# Treatment of newly diagnosed MM Non-Transplant Eligible

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# Disclosures

- **Thierry Facon**, University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France

– Any compensation received was provided directly to CHU Lille

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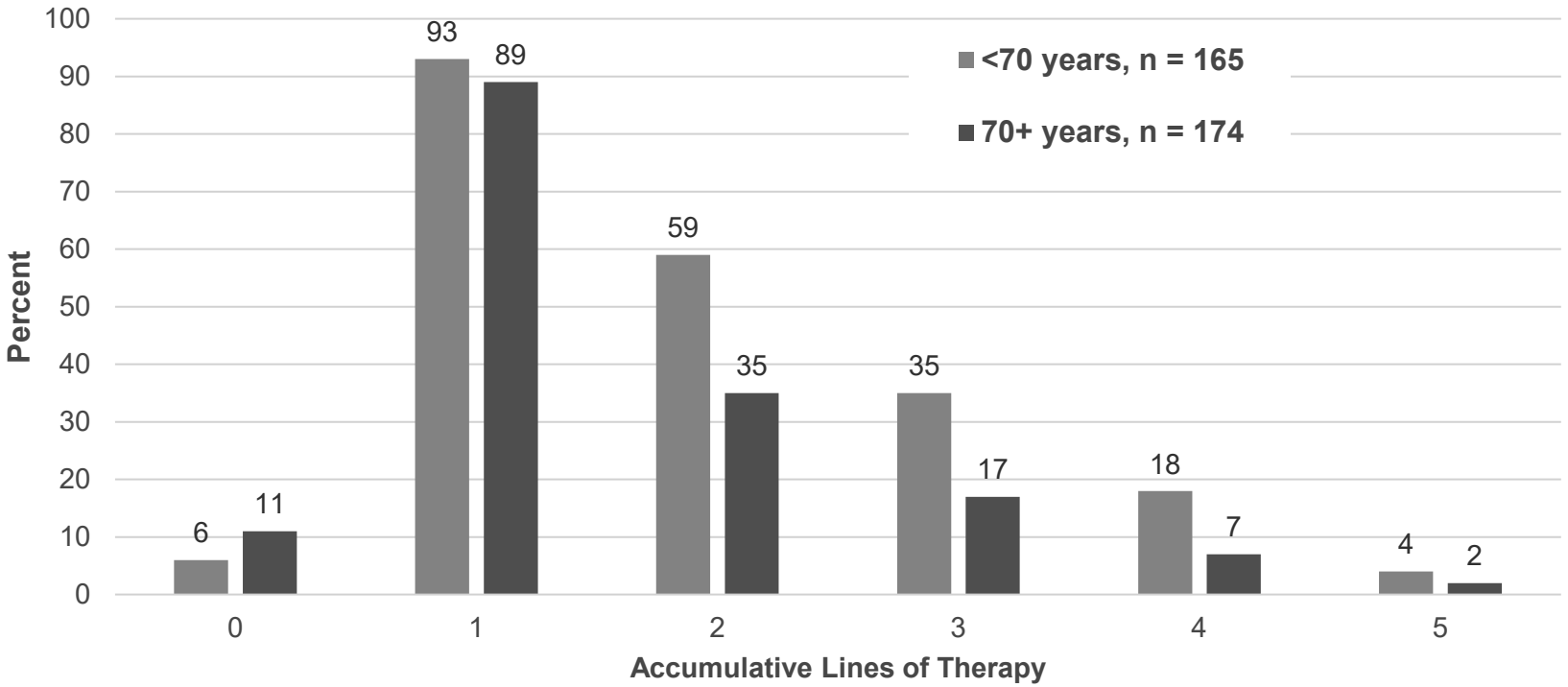
  - Advisory boards: Janssen, Bristol Myers Squibb, Takeda, Sanofi, Roche, Karyopharm, Oncopeptides, Amgen

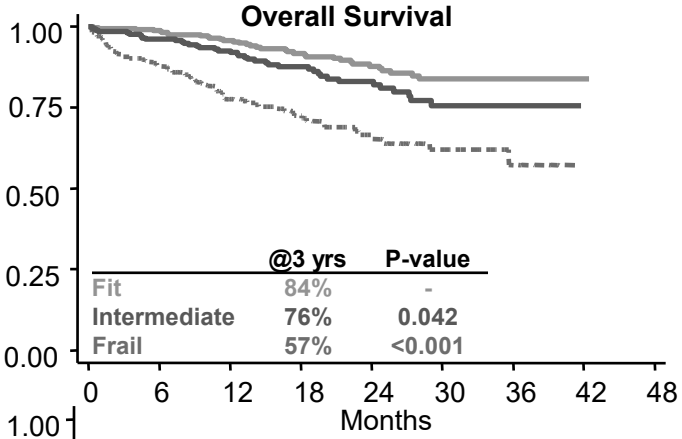
# General Considerations on Epidemiology and Frailty

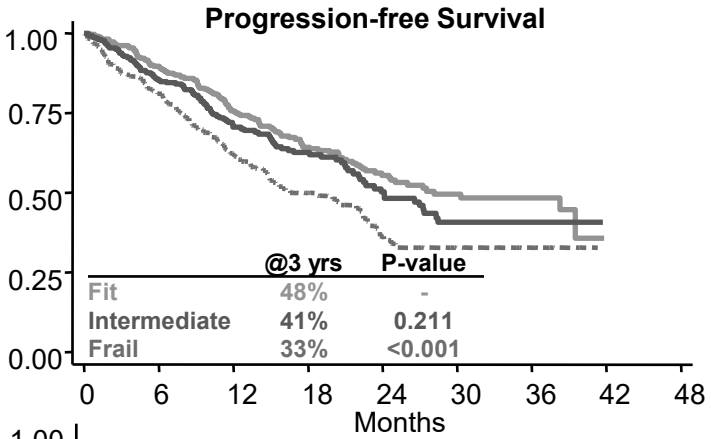
# Accumulative lines of therapy received by age at diagnosis

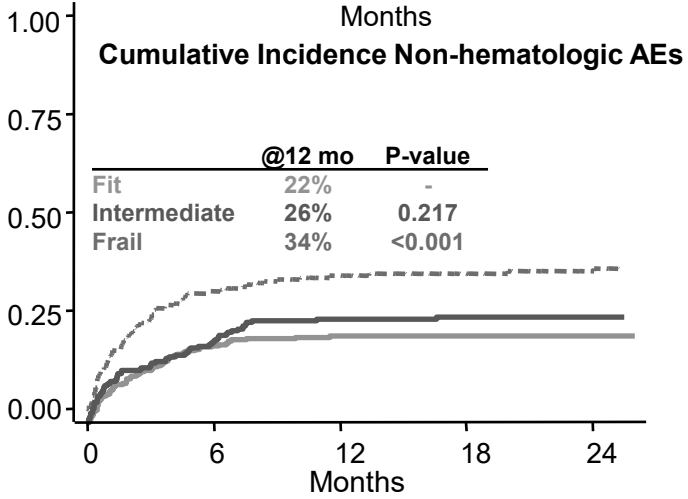


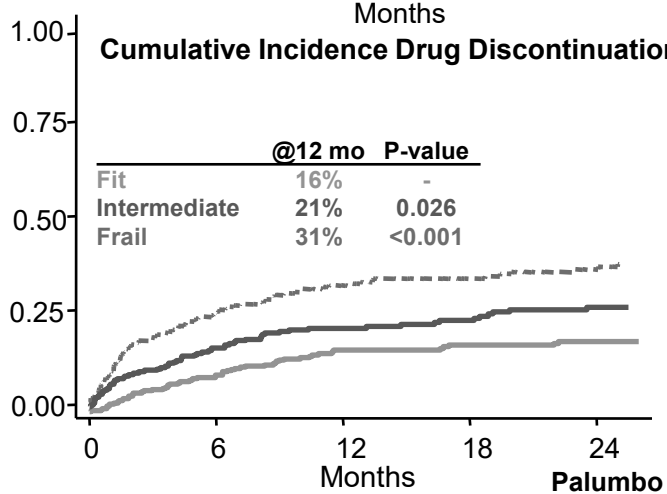

Courtesy of Dr A. Spencer

# IMWG frailty score: Long-term outcome



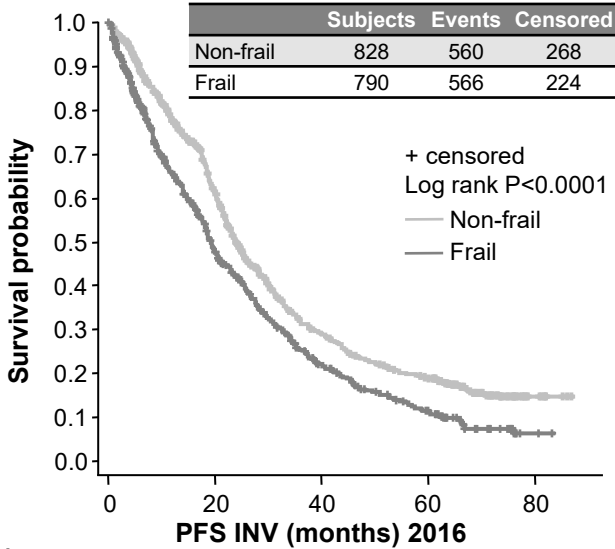




Palumbo A et al. Blood 2015;25:2068-2074.

# PFS and OS by frailty level in the FIRST study

**Product-limit survival estimates with number of subjects at risk**

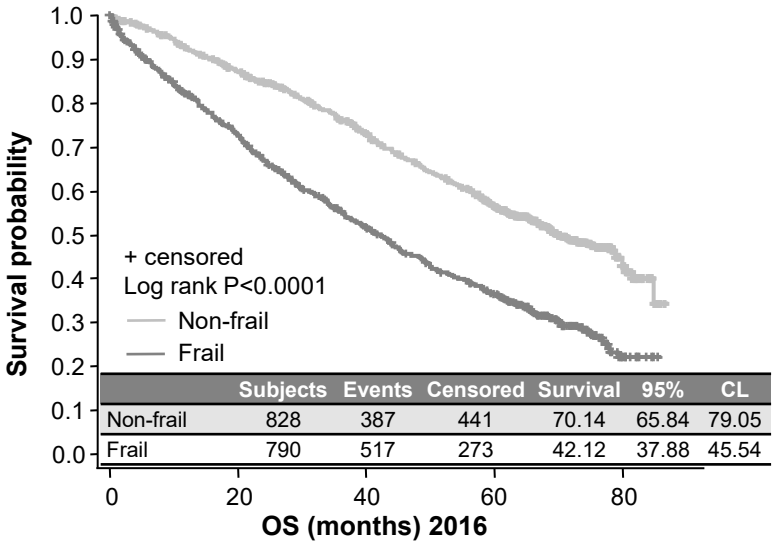
| | Subjects | Events | Censored | Survival | 95% | CL |
|---|---|---|---|---|---|---|
| Non-frail | 828 | 560 | 268 | 23.95 | 22.34 | 25.56 |
| Frail | 790 | 566 | 224 | 19.35 | 18.17 | 20.57 |




**N at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-frail | 828 | 588 | 414 | 252 | 176 | 133 | 107 | 52 | 12 | 0 |
| Frail | 790 | 458 | 292 | 187 | 117 | 76 | 50 | 17 | 2 | 0 |

**Product-limit survival estimates with number of subjects at risk**




| | Subjects | Events | Censored | Survival | 95% | CL |
|---|---|---|---|---|---|---|
| Non-frail | 828 | 387 | 441 | 70.14 | 65.84 | 79.05 |
| Frail | 790 | 517 | 273 | 42.12 | 37.88 | 45.54 |

**N at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Non-frail | 828 | 764 | 693 | 628 | 551 | 479 | 406 | 195 | 45 | 0 |
| Frail | 790 | 645 | 547 | 443 | 370 | 302 | 248 | 115 | 15 | 0 |

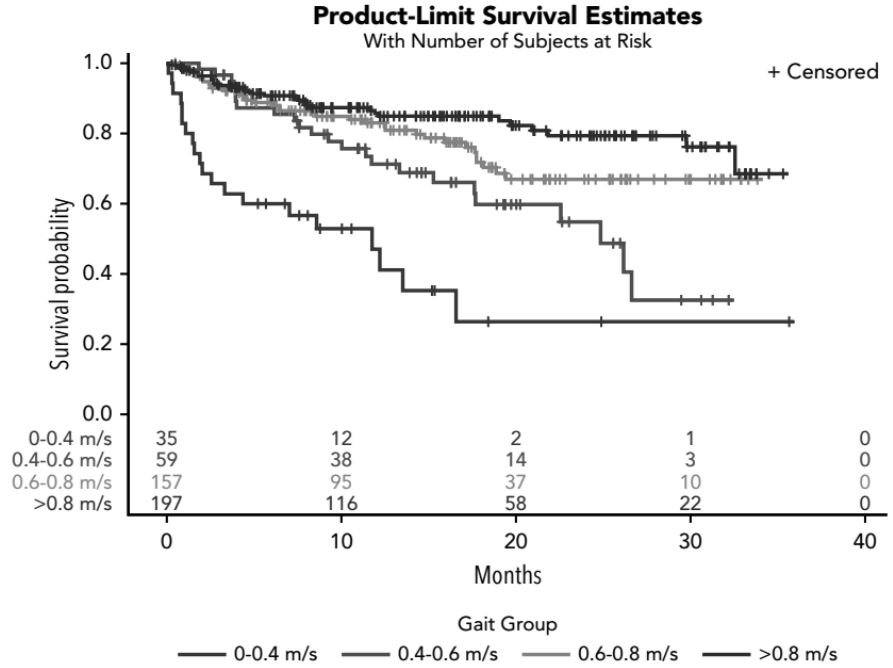
ifm

OS, overall survival; PFS, progression-free survival

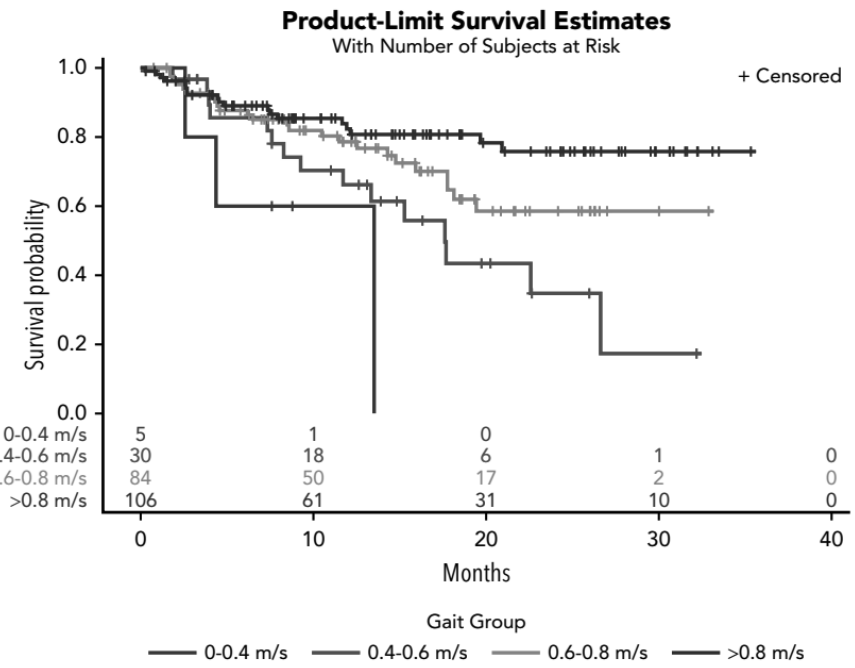

**Facon T et al. Leukemia 2020; 34:224-233**
**Steg et al.Leukemia 2020, Mian et al.Leukemia 2021**

# Gait speed and survival outcomes in elderly patients with hematological malignancies

## Survival by gait speed




## Survival by gait speed in patients with ECOG PS 0-1



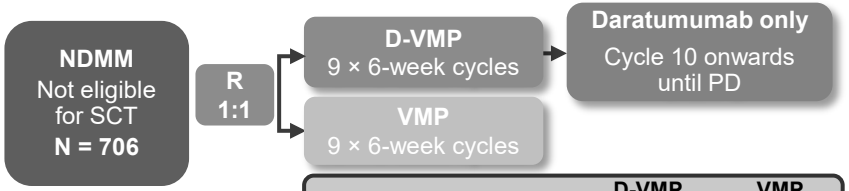

ECOG PS, Eastern Cooperative Oncology Group Performance Status

**Liu M et al. Blood 2019; 134(4):374-382**

# Major Treatment Regimens

# Key study designs in non stem-cell transplantation NDMM

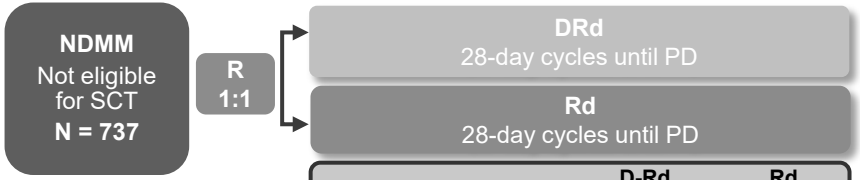
## ALCYONE[1]




**Primary endpoint: PFS**

| Characteristic | D-VMP (n = 350) | VMP (n = 356) |
|---|---|---|
| Median age (range), years | 71 (40–93) | 71 (50–91) |
| Age ≥ 75 years, % | 30 | 30 |
| ECOG PS 0/1/2, % | 22/52/26 | 28/49/24 |
| High-risk cytogenetics, % | 17 | 15 |

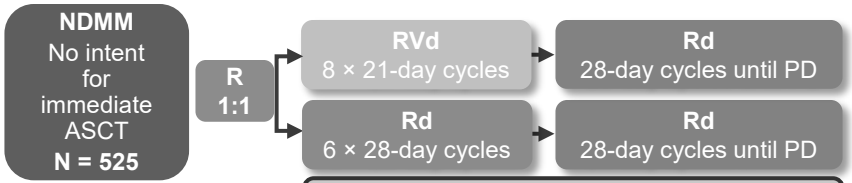
## MAIA[2]




**Primary endpoint: PFS**

| Characteristic | D-Rd (n = 368) | Rd (n = 369) |
|---|---|---|
| Median age (range), years | 73 (50–90) | 74 (45–89) |
| Age ≥ 75 years, % | 44 | 44 |
| ECOG PS 0/1/2, % | 35/48/17 | 33/51/16 |
| High-risk cytogenetics, % | 15 | 14 |

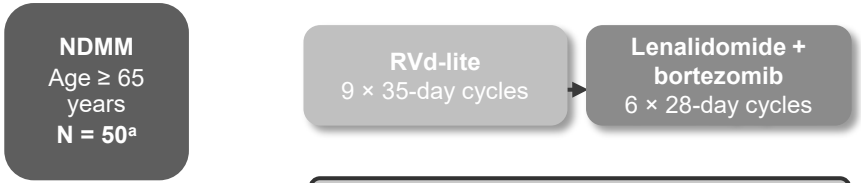
## SWOG S0777[3]




**Primary endpoint: PFS**

| Characteristic | RVd (n = 264) | Rd (n = 261) |
|---|---|---|
| Median age (range), years | 63 (-) | 63 (-) |
| Age ≥ 65 years, % | 38 | 48 |
| ECOG PS > 1, % | 12 | 16 |
| High-risk cytogenetics, % | - | - |

## RVd-lite[4,a]




**Primary endpoint: ORR**

| Characteristic | ITT (n = 50) |
|---|---|
| Median age (range), years | 73 (65–91) |
| Age ≥ 75 years, % | - |
| ECOG PS 0/1/2, % | 50/36/14 |
| High-risk cytogenetics, % | 12 |

These charts are provided for ease of viewing information from multiple trials.
Direct comparison between trials is not intended and should not be inferred.
[a] RVd lite is phase II, others phase III.
DRd, daratumumab, lenalidomide, low-dose dexamethasone; D-VMP; daratumumab, bortezomib, melphalan, prednisone; R, randomized; SCT, stem-cell transplantation.


1. Mateos MV et al. N Engl J Med 2018;378:518–28. 2. Facon T et al. N Engl J Med 2019;380:2104–15. 3. Durie BGM et al. Lancet 2017;389:519–27. 4. O'Donnell EK, et al. Br J Haematol 2018;182:222–30.

# SWOG 0777: PFS with RVd versus Rd[a]

**Regardless of age, treatment with RVd resulted in better responses compared with Rd**

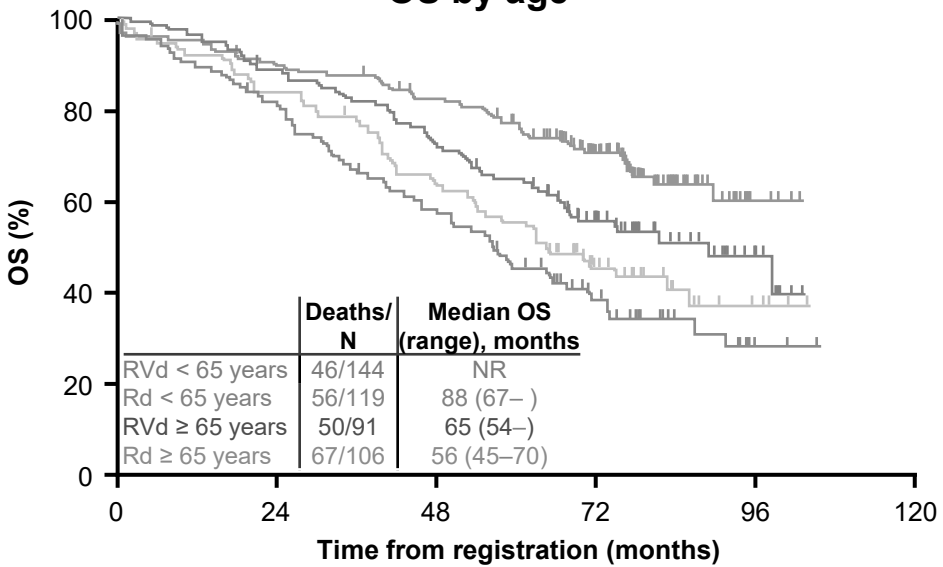
**Median PFS (months)[1]**

| Age (years) | RVd | Rd |
|---|---|---|
| < 65 | 48 | 34 |
| ≥ 65 | 34 | 24 |
| > 75 | 34 | 17 |

**Long term FU[2]**

**OS in pts ≥ 65 years: HR 0.769, p 0.168**

**OS by age[1]**



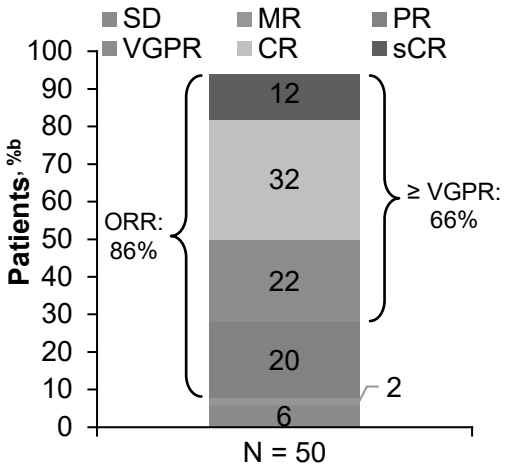

[a] For all analyses, both SWOG and IRC assessments have been conducted using the fully updated datasets with current data lock in May 2018.
D, dexamethasone; IRC, Independent Review Committee; OS overall survival; PFS, progression-free survival; R, lenalidomide, V bortezomib.


1. Durie B et al. Blood 2018;132:1992;
2. Durie B et al. Blood Cancer J 2020;10:53

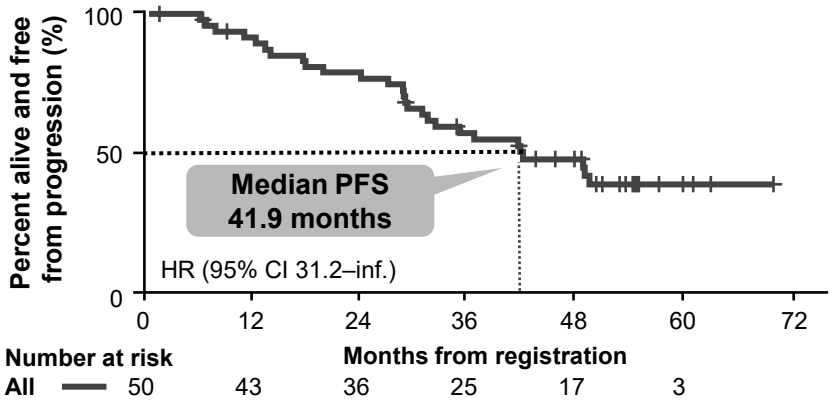
# Modified RVd (RVd-lite) in transplant-ineligible NDMM

| Baseline characteristics | N = 50 |
|---|---|
| Median age, years (range) | 73 (65–91) |
| **ISS stage at diagnosis, %** | |
| I | 38 |
| II | 34 |
| III | 28 |
| **ECOG PS score, %** | |
| 0 | 50 |
| 1 | 36 |
| 2 | 14 |

## Response rate




## PFS




≥ CR was 44% (ITT population; N = 50)
ORR was 86%; ≥ VGPR was 66% for patients evaluable for response[a] after 4 cycles (n = 46)
Median TTR was 1.1 months

Grade 3 or 4 AEs of interest:
- Peripheral neuropathy (2%), neutropenia (14%)

RVd-lite is Investigational only, not approved.
[a] The first 10 patients received bortezomib i.v. for cycle 1 only followed by s.c. administration; subsequent patients received bortezomib s.c.; [b] 6% of patients received < 4 cycles of therapy and were therefore not evaluable.
AE, adverse event; CR, complete response; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance status; ISS, International Staging System; MR, minimal response; ORR, overall response rate; PFS, progression-free survival; R, lenalidomide; sCR, stringent complete response; TTR, time to response; V, bortezomib; VGPR, very good partial response

O'Donnell EK et al. Br J Haematol 2018;182:222-30.
O'Donnell EK et al. ASH 2019; abstract 3178.

# Daratumumab Study designs

## ALCYONE

**Key eligibility criteria:**

- Transplant-ineligible NDMM
- ECOG PS score 0–2
- CrCl ≥ 40 mL/min
- No grade ≥ 2 PN or grade ≥ 2 neuropathic pain

1:1 Randomization (N = 706)

**VMP × 9 cycles (n = 356)**
**V:** 1.3 mg/m$^2$ SC
Cycle 1: twice weekly; Cycles 2–9: once weekly
**M:** 9 mg/m$^2$ PO days 1–4
**P:** 60 mg/m$^2$ PO days 1–4

**D-VMP × 9 cycles (n = 350)**
**D:** 16 mg/kg IV
Cycle 1: once weekly; Cycles 2–9: every 3 weeks
+
**Same VMP schedule**

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

**D:** cycles 10+

16 mg/kg IV Q4W, until PD

Follow-up for PD and survival

**Primary endpoint:**

- PFS

**Secondary endpoints:**

- ORR
- ≥ VGPR rate
- ≥ CR rate
- MRD (NGS; $10^{-5}$)
- OS
- Safety

**Stratification factors**

- ISS stage (I vs II vs III)
- Region (EU vs other)
- Age (< 75 vs ≥ 75 years)

**Statistical analyses**
360 PFS events: 85% power for 8-month PFS improvement[a]

CR, complete response; CrCl, creatinine clearance; D, daratumumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, European Union; M, melphalan; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; P, prednisone; PD, progressive disease; PN, peripheral neuropathy; V, bortezomib; VGPR, very good partial response.
[a] 8-month PFS improvement over 21-month median PFS of VMP.

Mateos MV, et al. *N Engl J Med.* 2018;378(6):518-528.

## MAIA

**Key eligibility criteria:**

- Transplant-ineligible NDMM
- ECOG PS score 0–2
- CrCl ≥ 30 mL/min

1:1 Randomization

**D-Rd (n = 368)**
**D:** 16 mg/kg IV[a]
Cycles 1, 2: QW; Cycles 3–6: Q2W; Cycles 7+: Q4W until PD
**R:** 25 mg PO daily days 1–21 until PD
**d:** 40 mg[b] PO or IV weekly until PD

**Rd (n = 369)**
**R:** 25 mg PO daily, days 1–21 until PD
**d:** 40 mg[b] PO or IV weekly until PD

**28-day cycles**

**Primary endpoint:**

- PFS

**Key secondary endpoints[c]:**

- ≥ CR rate
- ≥ VGPR rate
- MRD-negative rate (NGS; $10^{-5}$)
- ORR
- OS
- Safety

**Stratification factors**

- ISS stage (I vs II vs III)
- Region (NA vs other)
- Age (< 75 vs ≥ 75 years)

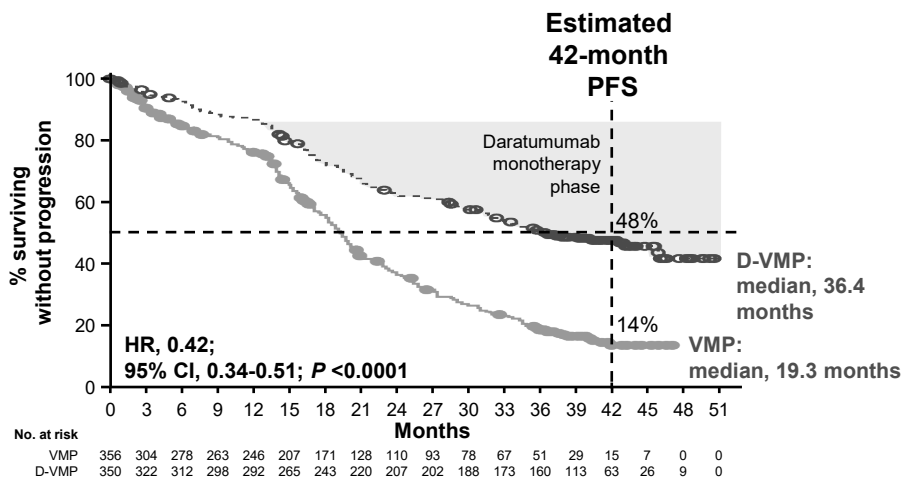
BMI, body mass index; D-Rd, daratumumab, lenalidomide, and dexamethasone; NA, North America.
[a] On days when DARA was administered, DEX was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication; [b] For patients > 75 years of age or with BMI < 18.5, DEX was administered at a dose of 20 mg weekly; [c] Efficacy endpoints were sequentially tested in the order shown.

Facon T et al. *Blood* 2019;132:LBA-2;
Facon T et al. *N Engl J Med* 2019;380:2104-15.

# PFS

## ALCYONE

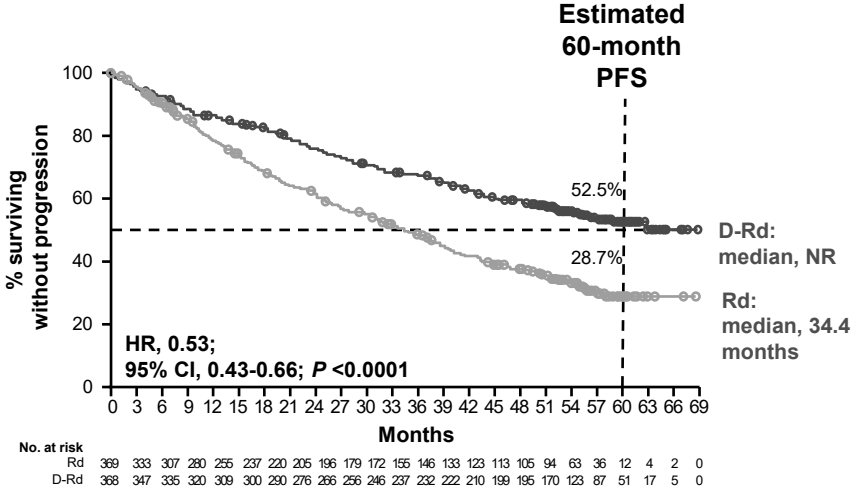
Median (range) follow-up: 40.1 (0-52.1) months




**D-VMP continued to demonstrate a significant PFS benefit with extended follow up**

## MAIA

Median follow-up: 56.2 months




- **D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd**
- **These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible**

D, daratumumab; PFS, progression-free survival; VMP, bortezomib, melphalan, prednisone; Rd, lenalidomide and dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached; NDMM, newly diagnosed multiple myeloma.

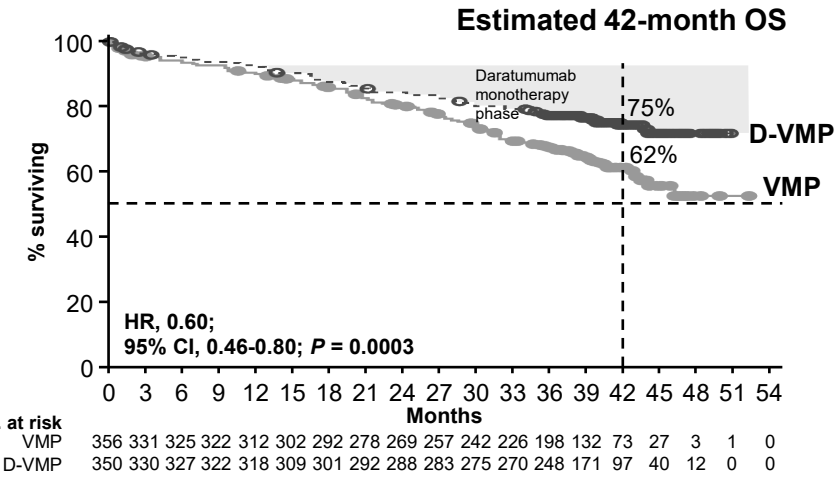
Mateos MVM et al. *Lancet*. 2019;395(10218):132-141.

Facon T et al. EHA 2021. LB1901.

# OS

## ALCYONE

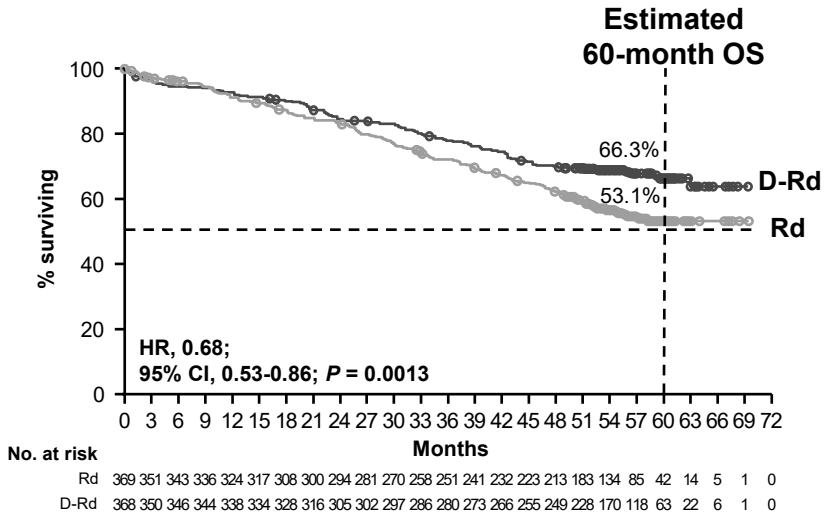
Median (range) follow-up: 40.1 (0-52.1) months
Pre-specified analysis triggered after 209 deaths were observed




**40% reduction in the risk of death in patients receiving D-VMP**

## MAIA

Median follow-up: 56.2 months




**D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible**

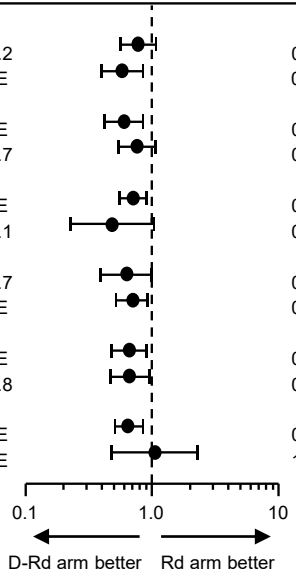
D, daratumumab; OS, overall survival; VMP, bortezomib, melphalan, prednisone; Rd, lenalidomide and dexamethasone; HR, hazard ratio; CI, confidence interval; NDMM, newly diagnosed multiple myeloma.

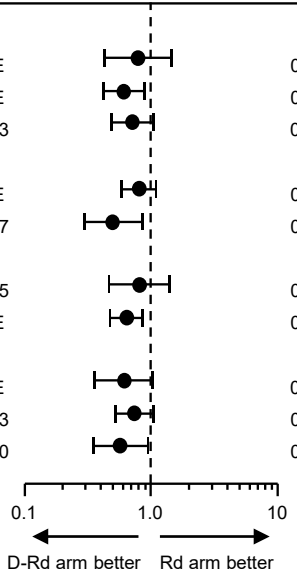
Mateos MVM et al. *Lancet*. 2019;395(10218):132-141.

Facon T et al. EHA 2021. LB1901.

# MAIA - Subgroup Analysis of OS

| | D-Rd No. of deaths/ total no. | Rd No. of deaths/ total no. | D-Rd Median OS (months) | Rd Median OS (months) | HR (95% CI) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 71/189 | 88/195 | NE | 57.2 | 0.78 (0.57-1.06) |
| Female | 46/179 | 68/174 | NE | NE | 0.58 (0.40-0.84) |
| Age | | | | | |
| <75 years | 52/208 | 80/208 | NE | NE | 0.60 (0.42-0.85) |
| ≥75 years | 65/160 | 76/161 | NE | 55.7 | 0.76 (0.55-1.06) |
| Race | | | | | |
| White | 106/336 | 138/339 | NE | NE | 0.71 (0.55-0.91) |
| Other | 11/32 | 18/30 | NE | 49.1 | 0.48 (0.23-1.03) |
| Region | | | | | |
| North America | 33/101 | 46/102 | NE | 55.7 | 0.63 (0.40-0.98) |
| Other | 84/267 | 110/267 | NE | NE | 0.70 (0.53-0.93) |
| Baseline renal function (CrCl) | | | | | |
| >60 mL/min | 59/206 | 89/227 | NE | NE | 0.66 (0.48-0.92) |
| ≤60 mL/min | 58/162 | 67/142 | NE | 54.8 | 0.67 (0.47-0.96) |
| Baseline hepatic function | | | | | |
| Normal | 104/335 | 144/340 | NE | NE | 0.65 (0.51-0.84) |
| Impaired | 13/31 | 12/29 | NE | NE | 1.05 (0.48-2.30) |
| ISS disease stage | | | | | |
| I | 19/98 | 24/103 | NE | NE | 0.79 (0.43-1.44) |
| II | 50/163 | 69/156 | NE | NE | 0.61 (0.42-0.88) |
| III | 48/107 | 63/110 | 62.8 | 47.3 | 0.72 (0.49-1.04) |
| Type of MM | | | | | |
| IgG | 74/225 | 90/231 | NE | NE | 0.80 (0.59-1.09) |
| Non-IgG | 22/74 | 37/76 | NE | 53.7 | 0.50 (0.30-0.86) |
| Cytogenetic risk at study entry | | | | | |
| High risk | 25/48 | 26/44 | 55.6 | 42.5 | 0.80 (0.46-1.39) |
| Standard risk | 80/271 | 116/279 | NE | NE | 0.64 (0.48-0.85) |
| ECOG PS score | | | | | |
| 0 | 24/127 | 36/123 | NE | NE | 0.61 (0.36-1.02) |
| 1 | 64/178 | 82/187 | NE | 58.3 | 0.74 (0.53-1.03) |
| ≥2 | 29/63 | 38/59 | 62.8 | 39.0 | 0.57 (0.35-0.94) |



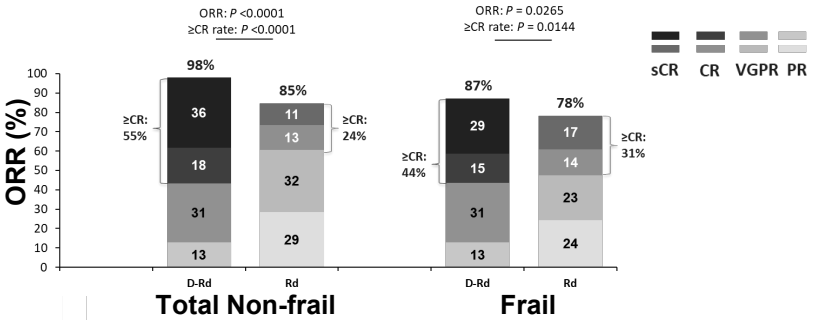




**OS benefit with D-Rd was generally consistent across patient subgroups**

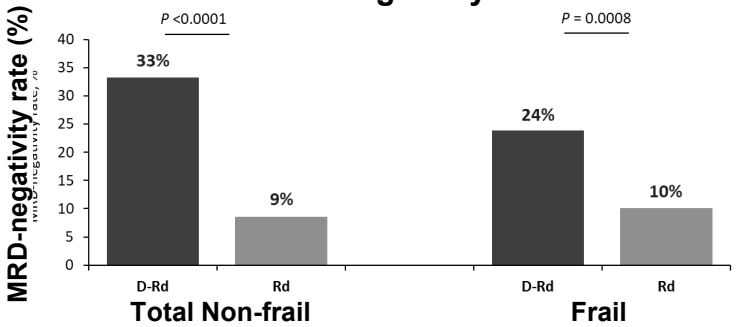
NE, not estimable; CrCl, creatinine clearance.

# Daratumumab plus lenalidomide and dexamethasone (D-Rd) vs lenalidomide and dexamethasone (Rd) in transplant-ineligible newly diagnosed multiple myeloma (NDMM): frailty subgroup analysis of MAIA

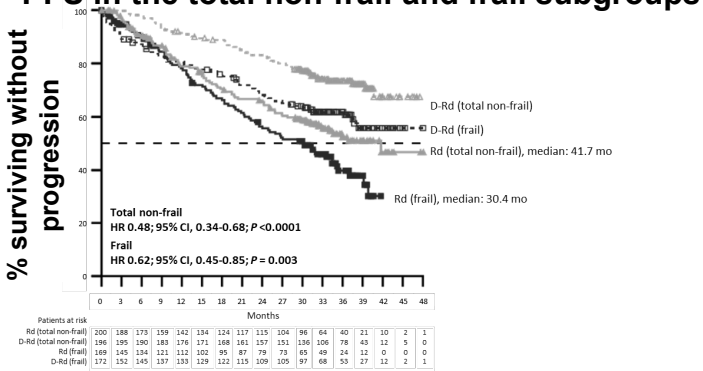
## ORR and ≥CR rate




## MRD-negativity




## PFS in the total non-frail and frail subgroups



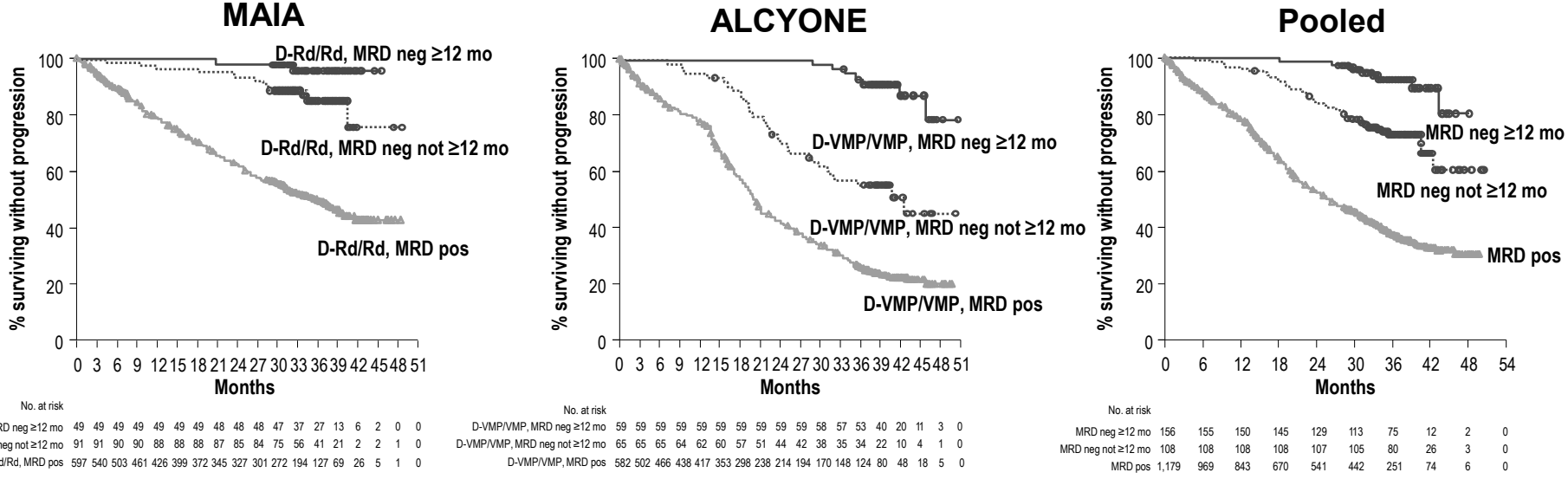

## Safety

| | Total Non-frail (n=395) | | Frail (n=334) | |
|---|---|---|---|---|
| n (%) | D-Rd (n=196) | Rd (n=199) | D-Rd (n=168) | Rd (n=166) |
| Patients with a TEAE with outcome of death | 7 (4) | 7 (4) | 20 (12) | 20 (12) |
| Patients with a serious TEAE | 123 (63) | 126 (63) | 125 (74) | 121 (73) |
| Treatment discontinuations due to TEAEs | 13 (7) | 31 (16) | 17 (10) | 32 (19) |
| Deaths | 26 (13) | 46 (23) | 57 (34) | 57 (34) |

**Our findings, although based on a retrospective assessment of frailty, support the clinical benefit of D-Rd in patients with transplant-ineligible NDMM enrolled in MAIA, regardless of frailty status**

Courtesy of S Zweegman, EMN 2021

# PFS based on sustained MRD negativity (NGS, $10^{-5}$) lasting ≥12 months in MAIA, ALCYONE and in both studies pooled

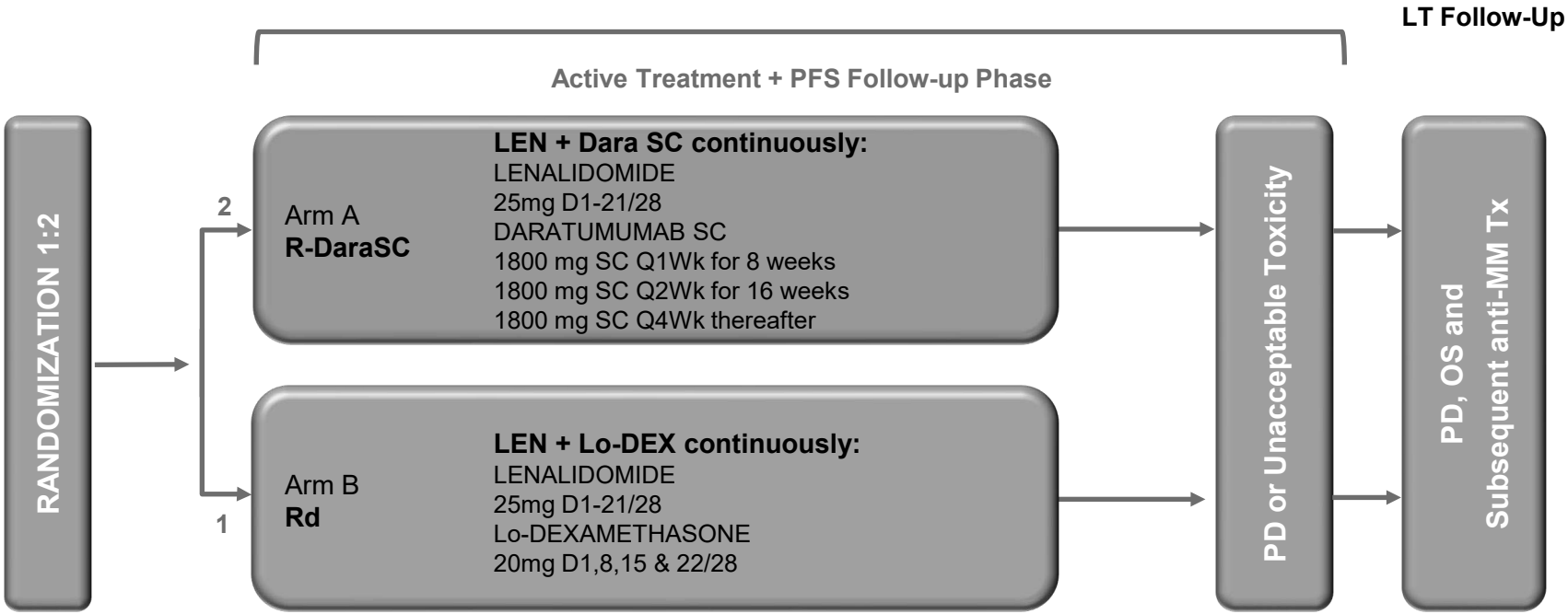



**Durable MRD negativity lasting ≥12 months improved PFS compared with MRD-negative patients who did not maintain MRD negativity for ≥12 months**

PFS, progression-free survival; MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

San Miguel J et al. ASH 2020; abstract 2317

# IFM 2017-03 for frail elderly NDMM patients
## A dexamethasone sparing study




***Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80***

***In Arm A low-dose dex (20mg/week) during Cycle 1 and 2 then methylprednisolone (with SC dara)***

LT, long term; OS, overall survival; PD, progressive disease;
PFS, progression-free survival; Q, every; SC, subcutaneous; Tx, treatment

https://clinicaltrials.gov/ct2/show/NCT03993912

# Phase III trials in NDMM not eligible for ASCT

| VMP |
| --- |
| **VMP vs MP:**<br>PFS: **24** vs 16m (▲8m **)**<br>OS: **56** vs 43m. (▲13 m) |

| Rd |
| --- |
| **Rd vs Rd18 vs MPT**<br>PFS: **26** vs 21m. (▲5m)<br>OS**: 59** vs 49m (▲10 m) |

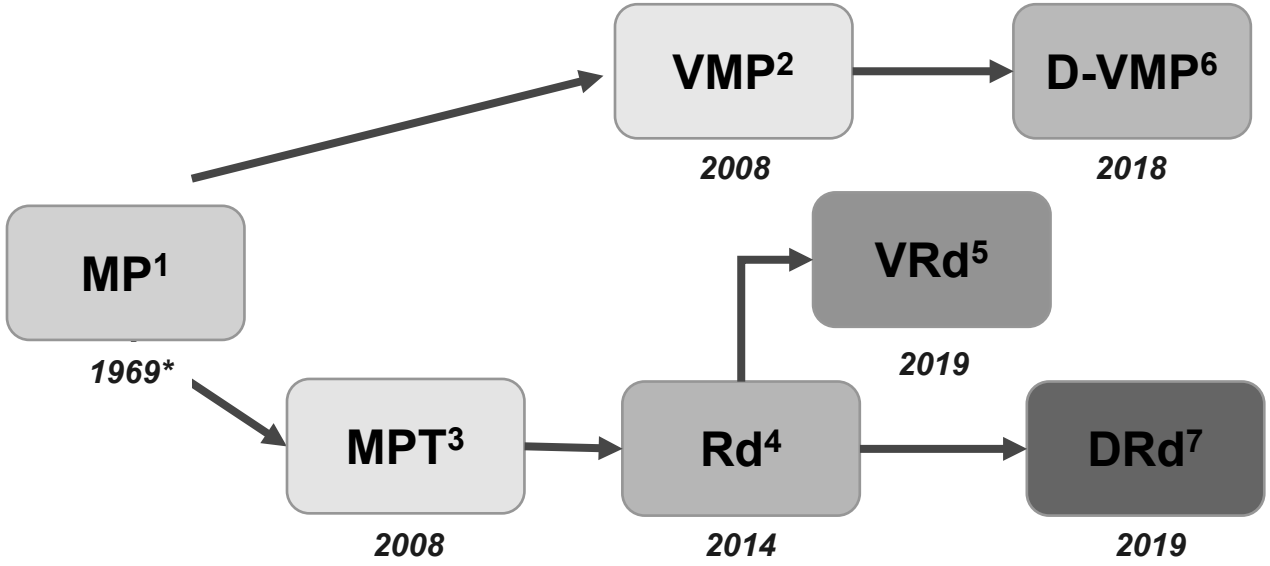
| | SWOG (N = 484) VRd vs Rd[1] | TOURMALINE (N = 705) IRd vs Rd[3] | ENDURANCE (N = 1087) KRd vs VRd[2] | ALCYONE (N = 706) DVMP vs VMP[4] | MAIA (N = 737) DRd vs Rd[5] |
| --- | --- | --- | --- | --- | --- |
| **PFS** (mos) **(▲**mos) | **34 vs 24**<br>▲ 10 | **35 vs 22**<br>▲ 13.5 | **34 vs 34**<br>**=** | **36 vs 19**<br>▲ 17 | **60+ vs 34**<br>▲ 26+ |
| **OS** | **65 mos** | **NA** | **84%@3y** | **78% vs 68%@3y** | **66% vs 53%@ 5y** |

ASCT, autologous stem cell transplant; d, dexamethasone; D, daratumumab; K, carfilzomib; M, melphalan; NA, not assessed; P, prednisone; R, lenalidomide; V, bortezomib

1. Durie B et al. Lancet 2017;389:519; 2. Kumar S et al. ASCO 2020; abstract LBA3;
3. Facon T et al. Blood 2021;. 4. Mateos. Lancet 2019; 395:132-41
5. Facon T. N Eng J Med 2019;380:2104 and Lancet Oncol 2021 in press.

# Treatment Landscape and Perspective in ND TNE Patients

## Regimens, Date of EMA approval, OS




**Ongoing/planned studies**
**Need for frailty assessement**

- **Dara-/Isa-VRd****
- **New IMiDs/CelMods**
- **Bispecific Antibodies**
- **CAR-T cells**
- **Continuous vs FDT**
- **Role of MRD**
- **Do not forget other aspects of MM (infections…)**

* Publication; OS Overall survival; **NCT03319667 et NCT03652064;
[1]MP, melphalan-prednisone; [2]VMP, bortezomib(Velcade)-melphalan-prednisone; [3]MPT, melphalan-prednisone-thalidomide; [4]Rd, lenalidomide(Revlimid)-dexamethasone; [5]VRd, bortezomib(Velcade)-lenalidomide (Revlimid)-dexamethasone; [6]D-VMP, daratumumab-bortezomib (Velcade)-melphalan-prednisone; [6]DRd, daratumumab-lenalidomide(Revlimid)-dexaméthasone; Isa = isatuximab; IMiDs = immunomodulateurs; BCMA = B cell maturation antigen; Ac = antibody; CAR-T cells = chimeric receptor T cells.

# IFM revised frailty algorithm with ECOG based on the FIRST study

| Category | Score |
|---|---|
| ≤ 75 years | 0 |
| 76-80 years | 1 |
| > 80 years | 2 |
| Charlson ≤ 1 | 0 |
| Charlson > 1 | 1 |
| ECOG = 0 | 0 |
| ECOG = 1 | 1 |
| ECOG ≥ 2 | 2 |
| Sum of Scores = 0 or 1 | → NON-FRAIL |
| Sum of Scores ≥ 2 | → FRAIL |

ECOG, Eastern Cooperative Oncology Group

Facon T et al. Leukemia 2020; 34:224-233