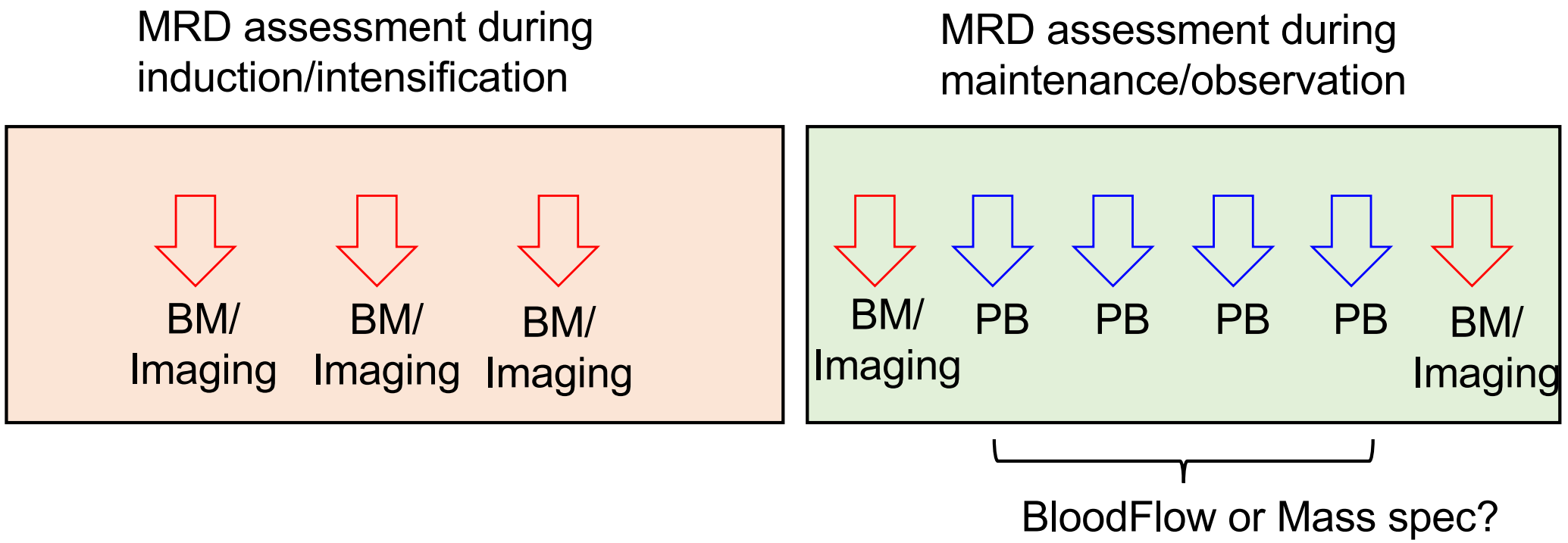


Forty-one patients have been enrolled from two MM Research Consortium sites into this phase 2 study (planned enrollment 45 patients). All patients receive 24 cycles of Dara-KRd in 28-day cycles without ASCT. With optional stem cell collection for ASCT-eligible candidates after cycle 4

Derman B et al HemaSphere | 2022; 6:S3

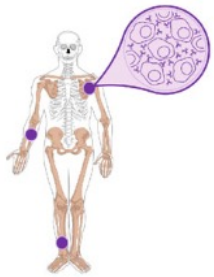
Minimally invasive MRD assessment at late time points

Hypothetical scenario to assess MRD in BM/PET and PB



Courtesy of Bruno Paiva, adpated

What technique in the future outside of clinical trials?



Baseline presentation

Patients with only **BM disease (no FL at PET/CT)**

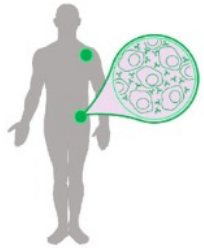
Initial MRD monitoring

PB MRD (MS or NGF/NGS)

If PB MRD neg: perform BM MRD

If BM MRD neg: need for sustained evaluation?

If BM MRD pos: repeat at later timepoint (after a clinical phase? After a fixed duration of time?)



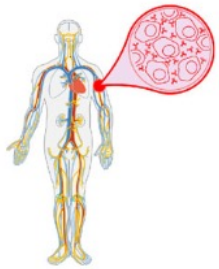
Patients with **EMD/focal lesions at PET/CT**

PB MRD (MS or NGF/NGS)

If PB MRD neg: perform PET/CT and BM MRD

If BM MRD and PET/CT neg: need for sustained MRD

If BM MRD pos: repeat at later time point (after a clinical phase? After a fixed duration of time?)



Patients with **circulating plasma cells**

PB MRD NGF (or MS/NGS)

If PB MRD neg: perform BM MRD and PET/CT

If BM MRD and PET/CT neg: need for sustained MRD? Only PB monitoring?

If BM MRD pos: repeat at later time point (after a clinical phase? After a fixed duration of time?)

For **high-risk patients**: high-risk CA, LDH, ISS II/III → consider multiple methods (imaging + BM)

Complementary multimodal methods

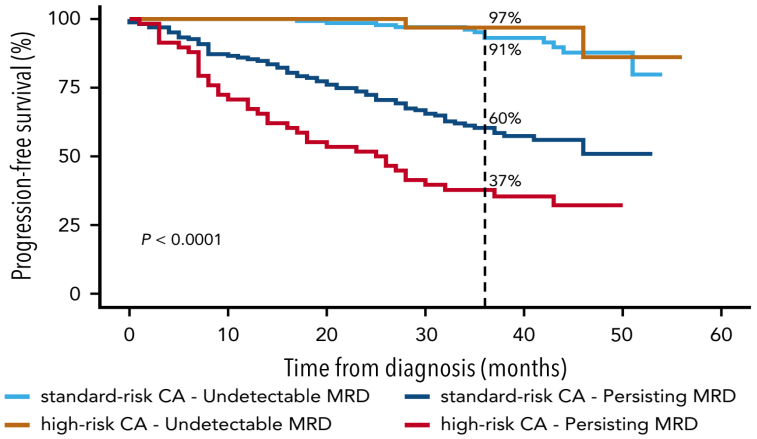
Bertamini L *et al* Current Hematologic Malignancy Reports 2021 16, pages 162–171 (2021)

Reaching MRD negativity can modulate the poor prognosis of high-risk chromosomal abnormalities

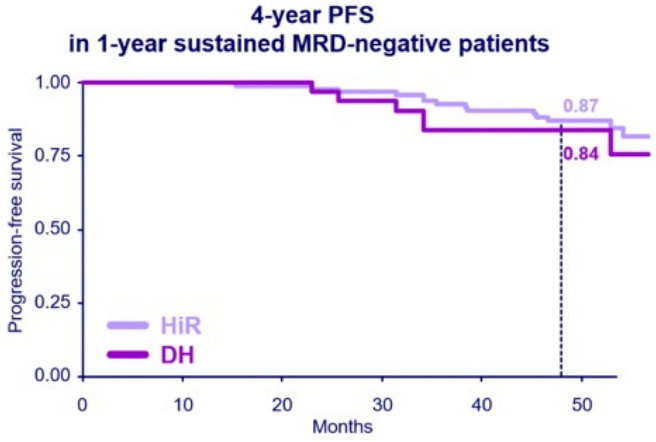
GEM2012MENOS65 trial (10^{-6})

FORTE trial (10^{-5})

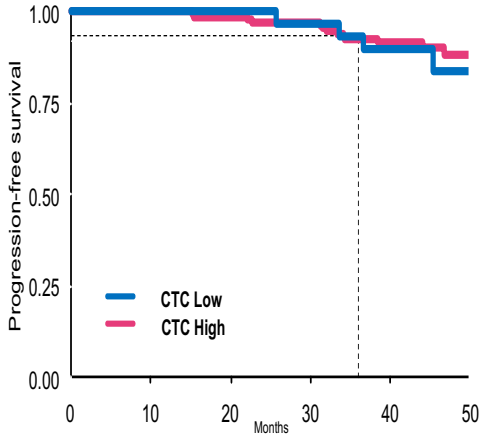
3-year PFS
In MRD negative patients



4-year PFS
in 1-year sustained MRD-negative patients



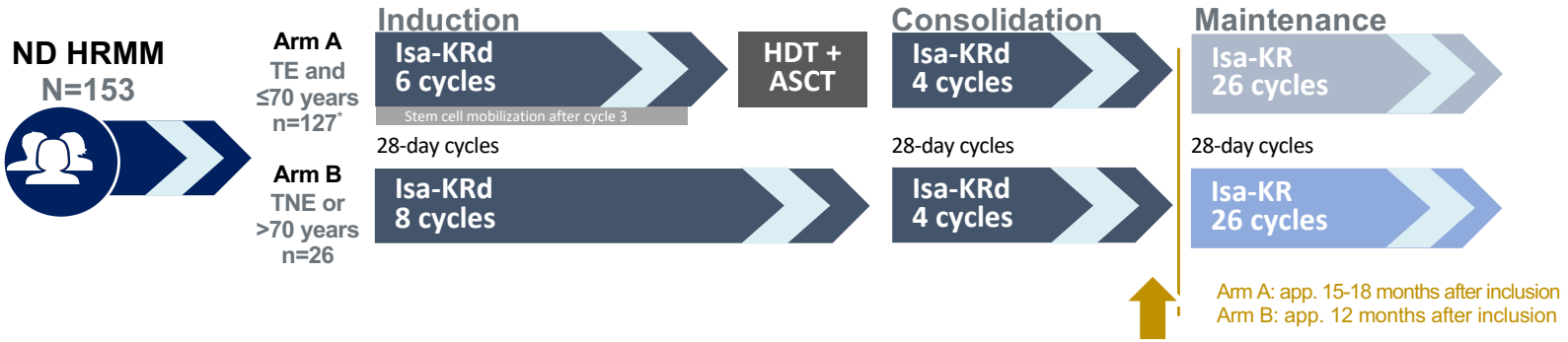
3-year PFS
in 1-year sust-MRD negative patients



CA, cytogenetic abnormalities; MM, multiple myeloma; MRD, minimal residual disease.; HiR, high risk; DH, double hit

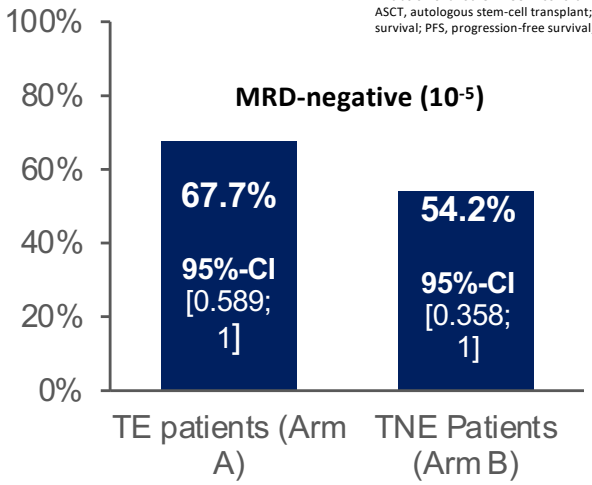
Goicoechea I et al. Blood 2021;137(1):49-60; Mina R et al Lancet Hematol 2022; Bertamini L. et al, JCO 2022.

MRD as primary objective for ND High risk myeloma: lesson from the Concept trial



Primary objective: MRD negativity after consolidation (NGF, 10^{-5})

Secondary objective: PFS; Key tertiary objectives: ORR, OS, safety



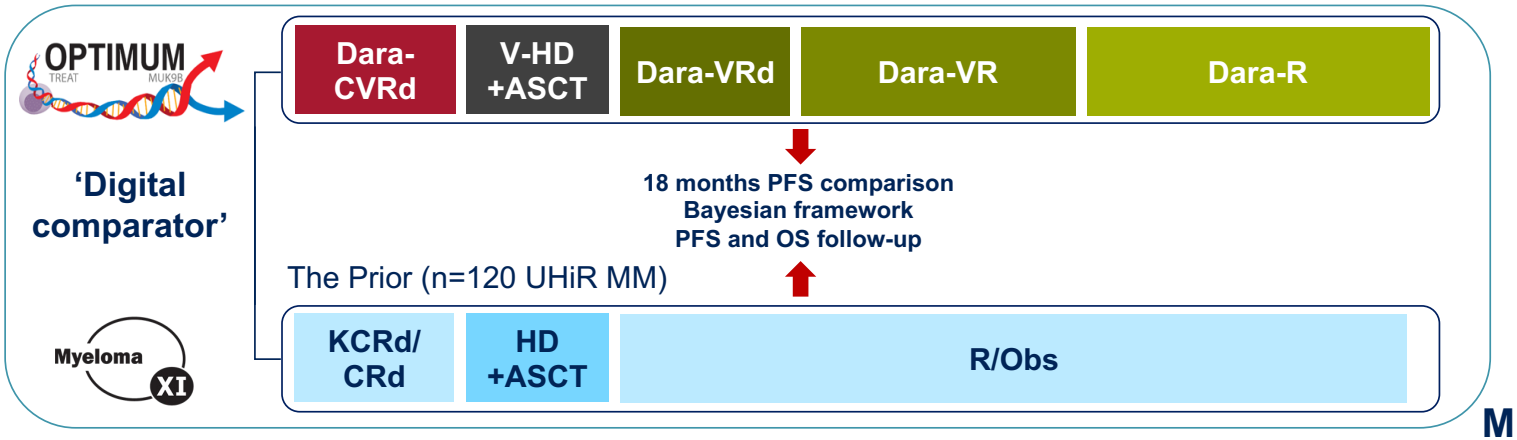
*Inclusion of another n=93 in cohort 2 from 2021-2022.

ASCT, autologous stem-cell transplant; d, dexamethasone; HDT, high-dose therapy; HRMM, high-risk multiple myeloma; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; ND, newly-diagnosed; NGF, next-generation flow; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, lenalidomide; TE, transplant-eligible; TNE, transplant-ineligible.

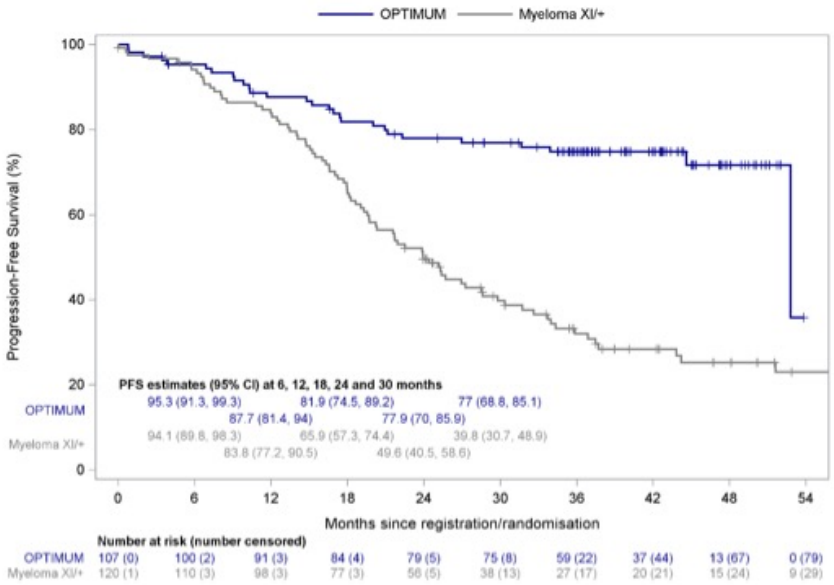
These data support the use of optimized quadruplet therapy in first-line treatment,
especially in patients with high-risk disease

Weisel K et al, abs #759 ASH 2022

MRD as primary objective for ND Ultra- High risk myeloma: lesson from the Optimum trial



MRD MFC 10^{-5} sensitivity



MRD Status	End of induction	Day 100-120 post-ASCT	End of Consolidation 2
MRD-	44 (41.1%)	68 (63.6%)	50 (46.7%)
MRD+	43 (40.2%)	15 (14.0%)	4 (3.7%)
Not evaluable	15 (14.0%)	13 (12.1%)	20 (18.7%)
Timepoint not reached	5 (4.7%)	11 (10.3%)	33 (30.8%)
Total	**107 (100%)**	**107 (100%)**	**107 (100%)**

84% of patients MRD- post-ASCT sustained MRD- at End Cons 2

Keiser M et al, abs #758 ASH 2022

How to use MRD in clinical practice: MRD to modulate treatments

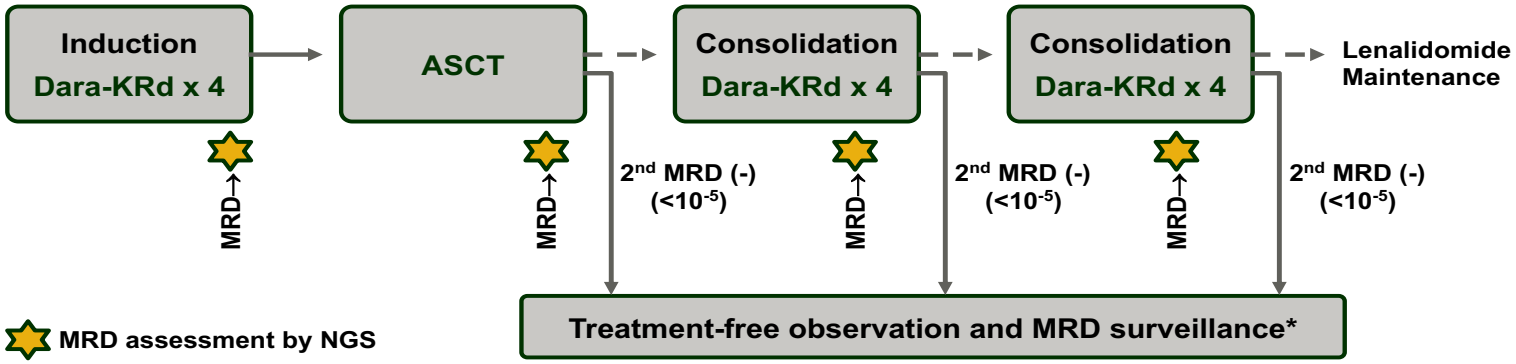
MRD driven approach

MASTER Phase 2 Trial: Design

Dara-KRd

- Daratumumab 16 mg/m^2 Days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg PO Days 1,8,15,22

Primary objective:
To determine the rate of MRD(-) responses (<10^{-5}) using NGS



- N=123, Median age 60 years, 57% MM high-risk cytogenetics (gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p))

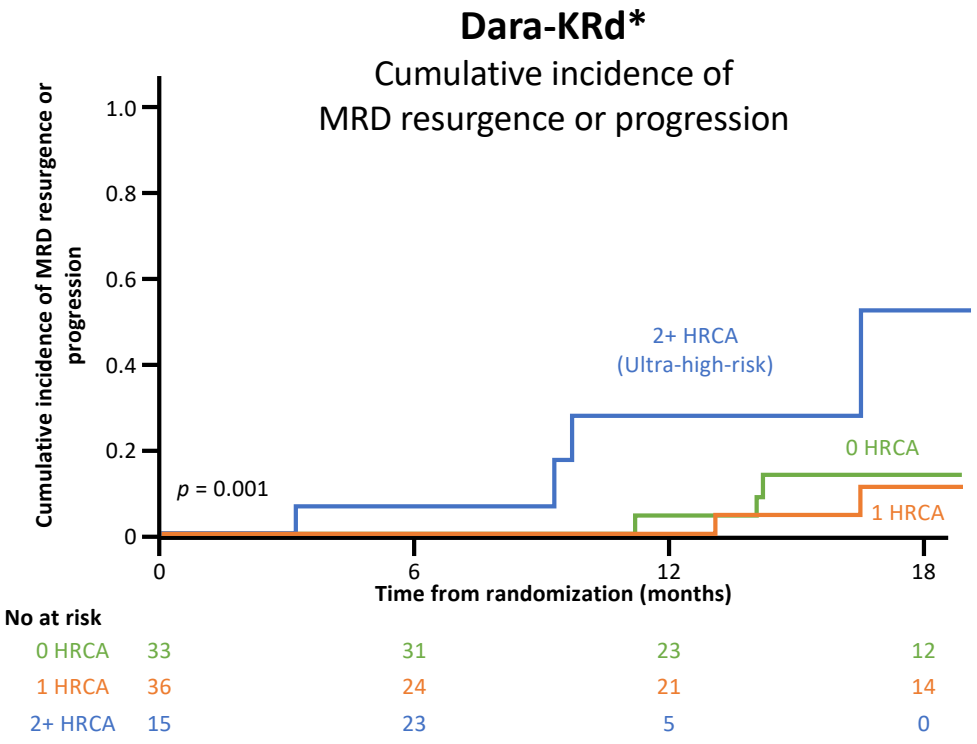
MASTER trial

*24 and 72 weeks after completion of therapy
ASCT, autologous stem cell transplant; MRD, minimal residual disease; NGS, next-generation sequencing

Costa L, et al. Blood 2021;138 (Suppl 1):481.

Sustained MRD negativity is crucial in high-risk patients
Lesson from the MASTER trial

- 84 patients achieved MRD-SURE
  - 0 HRCA – **62%**
  - 1 HRCA – **78%**
  - 2+ HRCA – **63%**
- Median follow-up in MRD-SURE: 14.2 months
- Risk of MRD resurgence or progression 12 months after treatment cessation
  - 0 HRCA – **4%**
  - 1 HRCA – **0%**
  - 2+ HRCA – **27%**
- None of the patients entering MRD-SURE died from MM progression



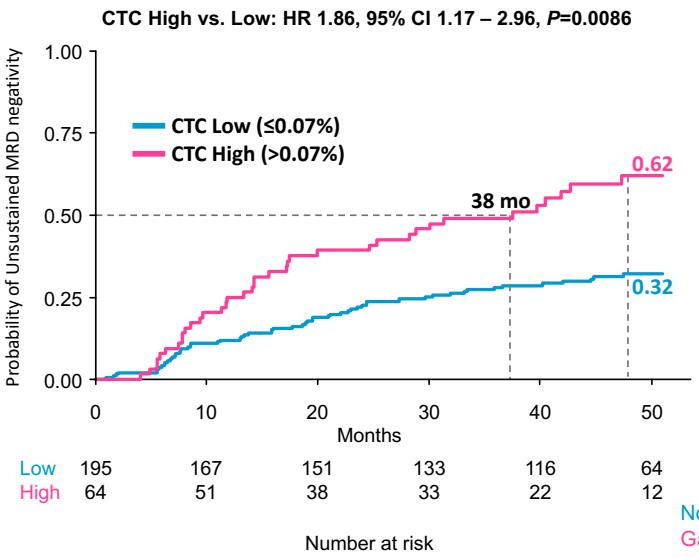
*This is not an approved regimen for carfilzomib; carfilzomib is not approved for the treatment of newly diagnosed multiple myeloma.
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p).
Amp, amplification; del, deletion; HRCA, high risk cytogenetic abnormalities; MRD, minimal residual disease.

Costa L et al. J Clin Oncol 2022;40(25):2901-2912

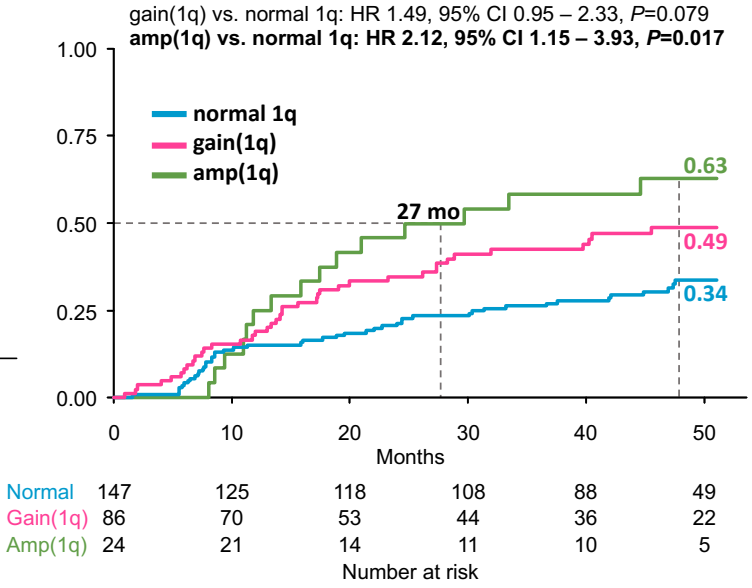
Risk factors for MRD resurgence and/or progression

FORTE TRIAL

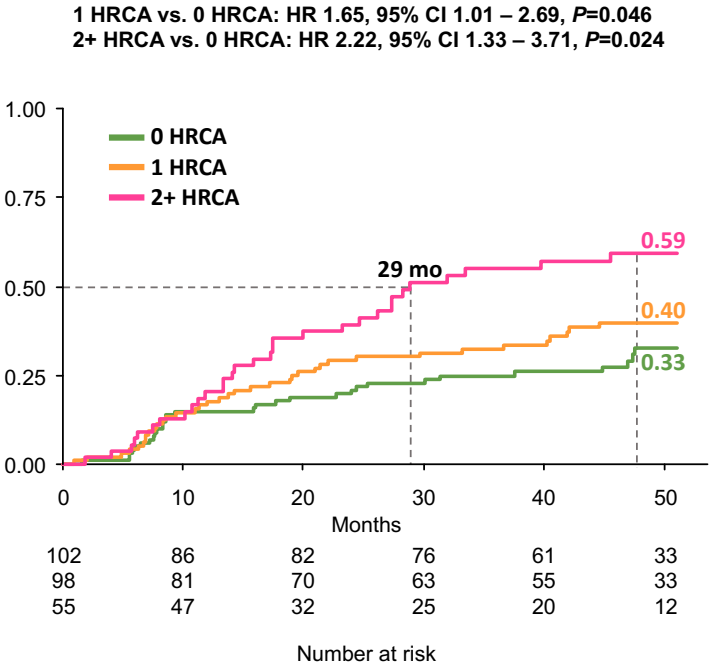
CTC



1q



Number of HRCA

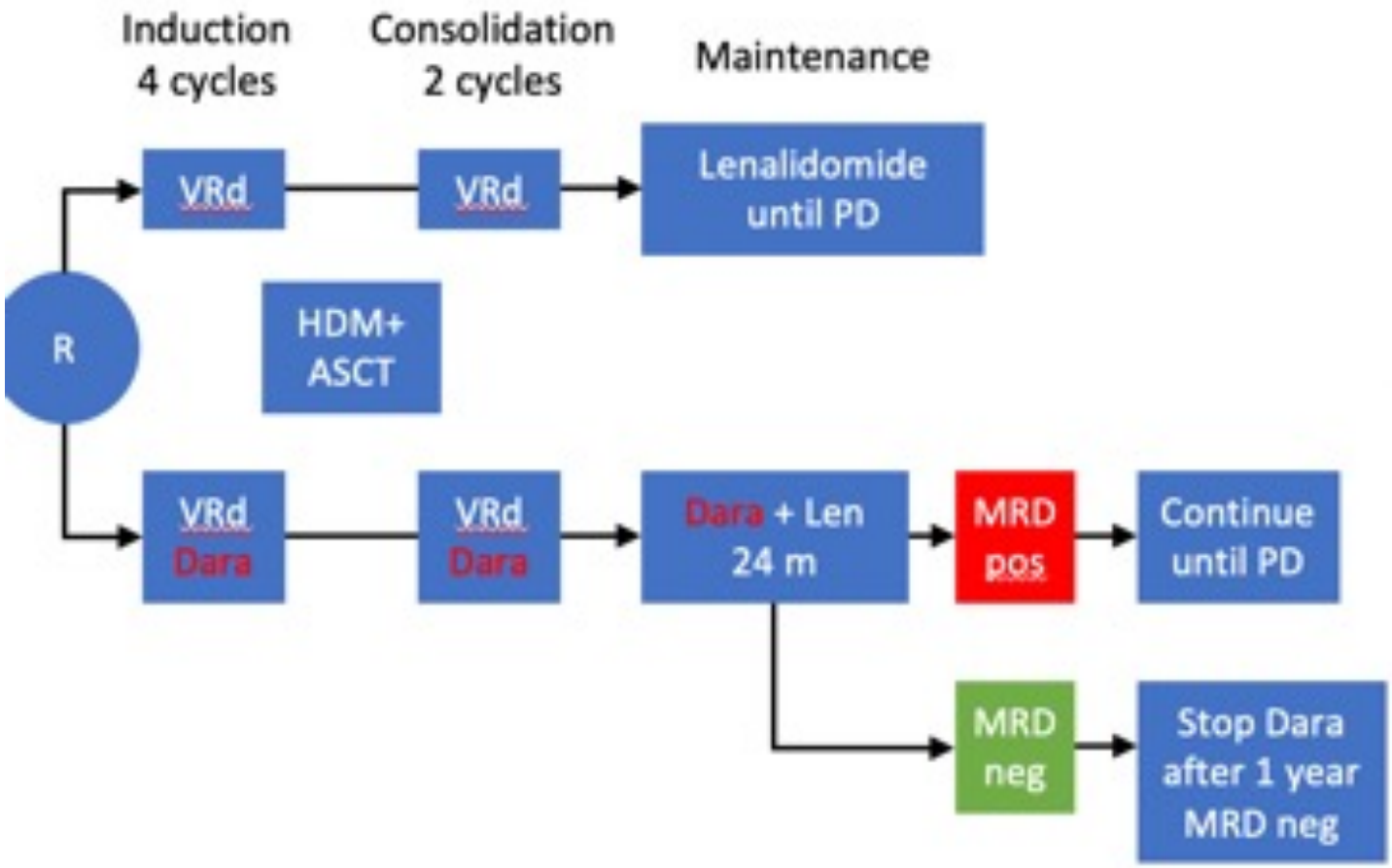


Despite the achievement of MRD negativity, high levels of CTC, amp(1q), and the co-occurrence of multiple HRCA identified a population of patients at higher risk of losing their MRD-negative status over time.

D' Agostino M et al IMS 2022

MRD as endpoint vs modifying treatment based on MRD – examples from clinical trials

Maintenance therapy de-escalation according to sustained MRD negativity: the PERSEUS2 study

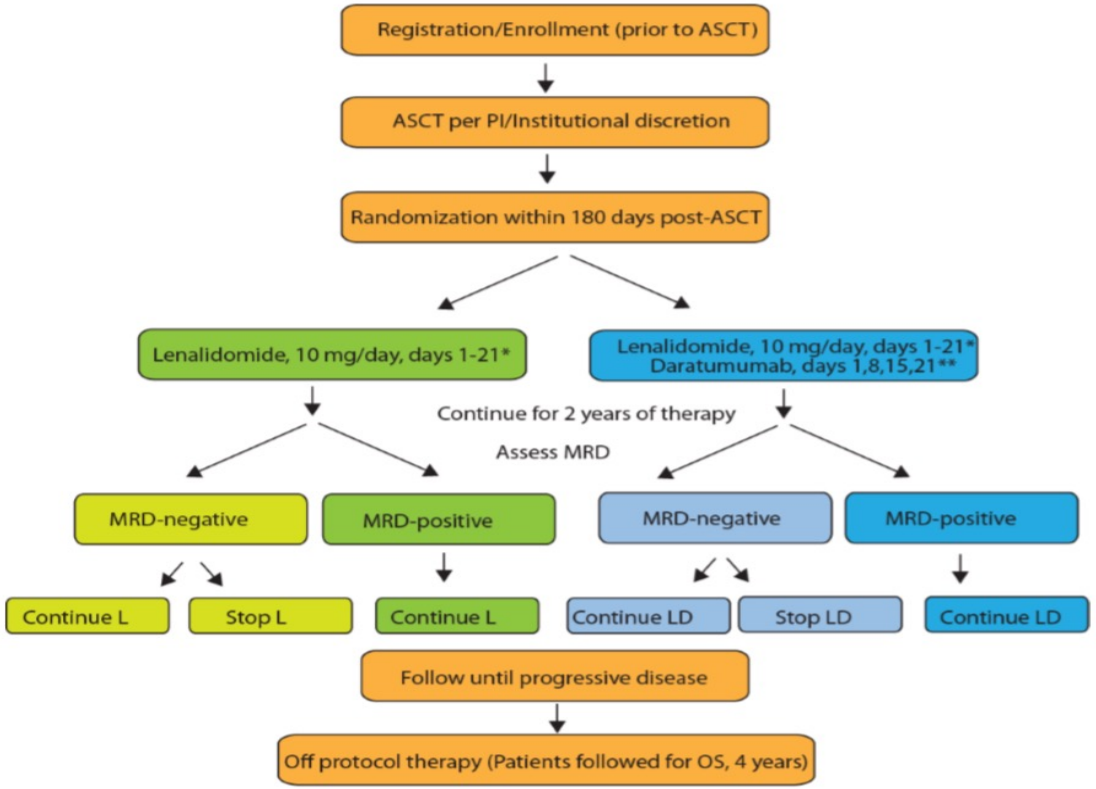


clinicalTrials.gov/NCT03710603

MRD as endpoint vs modifying treatment based on MRD – examples from clinical trials

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

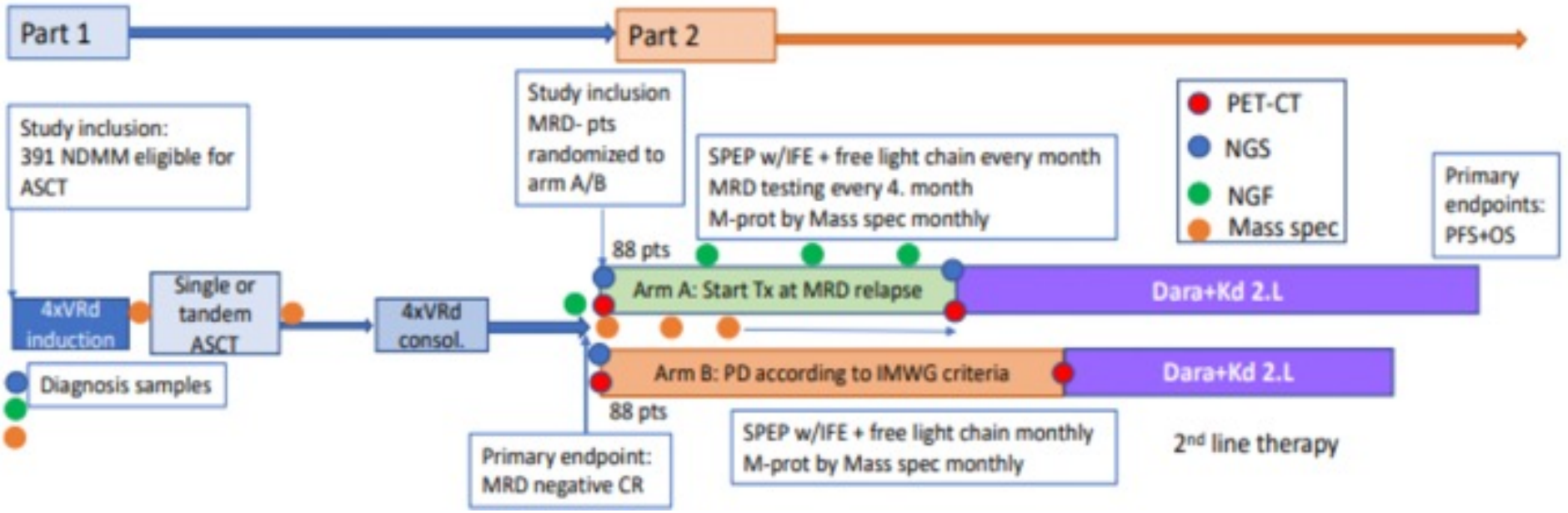
Treatment/Schema



*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

MRD as endpoint vs modifying treatment based on MRD – examples from clinical trials

The REMNANT study
Treatment at MRD resurgence vs clinical relapse

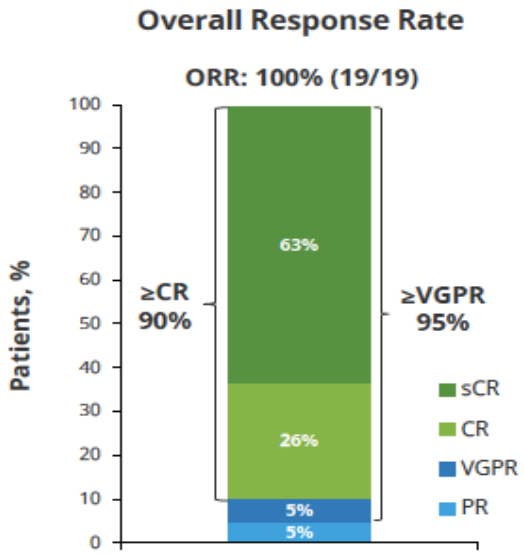


ASCT, autologous stem cell transplant; CR, complete response; IFE, immunofixation; IMWG, International Myeloma Working Group; Kd, carfilzomib, dexamethasone MRD, minimal residual disease; OS, overall survival; NGF, next-generation flow; NGS, next-generation sequencing; PFS, progression-free survival; SPEP, serum protein electrophoresis; VRd, bortezomib, lenalidomide, dexamethasone

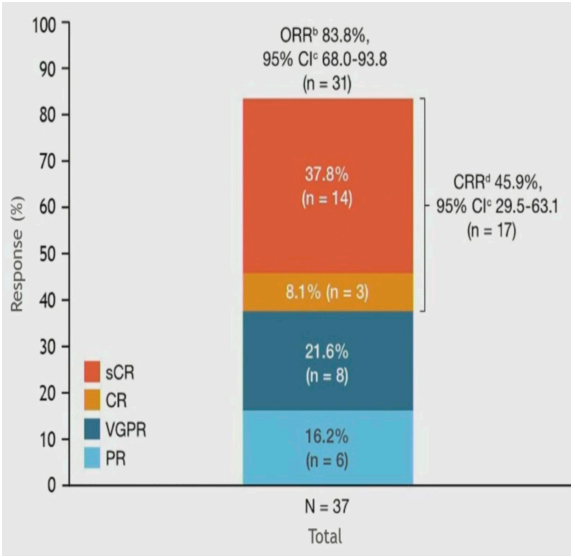
CAR-T IN EARLY LINES OF THERAPY: the rationale for potential use of T cell redirecting therapies in MRD positive patients

CARTITUDE-2 Cohort B:
Cilta-cel in patients with early relapse after initial therapy (n=19)
Progression ≤12 months from ASCT or induction therapy.

KarMMa-2:
Cohort 2a – Ide-cel for patients with an early relapse after ASCT



Median DOR was NR
12-month PFS rate was 89.5%



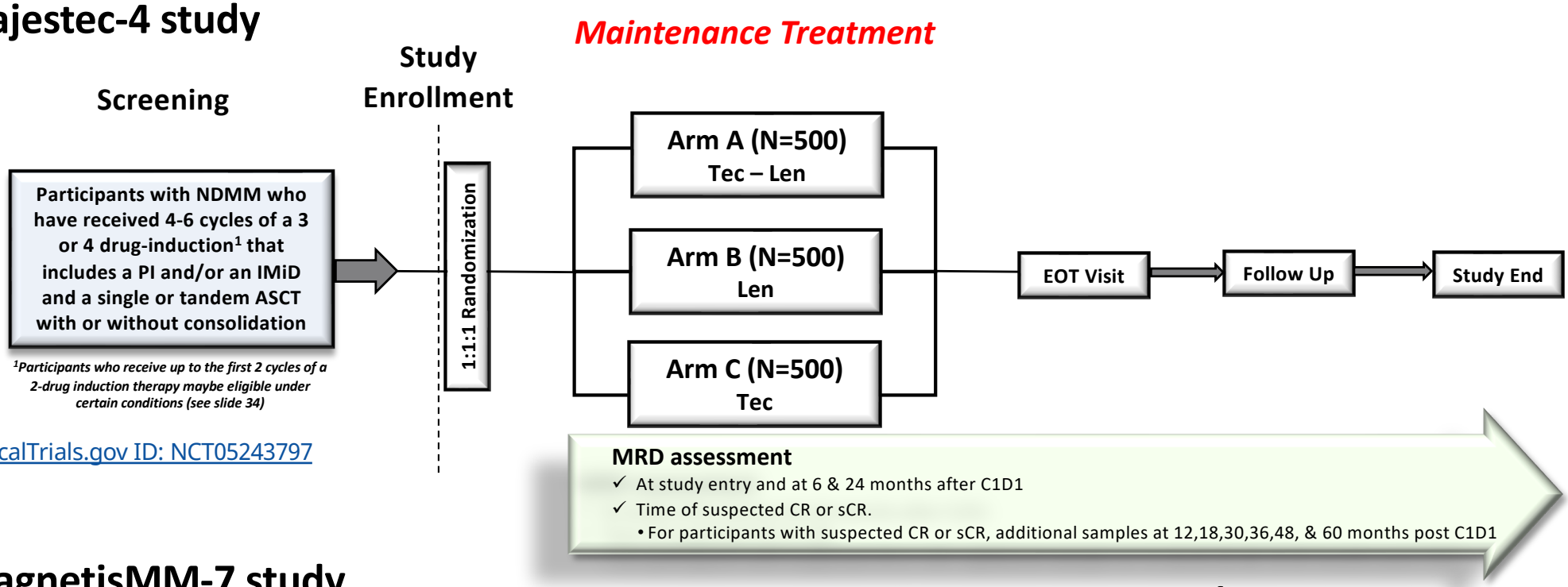
Median duration of response in responding patients: 15.7 months
Median duration of response in patients achieving a ≥CR: 23.5 months

CAR: chimeric antigen receptor; AE: adverse event; LOT: line of therapies; MNT:Movement and neurocognitive treatment-emergent; EMD: extramedullary disease; ORR: overall survival; CR: complete response; VGPR: very good partial response; DOR: duration of response; PFS: progression free survival; NR: not reached

van de Donk N et al. ASH 2022; abstract 3354 (poster presentation)

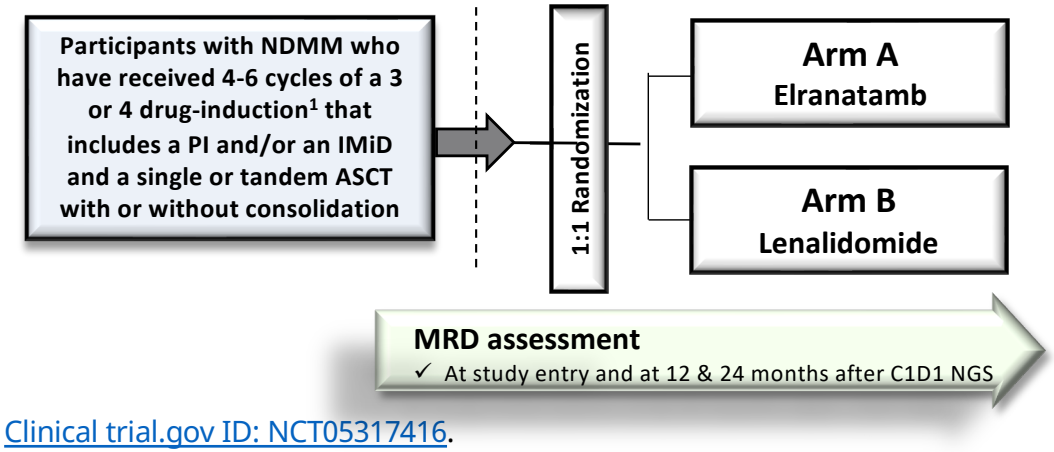
The potential use of T cell redirecting therapies in MRD positive patients

Majestec-4 study



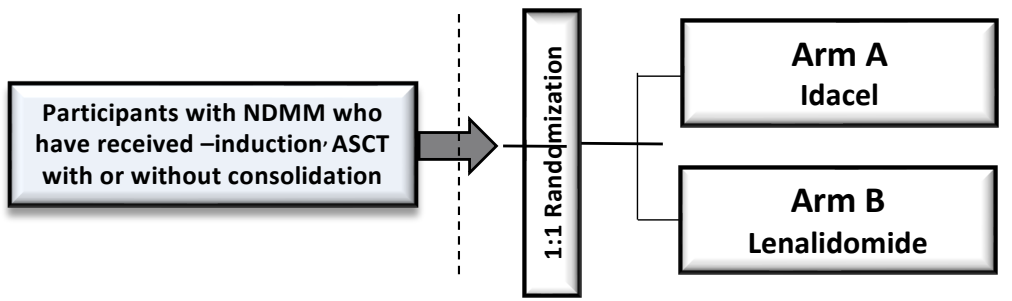
ClinicalTrials.gov ID: NCT05243797

MagnetisMM-7 study



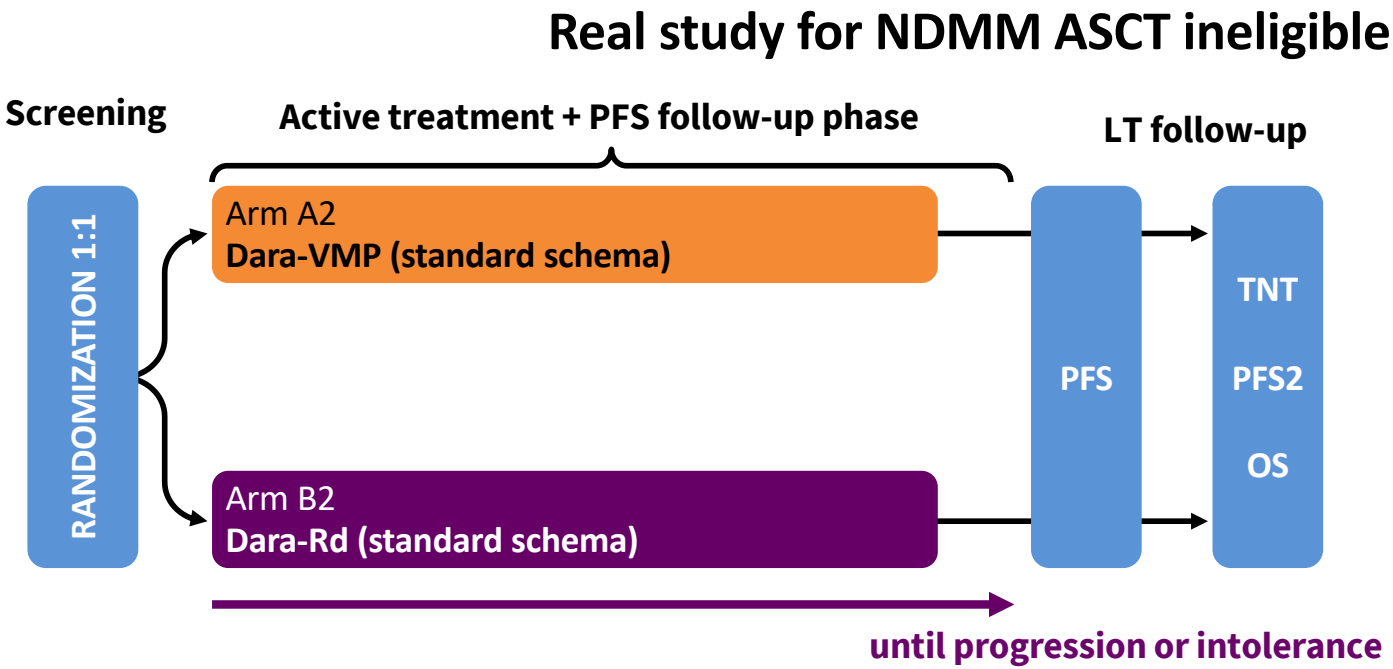
Clinical trial.gov ID: NCT05317416.

KarMMa-9 study



Clinical trial.gov ID: NCT06045806

The use of MRD in real life patients



MRD by NGF at 6^{th}-12^{th}-24^{th}-36^{th}-48^{th}-60^{th} months

Ongoing efforts to have MRD data form real life studies!

The need for armonization of MRD techniques

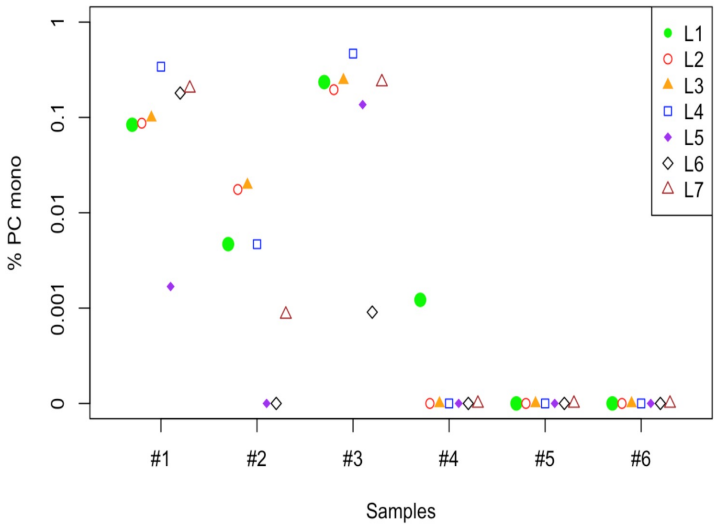
NGF. Dr Stefania Oliva

L1: Brescia (Roccaro, Chiarini)
L2: Catania (Romano, Parrinello)
L3: Padova (Zambello, Trimarco)
L4: Roma IFO (Cordone, Masi)
L5: Roma TVG (Buccisano, Consalvo)
L6: S. Giovanni Rotondo (Rossi, Carella)
L7: Torino (Oliva, Saraci)

NGS. Dr Carolina Terragna

L1: Bologna (Terragna, Martello Armuzzi)
L2: Pisa (Galimberti, Guerrini, Bono)
L3: Milano (Bolli, Lionetti)
L4: Torino (Drandi, Genuardi)

Preliminary data on NGF



100% of the participants were concordant for samples 1, 3, 5 and 6.

ICC=0.61, 95% CI 0.31-0.91 p<0.001

Ongoing efforts to armonize MRD in different laboratories of future use in clinical practice!

Conclusions

- MRD to deeply assess respons in clinical practice? YES, post induction, post ASCT, during maintenance
- Which technique? Let's use what we have available and reimbursed! NGS or NGF for BM
- PET/CT is complementary to BM, particularly for ED and high risk MM patients, PB? Yes but if negative is not enough!
- The achievement of MRD is crucial for *high risk* patients?→ sustained MRD!

Ongoing studies will provide important data concerning:

- Role of **autologous stem cell transplant** according to MRD status and cytogenetic risk
- Maintenance **de-escalation** or **discontinuation** in patients with sustained MRD negativity
- Maintenance **escalation** in patients with MRD positive status

NEED FOR REAL LIFE MRD DATA + ARMONIZATION OF TECHNIQUES

Aknowledgements

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Dr. Roberto Mina
Dr. Mattia D'Agostino
Dr. Giuseppe Bertuglia
Dr. Lorenzo Cani
Dr. Andrea Casson
Dr Tommaso Picardi

Laboratory Staff
Transplant Unit
Nurses
Data Managing Staff
Statisticians

European Myeloma Network (EMN)
Prof. Mario Boccadoro