POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

MM: first-line therapy

Massimo Offidani
Clinica di Ematologia
AOU delle Marche

DICHIARAZIONE

MASSIMO OFFIDANI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(Sanofi)**
- Partecipazione ad Advisory Board **(AbbVie, Amgen, BMS, GSK, Janssen, Roche, Sanofi, Takeda)**
- Onorari e partecipazione a congressi **(AbbVie, Amgen, BMS, GSK, Janssen, Roche, Sanofi, Takeda)**

SMM: curative strategy

Open-label phase II study

High-risk smoldering MM
(N = 87)

Treatment

INDUCTION
(***4-week cycles for 6 cycles***)
- Carfilzomib (36 mg/m² twice weekly or 56mg/m² weekly)
- Lenalidomide (25 mg daily for three weeks)
- Daratumumab (weekly for 8, every other week for 16 weeks)
- Dexamethasone 40 mg weekly

CONSOLIDATION
(***4-week cycles for 6 cycles***)
- Carfilzomib (36 mg/m² twice weekly or 56mg/m² weekly)
- Lenalidomide (25 mg daily for three weeks)
- Daratumumab (every 4 weeks)
- Dexamethasone 20 mg weekly

MAINTENANCE
(***4-week cycles for 12 cycles***)
- Lenalidomide (10 mg daily for 3 weeks)
- Daratumumab (q 8 weeks)

Selection criteria

- **Patients with SMM with high-risk disease**[1]
  - defined by the IMWG updated risk stratification criteria- presence of any two of the following: Serum M spike > 2 gm/dL OR an involved to uninvolved FLC ratio > 20 OR bone marrow PC% > 20%)
  - or a score of ≥9 using the risk scoring system using FLC ratio, serum M spike, marrow plasma cell % and presence of high-risk FISH
- Adequate marrow and organ function
- No evidence of amyloidosis
- Patients with significant comorbidities such as heart disease were excluded from the trial

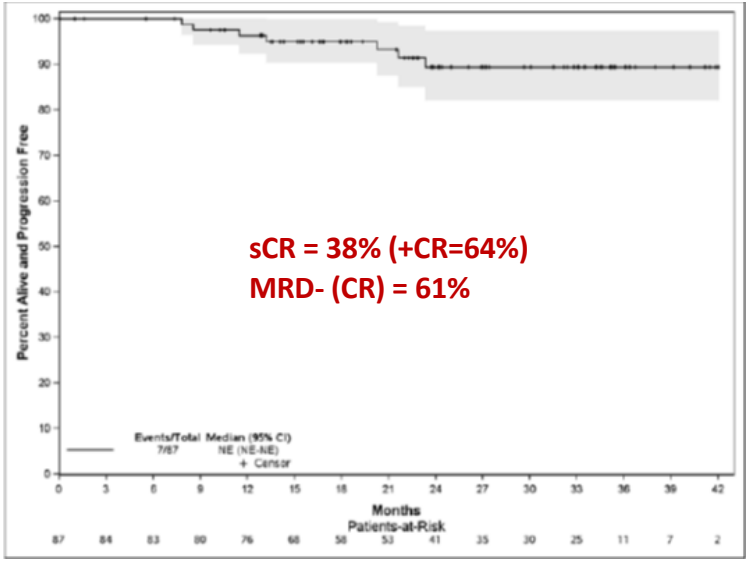
[1]Mateos, MV., Kumar, S., *et al. Blood Cancer J.* **10**, 102 (2020)

Trial objectives

- The ***primary endpoint*** of this trial is the rate of confirmed sCR
- ***Secondary objectives***:
  - To determine the toxicities
  - To determine the progression free survival and overall survival rate
  - To determine the MRD negativity rate (Euroflow, 10^{-5}) at the end of induction, consolidation, maintenance and at one year after the completion of treatment

Kumar S et al. ASH 2022, Abs 570

SMM: ASCENT



sCR = 38% (+CR=64%)
MRD- (CR) = 61%

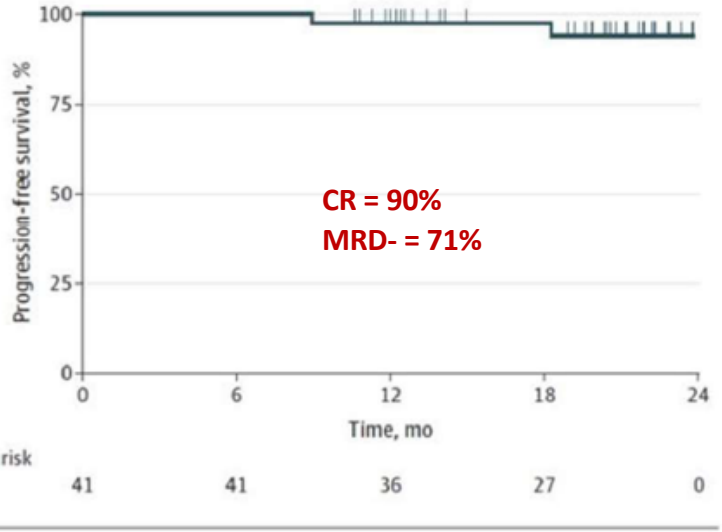
Progression: 4 pts

NonHeme AE grade ≥3= 44 (51%); Discontinuation 12 (14%)

Deaths on trial: 4 (4.6%): COVID-19 (n = 2), RSV (n = 1), PD (n = 1)

MM: MANHATTAN

KRd-Dara without ASCT

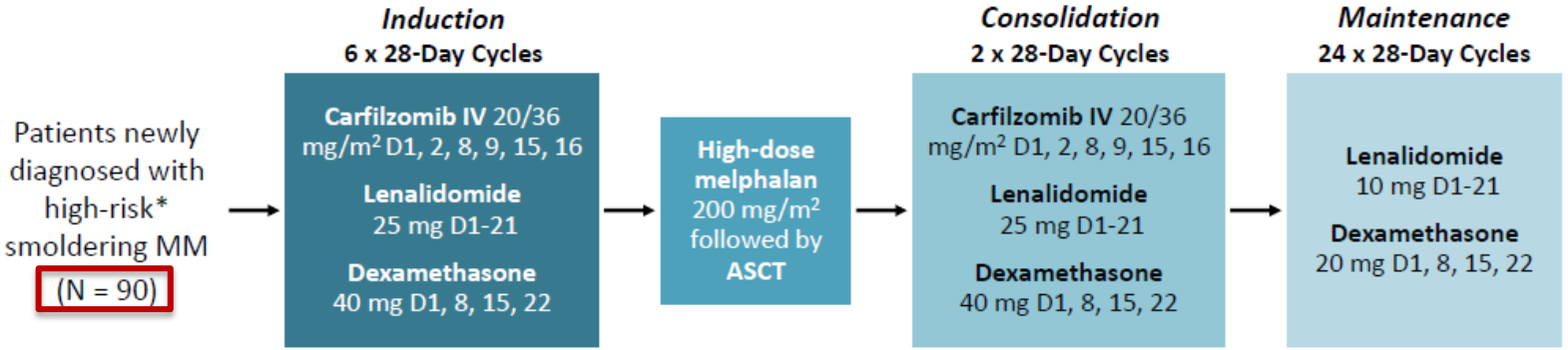


CR = 90%
MRD- = 71%

JAMA Oncol. doi:10.1001/jamaoncol.2021.0611
Published online April 15, 2021.

Phase II GEM-CESAR: Study Design

- Multicenter, open-label phase II trial



*Using Mayo and/or Spanish models (pre-2014 diagnostic criteria): ≥3 g/dL serum M-protein and ≥10% PCs in BM or either ≥3 g/dL serum M-protein or ≥10% PCs in BM and >95% of aberrant PCs within PCs in BM by immunophenotyping and immunoparesis.

- Patients included with ≥1 biomarker predictive for imminent risk of progression
- Patients with bone disease on CT or PET/CT at screening excluded

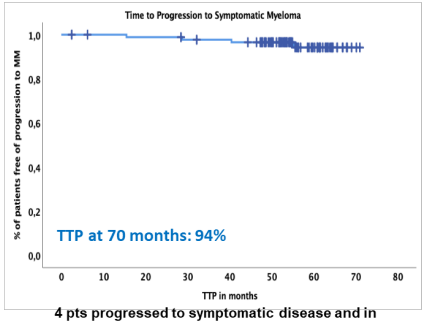
- **Primary endpoint:** MRD negativity (by flow cytometry) after HDT-ASCT and at 3 yr and 5 yr after HDT-ASCT
  - MRD assessment at 3 yr amended to 4 yr due to COVID-19 pandemic
- **Secondary endpoints:** response, TTP, PFS, OS, biochemical progression, safety

Mateos. ASH 2022. Abstr 118.

GEM-CESAR: Outcomes

Median follow-up: 54.6 (6.2-71) months

TTP to symptomatic disease



4 pts progressed to symptomatic disease and in 3 pts, the progression was first asymptomatic

Mateos et al ASH 2021 Abstr 1829

Factors associated with TTP

- **MRD+ve vs MRD-ve**
- **Ultra high risk vs high risk SMM**

Truly HR-SMM	98% at 70 mo
Ultra HR-SMM	86% at 70 mo

TT Biological Progression* was 72% at 5 yr

**Biochemical progression or conversion from MRD-ve into +ve*

Mateos et al ASH 2022 Abstr 118.

GEM-CESAR: Undetectable MRD 3 Mo and 4 Yr After ASCT (Primary Endpoint)

ITT

Undetectable MRD, n (%)	3 Mo After ASCT (n = 90)	4 Yr After ASCT (n = 90)
MRD negative at 10^{-5}	56 (62)	23 (25.5)
MRD negative at 10^{-6}	39 (43)	21 (23)

Per protocol

Undetectable MRD, n (%)	3 Mo After ASCT (n = 82)	4 Yr After ASCT (n = 58)
MRD negative at 10^{-5}	56 (68)	25 (43)
MRD negative at 10^{-6}	39 (48)	28 (48)

Rate of Progression at 2 years: modified scoring 2/20/20 including evolving pattern

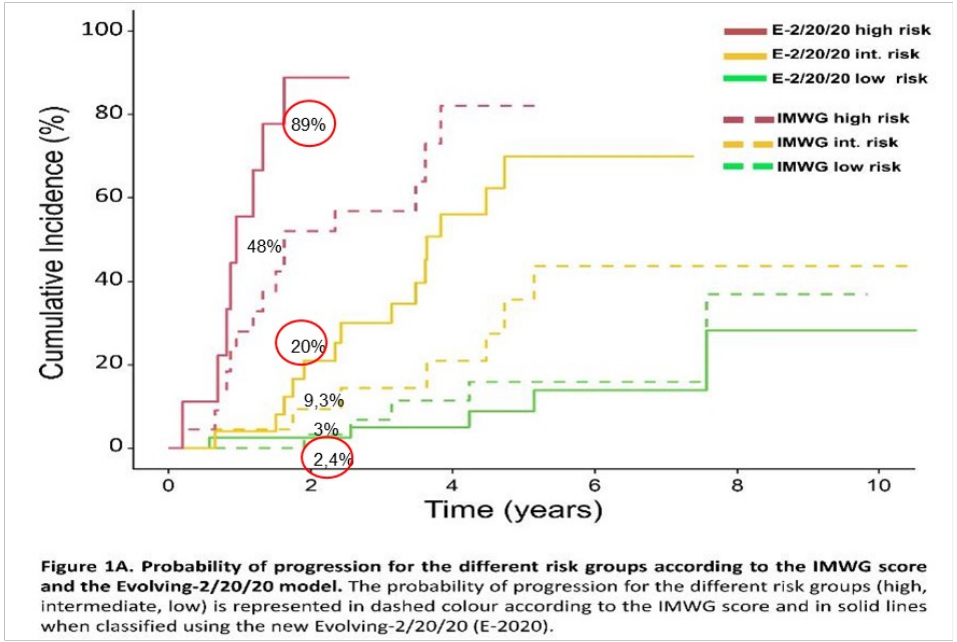


Figure 1A. Probability of progression for the different risk groups according to the IMWG score and the Evolving-2/20/20 model. The probability of progression for the different risk groups (high, intermediate, low) is represented in dashed colour according to the IMWG score and in solid lines when classified using the new Evolving-2/20/20 (E-2020).

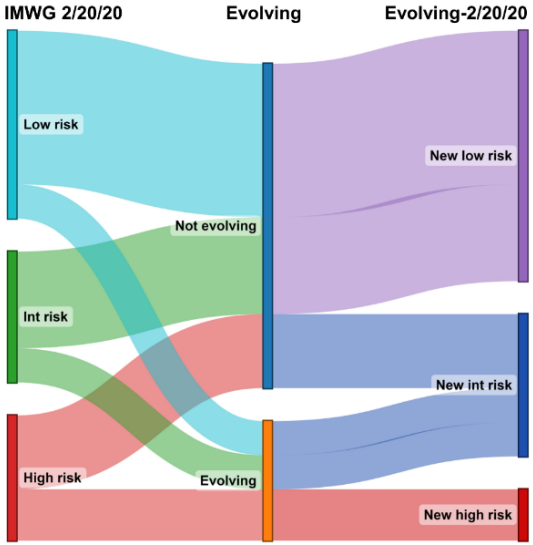


Figure 1B. Reclassification of the SMM patients in three risk groups. Sankey diagram showing the reassignment of the risk of progression with the new classification Evolving-2/20/20 with respect of the IMWG.

Evolving by itself: 48% at 2 yr

Rodríguez-Lobato et al. ASH 2022 Abstract 1892.

To treat or not to treat

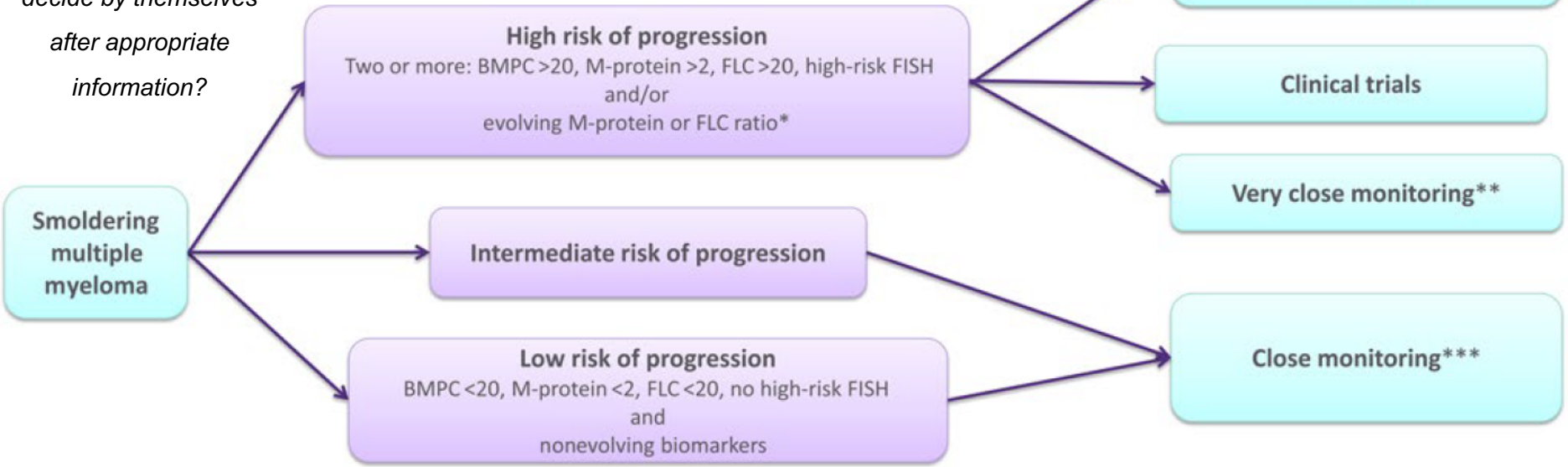
Should the doctor decide for the patient, or should the patients decide by themselves after appropriate information?

Suggested management of SMM

Sigrun Thorsteinsdottir[1,2] and Sigurdur Yngvi Kristinsson[1,3]

Hematology 2022 | ASH Education Program

In randomized trials conducted in specialized centers, we note 90% reduction in end organ damage with simple lenalidomide or Rd therapy compared with observation alone. Thus, attempting to delay therapy until the last minute and **intervene in time before end organ damage occurs is easier said than done** and had not been shown to be possible in clinical trials even with monthly follow-up. *Rajkumar et al BCJ 2022*

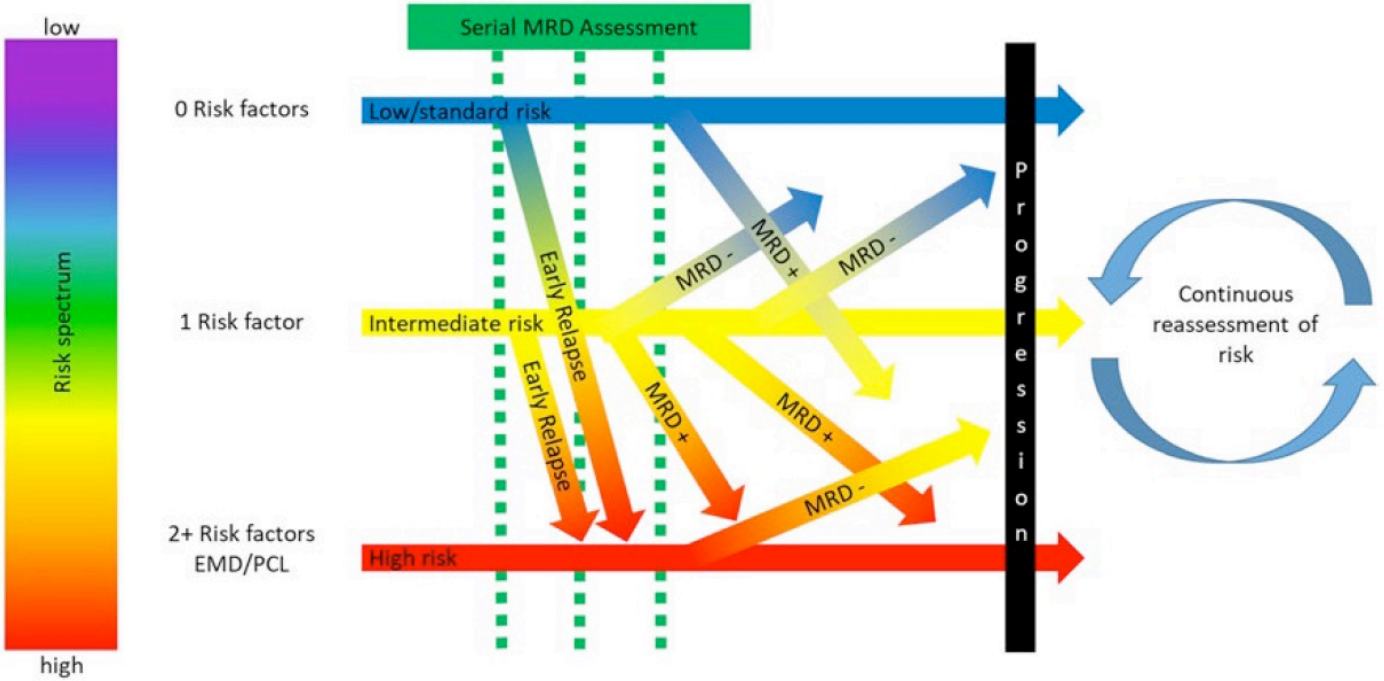


High-risk MM

Dynamics of risk assessment in MM

R-ISS?
R-ISS2?
mSMART?
Double-hit?
Others?

Risk factors at diagnosis:
- ISS 3
- Elevated LDH
- gain(1q)
- del(1p)
- t(4;14)
- t(14;16)
- t(14;20)
- del(17p)
- t(MYC;Ig)



GMMG CONCEPT trial: IsaKRd in HRMM

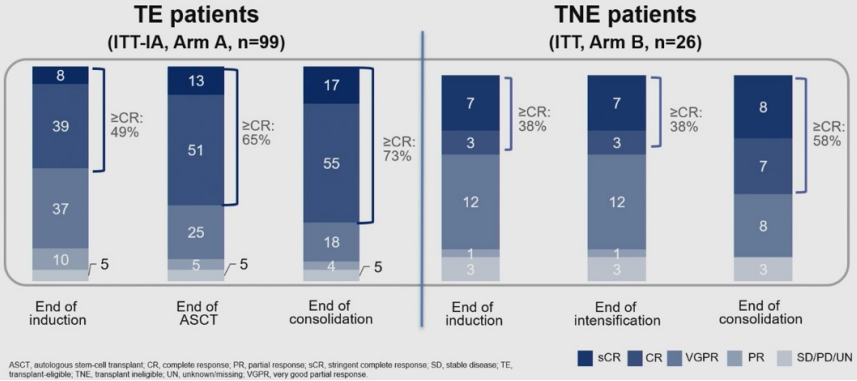
Key eligibility criteria:
- ✓ Age ≥18 years with NDMM
- ✓ HRMM

HRMM criteria:
- ISS stage II or III **PLUS**
- ≥1 of: del(17p), t(4;14), t(14;16) and/or >3 copies 1q21†

Patients can receive up to 1 cycle of anti-myeloma therapy before inclusion

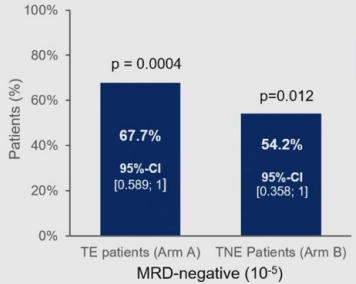
Primary objective: MRD negativity after consolidation (NGF, 10^{-5})
Secondary objective: PFS; Key tertiary objectives: ORR, OS, safety

Best response until end of consolidation



ASCT, autologous stem-cell transplant; CR, complete response; PR, partial response; sCR, stringent complete response; SD, stable disease; TE, transplant-eligible; TNE, transplant ineligible; UN, unknown/missing; VGPR, very good partial response.

Central response results: MRD



MRD status, n (%)	TE patients (Arm A) (n=93*)	TNE patients (Arm B) (n=24†)
Negative	**63 (67.7)**	**13 (54.2)**
Positive	3 (3.2)	0 (0)
Not done / missing	2 (2.2)	0 (0)
Timepoint not reached	25 (27.0)	11 (45.8)

6 TE and 2 TNE patients were not assessable

Of 72 TE patients reaching end of consolidation, 66 had an evaluable MRD-result and of those, 63 were MRD-negative

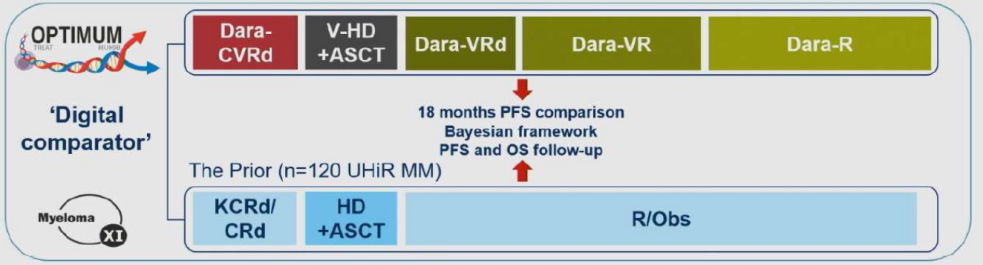
*MRD-IA population according to SAP; †MRD population according to SAP. IA, interim-analysis; MRD, minimal residual disease; SAP, statistical analysis plan; TE, transplant-eligible; TNE, transplant ineligible.

Weisel K et al, ASH 2022, abstract 759

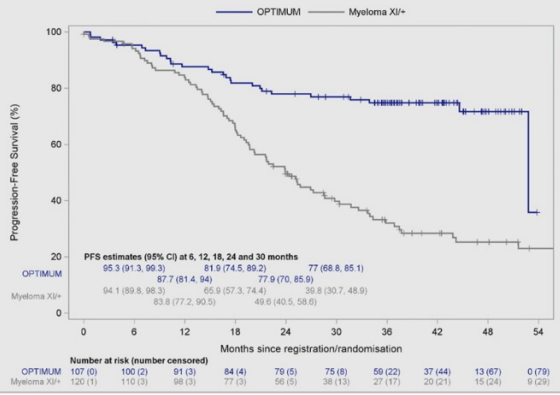
Kaiser M et al, ASH 2022, abstract 758

Extended intensified post-ASCT consolidation with Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (Dara-VRd) for Ultra-High Risk (UHiR) Newly Diagnosed Myeloma (NDMM) and Primary Plasma Cell Leukemia (pPCL): the UK OPTIMUM/MUKnine Trial.

Clinical UHiR context – digital comparator trial

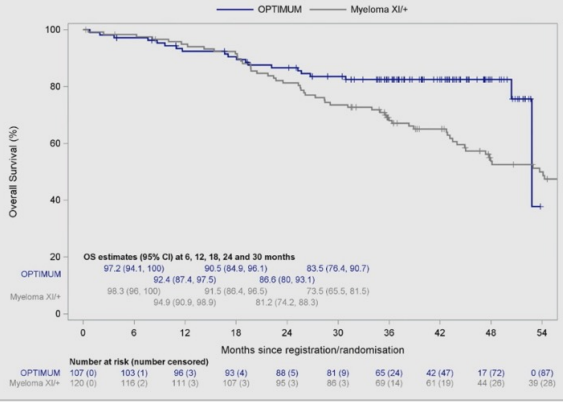


Extended Follow-up: End of Dara-VR Consolidation 2 OPTIMUM vs. Myeloma XI: PFS



Median follow-up 41.2 months

Extended Follow-up: End of Dara-VR Consolidation OPTIMUM vs. Myeloma XI: OS



Median follow-up 41.2 months

KRd *vs* VRd in HRMM at MSKCC

Tan CR et al, ASH 2022, Abstract 752

Study Design

- We conducted a retrospective chart review study with 154 consecutive HR-NDMM patients treated with KRd and VRd at Memorial Sloan Kettering
- Time period: January 1, 2015 to December 31, 2019
- Date of last follow-up: Sept. 30, 2022

Adults with high-risk newly diagnosed multiple myeloma
HR cytogenetic abnormalities defined as 1q+ (gain or amp), t(4;14), t(14;16), t(14;20), and/or del(17p) or monosomy 17
(N=154)

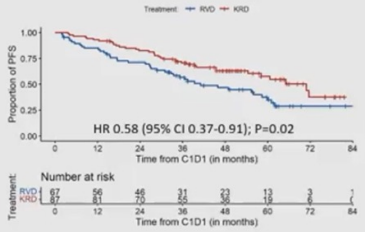
- Bortezomib Lenalidomide Dexamethasone N=67
  - Early ASCT* N=30
  - No early ASCT N=37
- Carfilzomib Lenalidomide Dexamethasone N=87
  - Early ASCT* N=47
  - No early ASCT N=40

Primary endpoint:
Progression Free Survival
Secondary endpoints:
- Overall response rate
- MRD negativity rate
- Event Free Survival
- Overall Survival

*Early ASCT: ASCT within 12 months of start of induction therapy without progressive disease
HR: high risk; NDMM: newly diagnosed multiple myeloma; VRd: Bortezomib, lenalidomide, dexamethasone; KRd: Carfilzomib, lenalidomide, dexamethasone; ASCT: Autologous stem cell transplant

American Society of Hematology

Progression Free Survival



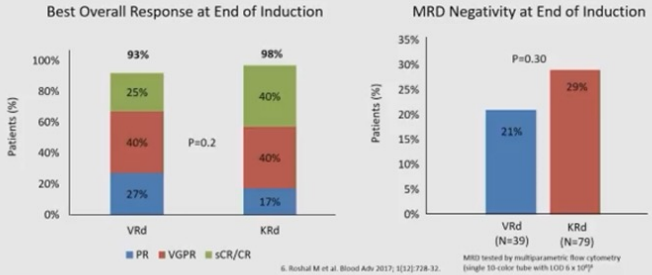
Median f/u for all patients: 55.8 mos (95%CI 50.9-62.6)
Median f/u VRd 61.7 mos (95%CI 53-67.1)
Median f/u KRd 51.6 mos (95%CI 49.1-63.5)

PFS	VRd (N=67)	KRd (N=87)
Median, mo (95%CI)	41 (32.8 – 61.1)	70.9 (58.2 – NR)*
5-yr estimate (95%CI)	35% (24% - 51%)	58% (47% - 71%)

*Median PFS is an estimate

American Society of Hematology

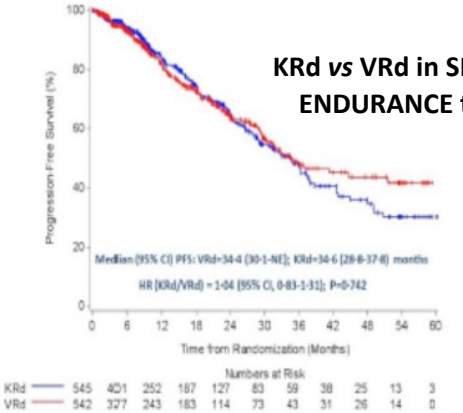
Responses



6. Roshal M et al. Blood Adv 2017; 1(12):728-32.

American Society of Hematology

KRd *vs* VRd in SRMM: ENDURANCE trial



Du J et al, ASH 2022, abstract 366

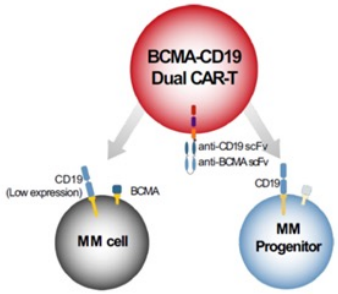
Phase I Open-Label Single-Arm Study of BCMA/CD19 Dual-Targeting FasTCAR-T Cells (GC012F) as First-Line Therapy for Transplant-Eligible Newly Diagnosed High-Risk Multiple Myeloma

Juan Du, *Weijun Fu, Jing Lu, Wanting Qiang, Haiyan He, Jin Liu, Ying Yang, Zhongyuan Feng, Lina Jin, Xiaoqiang Fan, Jia Liu, Qi Zhang, Lianjun Shen, Lihong Weng and Wei Cao*

Abstract 366

HR= citogenetica, ISS, LDH, EM disease, mSMART

GC012F: Introduction



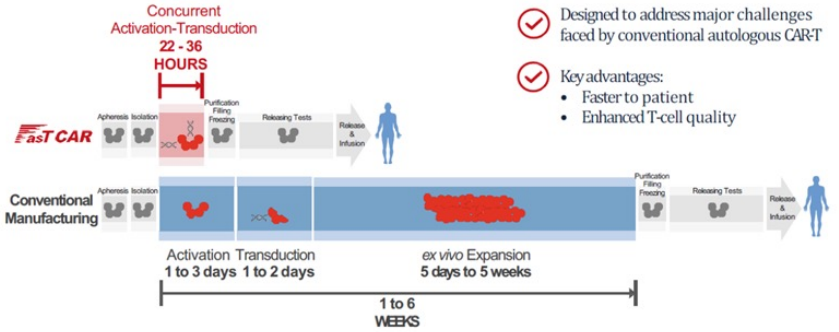
Targeting BCMA/CD19 is designed to drive fast, deep and durable responses in multiple myeloma (MM) patients

- BCMA is universally expressed on malignant plasma cells[1]
- CD19 is expressed on both multiple myeloma cells and their progenitors[2], making it a valid therapeutic target to treat multiple myeloma

1. Tai YT, Anderson KC. Immunotherapy. 2015;7(11):1187-1199.
2. Boucher K, Parquet N, Widen R, et al. Clin Cancer Res. 2012;18(22):6155-6168.

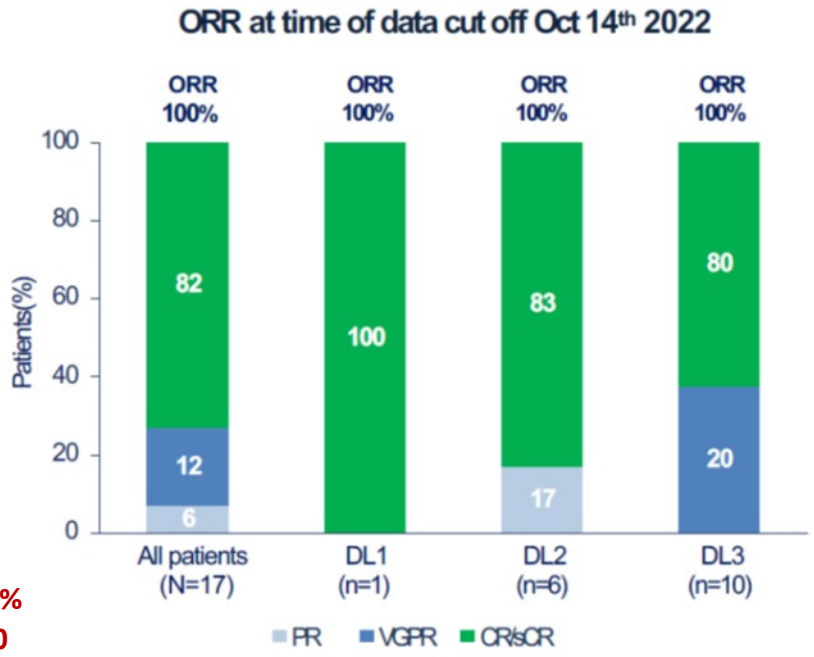
GC012F: FasTCAR Cuts Manufacturing Time to 22-36 Hours

Combines Activation & Transduction Steps, and Eliminates Need for *ex vivo* Expansion

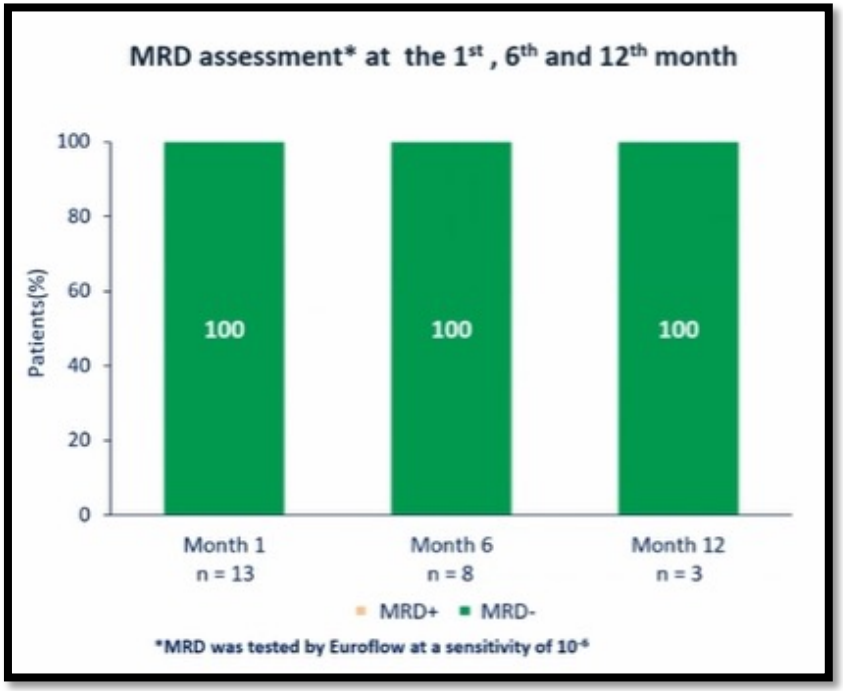


- Designed to address major challenges faced by conventional autologous CAR-T
- Key advantages:
  - Faster to patient
  - Enhanced T-cell quality

GC012F: Efficacy Assessment – ORR



CRS G2=8%
ICANS= 0



Personalized therapy in MM

Barriers and questions for the regular use and future prospects of MRD use in MM

Matthew Ho and Taxiarchis Kourelis

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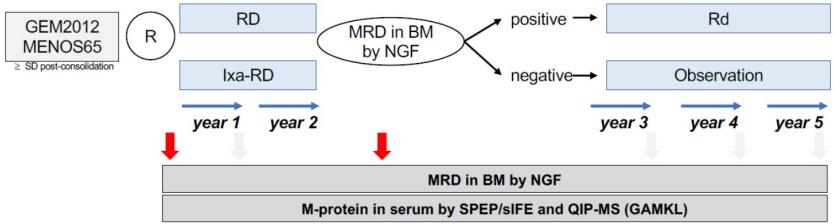
1. What is the most appropriate sensitivity threshold (10^{-5},10^{-6}, or higher) to determine MRD presence?
2. Should MRD− cutoffs or requirement for sustained MRD− be different according to disease risk?
3. What is the optimal timing for MRD assessment? What are the optimal intervals for sustained MRD assessment?
4. Can clinicians intensify or deintensify their therapeutic approaches based on MRD results at different time points?
5. How can blood-based and imaging methods complement BM-based MRD assessment?
6. Can MRD− be used as a surrogate marker for more clinically relevant end points (ie, PFS and ideally OS)? If yes, how "much more" MRD− is needed for a therapy to consistently lead to improve PFS/OS and in which setting (newly diagnosed vs relapsed disease, high-risk disease vs not)?
7. Are there tumor-extrinsic factors that can explain early relapse in MRD− non–high-risk patients (immunome, microbiome)?
8. What cells are responsible for relapse in MRD−? Are they malignant plasma cells truly present at very low thresholds, or are they phenotypically and genomically different than plasma cells? Are they amenable to sampling by BM aspiration, or are they adherent to the BM niche?

GEM2014MAIN

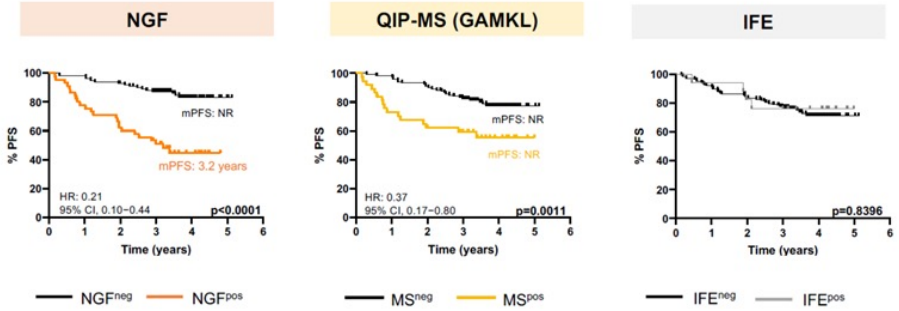
Puig N et al, ASH 2022, Abstract 866

Phase III, multicenter, open-label randomized trial

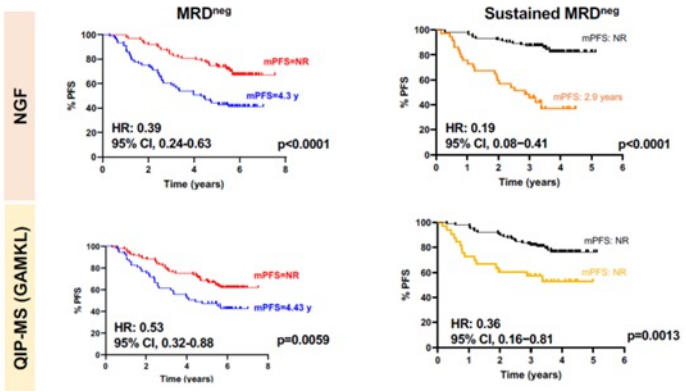
316 NDTE MM patients enrolled in the GEM2012 and achieving at least stable disease at the end of treatment



Progression-free survival according to the results of the three methods



The added clinical value of sustained MRD negativity



Ultra-Sensitive Assessment of Measurable Residual Disease (MRD) in Peripheral Blood (PB) of Multiple Myeloma (MM) Patients Using Bloodflow

Laura Notarfranchi, Anastasiia Zherniakova, Marta Lasa, PhD, Noemi Puig, MD, PhD, María Teresa Cedena, MD, PhD, Joaquín Martínez-Lopez, MD PhD, María José Calasanz, PhD Diego Alignani, PhD, Leire Burgos, Irene Manrique, Yi-Ju Huang, Jochen Fracowiak, Clara Gomez, Felipe De Arriba, PhD, Paula Rodríguez-Otero, MD, PhD, Luis Palomera, MD, PhD, Anna Sureda, María Esther Clavero Sanchez, Miguel Angel Alvarez, Angela Ibanez García, Miguel-Teodoro Hernández, MD, PhD, Albert Perez, Ana Pilar Gonzalez, PhD, Enrique M. Ocio, Juan Flores-Montero, Alberto Orfao, MD, PhD, Juan Jose Lahuerta, MD, PhD, María-Victoria Mateos, MD, PhD, Laura Rosiñol, MD, PhD, Joan Bladé Creixenti, MD, PhD, Jesús San-Miguel, MD, PhD and Bruno Paiva

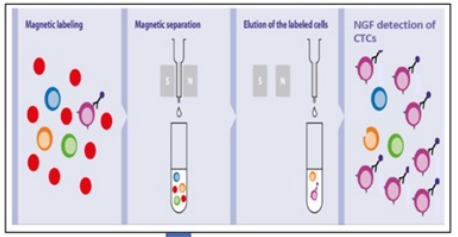
NEW Blood Flow Test

A new universally applicable and ultra-sensitive test to monitor MRD in PB

Before enrichment

NGS of cfDNA (VDJ & mutations) – H12O

Mass spectrometry - HUS

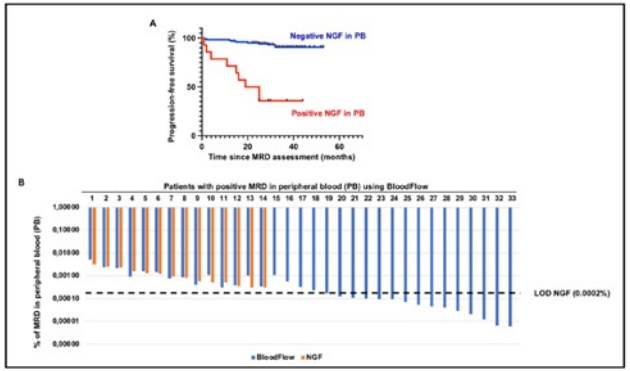


(CD138, CD269, CD229, CD317, CD319)

Abstract 865

Conclusion

MRD assessment in PB using NGF was prognostic in pts under maintenance or observation. Notwithstanding, a new method (BloodFlow) was developed to increase the NPV and showed an unprecedented sensitivity to detect MRD down to 10^{-8} in PB. BloodFlow detected MRD in PB more frequently than NGF, with a consequent decrease in the number of cases with persistent MRD in BM while undetectable in PB, which were more frequent during early and intensive treatment stages. These results suggest the possibility of periodic and ultra-sensitive MRD assessment in PB during maintenance/observation.

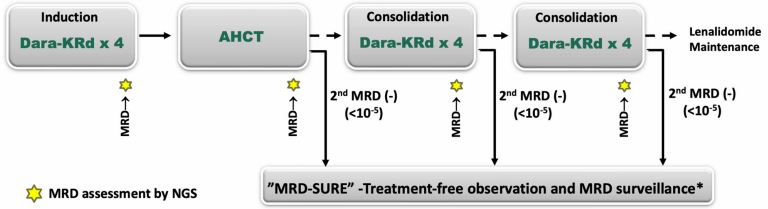


Notarfranchi L et al, ASH 2022, Ab 865

Treatment

Dara-KRd

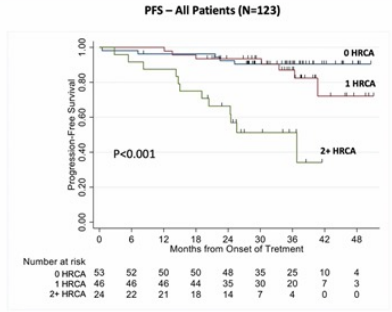
- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

MASTER trial

PFS and OS, median 34.1 mo.



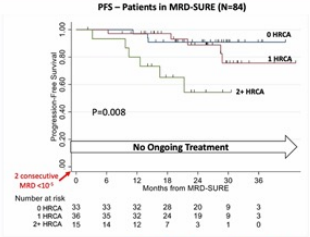
3-year PFS	0 HRCA	91%
	1 HRCA	87%
	2+ HRCA	51%
3-year OS	0 HRCA	96%
	1 HRCA	91%
	2+ HRCA	75%

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

MASTER trial

Patient disposition

- 118 patients with trackable MRD
  - 8% early discontinuation
  - 20% completed consolidation -> Lenalidomide Mainteance
  - 71% Entered MRD-SURE
- Likelihood of achieving MRD-SURE (N=84).
  - 0 HRCA – 66%
  - 1 HRCA- 82%
  - 2+ HRCA – 63%
- Median follow-up in MRD-SURE=24.8 mo.
  - 2 deaths from MM (21 and 24 mo after progression)
  - 2 deaths without progression (COVID-19 and fall).



	2-year PFS	2-year OS
0 HRCA	91%	100%
1 HRCA	89%	92%
2+ HRCA	54%	100%

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

MASTER trial

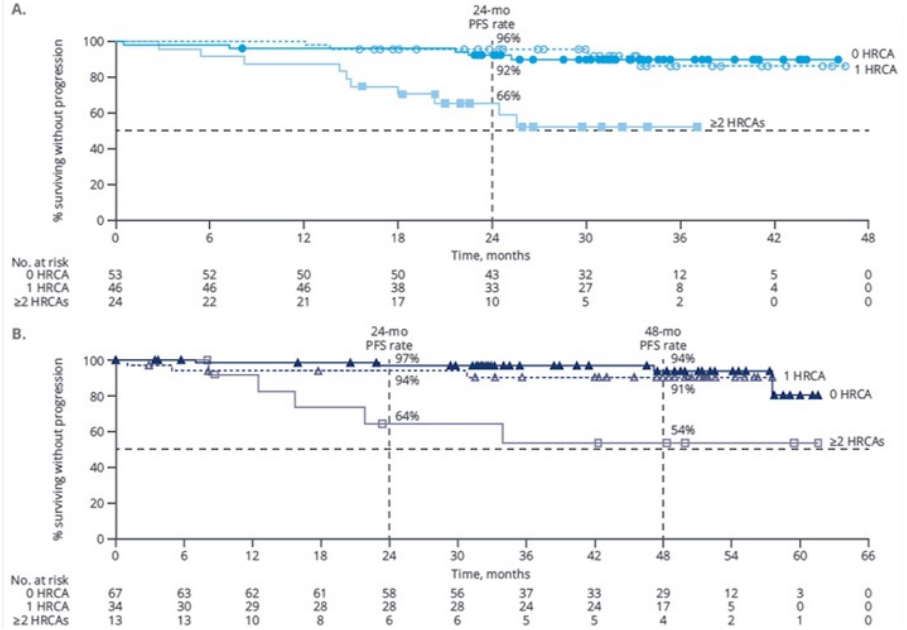
Costa LJM et al, ASH 2022, Abstract 3237

GRIFFIN+MASTER: HR SUBGROUP ANALYSIS

TABLE 3: MRD negativity by cytogenetic risk status[a] among patients who received D-KRd in MASTER and D-RVd in GRIFFIN

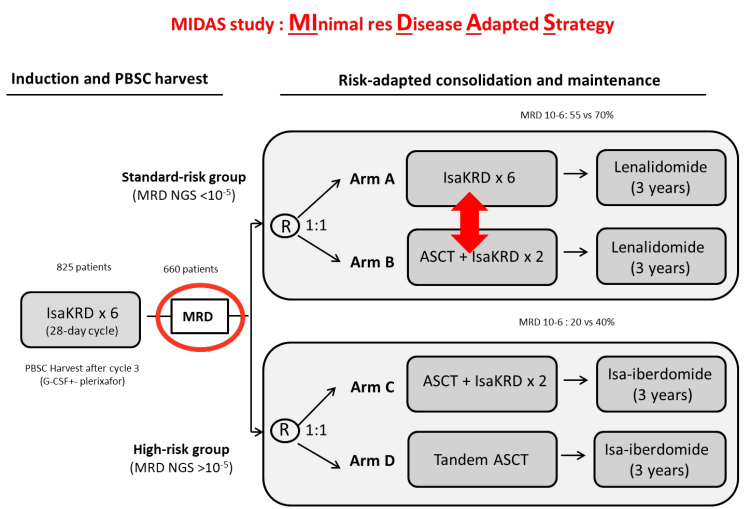
	D-KRd			D-RVd		
	0 HRCA	1 HRCA	≥2 HRCAs	0 HRCA	1 HRCA	≥2 HRCAs
MRD negative						
Evaluable population	n = 50[b]	n = 44[b]	n = 24[b]	n = 67[c]	n = 34[c]	n = 13[c]
10^{-5} sensitivity, %	80	86	83	76	56	62
10^{-6} sensitivity, %	68	80	67	45	26	15
In patients achieving ≥CR	n = 45	n = 39	n = 17	n = 60	n = 26	n = 8
10^{-5} sensitivity, %	84	90	94	75	53	54
Durable MRD negativity lasting ≥12 months						
Evaluable population	n = 50[b]	n = 44[b]	n = 24[b]	n = 67[c]	n = 34[c]	n = 13[c]
10^{-5} sensitivity, %	64	73	50	54	38	31
MRD (10^{-5}) conversion rate						
Evaluable population				n = 67[c]	n = 34[c]	n = 13[c]
MRD positive by the end of induction and then became MRD negative, %	NA	NA	NA	49	41	38
MRD positive by the end of consolidation and then became MRD negative, %	NA	NA	NA	19	12	23
Median time to MRD (10^{-5}) negativity,[b,c] months	7.5	7.1	7.6	8.5	8.6	19.6

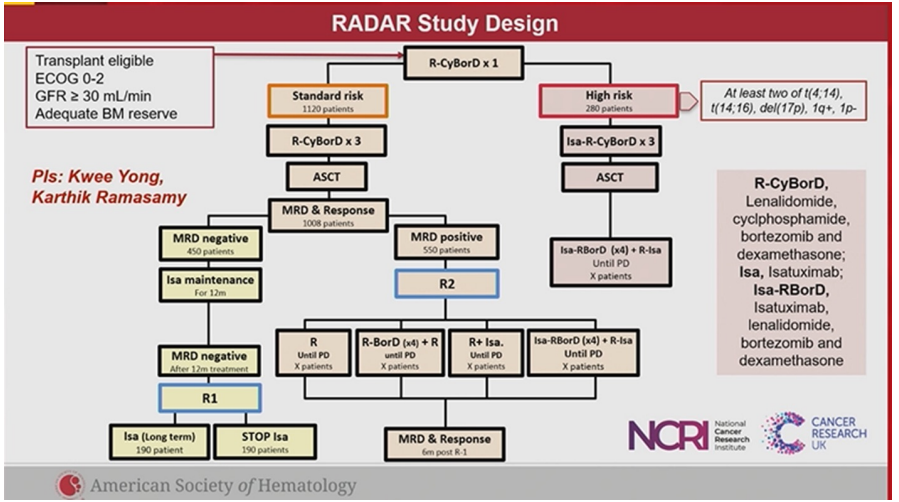
FIGURE 4: PFS by cytogenetic risk status[a] among patients who received (A) D-KRd in MASTER and (B) D-RVd in GRIFFIN



Callander N et al, ASH 2022, Abstract 4557

Ongoing randomized MRD-driven trials



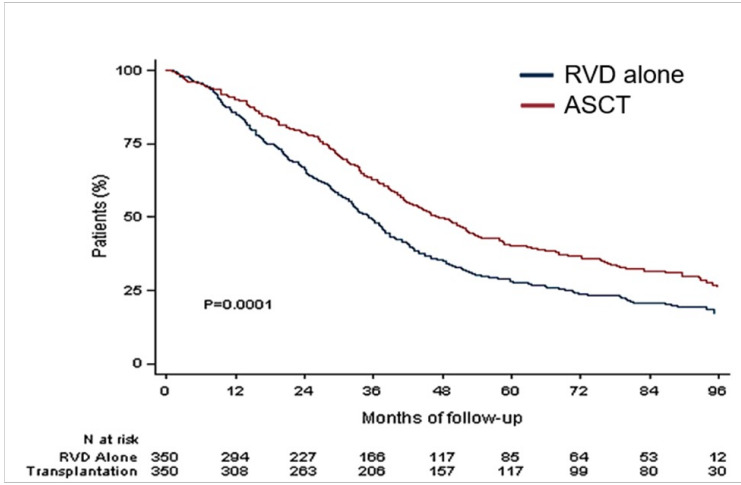


NCT04934475

Len 1 year vs Len until progression?

IFM-2009 Trial

Median PFS: 47.3 vs 35 mo

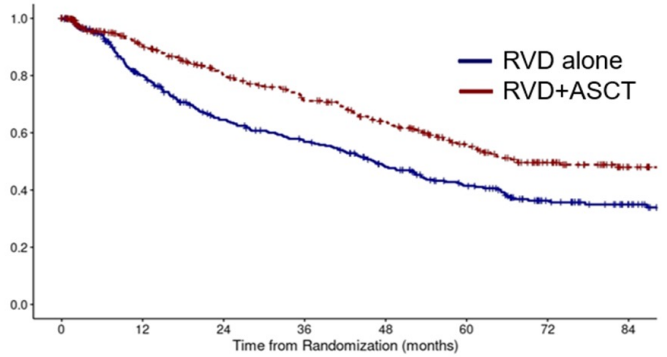


Attal et al. N Engl J Med 2017
Perrot et al. ASH 2020

DFCI 2009 Trial

Median PFS: 67.5 vs 46.2 mo

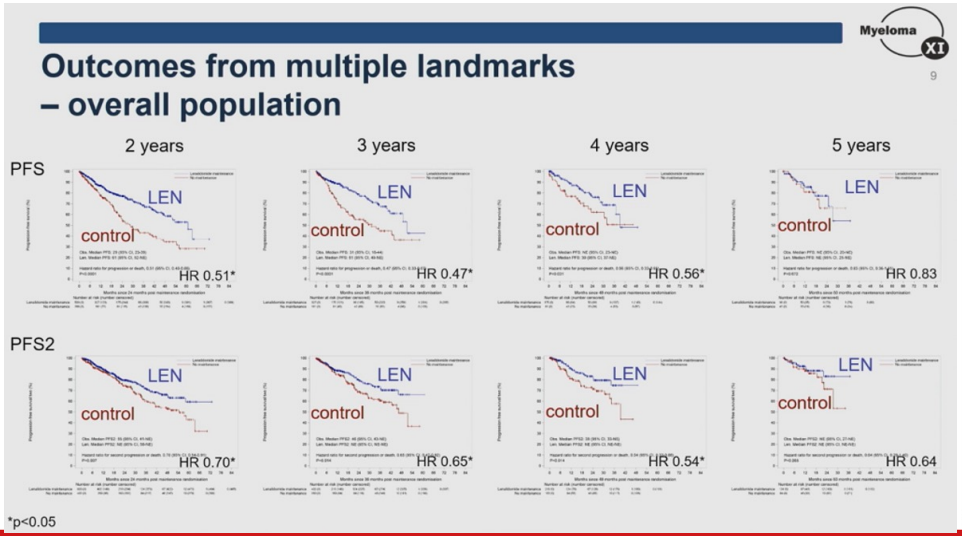
Benefit: maintenance until PD!

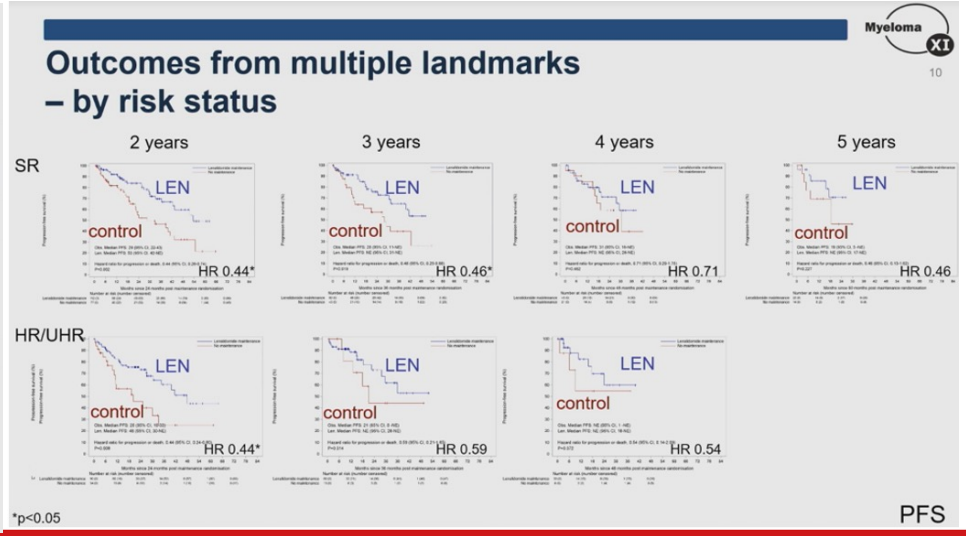


Richardson et al. N Engl J Med 2022

Myeloma XI

Defining the optimum duration of lenalidomide maintenance after autologous stem cell transplant – data from the Myeloma XI trial.

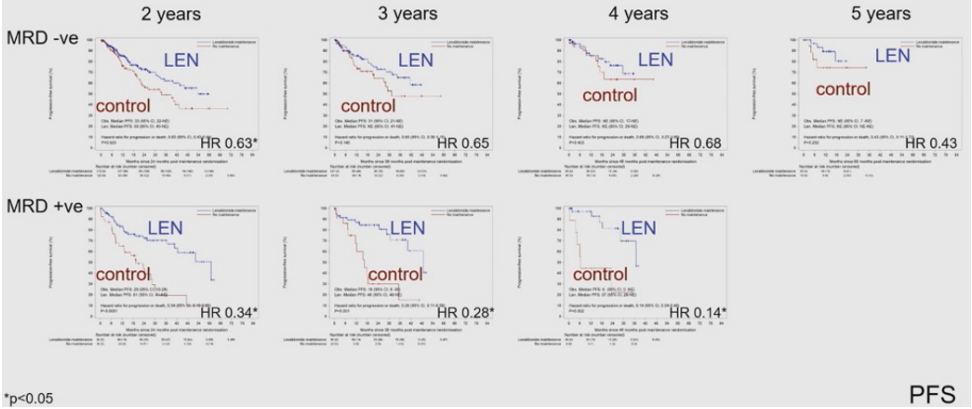




Outcomes from multiple landmarks – by MRD status

Myeloma XI

11



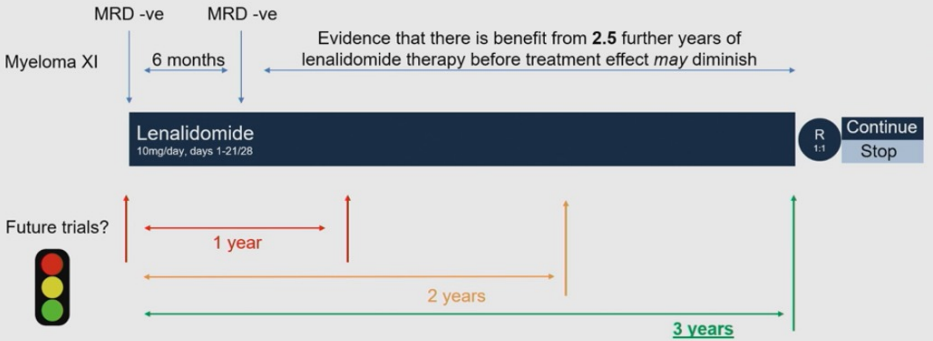
Can this help us personalise therapy?

Myeloma XI

14

MRD +ve – continue maintenance to progression

MRD –ve:

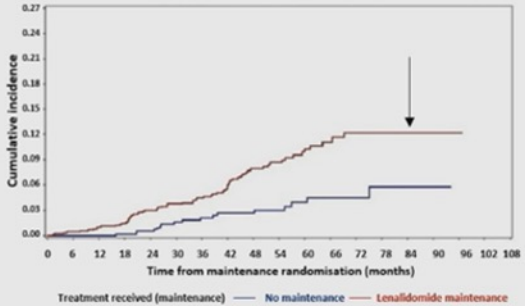


Pawlyn C N et al, ASH 2022, Abstract 570

Myeloma XI

Cumulative incidence of SPM according to maintenance treatment received

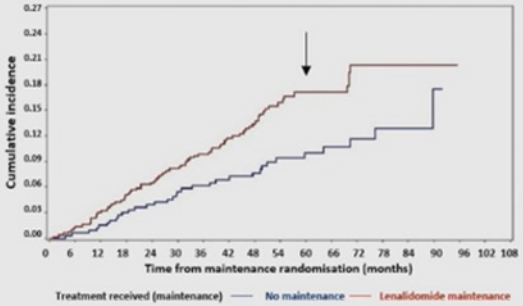
SPM cumulative incidence according to maintenance in ASCT eligible patients



7 year CI: Lenalidomide 12.2% vs 5.8% observation (p=0.006)

lenalidomide +/- vorinostat (n 875), Observed (n 566)

SPM cumulative incidence according to maintenance in non-ASCT eligible patients



5 year CI: Lenalidomide 17.1% vs 10% observation (p=0.10)

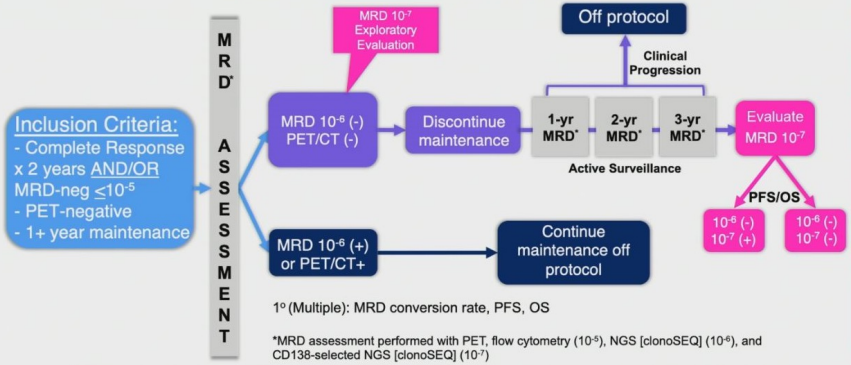
lenalidomide +/- vorinostat (n 493), Observed (n 340)

Significant increase in SPM incidence noted in ASCT patient who received lenalidomide maintenance
Higher incidence in non-ASCT patients, suggesting a predisposition to carcinogenesis in older myeloma patients

MRD2STOP trial

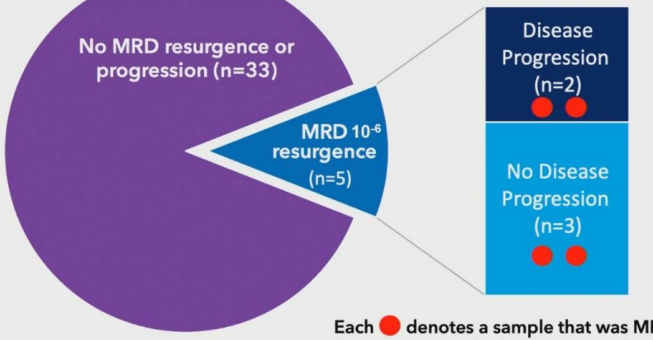
Derman BA et al, ASH 2022, abstract 870

MRD2STOP Schema



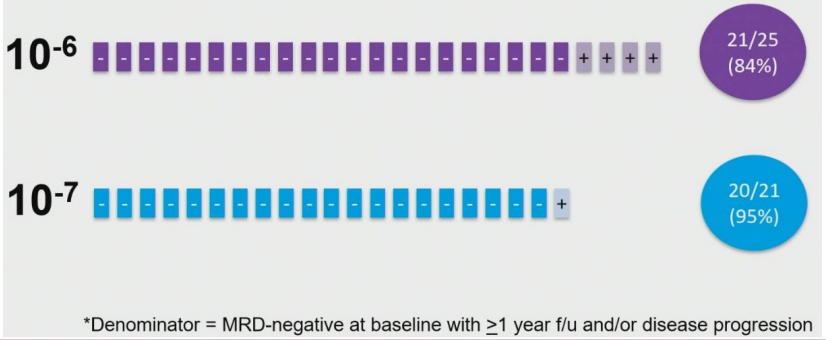
At data cutoff (July 13, 2022): 38 pts (of expected 45) have discontinued therapy

Patient Disposition



Each ● denotes a sample that was MRD(+) by the CD138-enriched NGS assay at baseline

Sustained MRD Negativity @ 12 Months

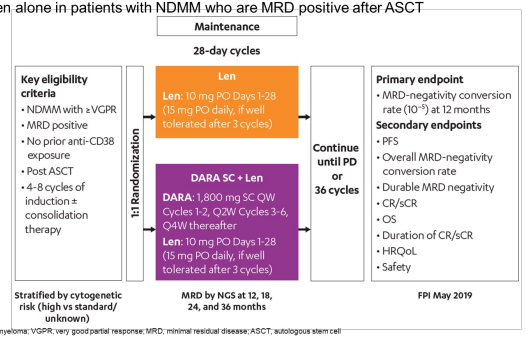


*Denominator = MRD-negative at baseline with ≥1 year f/u and/or disease progression

Ongoing randomized MRD-driven maintenance trials

AURIGA Phase 3 Study: Design

- Objective: to evaluate the conversion rate to MRD negativity after maintenance treatment with DARA SC plus len vs len alone in patients with NDMM who are MRD positive after ASCT

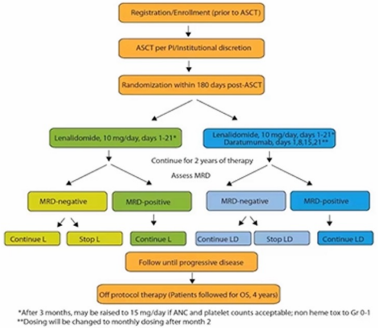


NDMM, newly diagnosed multiple myeloma; VGPR; very good partial response; MRD; minimal residual disease; ASCT; autologous stem cell transplant; len, lenalidomide; PO, oral; DARA SC, daratumumab subcutaneous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; NGS, next-generation sequencing; PD, progressive disease; PFS, progression-free survival; CR, complete response; sCR, stringent complete response; OS, overall survival; HRQoL, health-related quality of life; FPI, first patient in

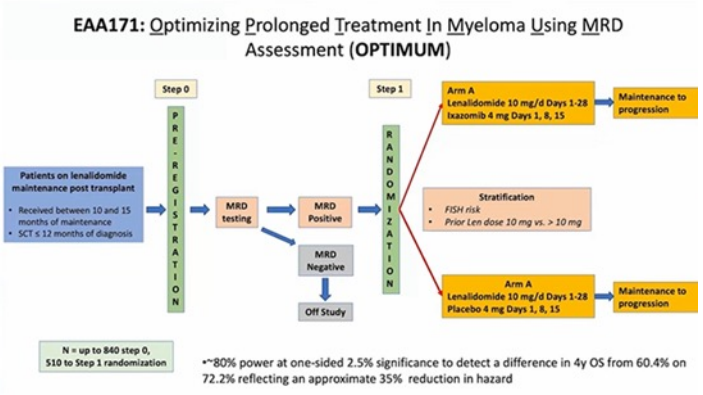
Shah N et al. ASH 2019; abstract 1829 (poster presentation)

Phase III Study of Daratumumab + Lenalidomide (LD) or Lenalidomide (L) as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients with Multiple Myeloma (MM) - DRAMMATIC

Treatment/Schema



EAA171: Optimizing Prolonged Treatment In Myeloma Using MRD assessment (OPTIMUM)



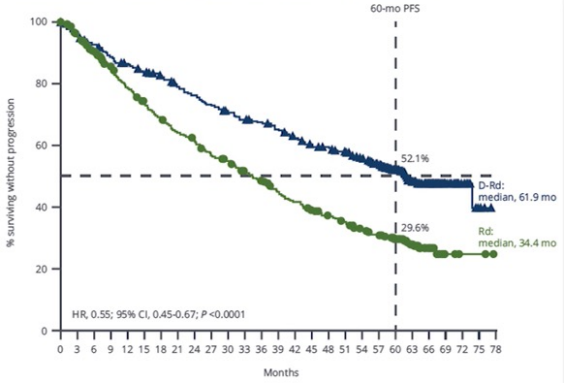
Shah N et al. ASH 2019; abstract 1829 (poster presentation)

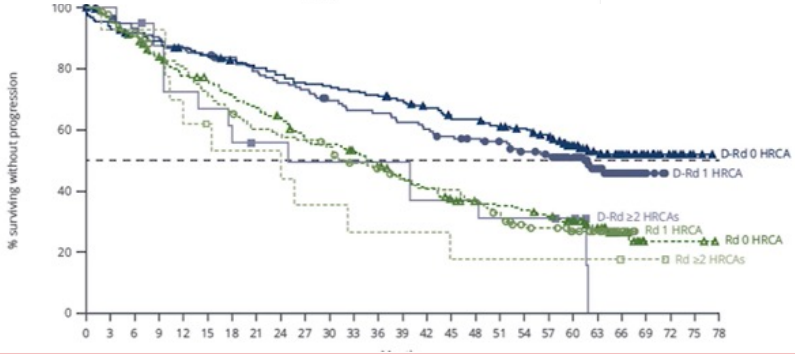
Not transplant eligible

Updates of phase 3 MAIA study

Kumar SK et al, poster 4559 Moreau P et al, poster 3245

FIGURE 1: PFS with D-Rd and Rd in the ITT population[a]





Updates of phase 3 ALCYONE study

Mateos MV et al, poster 4561

FIGURE 1: PFS based on investigator assessment with D-VMP and VMP in the ITT population

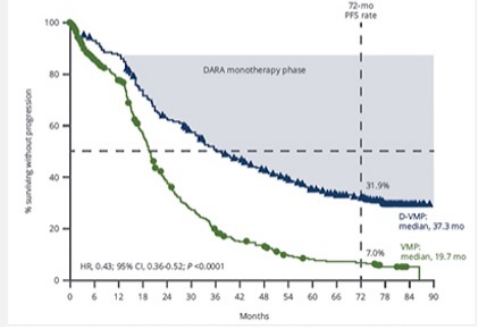
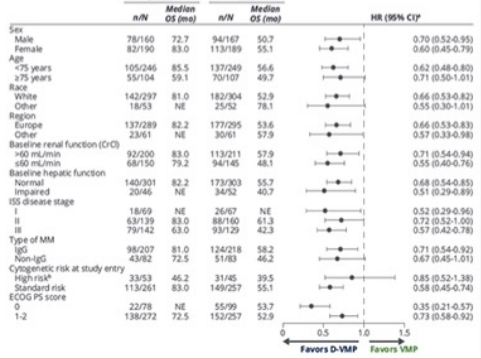
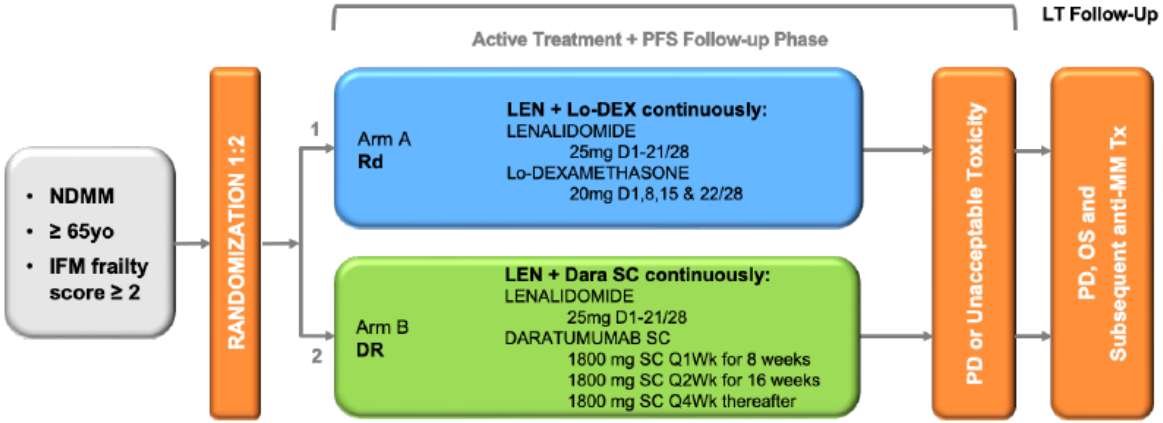


FIGURE 3: Analysis of OS in pre-specified patient subgroups



IFM 2017-03 - Study design



Randomization stratified by ISS (I vs II vs III) and age (<80 vs ≥80)
In Arm B low-dose dex (20mg/week) during Cycle 1 and 2 (with SC dara)

Primary endpoint: PFS

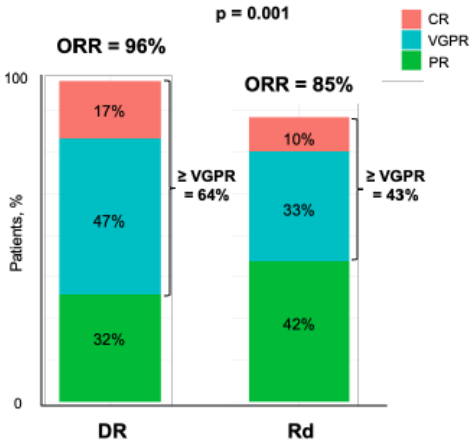
Interim analysis endpoints: 12-months-therapy data cut:

- overall response rate,
- VGPR or better rate,
- MRD rate
- occurrence of grade 3 or more side effects

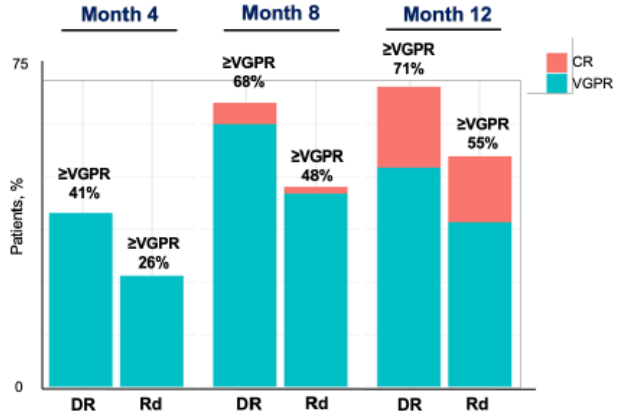
Manier S et al, ab 569 oral communication

IFM 2017-03 – Response and MRD rates

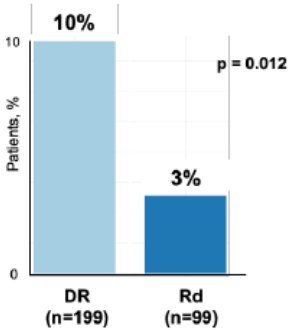
Best response



VGPR or better over time



MRD at 10^{-5} by NGS, in ITT analysis



Best overall response rate was significantly higher with DR and deeper responses were obtained with DR at all time points, including at early time points. DR improved rates of MRD negativity *vs.* Rd

IFM 2017-03 – Most common grade ≥3 AEs

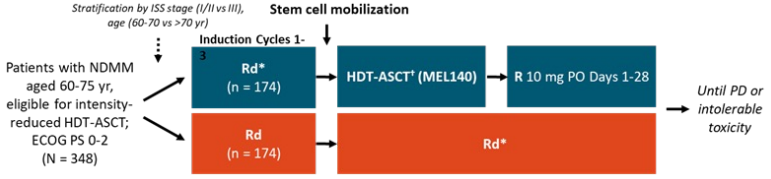
	DR group (n=199) Grade ≥ 3	Rd group (n=94) Grade ≥ 3	P value
All grade ≥ 3 AEs, % (n)	82% (164)	68% (64)	0.010
SAE, % (n)	55% (109)	63% (59)	0.21
Hematologic, % (n)	55% (109)	26% (24)	<0.0001
anemia	11% (21)	2% (2)	0.010
neutropenia	46% (91)	18% (17)	<0.0001
thrombocytopenia	9% (18)	3% (3)	0.089
Infection, % (n)	13% (26)	18% (17)	0.29
non-COVID infections	9% (17)	14% (13)	0.21
pneumonia	3% (5)	7% (7)	0.060
COVID	5% (9)	4% (4)	1

	DR group (n=199)	Rd group (n=94)	P value
Treatment discontinuation for AE, % (n)	14% (27)	16% (15)	0.65

DSMM XIII trial

DSMM XIII: Study Design

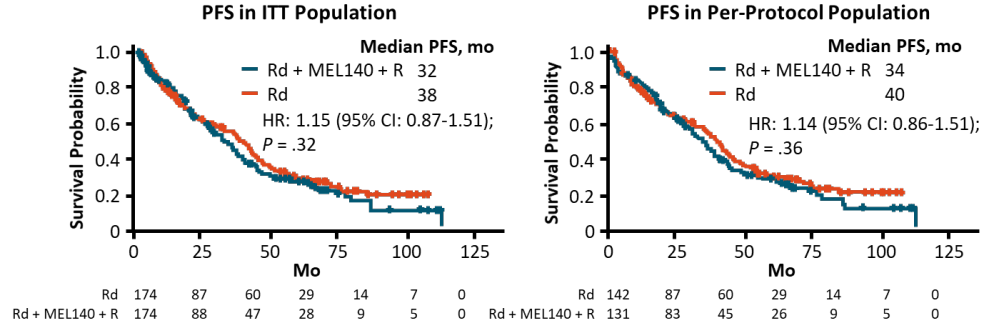
- Randomized, open-label phase III trial



- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, response, safety, impact of prognostic factors
- Median follow-up: 68 months
- Median cycles of maintenance R: 12 in ASCT arm, Median cycles of Rd: 16 in continuous arm

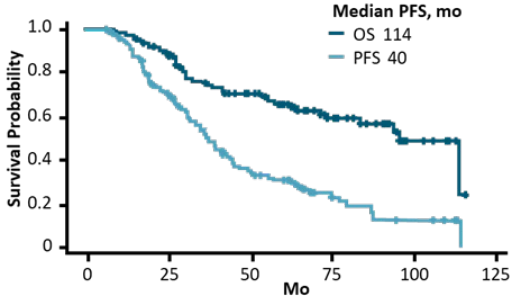
Straka. ASH 2022. Abstr 116.

DSMM XIII: PFS (Primary Endpoint)



DSMM XIII: PFS and OS in Transplant Recipients

- 115 (66%) patients in the transplant arm received a transplant during study treatment (38 single transplant; 77 double transplant)



Straka. ASH 2022. Abstr 116. Reproduced with permission.

Straka. ASH 2022. Abstr 116. Reproduced with permission.

Bringhen S et al, ASH 2022, Abstract 751

REAL-MM: Study design

Newly diagnosed MM with symptomatic disease and ineligible for transplant

231 patients
Randomization
1:1

VMP (N=114)
Bortezomib 1.3 mg/m² D1,4,8,11,22,25,29,32 cycle 1-4; 1.3 mg/m² D1,8,22,29 cycle 5-9
Melphalan 9 mg/m² D1-4
Prednisone 60 mg/ m² D1,8,15,22
(n=114)

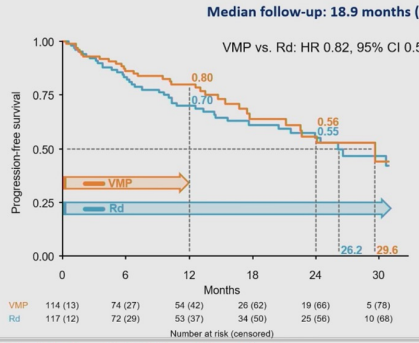
Up to nine 42-day cycles

Rd (N=117)
Lenalidomide 25 mg D1-21
Dexamethasone 40 mg/day* D1,8,15,22
(n=117)
* 20 mg/day D1,8,15,22 for patients ≥75 years

Until PD, death, or unacceptable toxicity

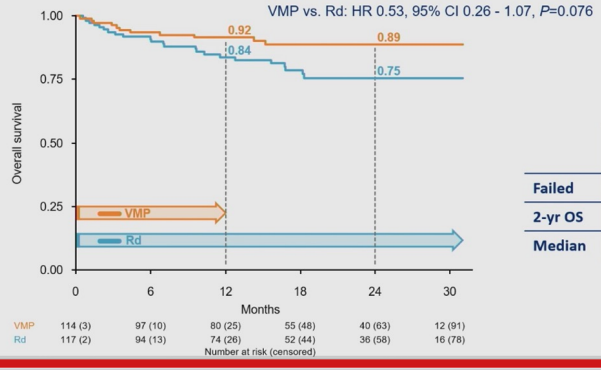
Stratification for:
- Cytogenetic risk
- Frailty

REAL-MM: Progression-free survival



	VMP n=114	Rd n=117
Failed	n=31	n=40
2-yr PFS	56%	55%
Median	29.6 mo	26.2 mo

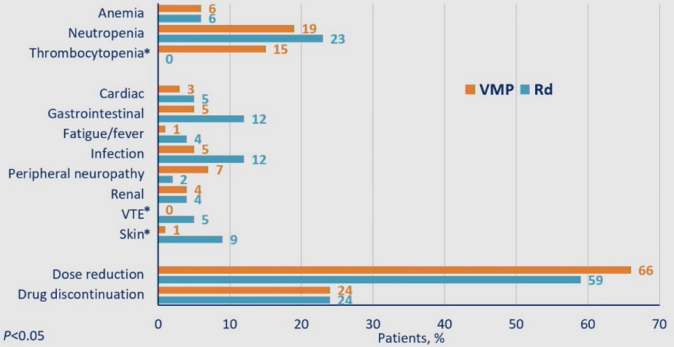
REAL-MM: Overall survival



	VMP n=114	Rd n=117
Failed	12	23
2-yr OS	89%	75%
Median	NR	NR

REAL-MM: Safety

Grade 3-4 adverse events and dose modification



*Significant P<0.05

REAL-MM: Progression-free survival