2021

# Progetto Ematologia Romagna

# La profondità della risposta

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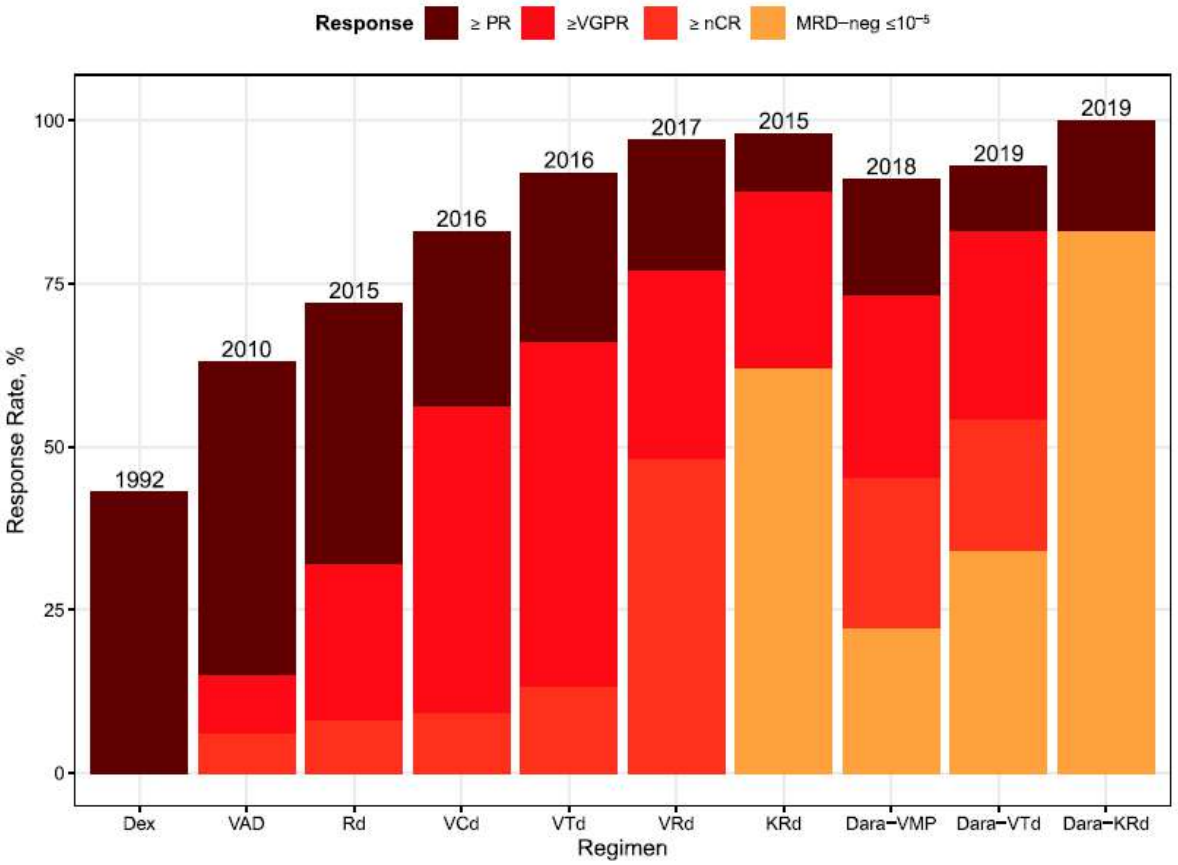
**Istituto di Ematologia "Seràgnoli"**

# Disclosures

Honoraria: Janssen, Amgen, Sanofi, GlaxoSmithKline

# Impact of modern therapies on response rates




- Increasing response rates with novel therapies
- Nevertheless a large majority of pts in remission eventually relapse

- Persistence of residual tumor cells **(MRD)**, clinically meaningful, undetectable by conventional serological/morphology-based tests, requiring additional sensitive methods

Diamond BT et al., Blood Reviews 46 (2021) 100732


# Beyond conventional CR
## MRD detection and novel response criteria

## International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

*Lancet Oncol* 2016; 17: e328–46

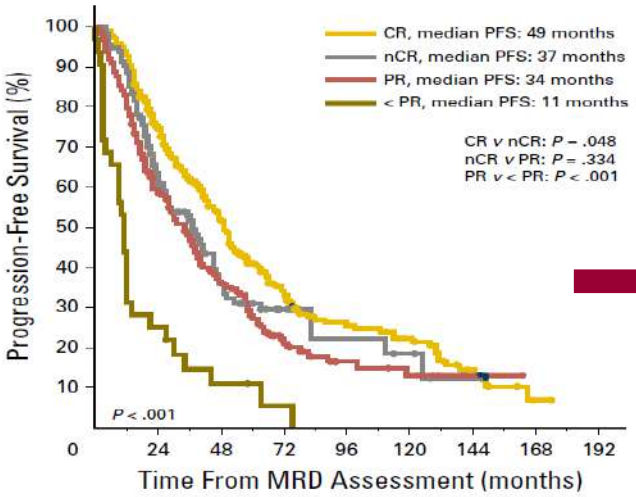
*Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efstathios Kastritis, Mario Boccadoro, Robert Orlowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, Elena Zamagni, Kazuyuki Shimizu, Sundar Jagannath, Hans E Johnsen, Evangelos Terpos, Anthony Reiman, Robert A Kyle, Pieter Sonneveld, Paul G Richardson, Philip McCarthy, Heinz Ludwig, Wenming Chen, Michele Cavo, Jean-Luc Harousseau, Suzanne Lentzsch, Jens Hillengass, Antonio Palumbo, Alberto Orfao, S Vincent Rajkumar, Jesus San Miguel, Herve Avet-Loiseau*

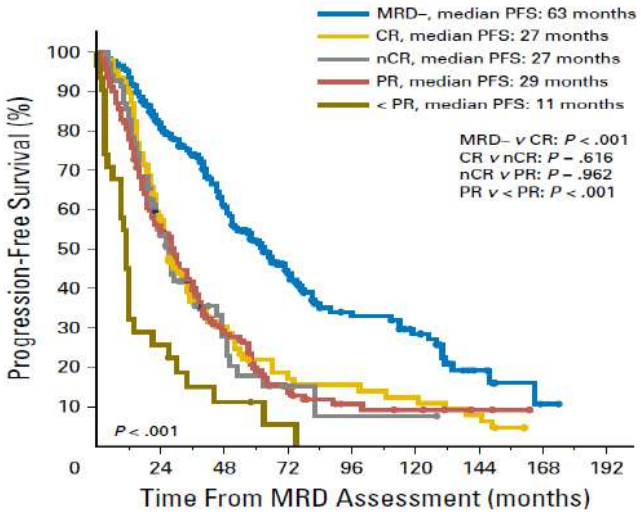
| | Response criteria* |
|---|---|
| **IMWG MRD criteria (requires a complete response as defined below)** | |
| Sustained MRD-negative | MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)† |
| Flow MRD-negative | Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher |
| Sequencing MRD-negative | Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells§ or higher |
| Imaging plus MRD-negative | MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶ |
| **Standard IMWG response criteria‖** | |
| Stringent complete response | Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)†† |
| Complete response | Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates |

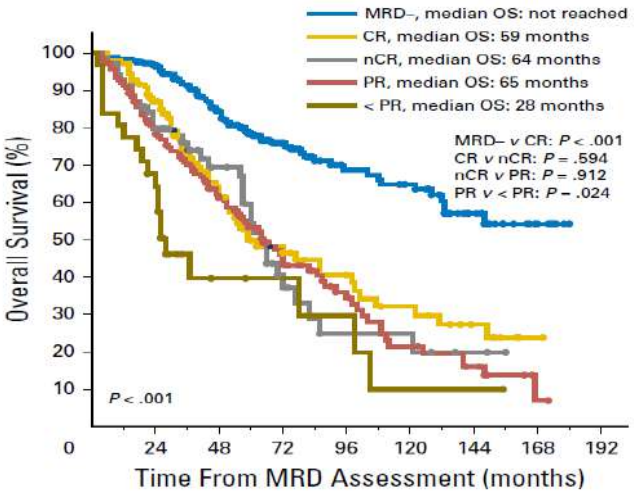
# Depth of response and survival: MRD surpasses CR

## Pooled analysis of 3 PETHEMA/GEM clinical trials

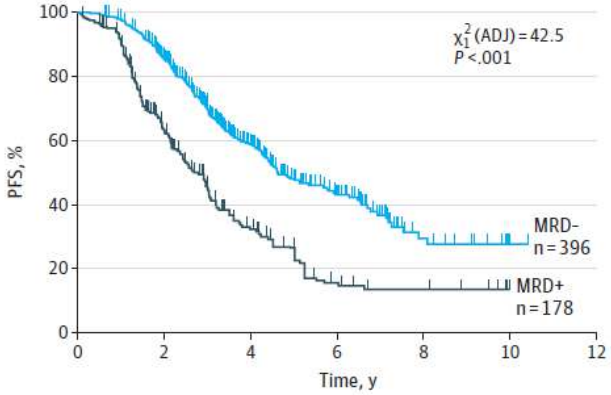
GEM2000 - GEM2005MENOS65 - GEM2010MAS65

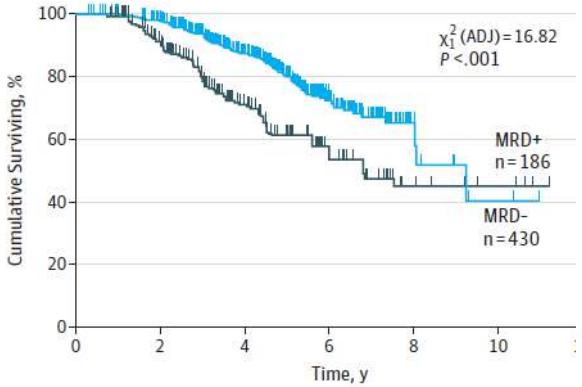



## Meta-analysis of MRD studies (CR patients)



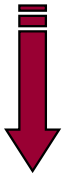



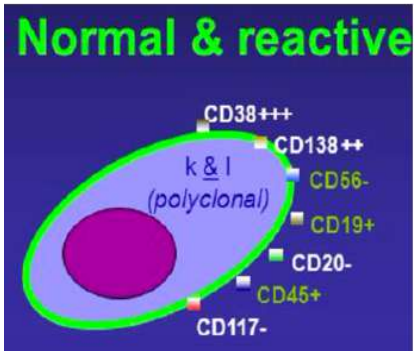

Lahuerta JJ, et al. JCO 2017;35(25):2900-10
Munshi et al. *JAMA Oncol*. 2017;3(1):28-35


# Detecting MRD in BM

## Cellular-based approach: study of aberrant phenotype

**Multiparameter Flow Cytometry (MFC)**

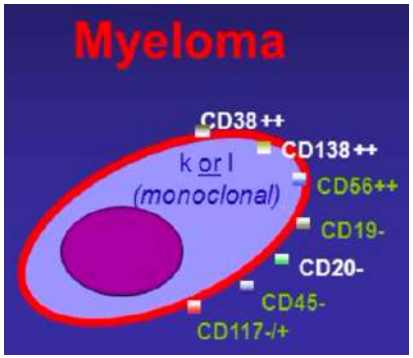





CD38, CD138
CD45, CD56

clg κ/λ chains

CD19, CD20, CD81,
CD27, CD117, CD200

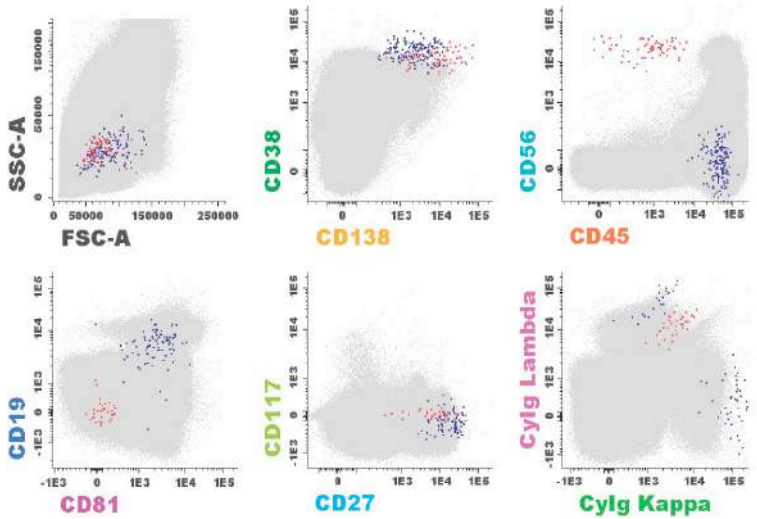



**Next Generation Flow (NGF)**

EuroFlow

**8-color, 2-tube panel**
(10-color, 1-tube assay, US model)

Simultaneous analysis of up
to 10 million cells
Sensitivity of 2 x $10^{-6}$



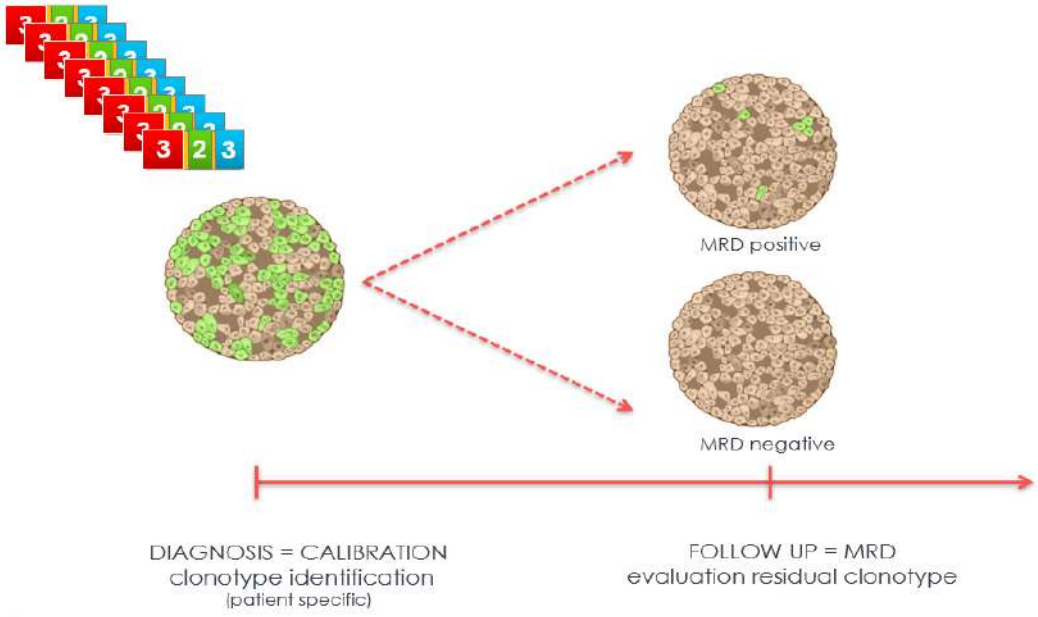

Flores-Montero et al, Cytometry Part B 2016
Flores-Montero et al, Leukemia (2017) 31, 2094–2103

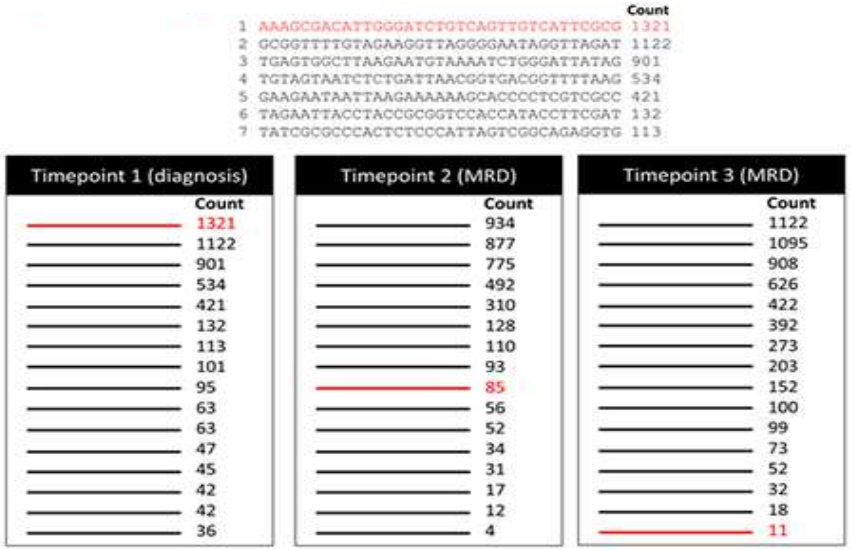
# Detecting MRD in BM

## Molecular-based approach: study of a tumor-specific marker

ASO-PCR, ddPCR → Next Generation Sequencing (NGS)

Clonal V(D)J rearrangement as a molecular marker of MM for one patient



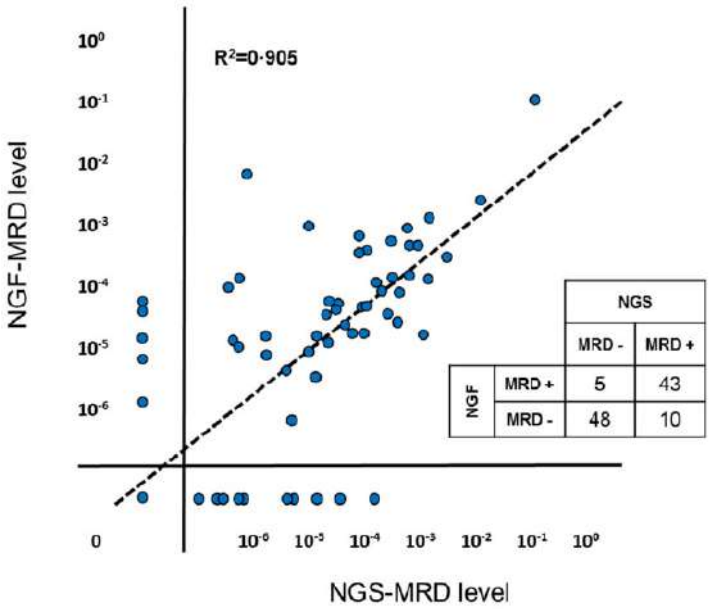

# MFC/NGF and NGS comparison

| | NGF | NGS |
|---|---|---|
| **Applicability** | Almost 100% of pts | 90-92% |
| **Availability** | Wide | Limited<br>(1 platform FDA approved, commercial; others ongoing) |
| **Sensitivity** | $10^{-5}$ / $10^{-6}$ | $10^{-5}$ / $10^{-6}$ |
| **Quantitative** | Yes | Yes |
| **Nr of cells required** | 20 x $10^{6}$ | 2-3 x $10^{6}$ |
| **Processing requirements** | Fresh sample (within 24-36 h) | Fresh or stored sample |
| **Baseline diagnostic sample** | Not needed | Mandatory |
| **Standardization** | Yes (EuroFlow Consortium) | Yes (Adaptive Biotechnologies) |
| **Turnaround** | 3-4 hours | 1-2 weeks |
| **Complexity** | Flow cytometry skills required (automated software available) | Bioinformatic support required |
| **Cost** | + | ++ |

# MFC/NGF and NGS comparison

## GEM2012 trial

MRD evaluated 3 mos after ASCT

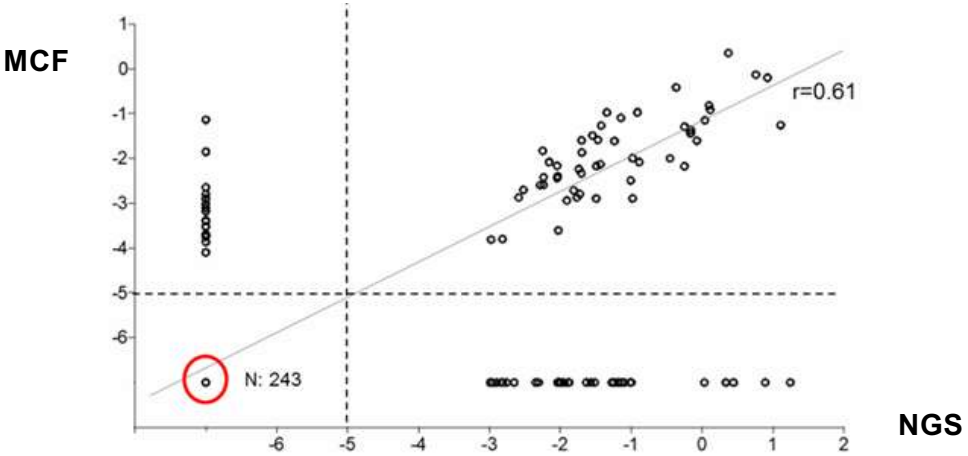



| | | NGS | |
|---|---|---|---|
| | | MRD - | MRD + |
| NGF | MRD + | 5 | 43 |
| | MRD - | 48 | 10 |

91/106 (85.8%) were concordant between techniques
Only 15/106 cases (14.2%) were discordant

Medina A, et al. Blood Cancer J. 2020;10(10):108

## FORTE trial



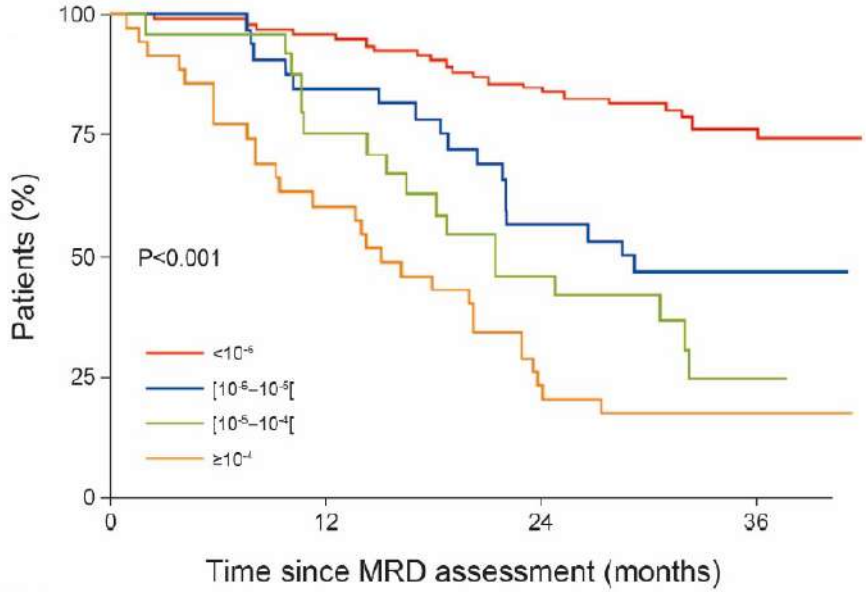

| | | | NGS | | |
|---|---|---|---|---|---|
| MRD⁻ and ≥CR, n (%) $10^{-5}$ | Flow cytometry | Total | Positive | Negative | Observed agreement |
| MRD status, n (%) | Positive | 56 | 46 (82) | 10 (18) | 86% |
| | Negative | 279 | 36 (13) | 243 (87) | |
| | | | NGS | | |
| MRD⁻ and ≥CR, n (%) $10^{-6}$ | NGF | Total | positive | Negative | Observed agreement |
| MRD status, n (%) | Positive | 21 | 19 (90) | 2 (10) | 78% |
| | Negative | 35 | 10 (28) | 25 (72) | |

Oliva et al. ASCO metting 2020, abstract #8533

# MRD sensitivity: the deeper the better…

## IFM 2009 trial

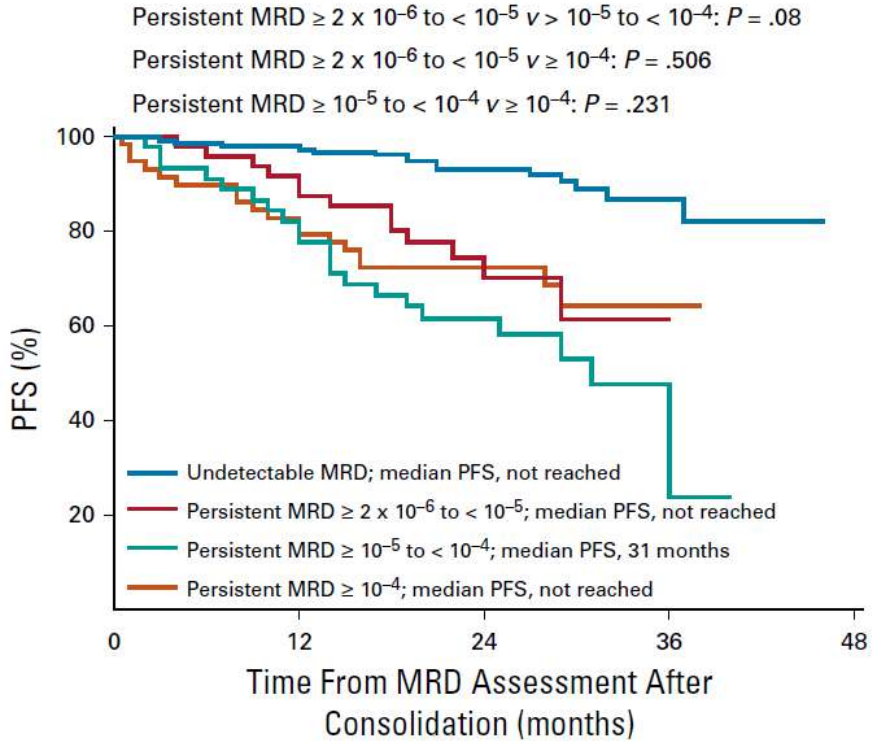
PFS according to MRD level after 12 mos of maintenance in pts ≥ VGPR




| No. at Risk | | | | |
|---|---|---|---|---|
| <10⁻⁶ | 92 | 88 | 77 | 42 |
| [10⁻⁶–10⁻⁵[ | 32 | 27 | 18 | 11 |
| [10⁻⁵–10⁻⁴[ | 24 | 18 | 11 | 4 |
| ≥10⁻⁴ | 35 | 21 | 8 | 3 |

Perrot et al. Blood 2018;132(23):2456-64

## PETHEMA/GEM2012MENOS65 trial



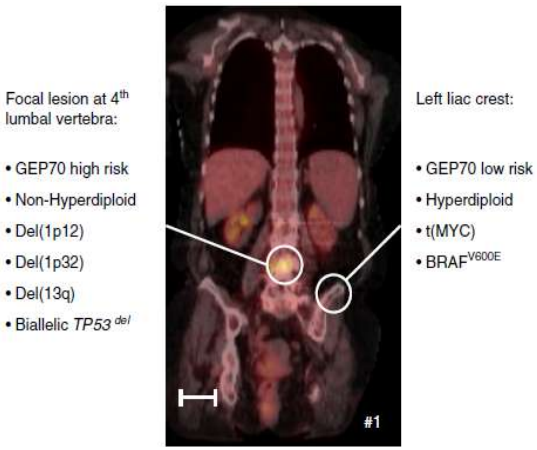

All pairwise comparisons MRDneg vs pos significant (P<.001)

No statistically significant differences in PFS of pts with pos MRD in all the logarithmic range

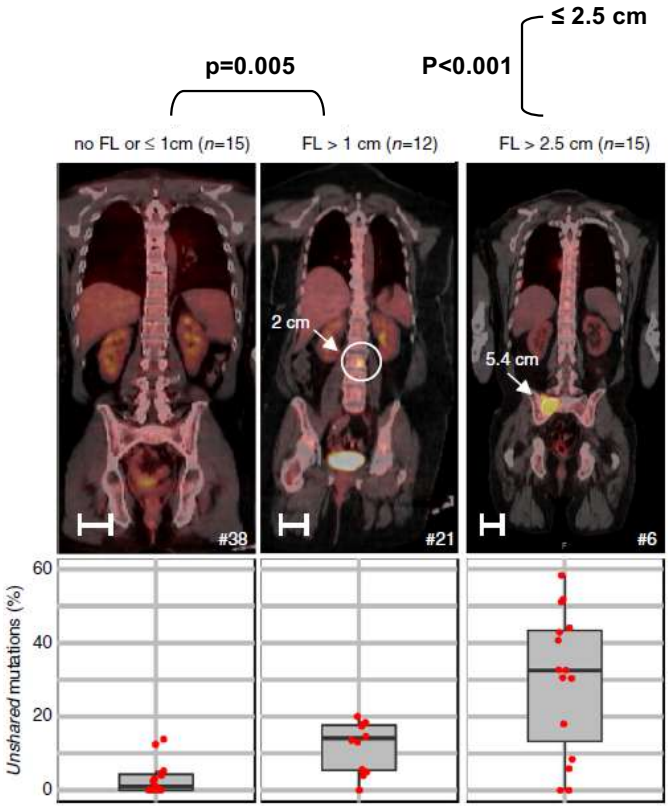
Paiva et al. J Clin Oncol 2019;38:784-92

# The impact of spatial heterogeneity on MRD diagnostic

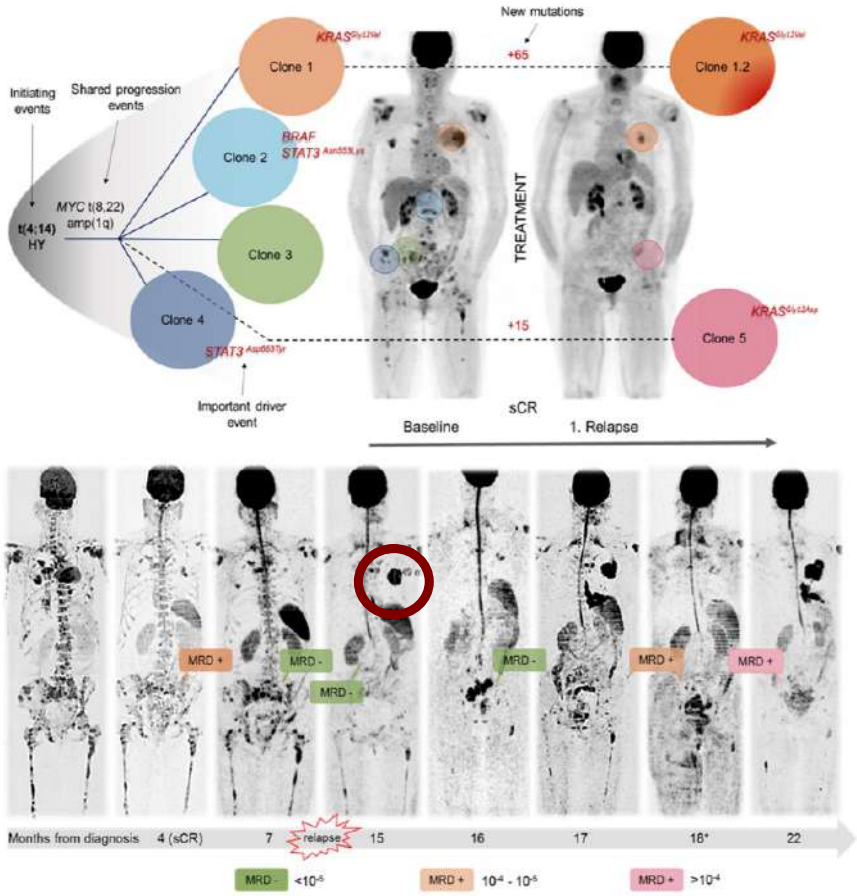
## Discrepancy between BM MRD and imaging




Different GEP profile between BM and FL




Growing heterogeneity with growing size of the lesions



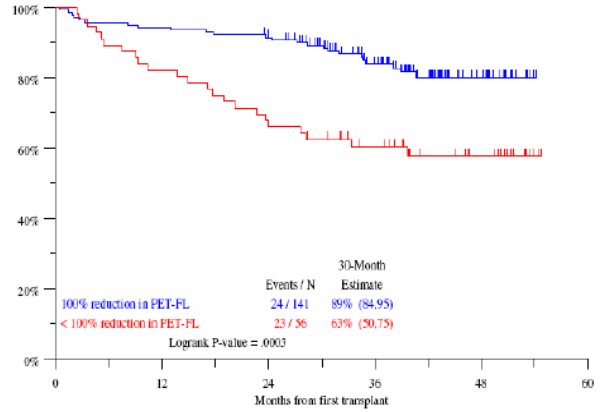

Imaging relapse while maintaining MRD negativity


Rasche L et al. Nature Comm 2017
Rasche L et al. Leukemia 2019

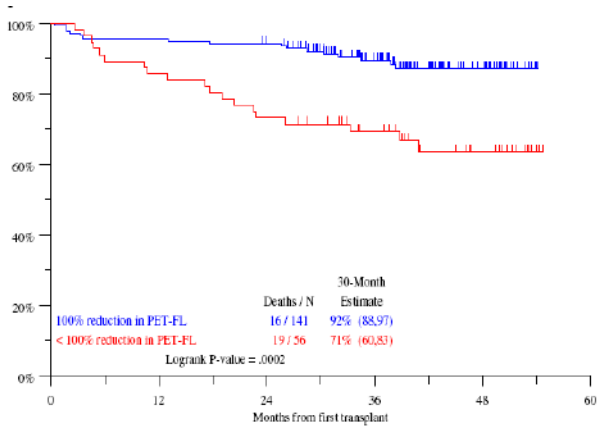
# 2021 FDG PET/CT for evaluation of metabolic response and MRD

## Before ASCT

PFS

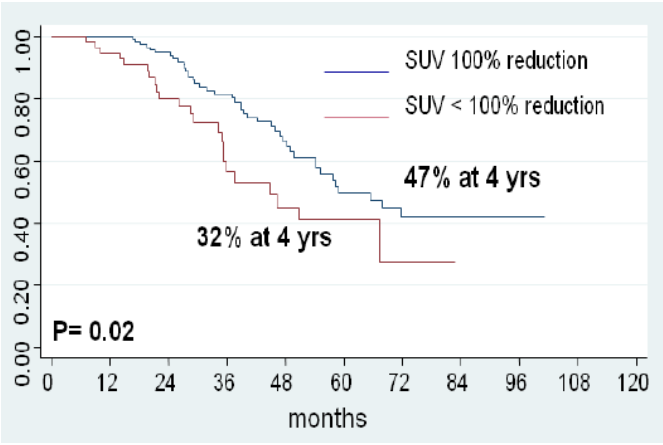


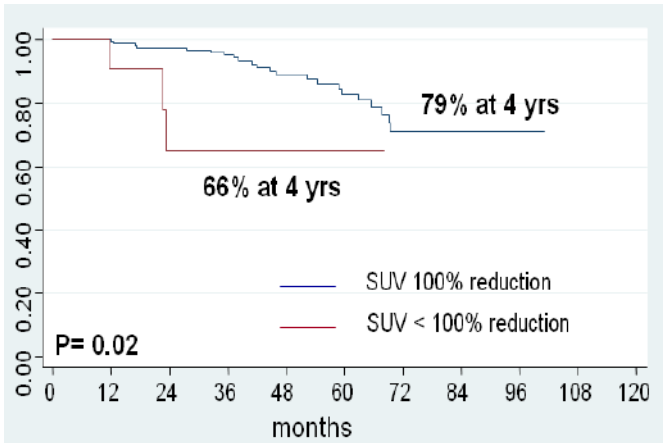

OS




Bartel et al, Blood 2009 114: 2068-76

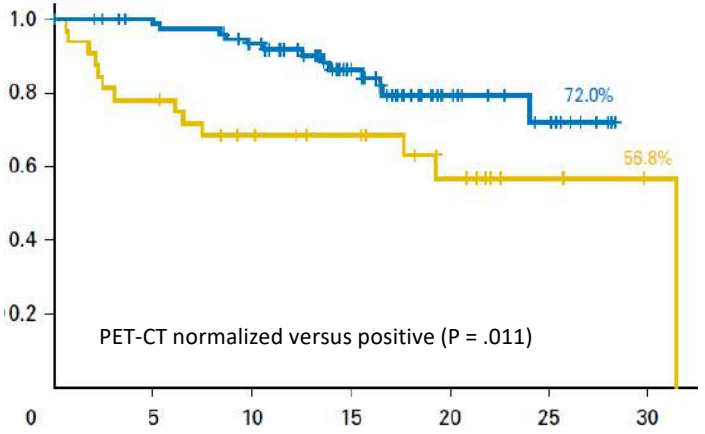
## After ASCT

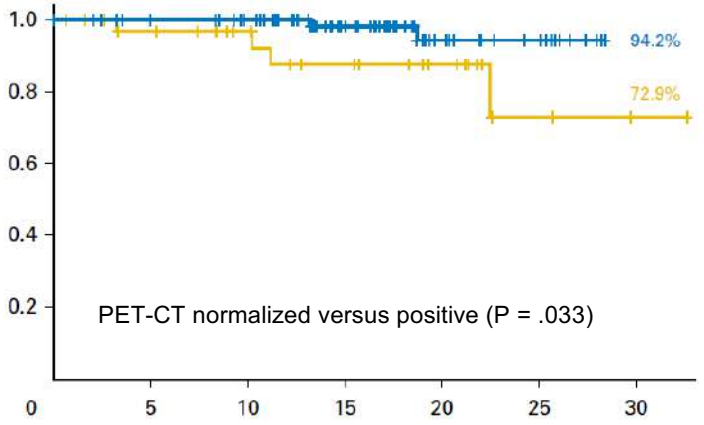



Zamagni et al. Blood. 2011;118:5989-95

## Before maintenance



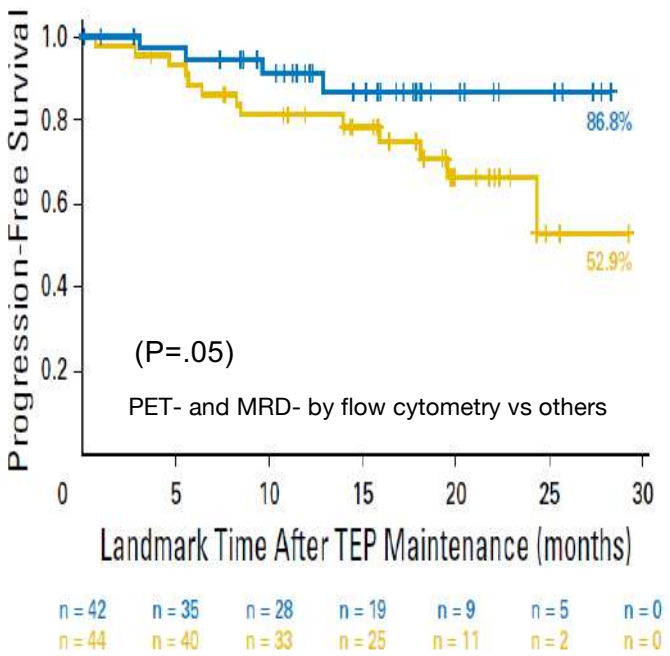




Moreau, et al. JCO2017;35(25):2911-18

# Complementarity between NGF/NGS and PET/CT

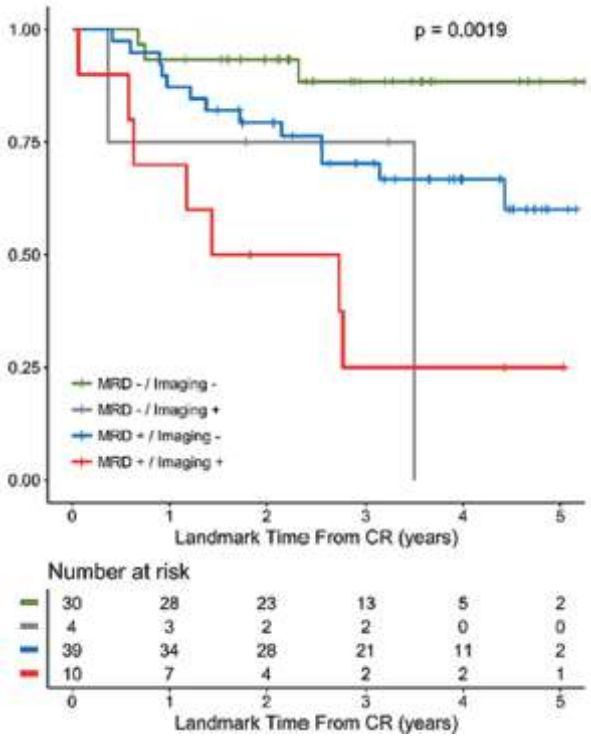
## Patients with double-negative MRD have better outcome

### IMAJEM Study



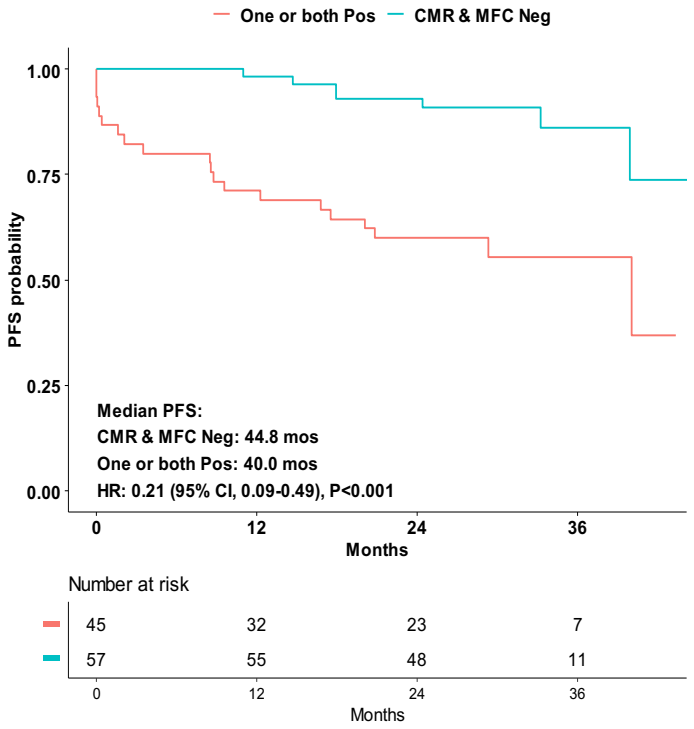

Moreau, et al. JCO2017;35(25):2911-18

### University of Arkansas




Rasche et al. Leukemia. 2019;33:1713-22

### FORTE trial




Zamagni et al. ASH 2020

2021

# Reproducibility and harmonization of data

Leukemia (2021) 35:18–30
https://doi.org/10.1038/s41375-020-01012-4

REVIEW ARTICLE

Multiple myeloma gammopathies

## International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials

Luciano J. Costa[1] · Benjamin A. Derman[2] · Susan Bal[1] · Surbhi Sidana[3] · Saurabh Chhabra[4] · Rebecca Silbermann[5] · Jing C. Ye[6] · Gordon Cook[7] · Robert F. Cornell[8] · Sarah A. Holstein[9] · Qian Shi[10] · James Omel[11] · Natalie S. Callander[12] · Wee Joo Chng[13] · Vania Hungria[14] · Angelo Maiolino[15] · Edward Stadtmauer[16] · Sergio Giralt[17] · Marcelo Pasquini[4] · Andrzej J. Jakubowiak[2] · Gareth J. Morgan[18] · Amrita Krishnan[19] · Graham H. Jackson[20] · Mohamad Mohty[21] · Maria Victoria Mateos[22] · Meletious A. Dimopoulos[23] · Thierry Facon[24] · Andrew Spencer[25] · Jesus San Miguel[26] · Parameswaran Hari[4] Saad Z. Usmani[27] · Salomon Manier[28] · Phillip McCarthy[29] · Shaji Kumar[30] · Francesca Gay[31] · Bruno Paiva

- to improve the quality and reproducibility of MRD dectection in future trials and ensure uniform reporting of MRD results → better inter-trials comparison
- to validate MRD as a survival surrogate endpoint for accelerating drug approval

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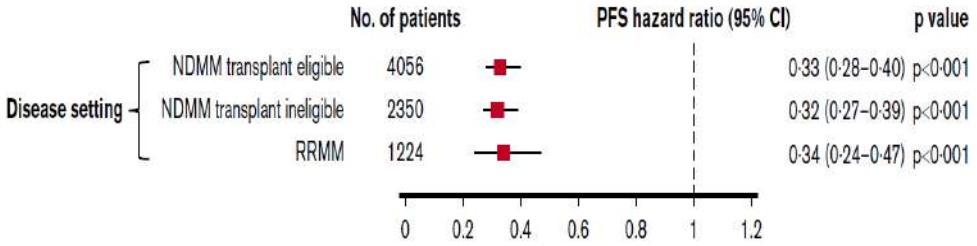
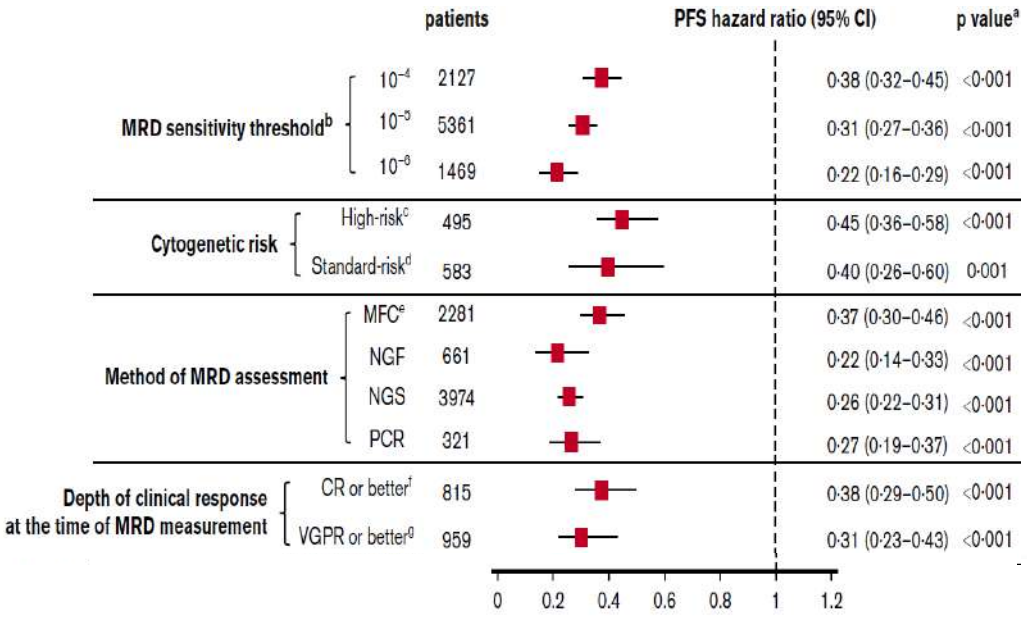
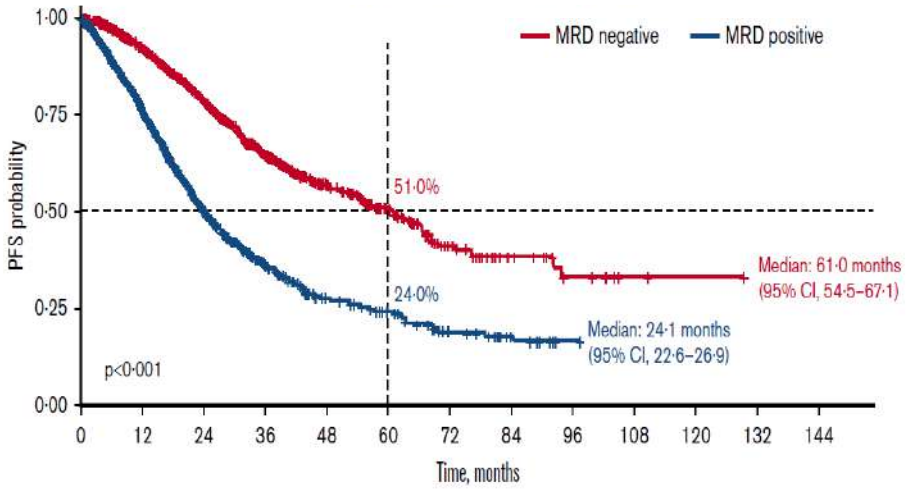
# MRD best predictor of outcome

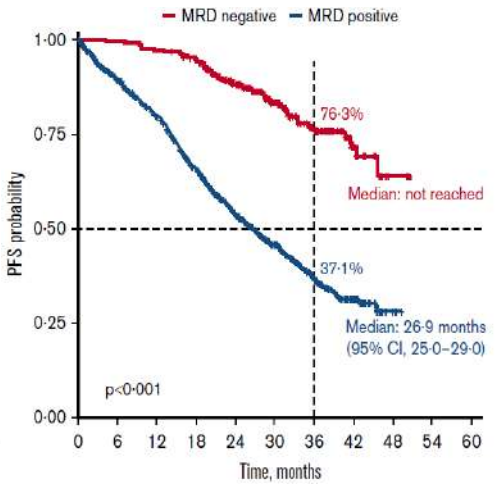
## Meta-analysis of MRD studies (44, >8000 pts)

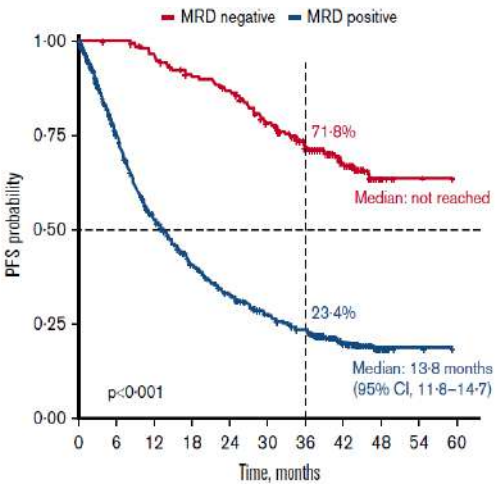
Munshi et al. Blood Adv. 2020 Dec 8;4(23):5988-5999



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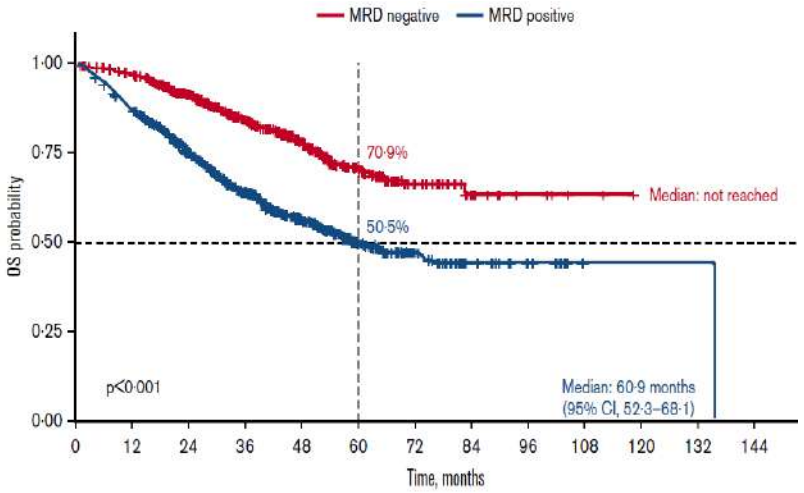
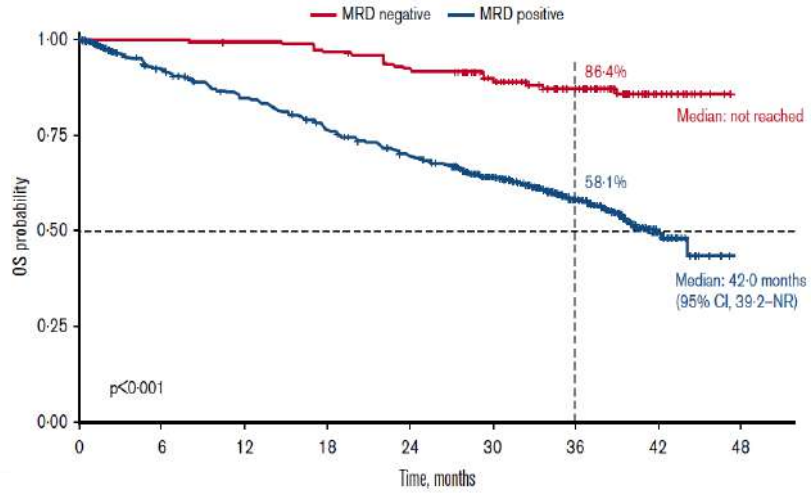
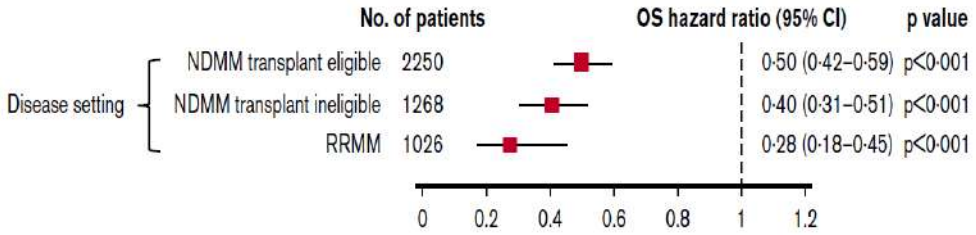
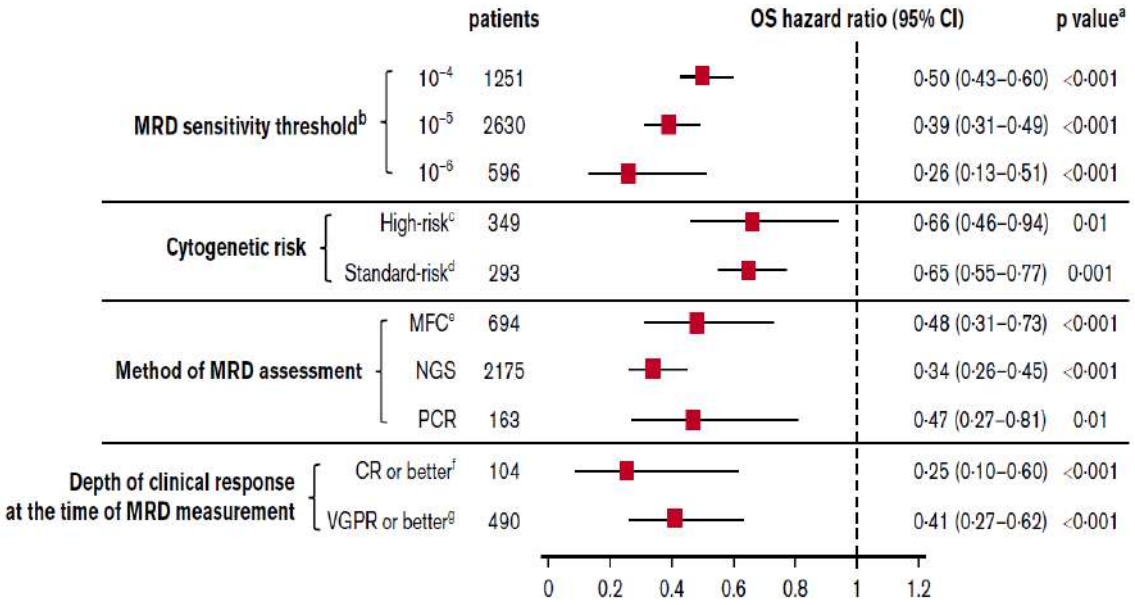
# MRD best predictor of outcome



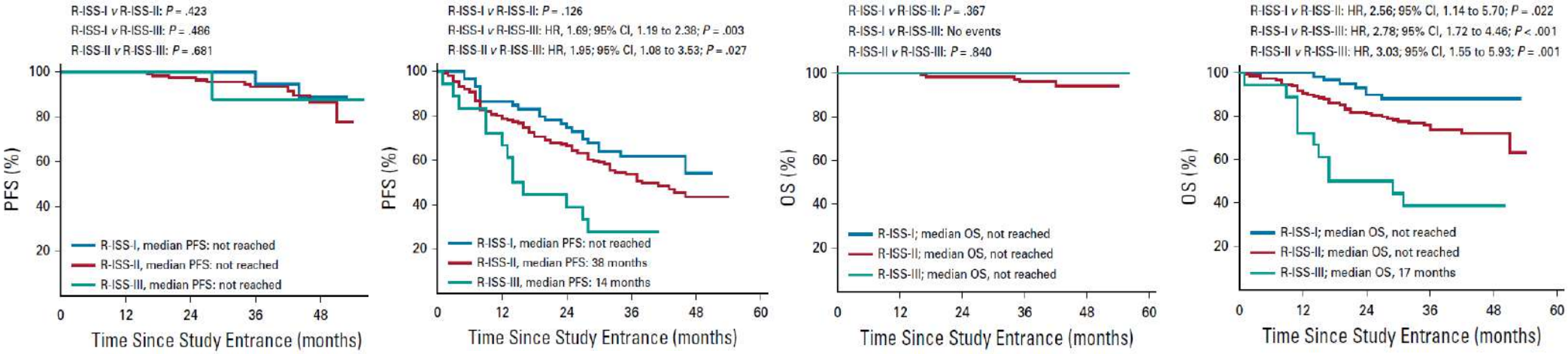




Munshi et al. Blood Adv. 2020 Dec 8;4(23):5988-5999

# MRD and HIGH RISK patients

## Modulating pts' risk at diagnosis according to depth of response after treatment

## Impact on PFS/OS of R-ISS in pts with undetectable vs persistent MRD

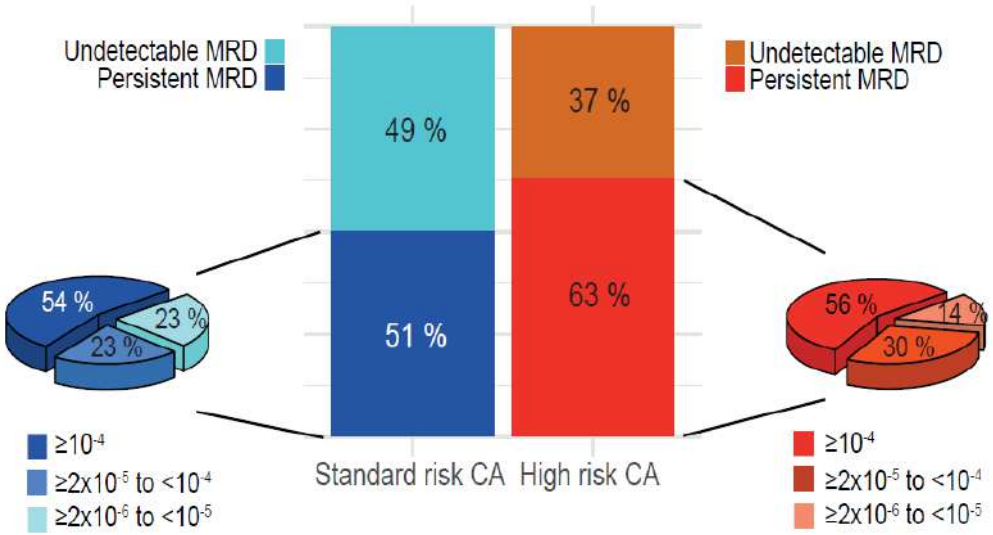



**patients with adverse prognosis shift into a favorable one upon achieving deep responses to treatment**

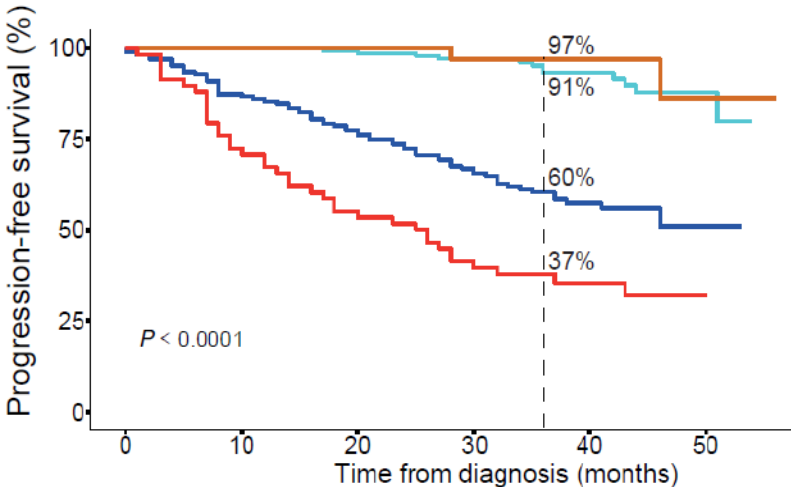
Paiva et al. J Clin Oncol 2019;38:784-92

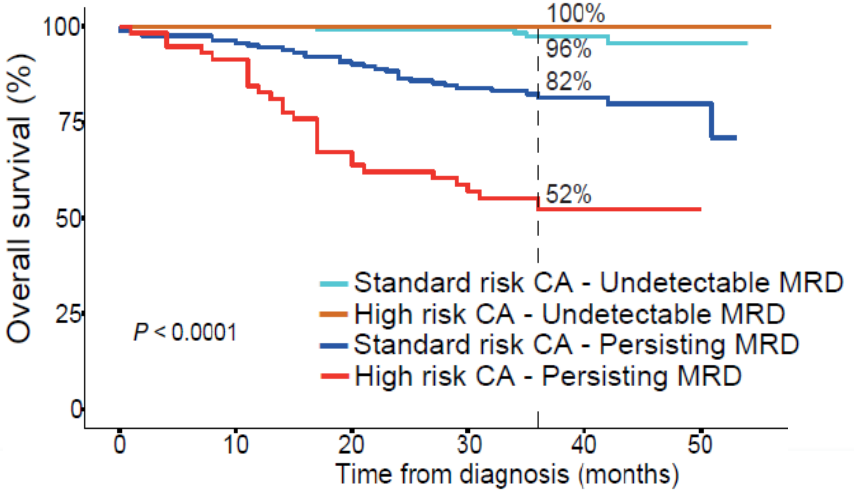
# MRD and HIGH RISK patients

## MRD status according to cytogenetic risk in the PETHEMA/GEM2012MENOS65 clinical trial




**Undetectable MRD overcomes the dismal survival of MM patients with high risk CA**

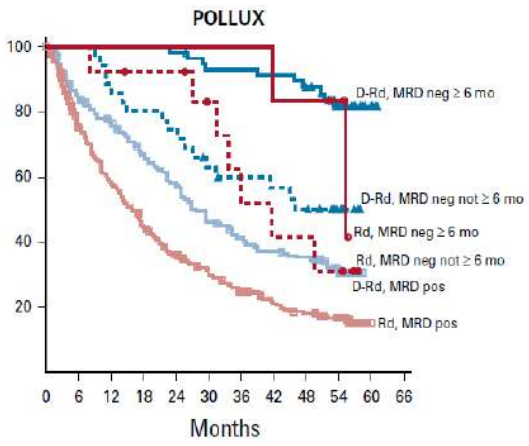


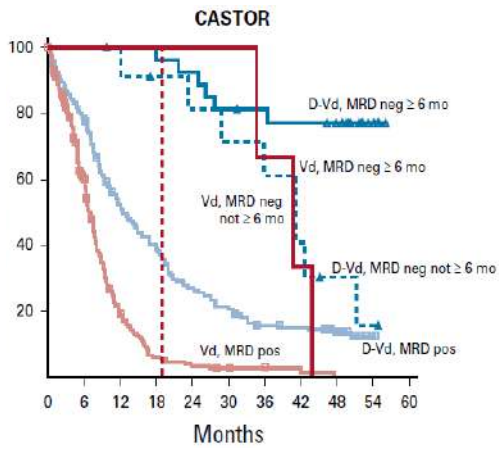



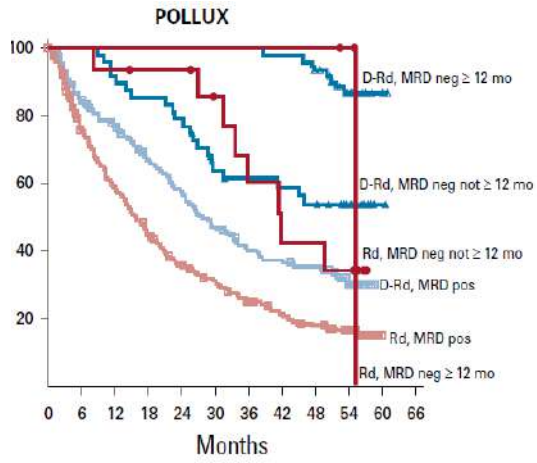

Goicoechea et al. Blood 2020

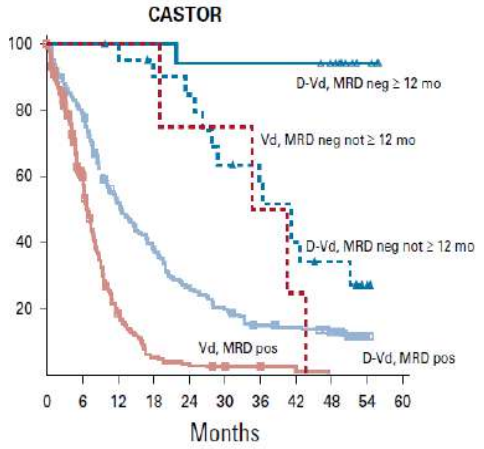

# Durability of response: sustained MRD negativity

| | POLLUX | | | CASTOR | | |
|---|---|---|---|---|---|---|
| MRD Negativity ($10^{-5}$) | D-Rd (n = 286) | Rd (n = 283) | *P*[a] | D-Vd (n = 251) | Vd (n = 247) | *P*[a] |
| ITT | 93 (32.5%) | 19 (6.7%) | < .000001 | 38 (15.1%) | 4 (1.6%) | < .000001 |
| ≥ 6 months sustained[b] | 58 (20.3%) | 6 (2.1%) | < .0001 | 26 (10.4%) | 3 (1.2%) | < .0001 |
| ≥ 12 months sustained[c] | 46 (16.1%) | 4 (1.4%) | < .0001 | 17 (6.8%) | 0 (0.0%) | < .0001 |




**Achievement of sustained MRD negativity consistently demonstrated longer PFS for DARA-containing regimens vs those without sustained MRD negativity in the ITT population**

Avet-Loiseau et al. J Clin Oncol 2021;39:1139-1149

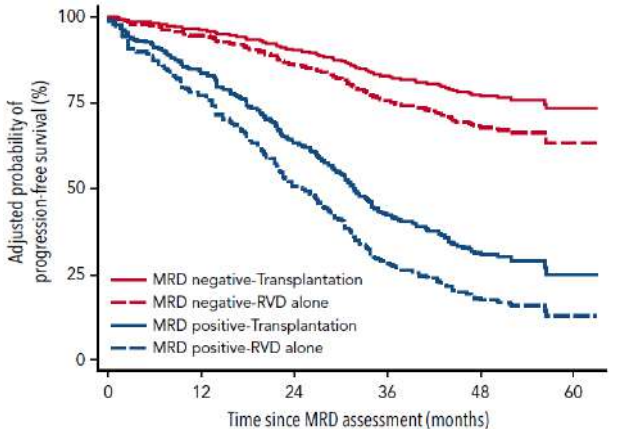
# MRD evaluation in clinical trials

## IFM 2009

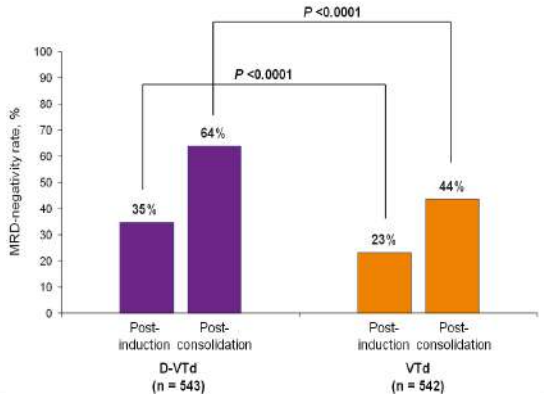
Attal NEJM 2017
Perrot Blood 2018

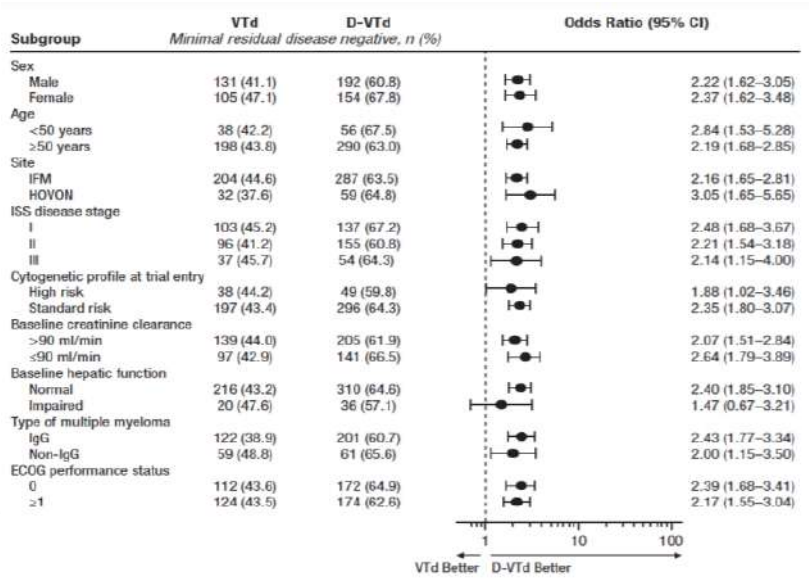
### Response

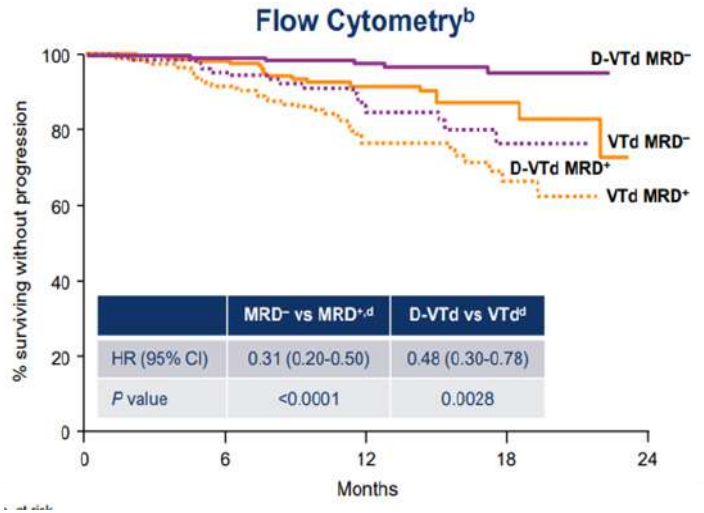
| Outcome | RVD-Alone Group (N=350) | Transplantation Group (N=350) | Adjusted P Value† |
|---|---|---|---|
| Best response during the study — no. (%) | | | 0.02 |
| Complete response | 169 (48) | 205 (59) | |
| Very good partial response | 101 (29) | 102 (29) | |
| Partial response | 70 (20) | 37 (11) | |
| Stable disease | 10 (3) | 6 (2) | |
| Complete response — no. (%) | 169 (48) | 205 (59) | 0.03 |
| Complete response or very good partial response — no. (%) | 270 (77) | 307 (88) | 0.001 |
| Minimal residual disease not detected during the study — no./ total no. with complete or very good partial response (%)‡ | 171/265 (65) | 220/278 (79) | <0.001 |




## CASSIOPEIA



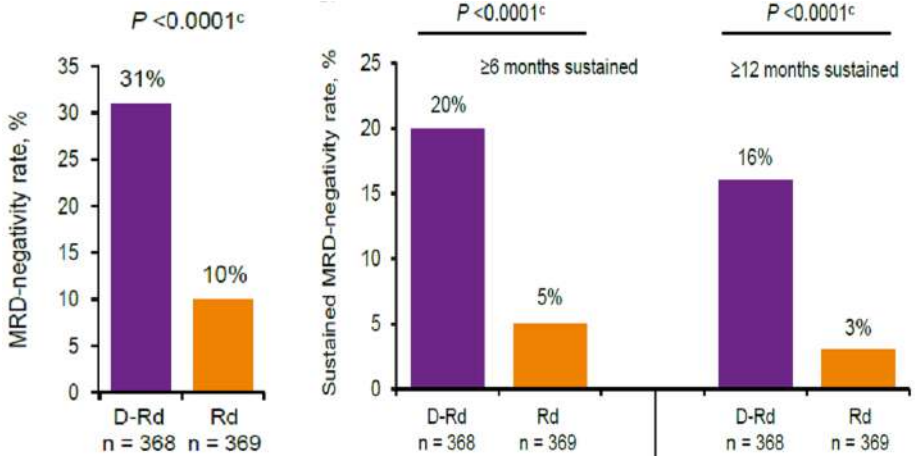



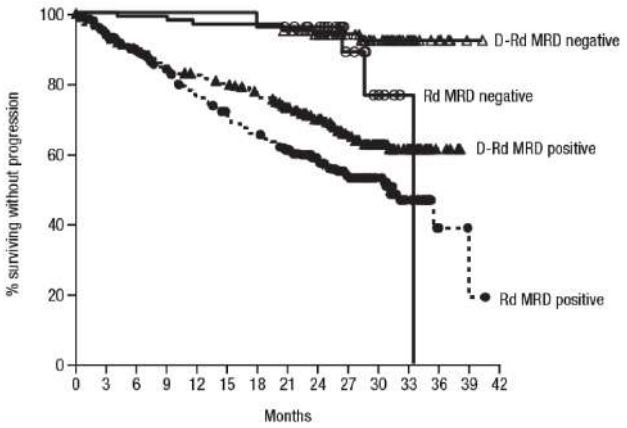

Moreau P, Lancet 2019 / Avet-Loiseau EHA 2019

# MRD evaluation in clinical trials

## MAIA

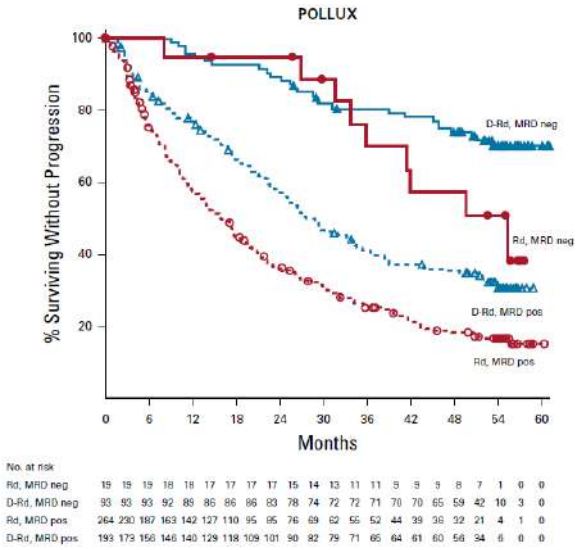
Facon et al. NEJM 2019
Kumar et al. ASH 2020

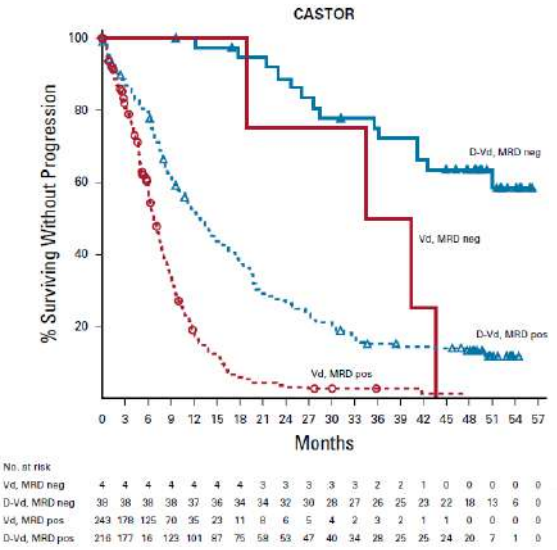



## CASTOR + POLLUX

| | POLLUX | | CASTOR | |
|---|---|---|---|---|
| | D-Rd N = 286 (ITT) | Rd N = 283 (ITT) | D-Vd N = 251 (ITT) | Vd N = 247 (ITT) |
| **MRD negative ($10^{-5}$) at ≥1 time point** | n = 93 | n = 19 | n = 38 | n = 4 |
| Median (95% CI) PFS, months | NR (NE-NE) | 55.3 (33.6-NE) | NR (41.3-NE) | 37.6 (19.0-43.7) |
| Hazard ratio (95% CI)[a] | 0.53 (0.25-1.12) | | 0.27 (0.09-0.83) | |
| *P*-value[b] | *P* = 0.0923 | | *P* = 0.0138 | |
| **MRD positive** | n = 193 | n = 264 | n = 213 | n = 243 |
| Median (95% CI) PFS, months | 27.5 (23.9-34.1) | 15.7 (12.9-18.5) | 12.4 (10.3-15.8) | 6.8 (6.2-7.6) |
| Hazard ratio (95% CI)[a] | 0.61 (0.49-0.76) | | 0.41 (0.33-0.51) | |
| *P*-value[b] | *P* <0.0001 | | *P* <0.0001 | |




Avet-Loiseau et al. J Clin Oncol 2021;39:1139-1149

# MRD status- adapted therapies: MASTER trial

## MRD response-adapted Dara-KRd sequential therapy in transplant-eligible NDMM patients

Key inclusion criteria
- NDMM*
- ECOG PS 0-2
- CrCl ≥ 40 mL/min

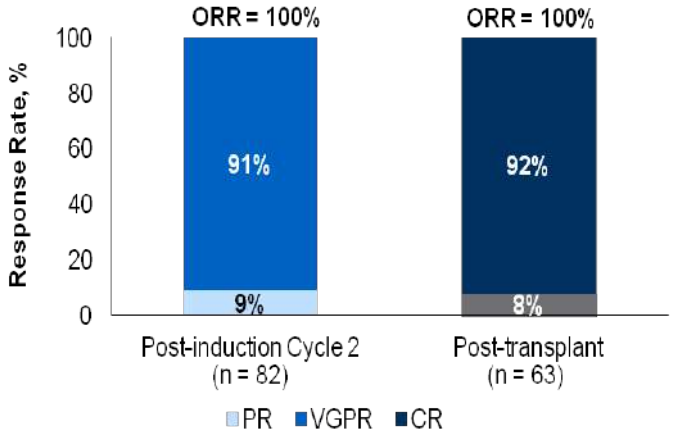
→ **Induction** Dara-KRd x 4 cycles → **AHCT** → **Consolidation** Dara-KRd x 4 cycles → **Consolidation** Dara-KRd x 4 cycles → ***Lenalidomide maintenance***

Dara-KRd dosing: D 16 mg/m² on days 1,8,15,22 (days 1,15 of Cycles 3-6; Day 1 Cycle > 6); K 56 mg/m² days 1,8,15; R 25 mg days 1-21; d 40 mg PO Days 1,8,15,22. *1 VCD cycle permitted.

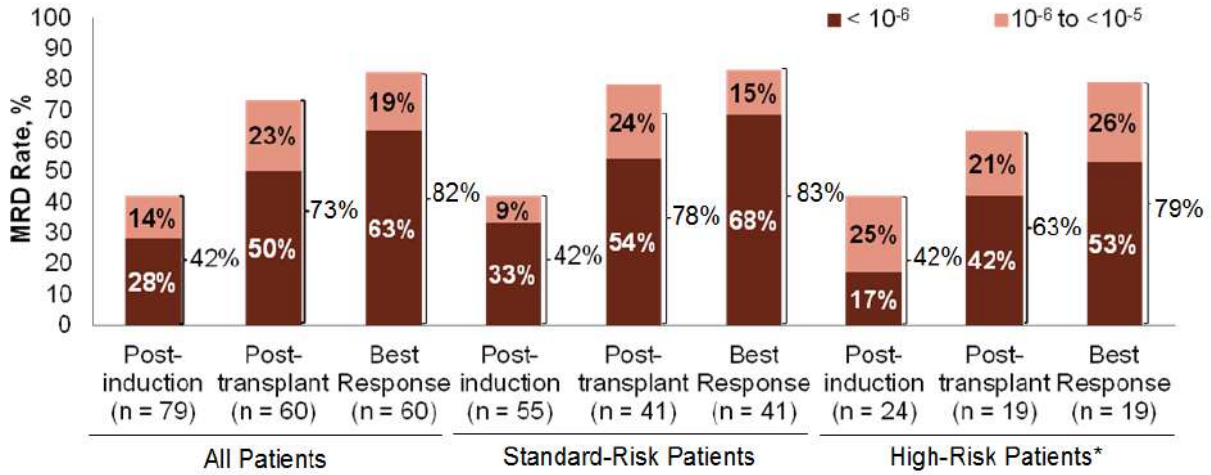
**Primary Endpoint:** MRD-negative remission

**MRD assessment after each treatment phase; pts with confirmed (2nd) MRD-negative status (< $10^{-5}$) entered treatment-free observation phase with MRD assessment at 24 and 72 wks after EOT**

### Response rates




### MRD rates

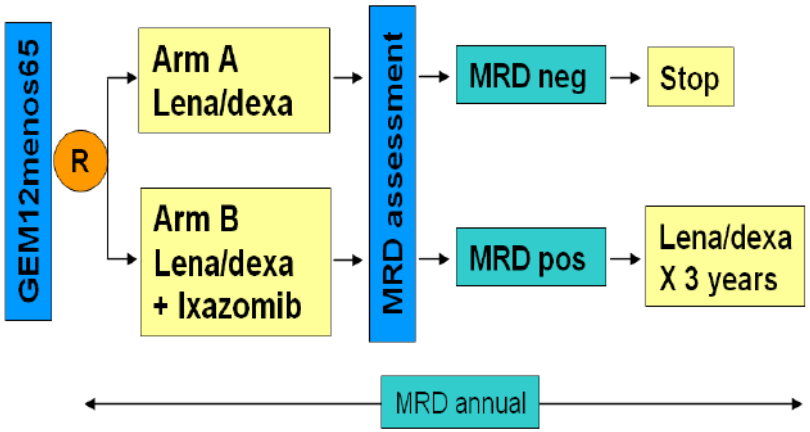



*del17p, t(4;14) or t(14;16)

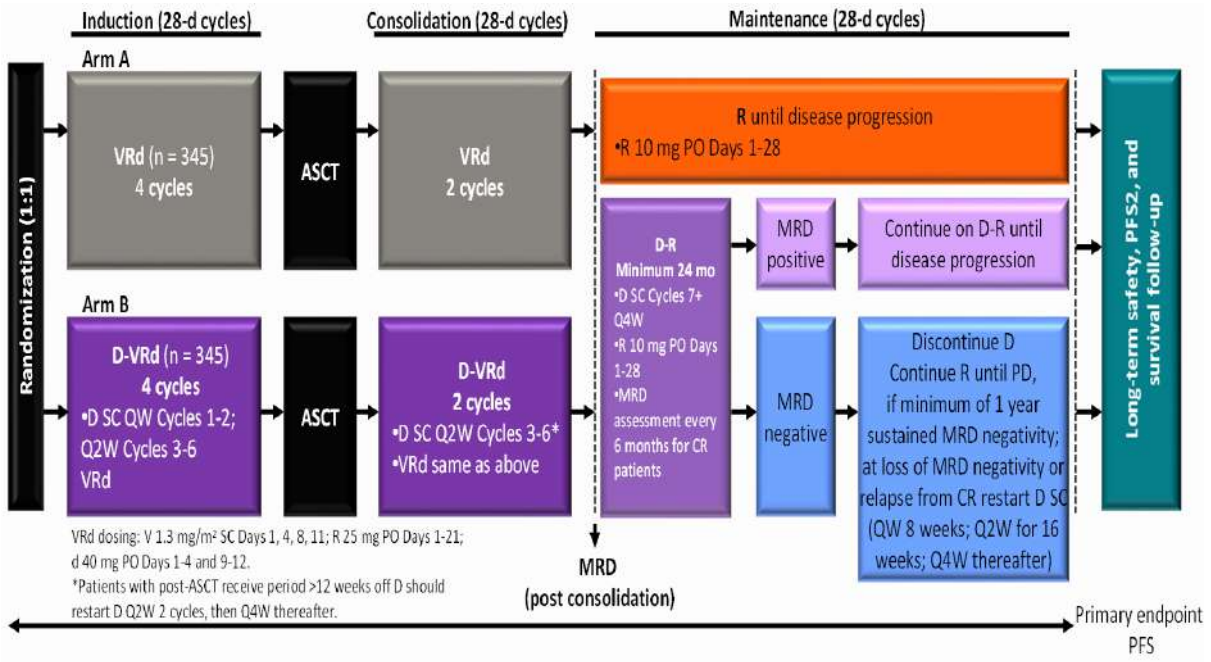
Costa LJ et al, EHA 2020

# Current trials with MRD-driven maintenance

## GEM14 phase 3 trial
(NCT02406144)




## PERSEUS phase 3 trial
(NCT03710603)

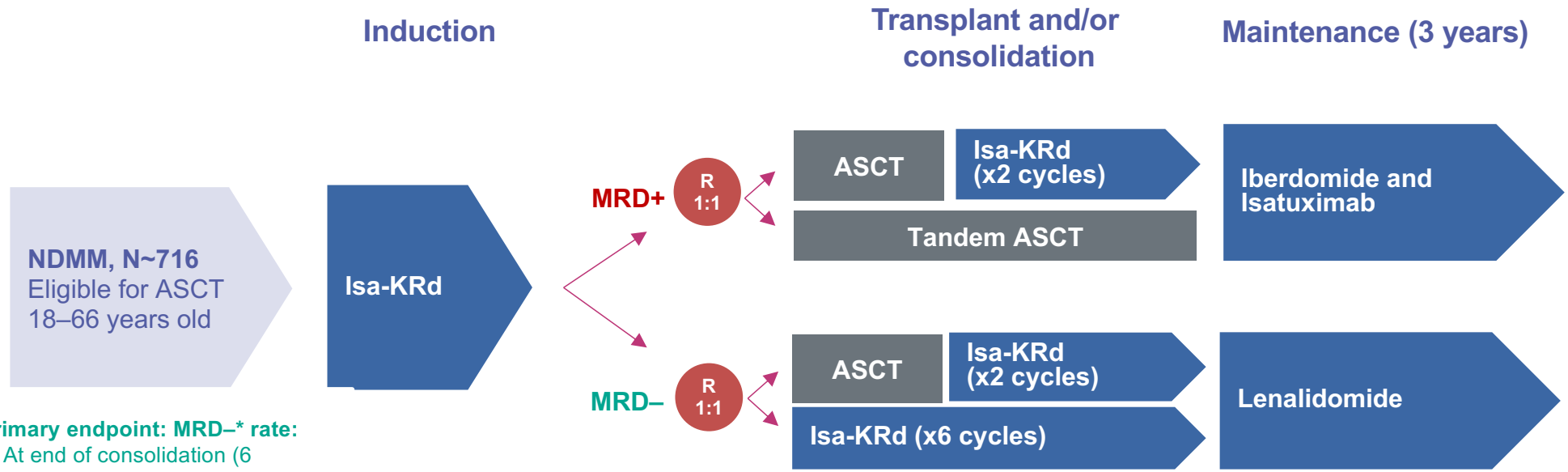


# Current trials with MRD-driven maintenance

## Minimal Residual Disease Adapted Strategy (MIDAS)

*Sponsor: Intergroupe Francophone du Myelome (IFM)*

*Estimated primary completion: September 2024*




**Primary endpoint: MRD–* rate:**

- At end of consolidation (6 months)
- 1, 2, and 3 years post induction

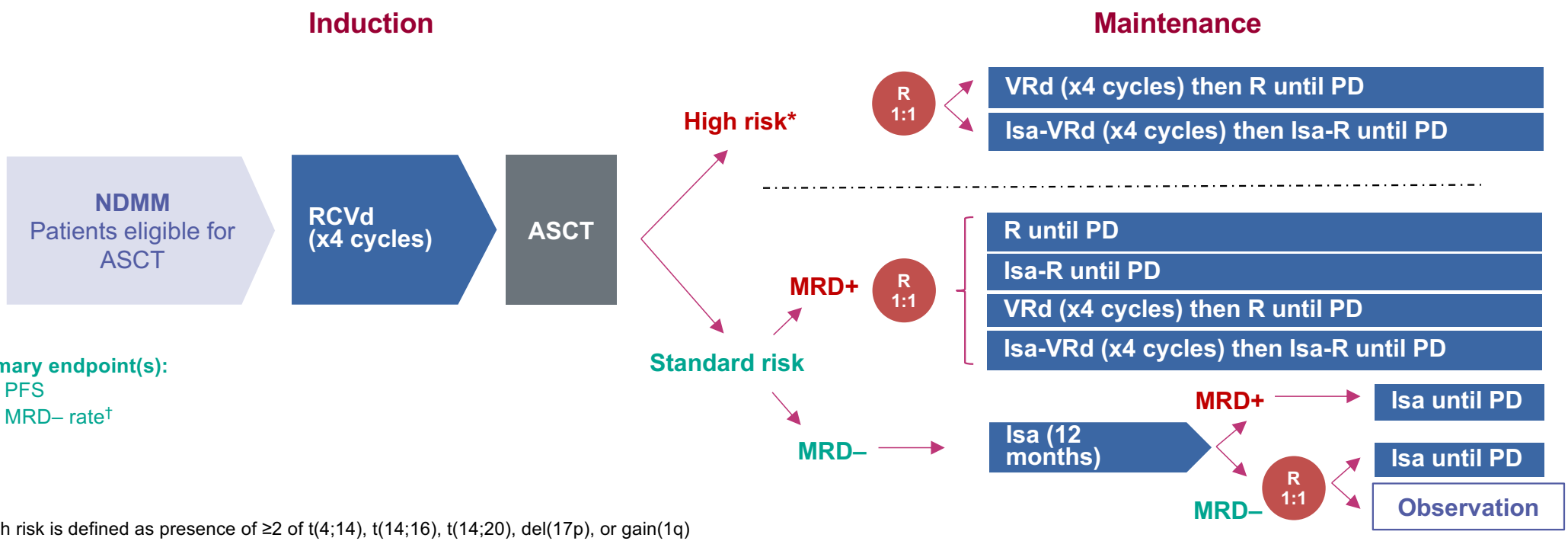
*Primary analysis will evaluate MRD (NGS, $10^{-6}$ threshold)

https://clinicaltrials.gov/ct2/show/NCT04934475

# Current trials with MRD-driven maintenance

## Risk-Adapted therapy Directed According to Response (RADAR)

*Sponsor: University of Leeds*
*Estimated primary completion: Not available*




**Primary endpoint(s):**
- PFS
- MRD– rate†

*High risk is defined as presence of ≥2 of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q)
†6 months post-ASCT for pts allocated to maintenance only, and 7 months for pts allocated to consolidation then maintenance.
MRD assessed at 10–5, confirmed by central lab

https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001258-25/GB

2021

# Ongoing clinical trials including MRD status in patients' enrollment and/or MRD-driven interventions

| Identifier | Phase | Regimen/Purpose | Subjects | MRD-driven decision | Primary endpoint | Status |
|---|---|---|---|---|---|---|
| NCT04108624 (MRD2STOP) | PO | Maintenance cessation | 56 multimodality$^{\&}$MRD$^{neg}$ MM patients on a single-agent maintenance for ≥1year | Maintenance cessation | MRD conversion rate, PFS, OS | Not yet recruiting |
| NCT04221178 | PO | Maintenance cessation | 50 MRD$^{neg}$ MM patients for ≥3 years while on continuous maintenance | Maintenance cessation | MRD negativity rate ($10^{-5}$) a year after enrolling | Recruiting |
| NCT03490344 | 2 | Daratumumab effect on MRD$^{pos}$ patients post induction | 25 MRD$^{pos}$ patients post induction with without consolidative HDT/ASCT | - | MRD negativity rate by MFC | Recruiting |
| NCT03992170 (DAR4MM) | 2 | Daratumumab effect on MRD$^{pos}$ patients | 50 MRD$^{pos}$ patients with ≥VGPR after any previous therapy | All patients will receive Dara for 24 weeks<br>MRD$^{neg}$ (NGF): treatment cessation<br>MRD$^{pos}$: Daratumumab every 4 weeks for 80 more weeks | MRD negativity rate | Recruiting |
| NCT03901963 (AURIGA) | 3 | DaraR vs. R alone as maintenance treatment | 214 MRD$^{pos}$ (≥$10^{-5}$)patients post ASCT | - | MRD conversion rate tested by NGS ($10^{-5}$) | Recruiting |
| NCT03697655 (PREDATOR) | 2 | Preventive role of Daratumumab (Dara vs. no intervention) in reappearance of MRD | 274 MRD$^{neg}$ patients after one or two prior lines of therapy | - | EFS | Recruiting |
| NCT02389517 | 2 | Ixa-Rd vs. R alone as maintenance therapy | 86 MRD$^{pos}$ patients after ASCT | - | MRD negativity rate by MFC | Recruiting |
| NCT02969837 | 2 | Elo-KRd as initial therapy | 55 NDMM non-transplant or transplant eligible agreed to defer ASCT | All with receive Elo-KRD for 12 cycles and then:<br>MRD$^{neg}$: Elo-Rd maintenance until PD<br>MRD$^{pos}$: Elo-KRd for 6 more cycles and then Elo-Rd maintenance until PD | sCR rate, MRD negativity rate by NGS (clonoSIGHT) | Recruiting |
| NCT04071457 (DRAMMATIC) | 3 | DARArHuPH20 + R vs. R alone as maintenance therapyto direct therapy duration | 1100 patients post ASCT | After 2 years of maintenance with each arm:<br>MRD$^{pos}$ >$10^{-6}$: Continue with assigned treatment<br>MRD$^{neg}$ (≤$10^{-6}$): Randomization to either stop or continue assigned treatment for up to 7 years | OS | Recruiting |
| NCT02659293 | 3 | KRd vs. R alone after ASCT | 180 post ASCT that received a maximum of 2 induction regimens and have ≥SD at d100 post ASCT | Carfilzomib cycles 5–8 for MRD- patients that have no risk factors at the end of cycle 6<br>Carfilzomib: cycles 5 - 36 for MRD$^{pos}$ patients with high risk factors at the end of cycle 6 | PFS | Recruiting |
| NCT04096066 | 3 | KRd vs. Rd alone | 340 elderly NDMM not eligible for ASCT | Patients with ≥VGPR & MRD$^{neg}$ ($10^{-5}$) for ≥ 1 year in the KRD arm will stop K (after ≥ 2 years of treatment) and continue with RD until PD or intolerance | MRD negativity rate, PFS | Recruiting |
| NCT04140162 | 2 | DaraRd induction ± DaraVRd consolidation + DaraR maintenance | 50 NDMM eligible and not for ASCT | Only those with MRD positive status after 6 cycles of induction will receive consolidation | MRD negativity rate after induction and/or consolidation | Not yet recruiting |
| NCT03710603 (PERSEUS) | 3 | DaraVRd arm: DaraVRd for induction and consolidation, DaraR for maintenance<br>VRd arm: VRd for induction and consolidation, R for maintenance | 690 NDMM eligible for ASCT | Patients in DaraVRd group with sustained MRD negativity ($10^{-5}$) for 12 months and minimum 24 months of maintenance will stop Dara until PD or intolerance<br>Upon recurrence of MRD or loss of CR, patients will restart Dara until PD or intolerance | PFS | Recruiting |
| NCT03224507 (MASTER) | 2 | DaraKRd for induction, ASCT ± DaraKRd consolidation ± R maintenance | 82 NDMM eligible for ASCT | MRD ($10^{-5}$) is evaluated post induction, post ASCT and during each 4-cycle block of Dara-KRd consolidation<br>MRD$^{neg}$ patients after two consecutive evaluations will stop therapy and will be monitored for MRD resurgence (In 6 and 18 months.<br>MRD$^{pos}$ patients post ASCT will complete all cycles of consolidation and if MRD persists, they will receive R maintenance until PD or intolerance | MRD negativity rate by NGS (clonoSEQ) | Recruiting |

Kostopoulous et al. Frontiers in Oncology 2021

# Take home messages

- MRD is the best biomarker to predict outcome
- Modern triplet/quadruplet combinations (both in newly diagnosed and relapse/refractory setting) ultimately result in higher rates of MRD negativity
- MRD negativity should be attained at the deepest sensitivity level (whatever the method) and possibly sustained
- MRD negativity (at high sensitivity level) can overcome poor prognosis in HR pts
- Spatial disease heterogeneity and dissemination, possibility of EMD relapse → combination of BM-based methods and imaging might improve and complete the prognosis and risk assessment of pts
- The use of MRD to drive treatment decisions is under investigation: results of several ongoing phase III trials in the field are eagerly awaited
- Open issues: timing, costs, applicability in daily clinical practice