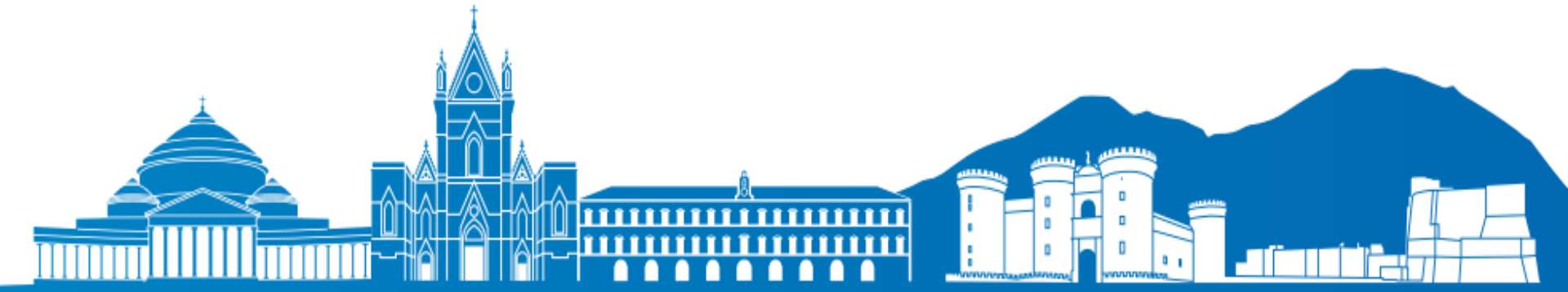


Nuove prospettive nel

MIELOMA MULTIPLO

NAPOLI Royal Hotel Continental

7-8 MARZO 2022

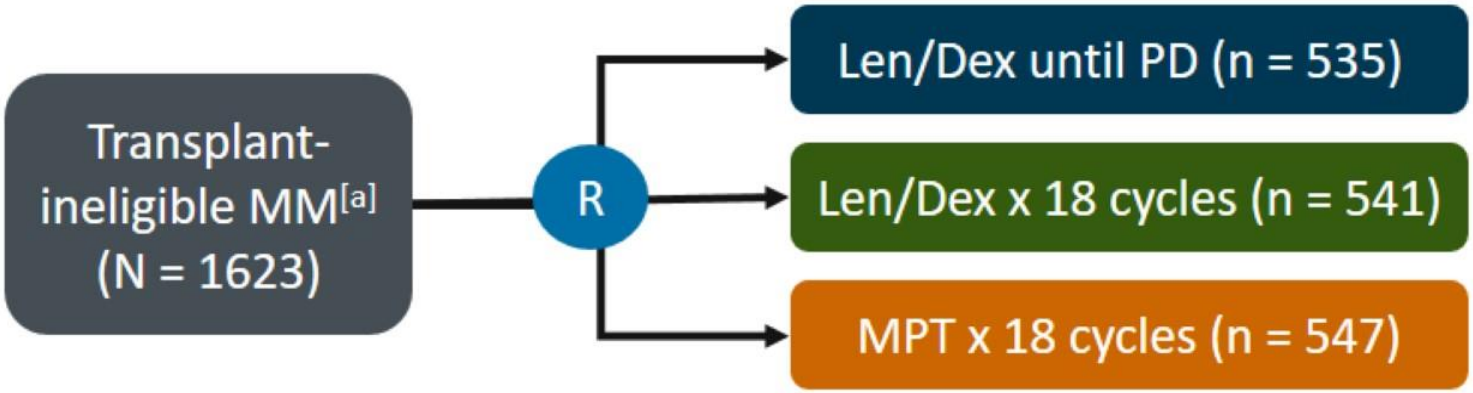
Innovazioni nella terapia del paziente non candidabile a trapianto

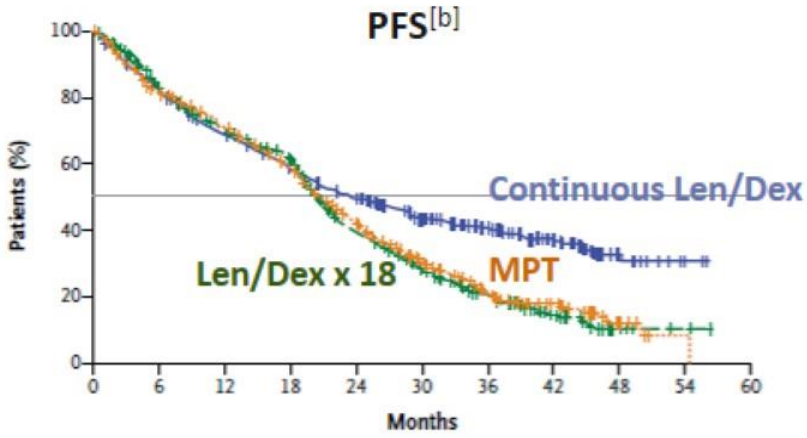
Francesco Di Raimondo

Università di Catania

FIRST Study

Continuous Therapy for Transplant-Ineligible Patients



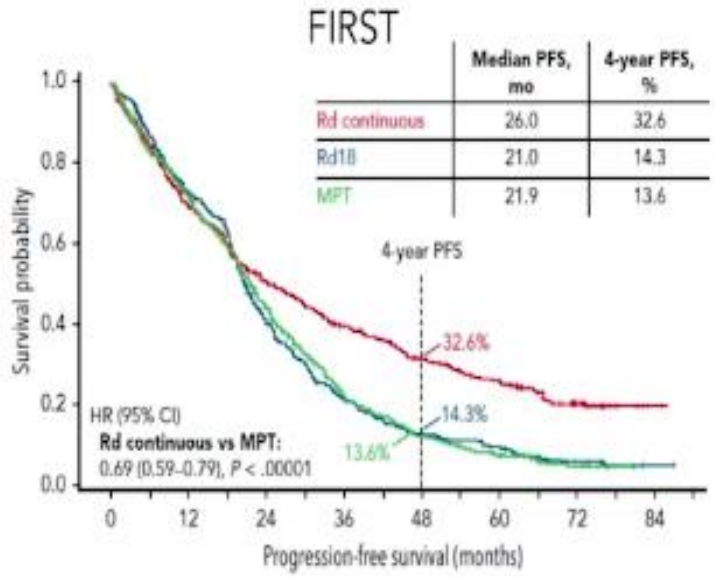


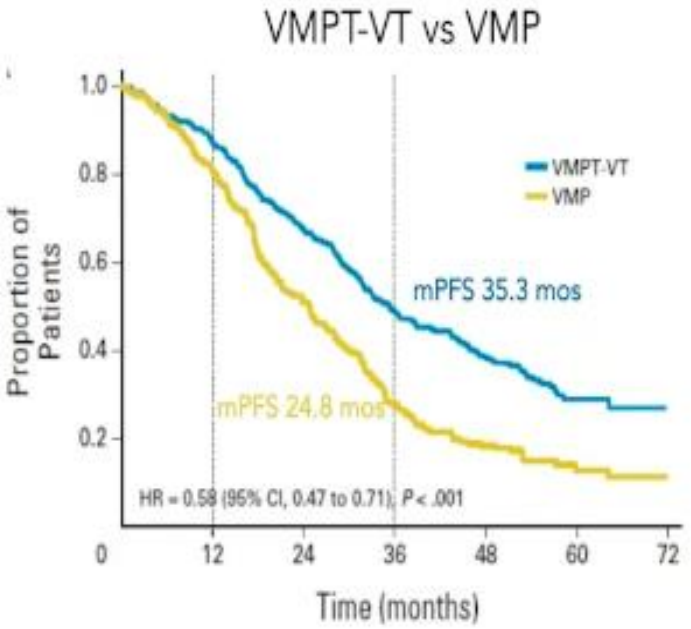
Survival Outcomes[b]	Continuous Len/Dex (n = 535)	Len/Dex x 18 Cycles (n = 541)	MPT x 18 Cycles (n = 547)
Median PFS, mo	26*	21†	21
Median OS, mo	59	56	51

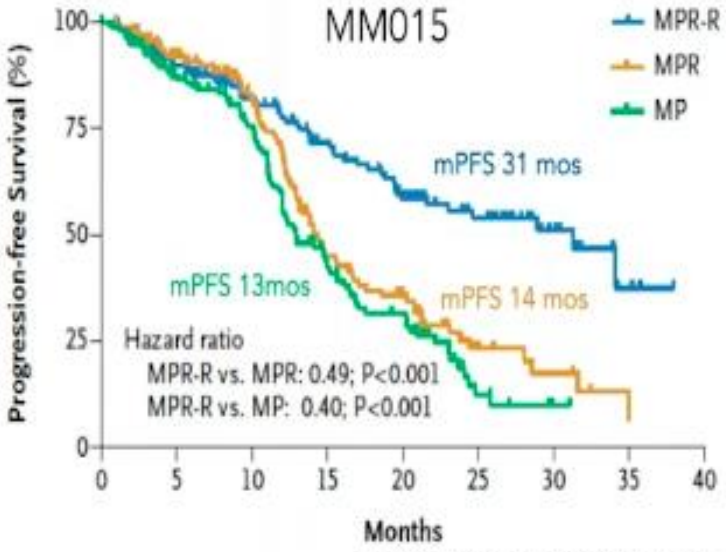
*HR for continuous Len/Dex vs MPT: 0.72 ($P < .001$). †HR for continuous Rd vs 18 cycles Rd: 0.70 ($P < .001$).

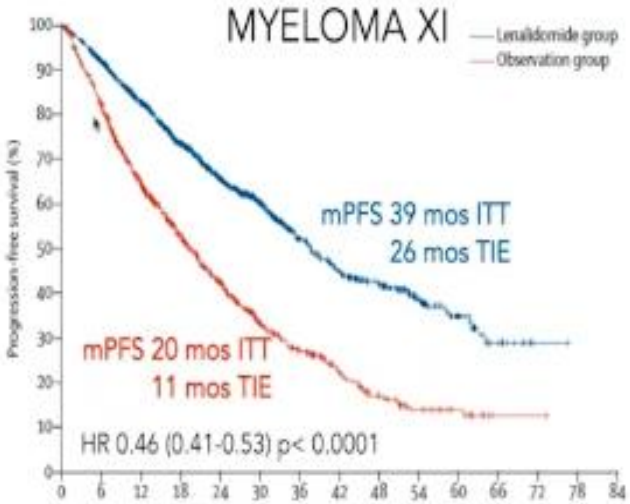
a. Facon T, et al. *Blood*. 2018;131:301-310; b. Benboubker L, et al. *N Engl J Med*. 2014;371:906-917.

Superior survival (PFS) outcomes with continuous vs fixed therapy









Facon et al Blood 2018; Palumbo et al JCO 2014; Palumbo et al NEJM 2012; Jackson et al Lancet Oncol 2019

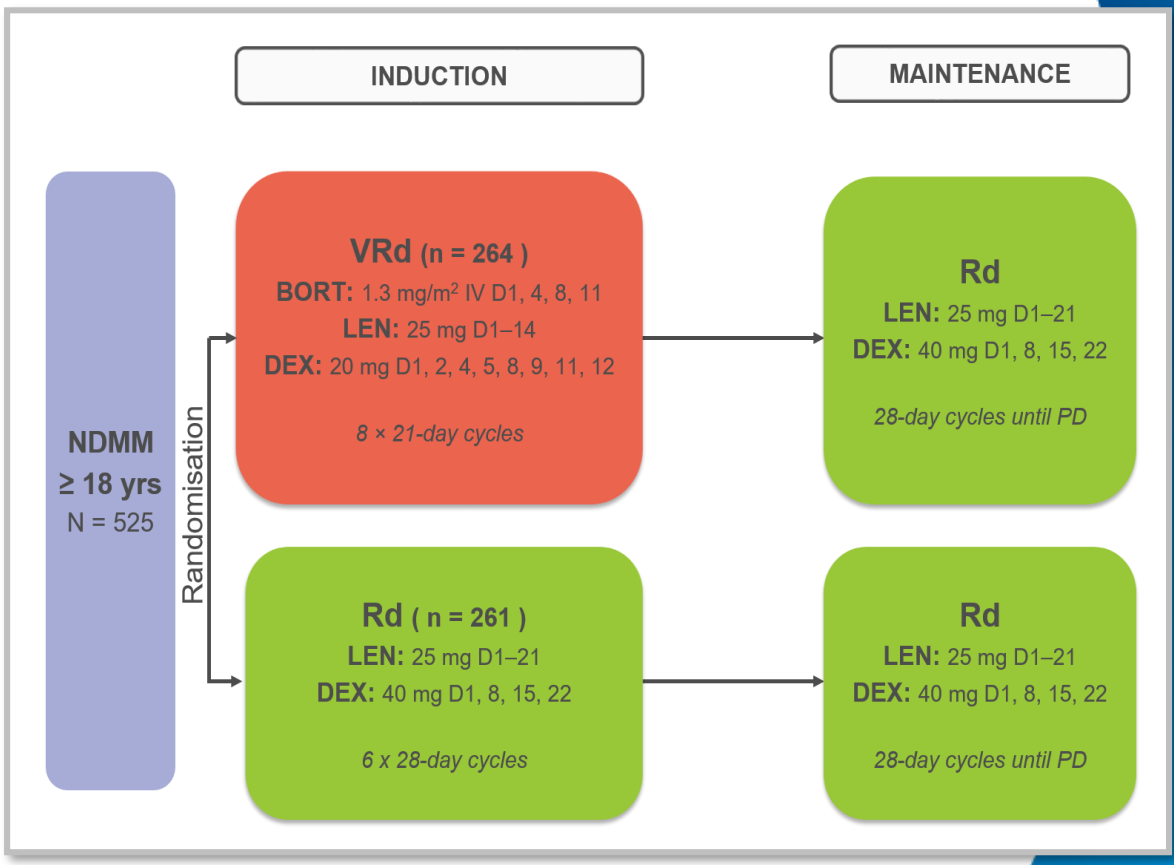
SWOG S0777: Study Design

Phase 3 trial of RVD versus RD as initial therapy in NDMM patients with no immediate intent to undergo ASCT, irrespective of eligibility

- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, ORR, safety

• Lo studio è stato condotto in 139 centri SWOG e del *National Cancer Trials Network*

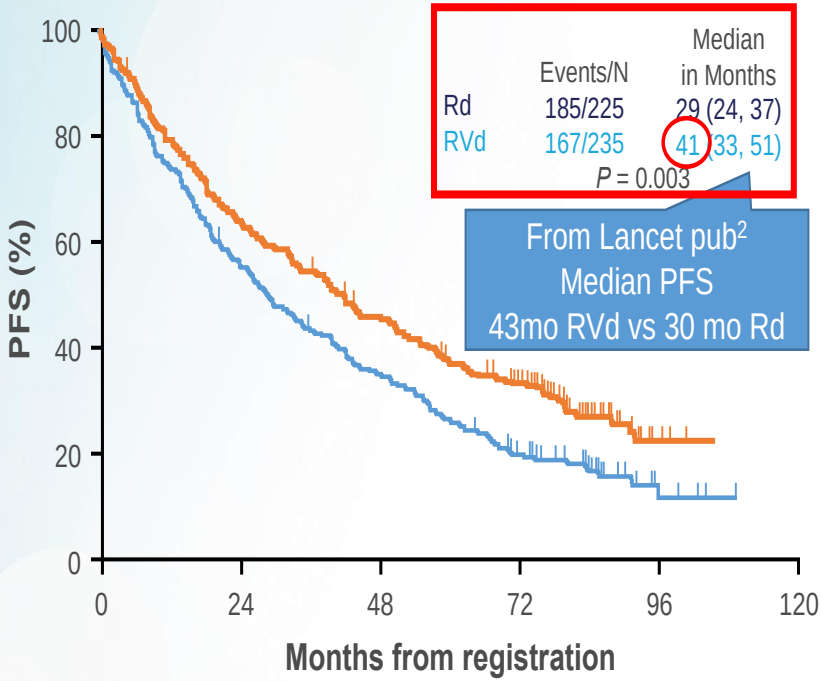
• I pazienti sono stati randomizzati tra aprile 2008 e febbraio 2012



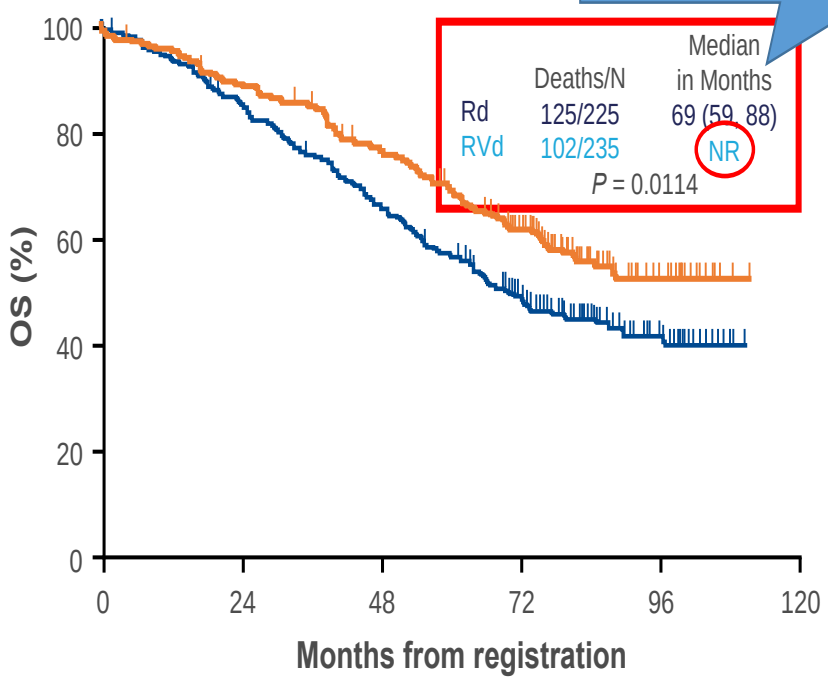
SWOG S0777: Updated PFS and OS

Median follow-up 84 mos (7 years)[1]

PFS[1]



OS[1,a]



Clinically meaningful and statistically significant benefit in favour of RVD

[a] RVd: 55% OS at 7 years.

Mo, months; NR, not reached; OS, overall survival; PFS, progression-free survival; pub, publication; Rd, lenalidomide and dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone.

1. Durie B. ASH 2018. Abstract 1992; 2. Durie B, et al. Lancet. 2017;389:519–527. Durie B. Blood Cancer Journal 2020 (10) 53

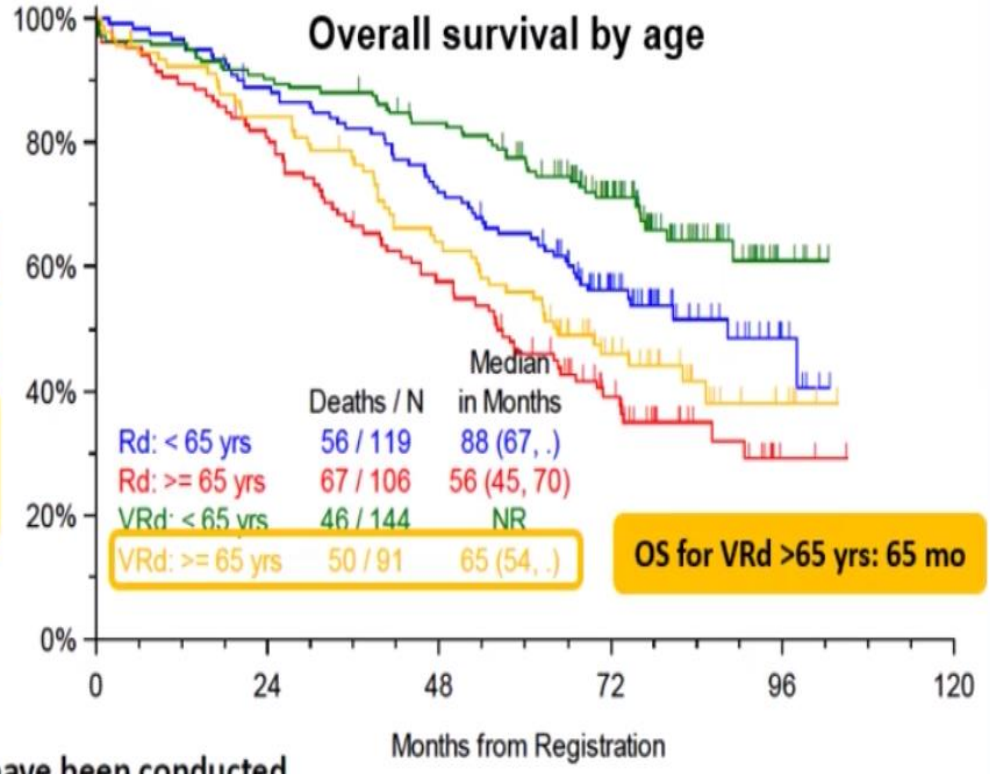
VRd-Rd vs continuous Rd: SWOG SO777 trial

Impact of age on outcomes

Age ≥65 years 43% overall, VRd 38%

Median PFS (months)

Age (years)	VRd	Rd
<65	48	34
≥65	34	24
>75	34	17



*For all analyses, both SWOG and IRC assessments have been conducted using the fully updated datasets with current datalock in May 2018

VRd improved outcome compared with Rd, irrespective of age

Durie B et al. ASH 2018, abstract 1992, poster presentation; Durie B et al BCJ 2020

V, bortezomib; R, lenalidomide; d, dexamethasone; PFS, progression-free survival; OS, overall survival; p, p-value; yrs, years, mo, months.

Modified VRd (VRd-lite)

Phase 2 Study

Induction (cycles 1-9)
Repeat q35 days × 9 cycles

Lenalidomide 15 mg po days 1-21
Bortezomib 1.3 mg/m^2 sc* days 1, 8, 15, 22
Dexamethasone 20 mg po days 1, 2, 8, 9, 15, 16, 22, 23 (patients ≤75 years)
Dexamethasone 20 mg po days 1, 8, 15, 22 (patients >75 years old)

↓

Consolidation (cycles 10-15)
Repeat q28 days × 6 cycles

Lenalidomide 15 po days 1-21 (or last tolerated dose as of cycle 9)
Bortezomib 1.3 mg/m^2 sc days 1, 15 (or last tolerated dose as of cycle 9)

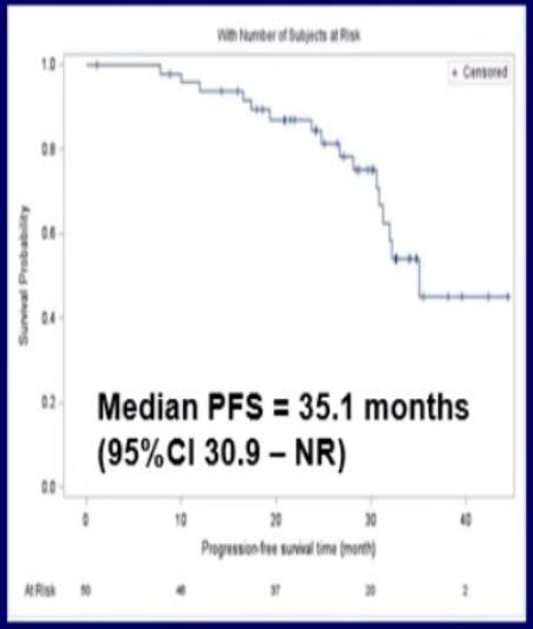
* The first 10 patients received bortezomib intravenously for cycle 1 only followed by subcutaneous administration. Subsequent patients received bortezomib subcutaneously.

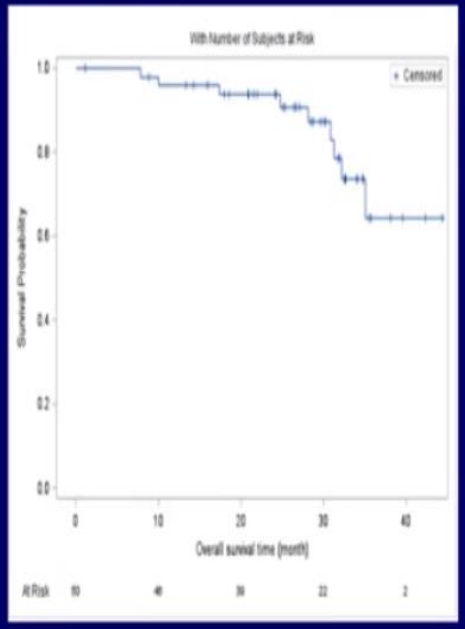
Median age 73 years

ORR 86%, ≥VGPR 66%, ≥CR 44%

Any grade PN 60%, Grade 3-4 PN 2%

Grade 3-4 AEs: Fatigue 16%, Rash 10%, Neutropenia 14%





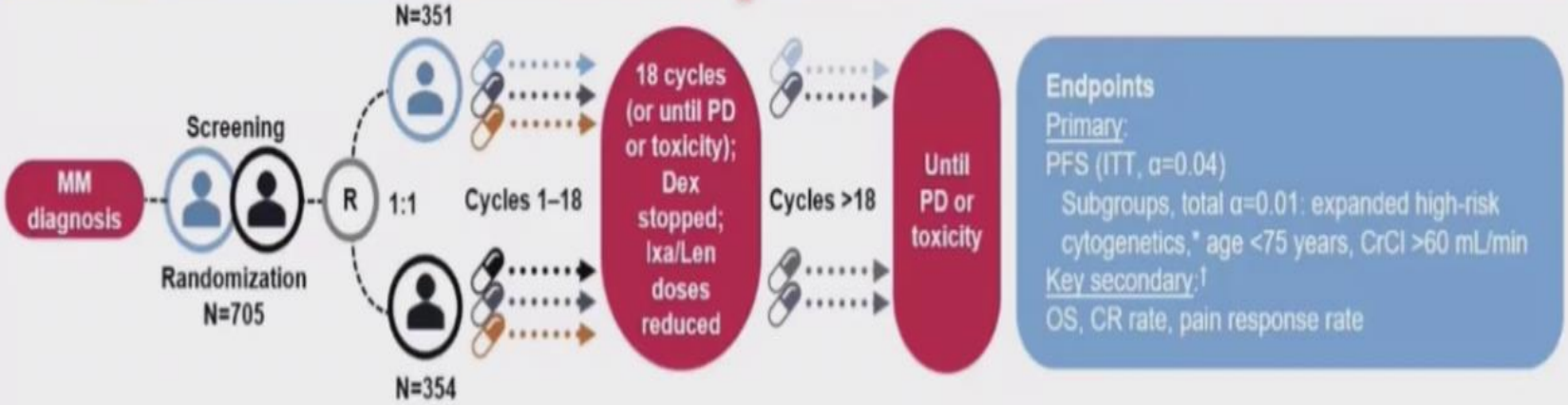
VRd-lite is well-tolerated and highly effective in TNE patients with robust PFS and OS.

MM, multiple myeloma; V, bortezomib; R, lenalidomide; d, dexamethasone; No., N, number.

O'Donnell et al, Br J Haematol 2018;182:222

TOURMALINE-MM2: Phase 3 study of ixazomib-Rd vs placebo-Rd in transplant-ineligible NDMM patients

Inclusion criteria	Exclusion criteria
Adult NDMM patients with measurable disease diagnosed per IMWG criteria	Prior treatment for MM
Eligible for Rd treatment and ineligible for ASCT	Current uncontrolled cardiovascular conditions
ECOG PS of 0–2	Inability or unwillingness to receive thromboembolism prophylaxis
Adequate hematologic and hepatic function	Localized radiotherapy, major surgery, or serious infection within 14 days prior to randomization
Calculated CrCl ≥30 mL/min	Peripheral neuropathy of grade ≥2 or grade 1 with pain

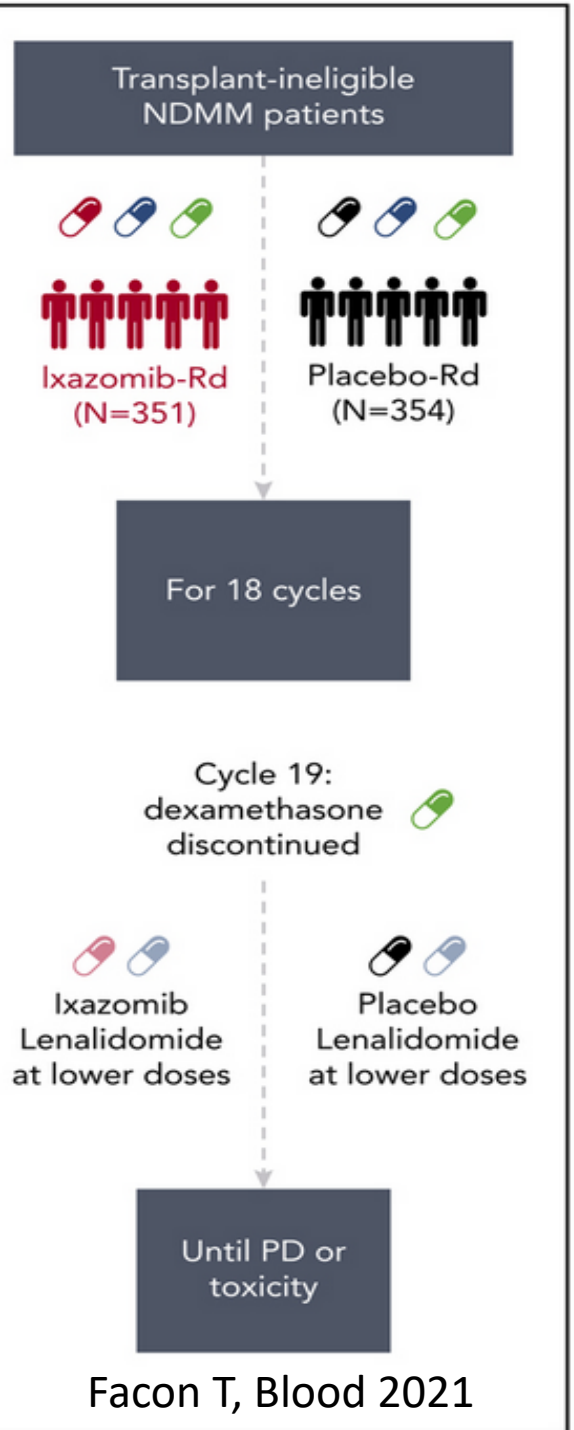


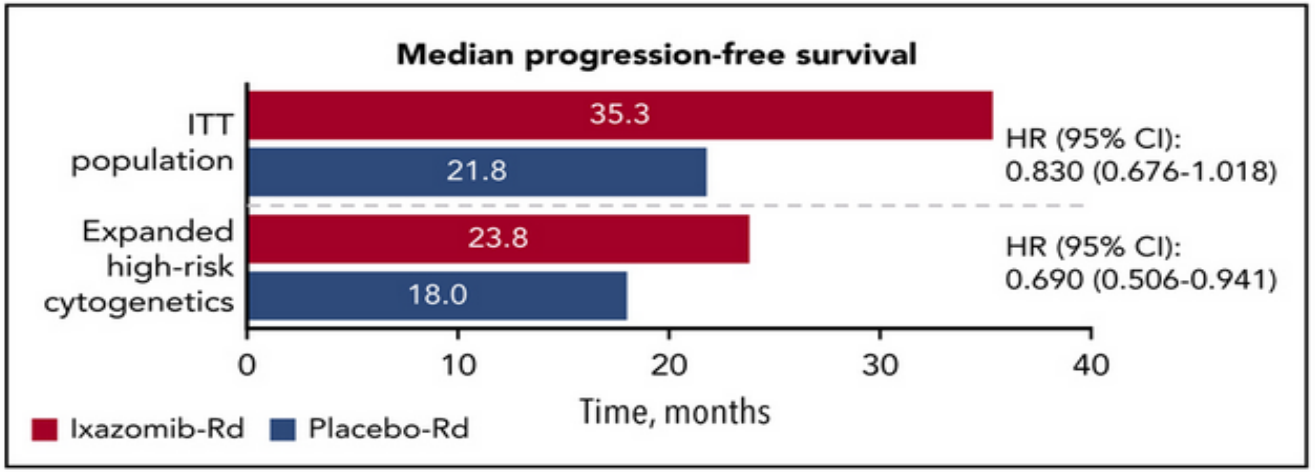
Stratification:
- Age <75 vs ≥75 years
- ISS disease stage at screening: I or II vs III
- BPI-SF worst pain score: <4 vs ≥4

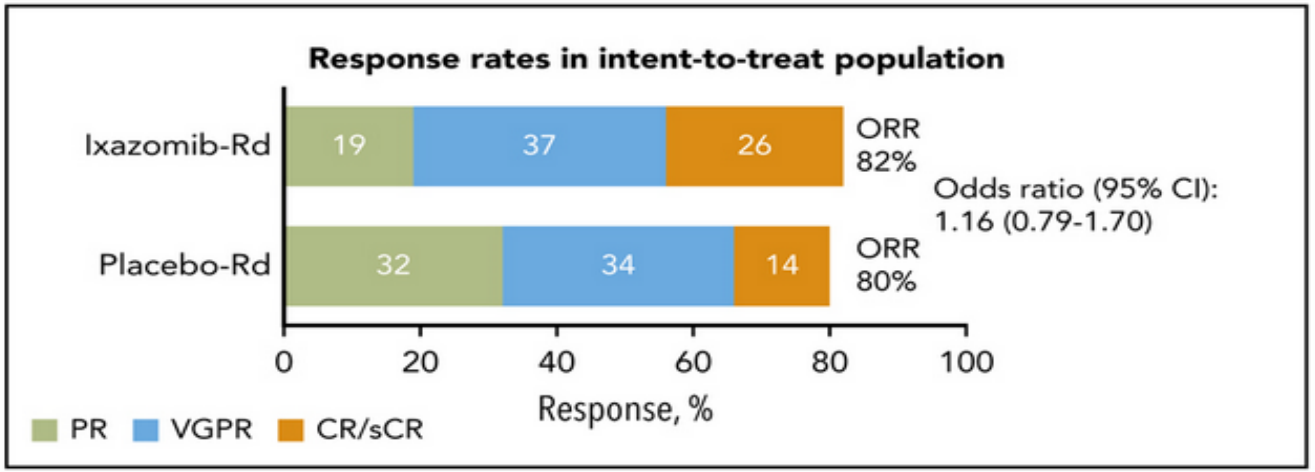
Ixa 4 mg	Ixa 3 mg	Days 1, 8, 15	28-day cycles
Len 25 (10‡) mg	Len 10 mg	Days 1–21	
Placebo	Placebo	Days 1, 8, 15	
Dex 40 (20§) mg		Days 1, 8, 15, 22	

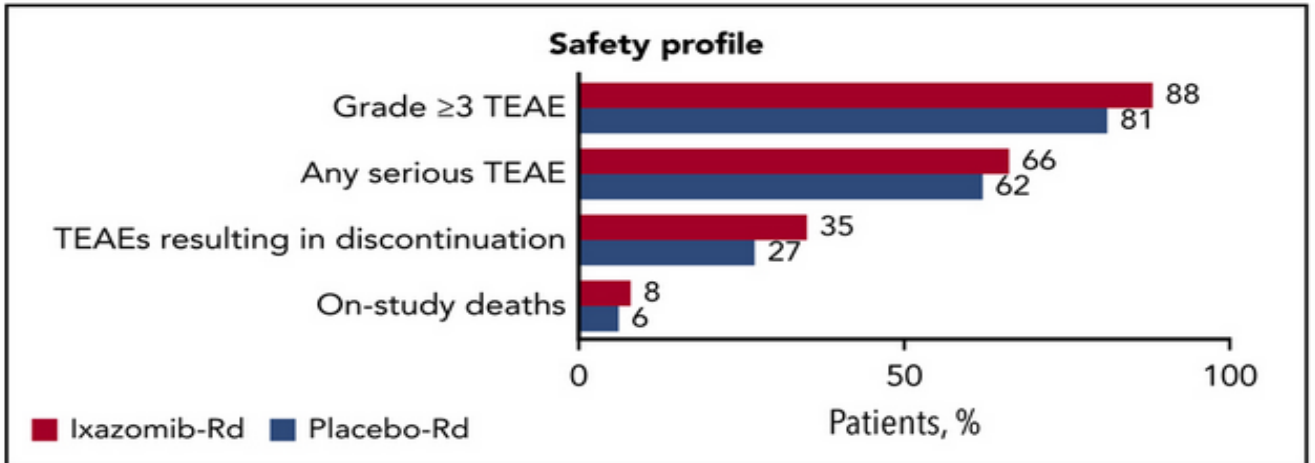
*Includes t(4;14), t(14;16), del(17p), amp(1q21); †Additional secondary endpoints included TTP and safety; ‡Patients with renal impairment; §Patients aged >75 years.
ASCT, autologous stem cell transplant; BPI-SF, Brief Pain Inventory-Short Form worst pain; CR, complete response; CrCl, creatinine clearance; Dex, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; ISS, International Staging System; ITT, intent-to-treat; Ixa, ixazomib; Len, lenalidomide; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomization; TTP, time to progression.

Facon, ASH 2020

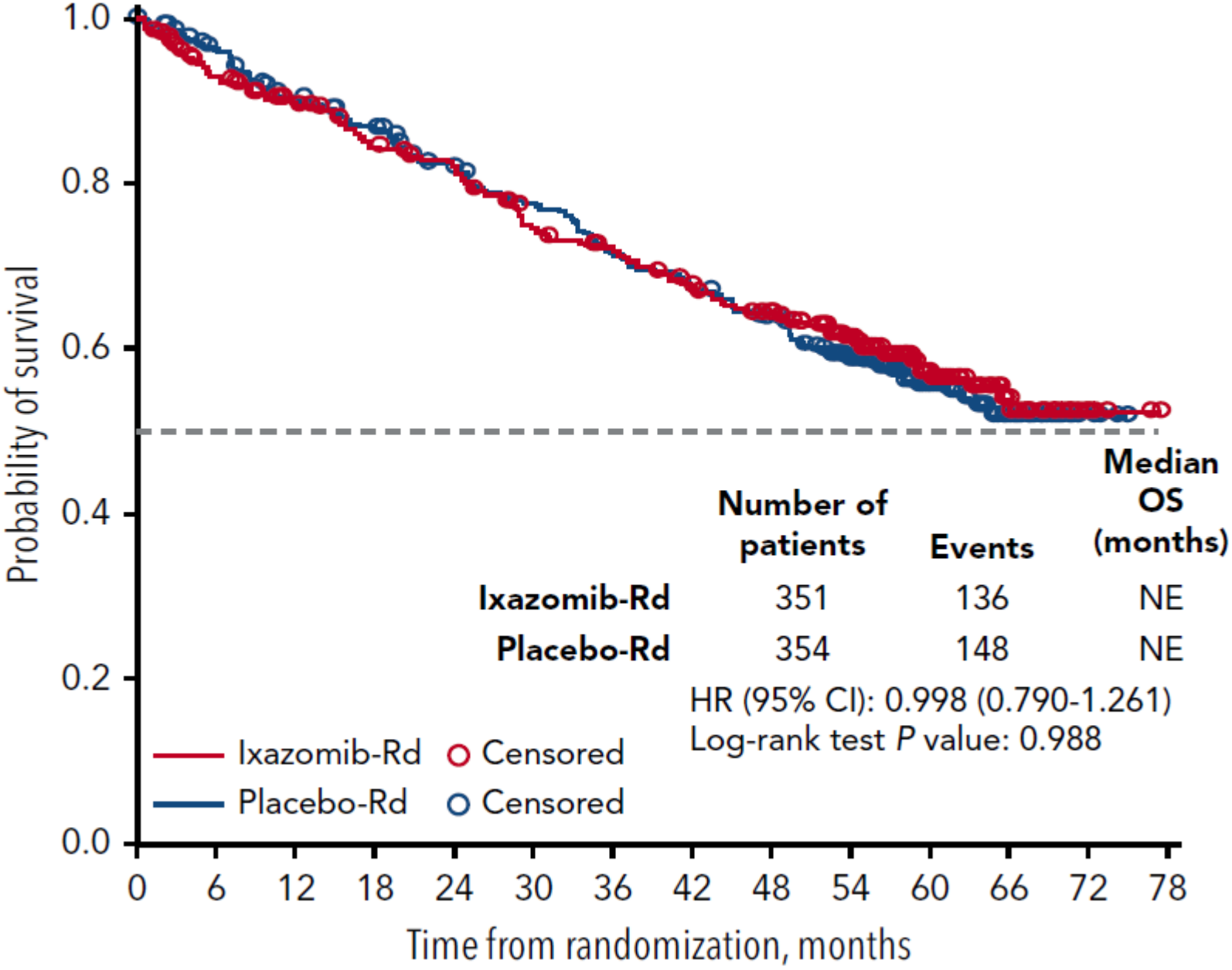






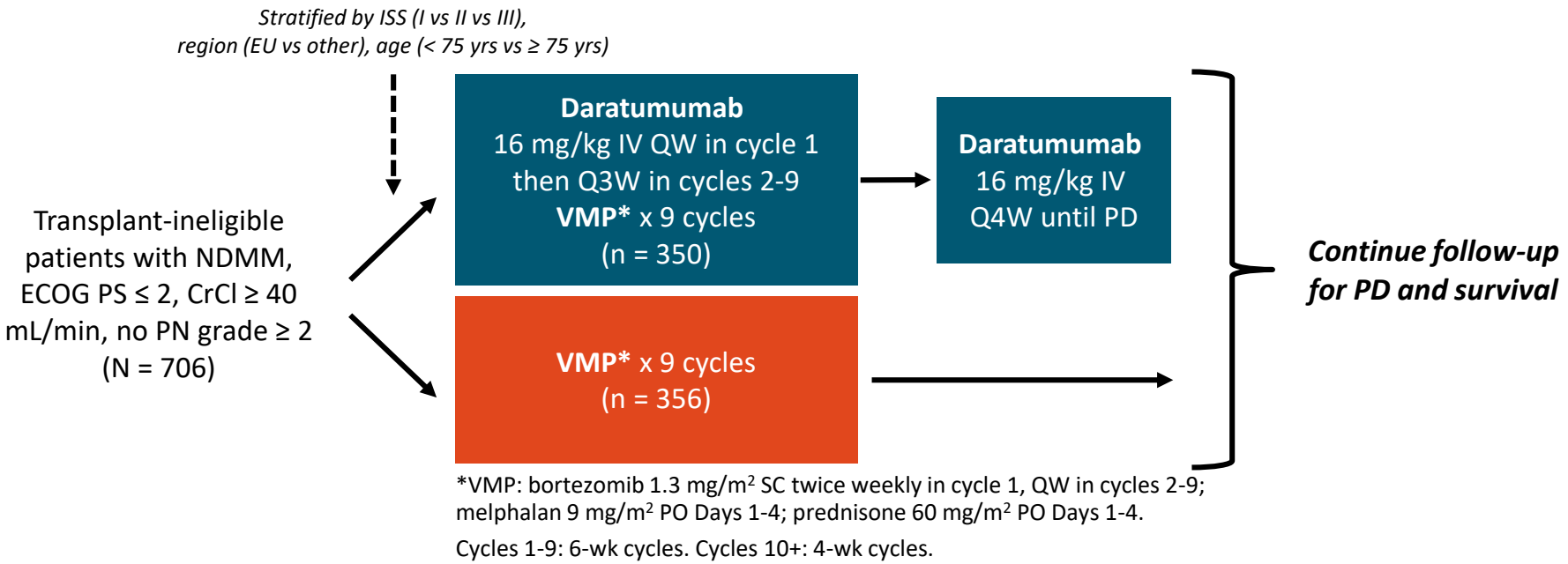


Facon T, Blood 2021



Facon T, Blood 2021

ALCYONE: Open-Label Phase III Study Design

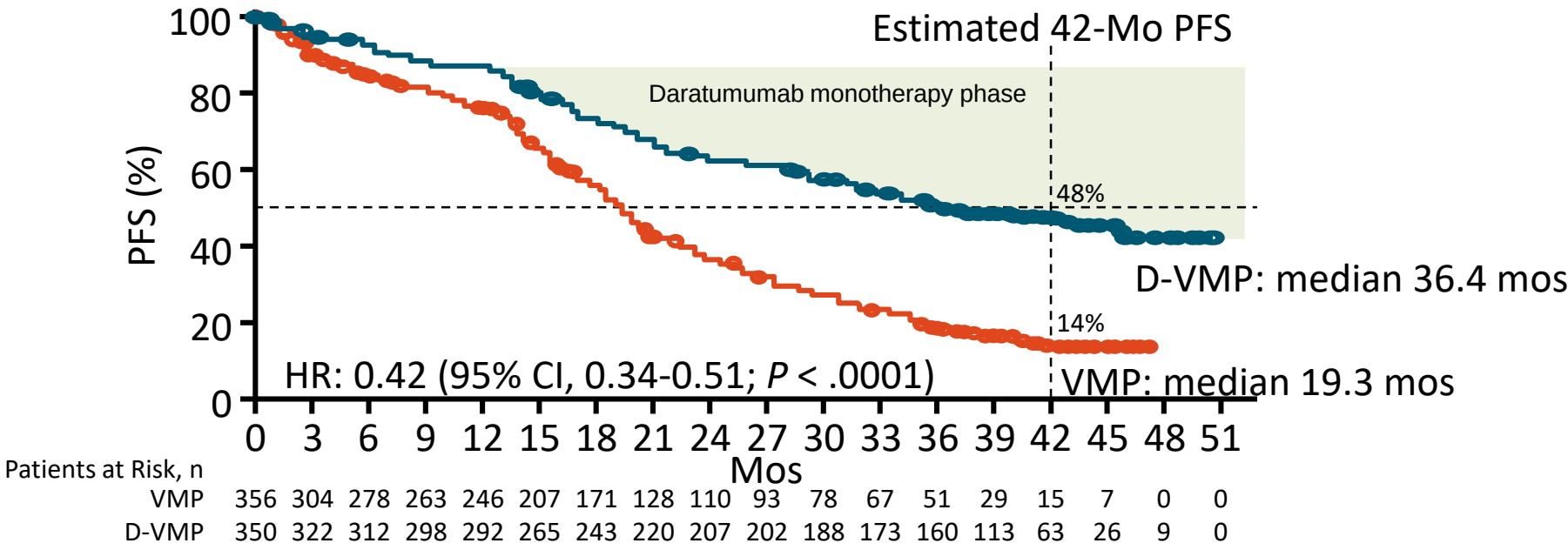


*VMP: bortezomib 1.3 mg/m^2 SC twice weekly in cycle 1, QW in cycles 2-9; melphalan 9 mg/m^2 PO Days 1-4; prednisone 60 mg/m^2 PO Days 1-4.

Cycles 1-9: 6-wk cycles. Cycles 10+: 4-wk cycles.

Mateos. ASH 2019. Abstr 859.

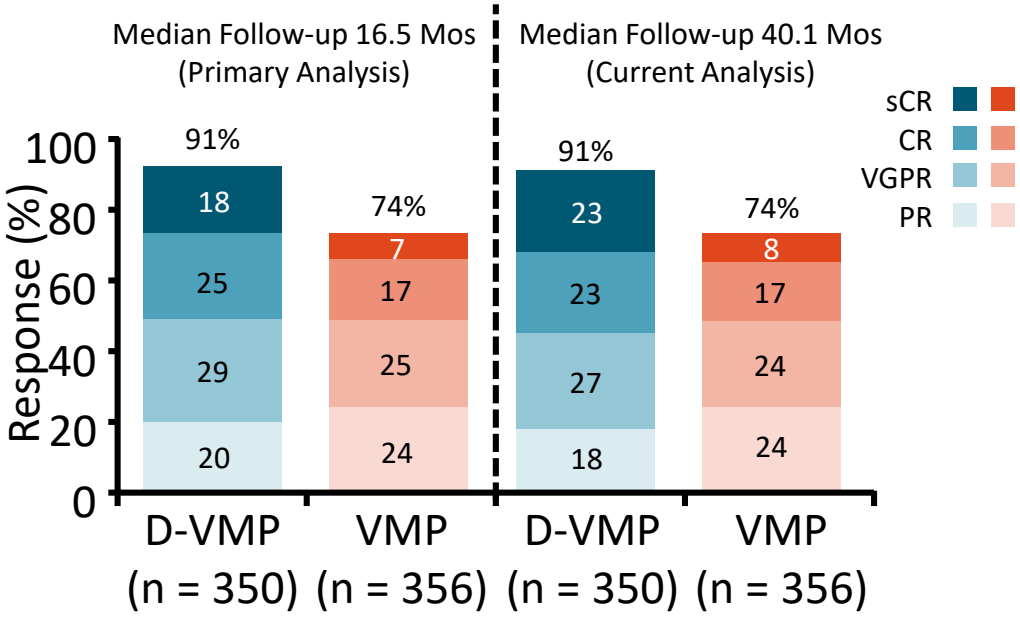
ALCYONE: PFS

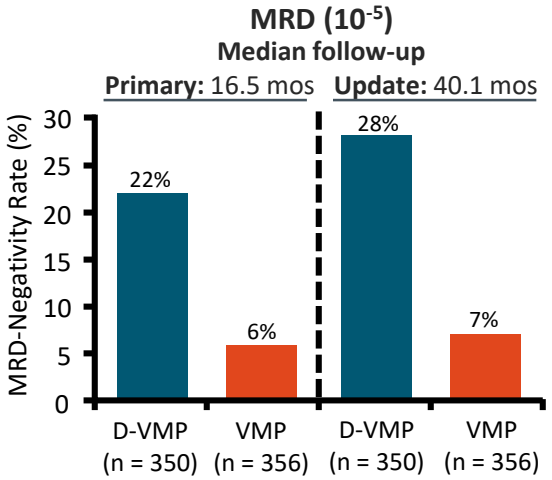


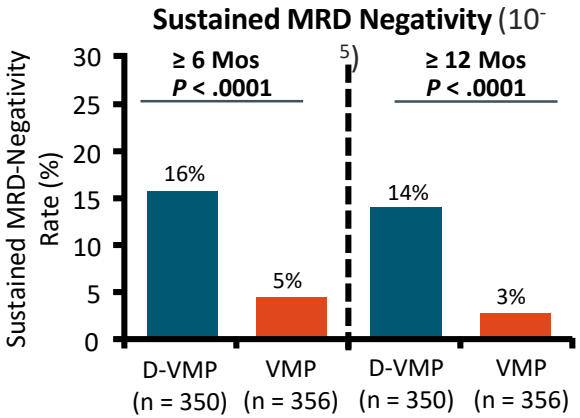
- D-VMP also conferred PFS2 benefit vs VMP: Estimated 42-Mo PFS2: 68% vs 50% (HR: 0.55; 95% CI: 0.43-0.71; *P* < .0001)

Mateos. ASH 2019. Abstr 859.

ALCYONE: Response



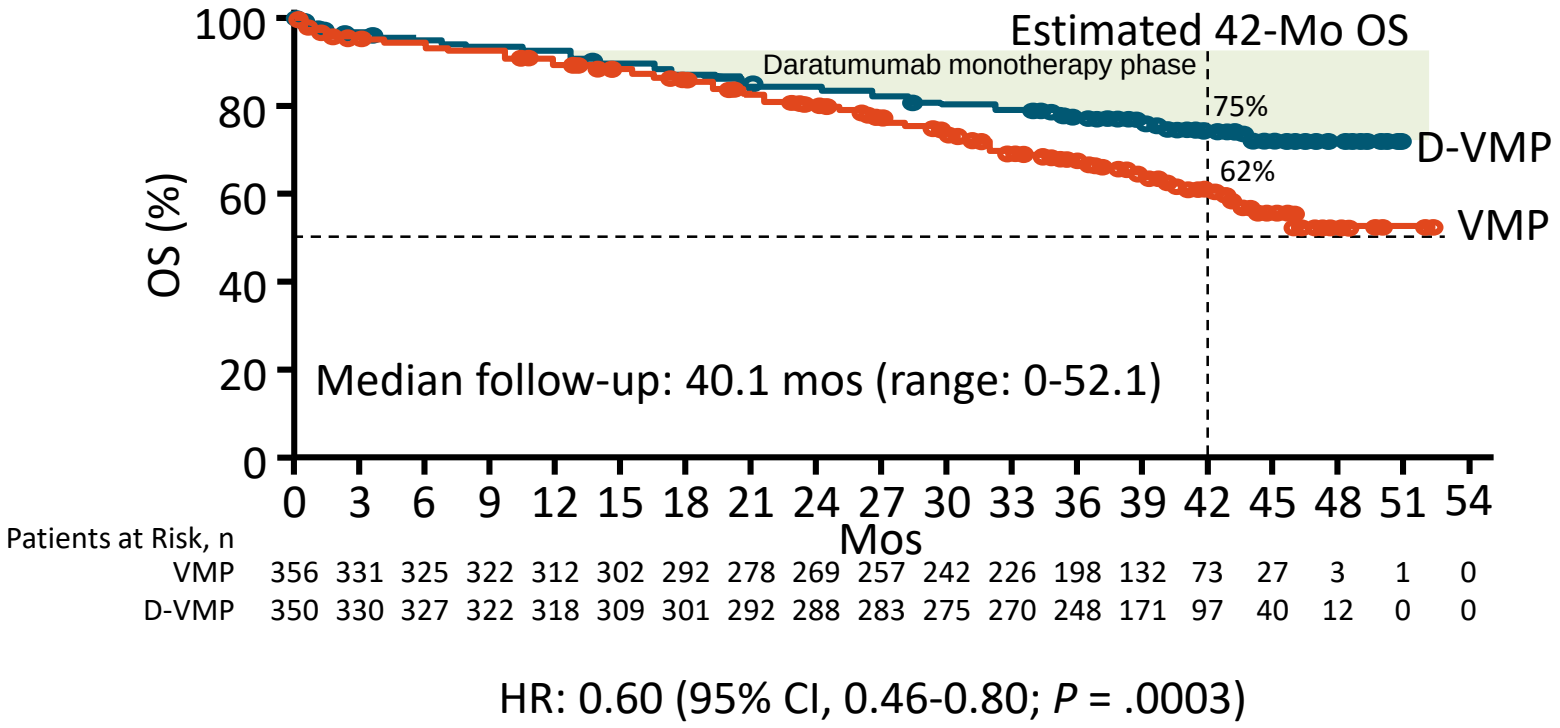




Mateos. ASH 2019. Abstr 859

ALCYONE: OS

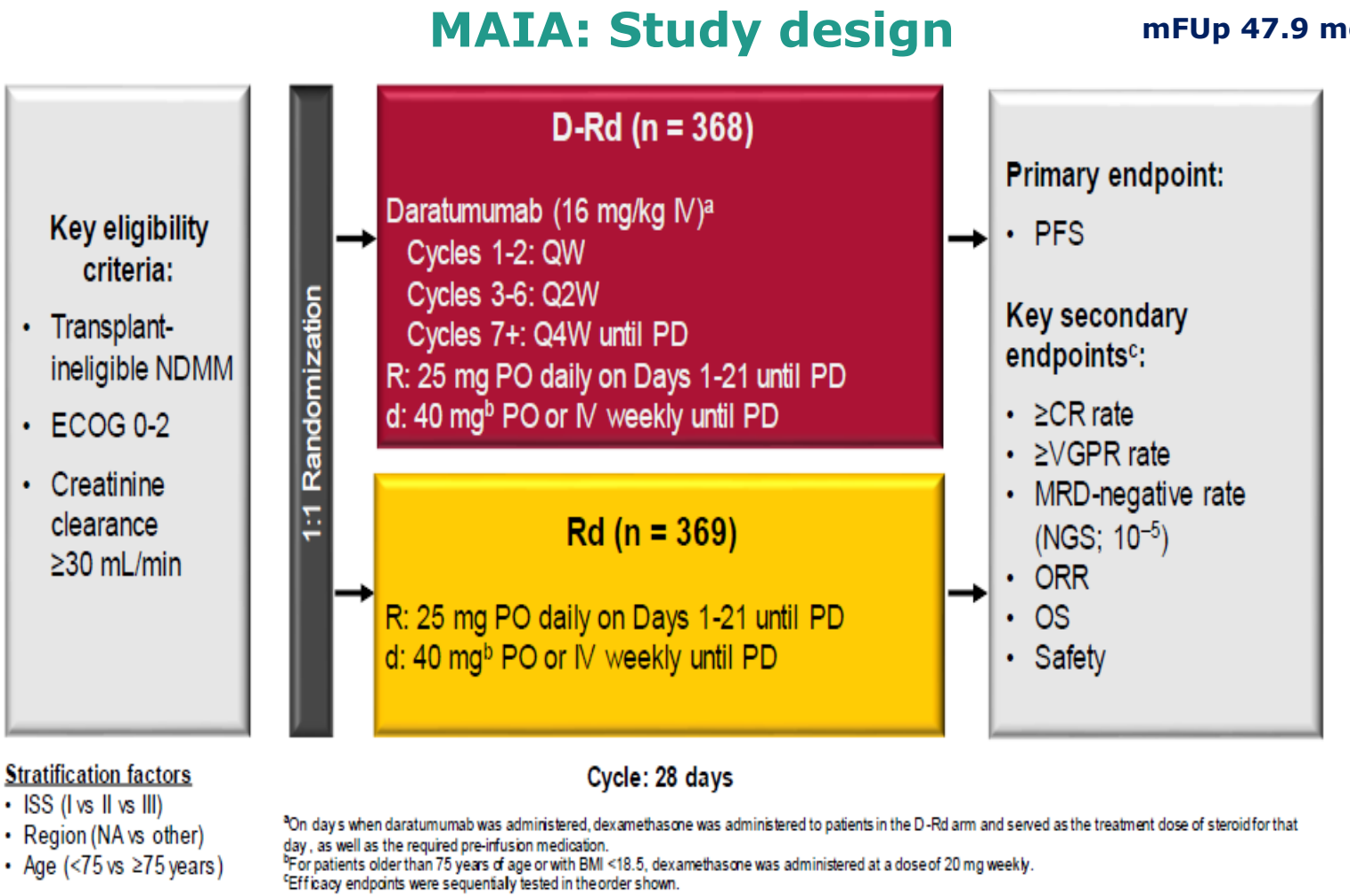
- Pre-specified analysis after 209 deaths occurred



HR: 0.60 (95% CI, 0.46-0.80; *P* = .0003)

Mateos. ASH 2019. Abstr 859

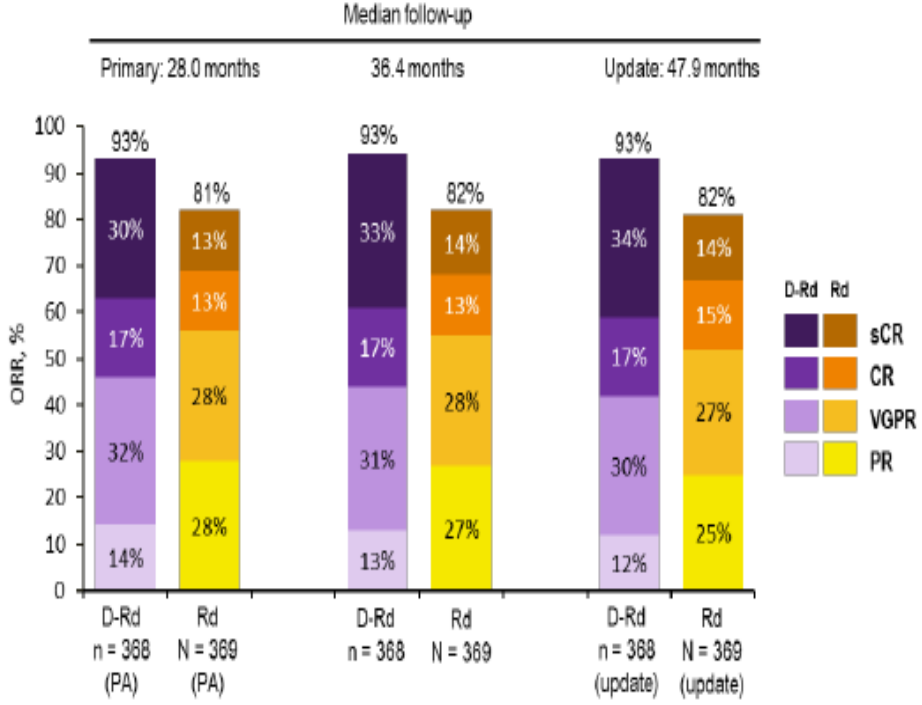
Daratumumab in combination with VMP or RD regimen are a new treatment options for NDMM patients



Kumar et al. Abstract: #2276 62nd ASH Annual

Phase 3 MAIA Study: Updated Response

- Most common grade 3/4 AEs: neutropenia (50.0% vs 35.3%), anemia (11.8% vs 19.7%), lymphopenia (15.1% vs 10.7%), and pneumonia (13.7% vs 7.9%)

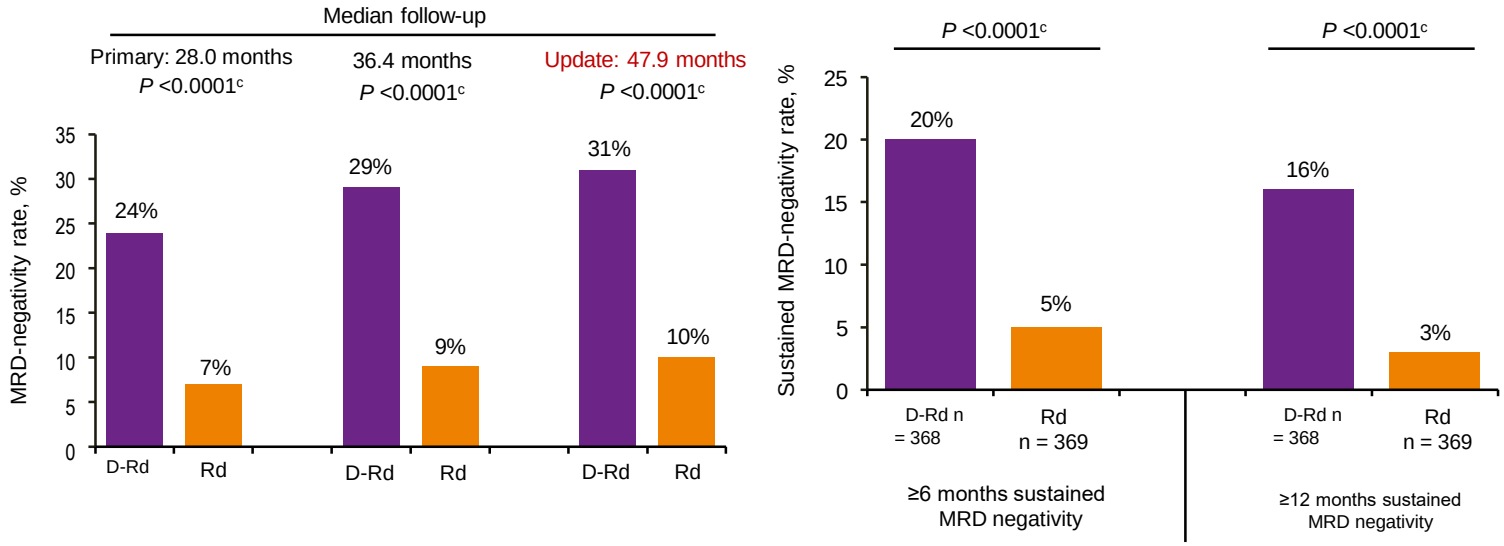


Adding DARA to Rd resulted in deeper responses with higher rates of ≥CR and ≥VGPR, compared with Rd alone

Kumar S et al, ASH 2020; abstract 2276

MRD-negativity Rate and Sustained MRD Negativity in Patients Treated with D-Rd versus Rd

mFUp 47.9 mo

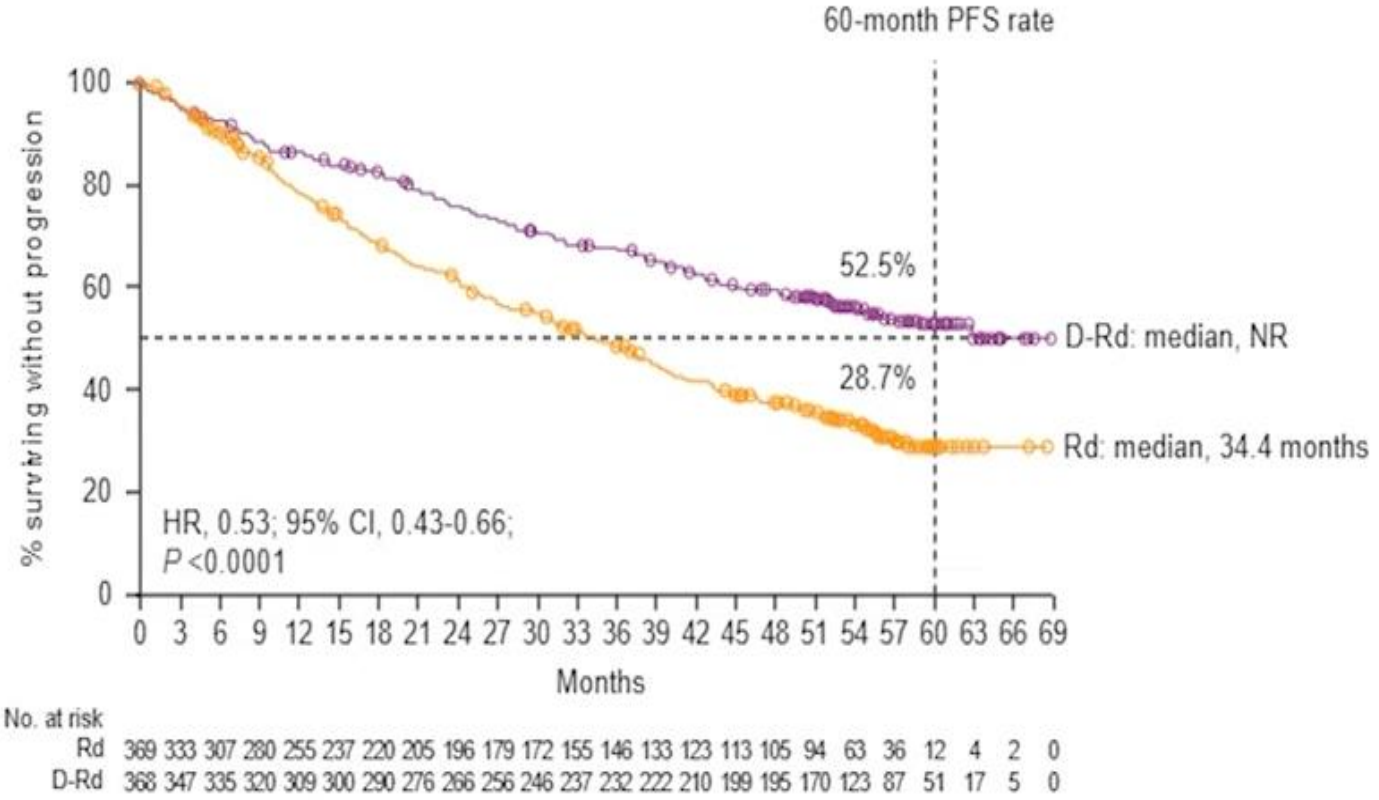


Significantly higher rates of MRD negativity and sustained MRD negativity were observed with D-Rd versus Rd alone

MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; PA, primary analysis; ITT, intent-to-treat. [a]ITT population. [b]Median follow-up of 47.9 months. [c]*P* value was calculated using Fisher's exact test.

Kumar et al. Abstract: #2276 62nd ASH Annual Meeting 2020

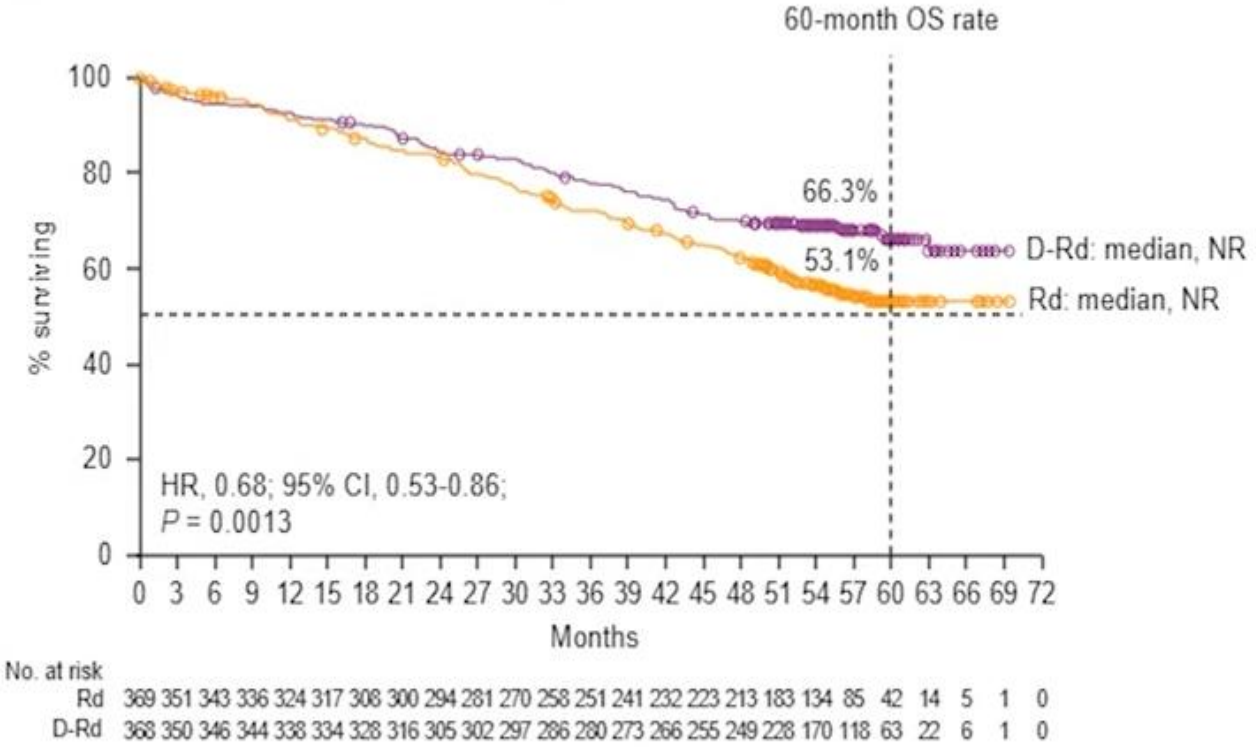
Progression Free Survival (PFS) data



- **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**

Facon T, EHA 2021

Overall Survival (OS) data



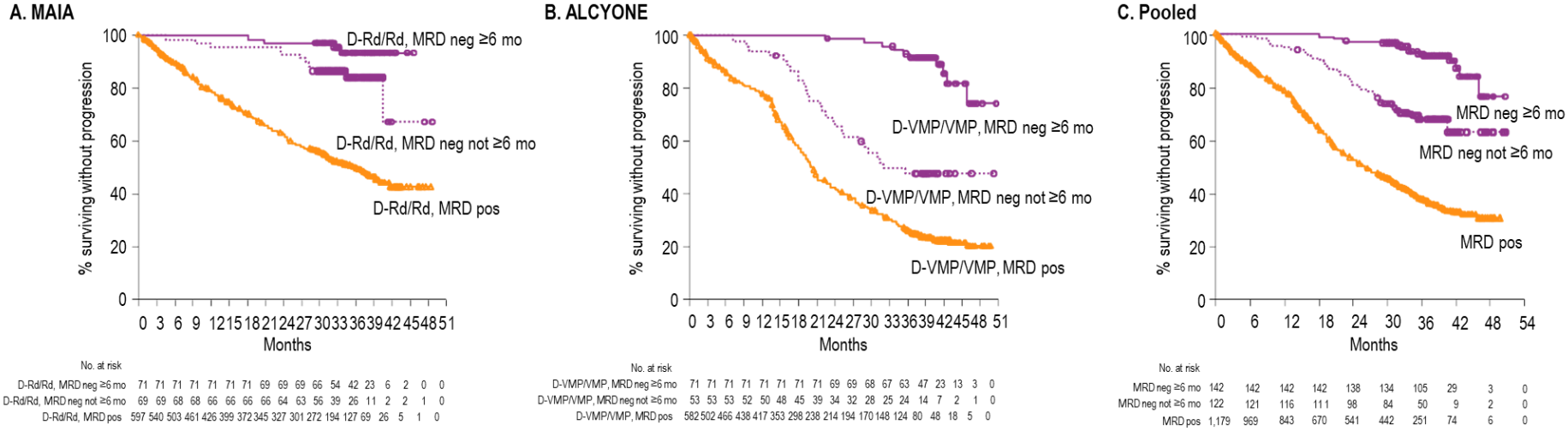
D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

Facon T, EHA 2021

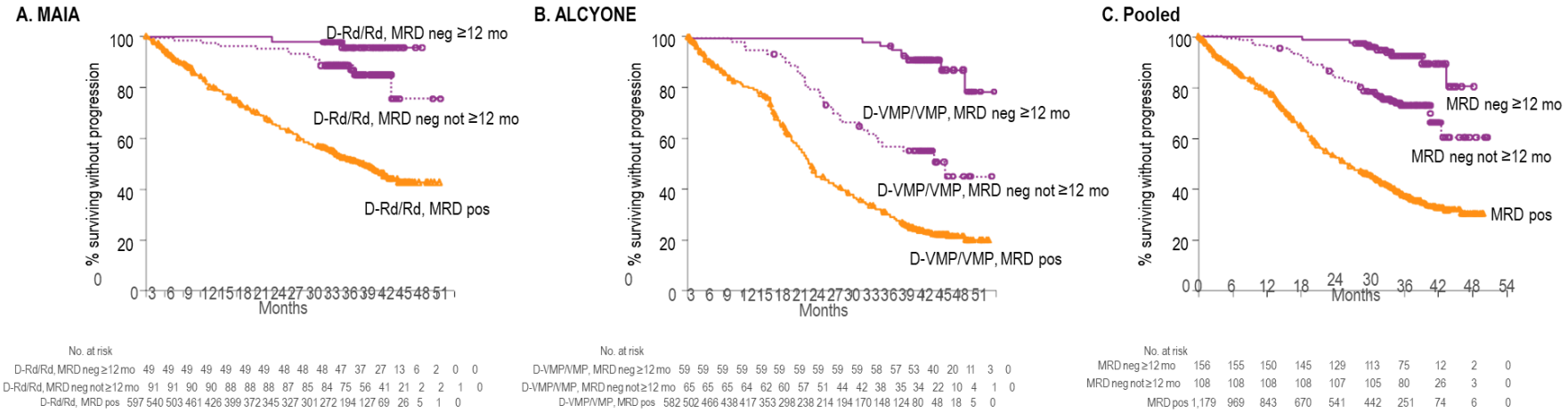
MAIA and ALCYONE: PFS Based on Sustained MRD

MAIA FUp 36.4 mo
ALCYONE FUp 40.1 mo

≥6 months



≥12 months

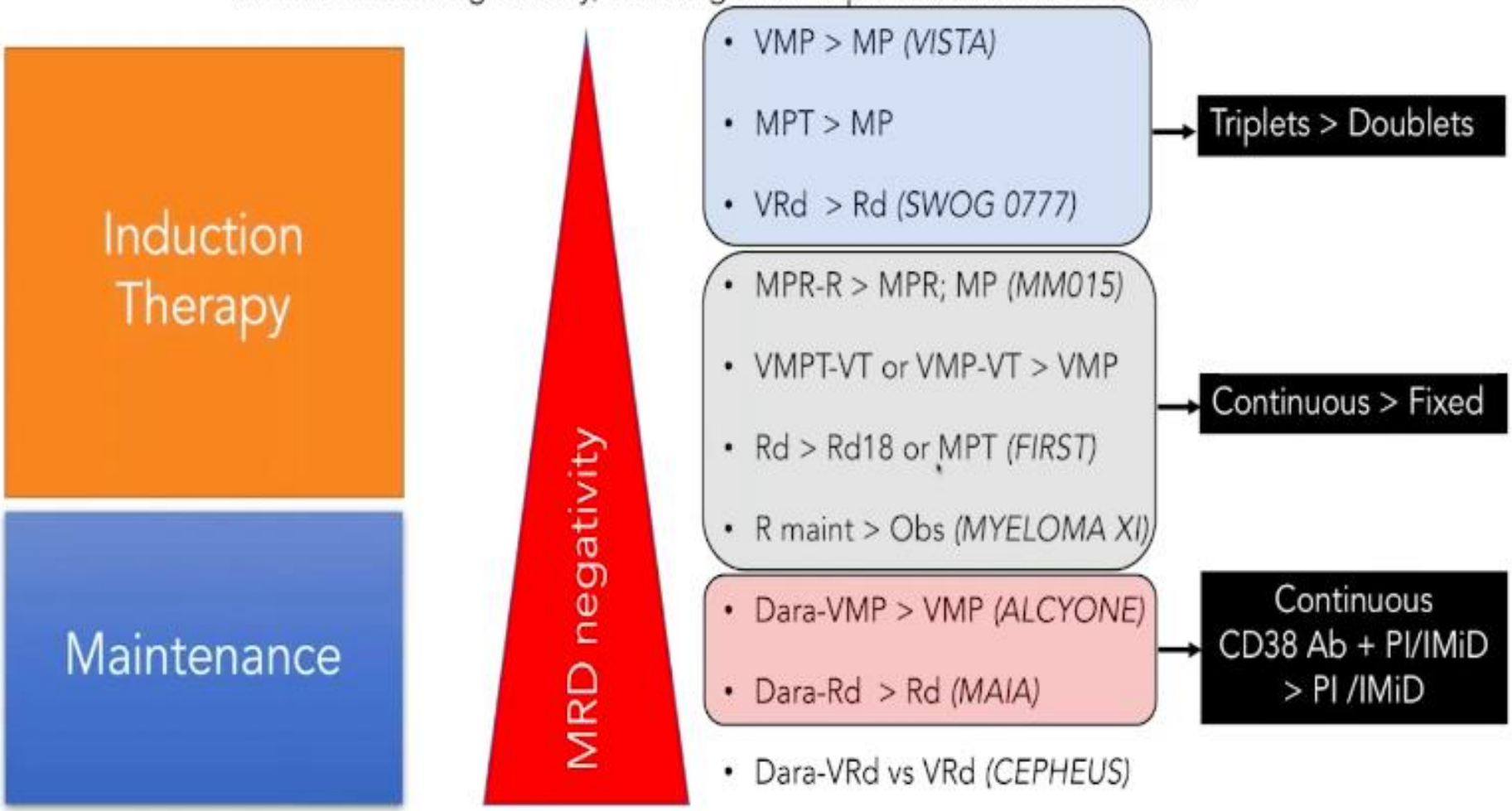


Both in MAIA and ALCYONE individually, as well as in the pooled analysis, durable MRD negativity lasting ≥6 & ≥12 months improved PFS compared with MRD-negative patients

San-Miguel et al. Abstract: #2317_ASH 2020

Therapy for **Transplant Ineligible** Newly Diagnosed Multiple Myeloma

The goal is to maximize the rate and durability of MRD negative disease, without increasing toxicity, resulting in an improved survival outcomes



NCCN Guidelines V.3.2022: Multiple Myeloma Primary Therapy for Non-Transplant Candidates

- Preferred Regimens
  - Bortezomib/lenalidomide/dexamethasone (category 1)
  - Daratumumab/lenalidomide/dexamethasone (category 1)
- Other recommended regimens
  - Carfilzomib/lenalidomide/dexamethasone
  - Ixazomib/lenalidomide/dexamethasone
  - Daratumumab/bortezomib/melphalan/prednisone (category 1)
  - Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Useful in certain circumstances
  - Bortezomib/dexamethasone
  - Bortezomib/cyclophosphamide/dexamethasone
  - Carfilzomib/cyclophosphamide/dexamethasone
  - Lenalidomide/low-dose dexamethasone (category 1)
  - Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients

NCCN Guidelines: Multiple Myeloma. V4.2022. Updated 12/14/21. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1445. Accessed 12/20/21.

Key Points: Yes, VRd is the preferred regimen in transplant-ineligible NDMM

- VRd has been the preferred initial regimen in transplant-ineligible MM patients since 2017. This regimen includes 2 highly active anti-myeloma drugs and significantly improves outcomes vs Rd alone
- While it is a positive that Dara-Rd has emerged as an alternate option, there are enduring benefits of VRd relative to Dara-Rd:
  - generalizability of VRd across the entire population
  - an opportunity for older, frailer patients to be able to continue on an all-oral regimen
  - increased convenience and flexibility - infusion center visits are not required
  - decreased risk of neutropenia, which may lead to significant infections, and
  - an option for continuous therapy… that both SWOG and MAIA showed the importance of
- In the absence of phase III data proving an OS benefit vs. Dara-Rd, VRd is still the 'go-to option' in this setting

Clinical Questions

In patients with newly diagnosed myeloma not eligible for transplant, should we use our best treatment first, or save them for later?

Is it better to use VRd first and a daratumumab-based regimen as subsequent treatment?

Is it better to use D-Rd first and a carfilzomib- or pomalidomide-based regimen as subsequent treatment?

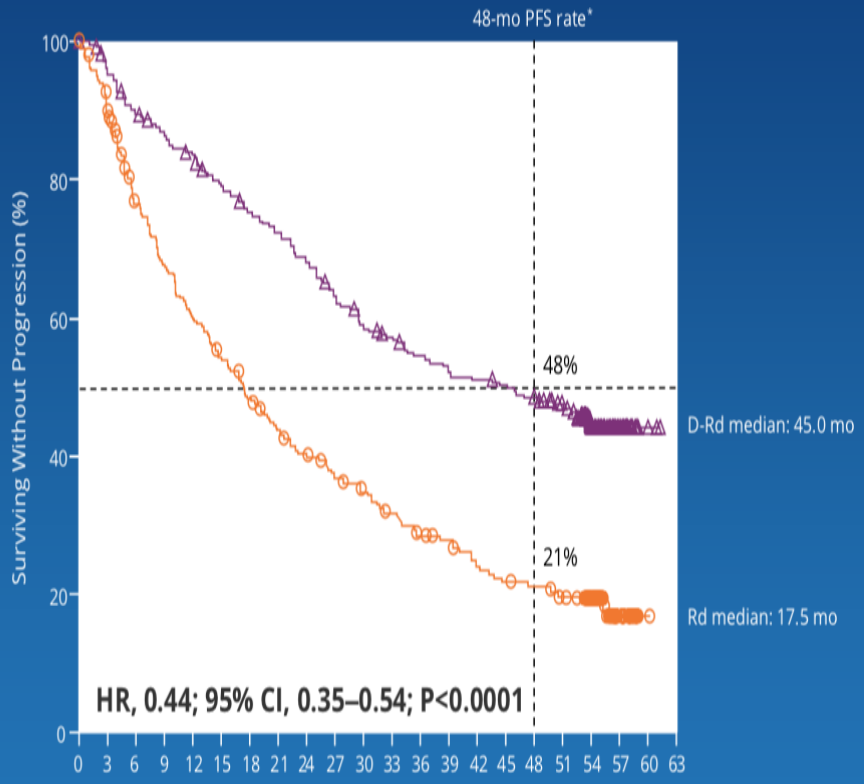
D-Rd, daratumumab, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone

Fonseca R, ASH 2021

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

POLLUX Showed a PFS Benefit of D-Rd vs Rd in RRMM

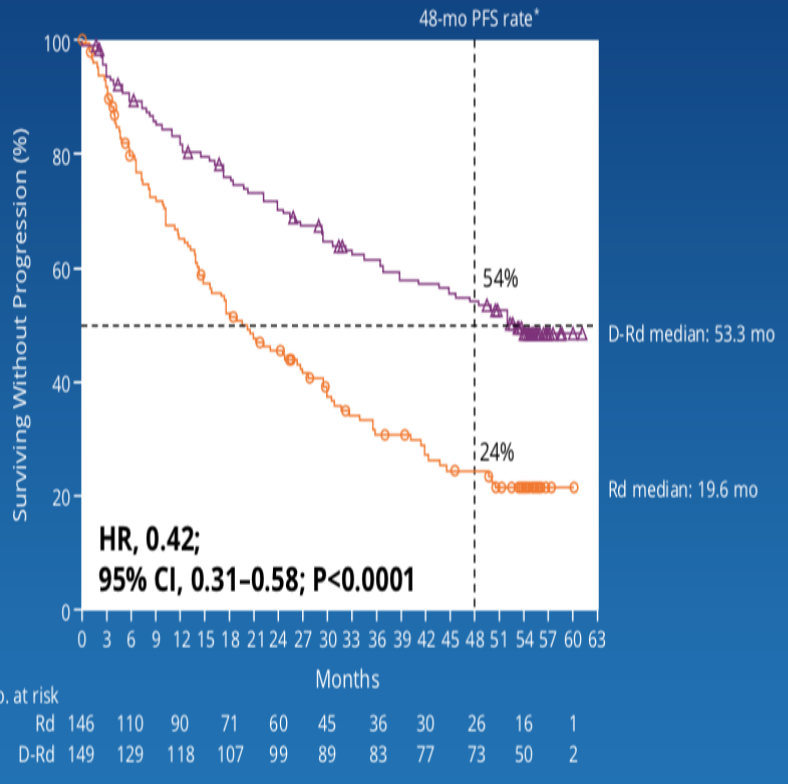
ITT Population



No. at risk

Rd	283	206	160	127	102	83	66	53	45	28	1
D-Rd	286	249	229	204	184	156	143	134	125	76	3

Patients With 1 Prior LOT



No. at risk

Rd	146	110	90	71	60	45	36	30	26	16	1
D-Rd	149	129	118	107	99	89	83	77	73	50	2

	MAIA	POLLUX
Median age, years	73	65
Prior ASCT, %	0	63

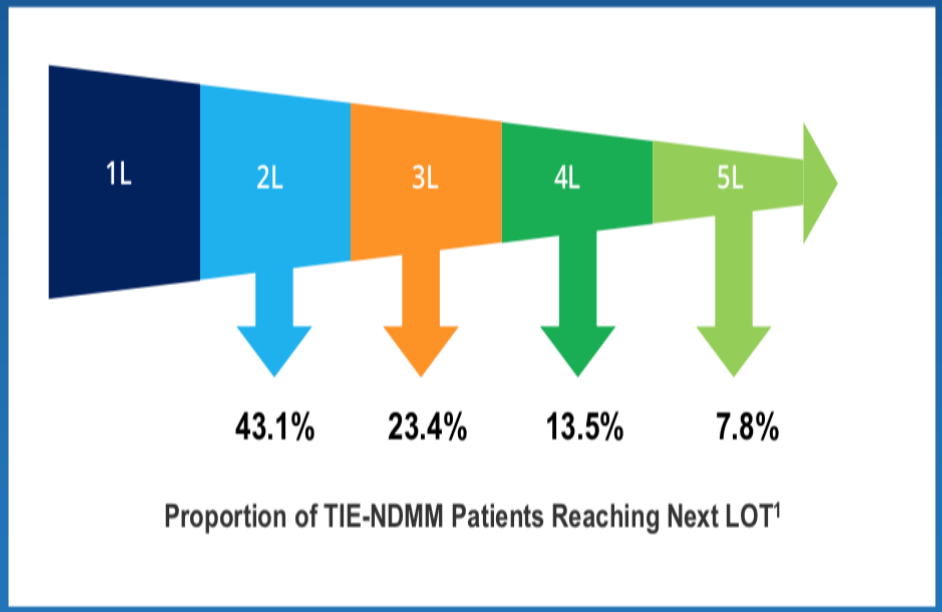
*Kaplan-Meier estimate

ASCT, autologous stem cell transplant; D-Rd, daratumumab, lenalidomide, and dexamethasone; HR, hazard ratio; ITT, intent-to-treat; LOT, line of therapy; MM, multiple myeloma; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma

Kaufman JL, et al. ASH 2019, Poster 1866.

Attrition Rates: >50% of Patients Receive Only First-Line Therapy in TIE NDMM

- Attrition rates between lines of therapy are high in MM[1-5]
- For patients who do receive >1 LOT, response rate and duration of response worsen with each subsequent LOT[2-5]
- Achieving the longest initial PFS is critical and enables more patients to benefit from next-generation treatments that are currently in development



L, line; LOT, line of therapy; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; TIE, transplant-ineligible

1. Fonseca R, et al. *BMC Cancer* 2020; 20:1087. 2. Raab MS, et al. *Br J Haematol* 2016; 175:66-76. 3. Yong K, et al. *Br J Haematol* 2016; 175:252-64. 4. Szabo AG, et al. *Clin Hematol Int* 2019; 1:220-28. 5. Verelst SGR, et al. *Hemasphere* 2018; 2:e45. Figure adapted from Fonseca et al. *BMC Cancer* 2020; 20:1087.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Data Sources and Assumptions Included in the Simulation

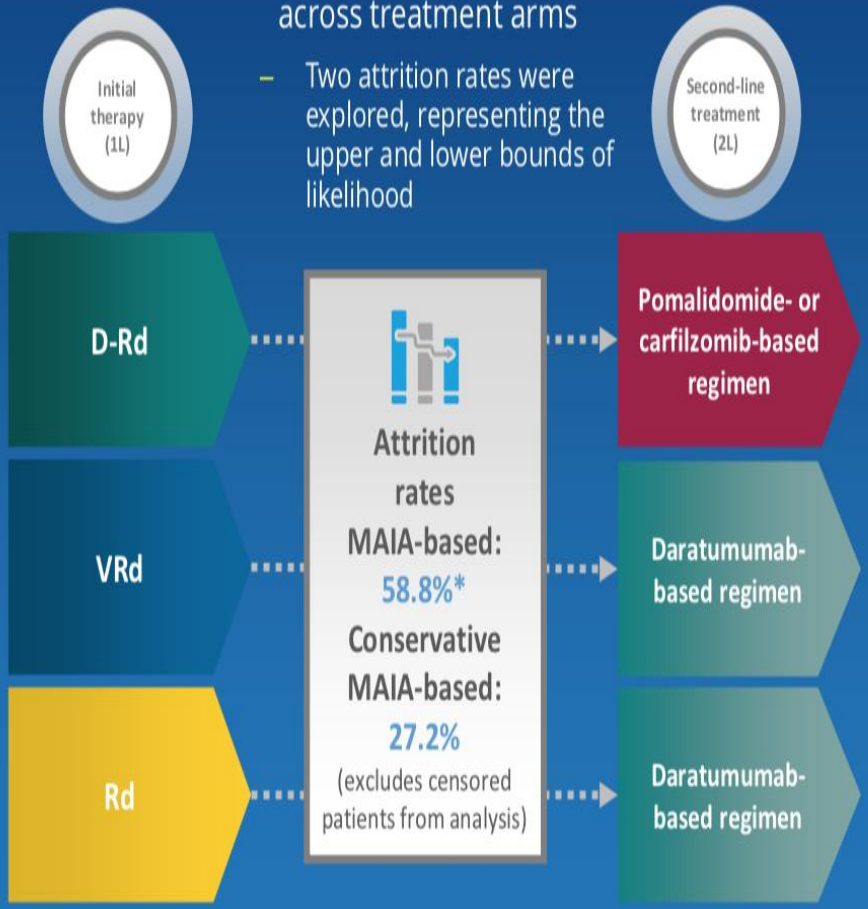
1. Time spent in 1L

- Derived from MAIA[1] (D-Rd, Rd) and Flatiron[2] (VRd)

Health state	Data source	Time period
1L D-Rd/Rd	MAIA	2015–2021
1L VRd	Flatiron	2011–2019

2. Attrition rates

- Assumed to be the same across treatment arms
  - Two attrition rates were explored, representing the upper and lower bounds of likelihood



3. Time spent in 2L

- Derived from real-world data from the Flatiron Health database

Health state	Data source	Time period
2L DARA/POM/ CAR based	Flatiron	2011–2021

- Real-world data were used as patients in RRMM RCTs do not reflect patients who would progress after MAIA
  - Patients in RRMM trials are younger than in MAIA and may have had prior ASCT

	MAIA	POLLUX	RRMM†
Median age, years	73	65	64–67
Prior ASCT, %	0	63	56–63

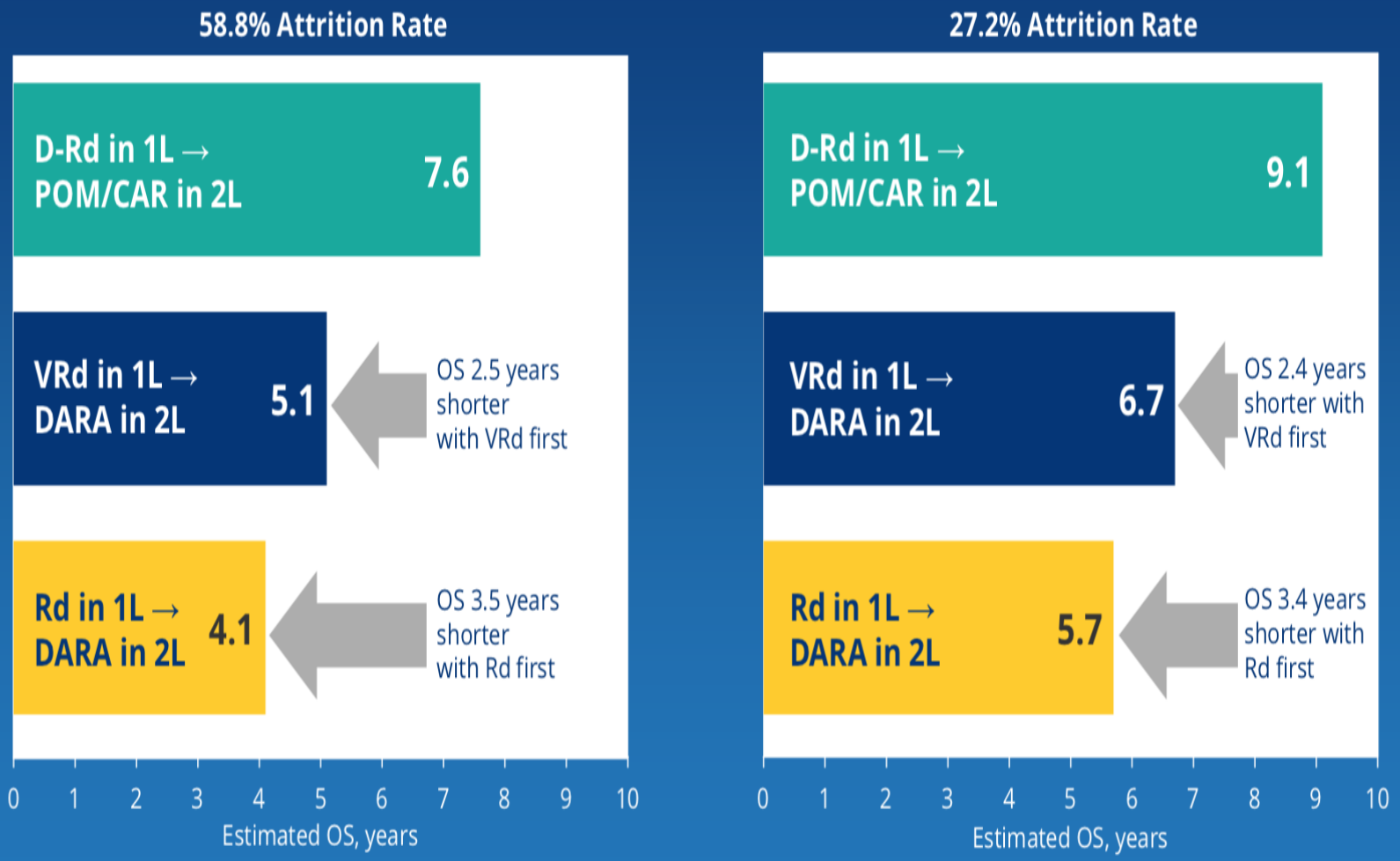
*Of the 729 patients who received ≥1 dose of study treatment, 300 (41.2%) received subsequent therapy and 429 (58.8%) did not. At a median follow-up of 56.2 months, 222 patients remained on study treatment (155 on D-Rd and 67 on Rd). †CASTOR, POLLUX, APOLLO, CANDOR, ENDEAVOR, ASPIRE.

1L, first line; 2L, second line; ASCT, autologous stem cell transplant; CAR, carfilzomib; D-Rd, daratumumab, lenalidomide, and dexamethasone; DARA, daratumumab; POM, pomalidomide; RCT, randomized controlled trial; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma; VRd, bortezomib, lenalidomide, and dexamethasone

1. Facon T, et al. *Lancet Oncol* 2021; 22:1582-96. 2. Durie BGM, et al. *Am J Hematol* 2020; 95:1486-94.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Additional Median OS Benefit in This Clinical Simulation Was Consistently >2 Years When D-Rd Was Used First



Results were consistent with varying attrition rates (58.8% and 27.2%)

1L, first line; 2L, second line; CAR, carfilzomib; D-Rd, daratumumab, lenalidomide, and dexamethasone; DARA, daratumumab; OS, overall survival; POM, pomalidomide; Rd, lenalidomide and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

FRAGILITA'

- Stato fisiologico che può passare da una fase di equilibrio a una di disabilità anche in seguito a stress minimi

Tabella 1 Valutazione multidisciplinare geriatrica e mieloma multiplo (MM)

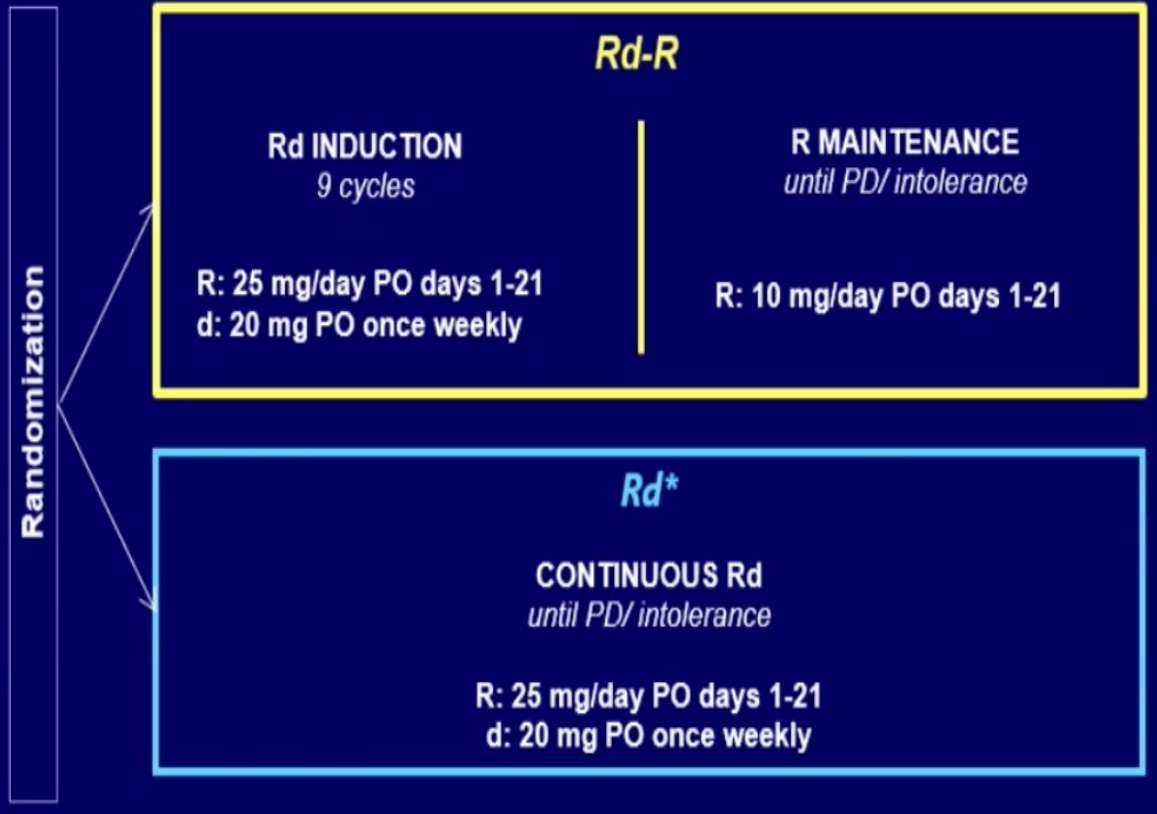
	IMWG frailty index	R-MCI	ECOG-PS frailty score
Studio	*Palumbo et al.* (14)	*Engelhardt et al.* (15)	*Facon et al.* (16)
Fattori considerati	Età CCI ADL IADL	KPS (Karnofsky) Funzione renale (eGFR) Funzione polmonare Fragilità Età ±Citogenetica	Età CCI ECOG-PS
Fit/Intermediate-fit/Frail	39%, 31%, 30%	31%, 56%, 23%	52%, 48%
Età mediana	74 (46% ≥75)	63 (13% ≥75)	73 (35% ≥75)

Bertamini L, Progressi in Ematologia 2020

Dose/Schedule-Adjusted Rd-R vs continuous Rd in unfit patients

RV-MM-PI-0752 Phase III Randomized Study

199 intermediate-fit (unfit) patients have been enrolled and could be evaluated



*The dose and schedule of continuous Rd was the one adopted in patients >75 years in the FIRST trial (Hulin C et al. JCO 2016)

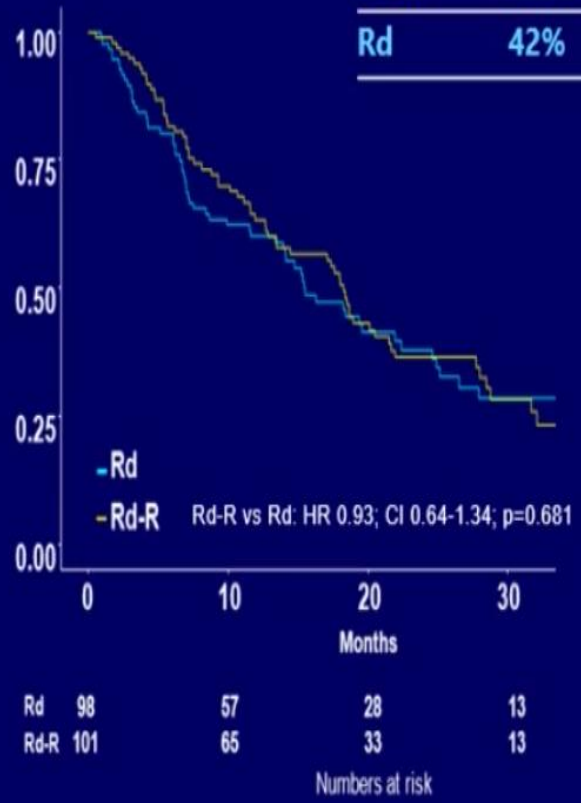
R, lenalidomide; d, dexamethasone; PO, orally; PD, progressive disease

Larocca A, et al. ASH 2018, abstract 305

Dose/Schedule-Adjusted Rd-R vs Rd in unfit patients

Progression-free survival

	20-month PFS
Rd-R	43%
Rd	42%

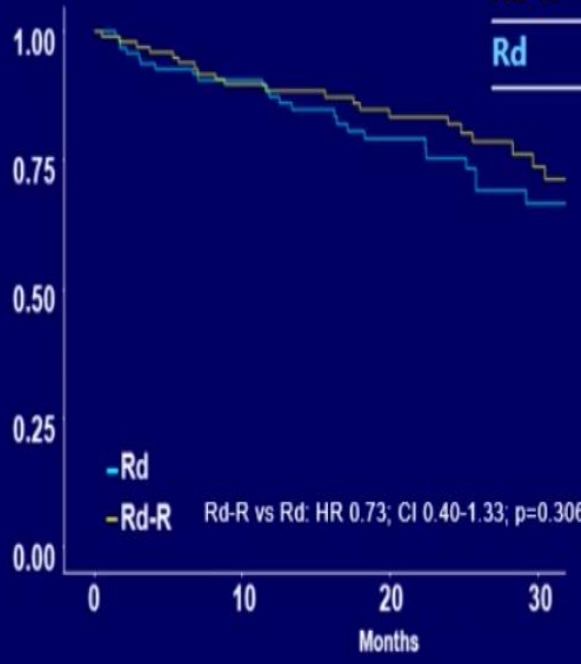


Rd	98	57	28	13
Rd-R	101	65	33	13

Numbers at risk

Overall survival

	20-month OS
Rd-R	84%
Rd	79%



Rd	98	82	48	22
Rd-R	101	84	61	31

Numbers at risk

Reduced dose intensity Rd-R and sparing steroid do not affect outcome in unfit patients

R, Lenalidomide; d, dexamethasone; PFS, progression-free survival, OS, overall survival.

Larocca A, et al. ASH 2018, abstract 305

Ixazomib-Daratumumab-low dose dexamethasone

Phase II HOVON 143 trial

Induction

9 cycles of 4 weeks

Ixazomib 4 mg day 1, 8, 15

Daratumumab 16 mg/kg

cycle 1-2 day 1, 8, 15, 22

cycle 3-6 day 1, 15

cycle 7-9 day 1

Dexamethasone

cycle 1-2 20 mg day 1, 8, 15, 22

cycle 3-6 10 mg day 1, 15

cycle 7-9 10 mg day 1

Maintenance

8-week cycles (until progression for a maximum of 2 years)

Ixazomib 4 mg day 1, 8, 15, 29, 36, 43

Daratumumab 16 mg/kg day 1

Dexamethasone 10 mg day 1

Median Age 76 years for unfit, 82 years for frail

	Unfit	Frail
ORR	74%	78%
PFS	23 months	12 months
Discontinuation	2%	7%
Early death	2%	9%
Grade 3-4 infections	9%	13%

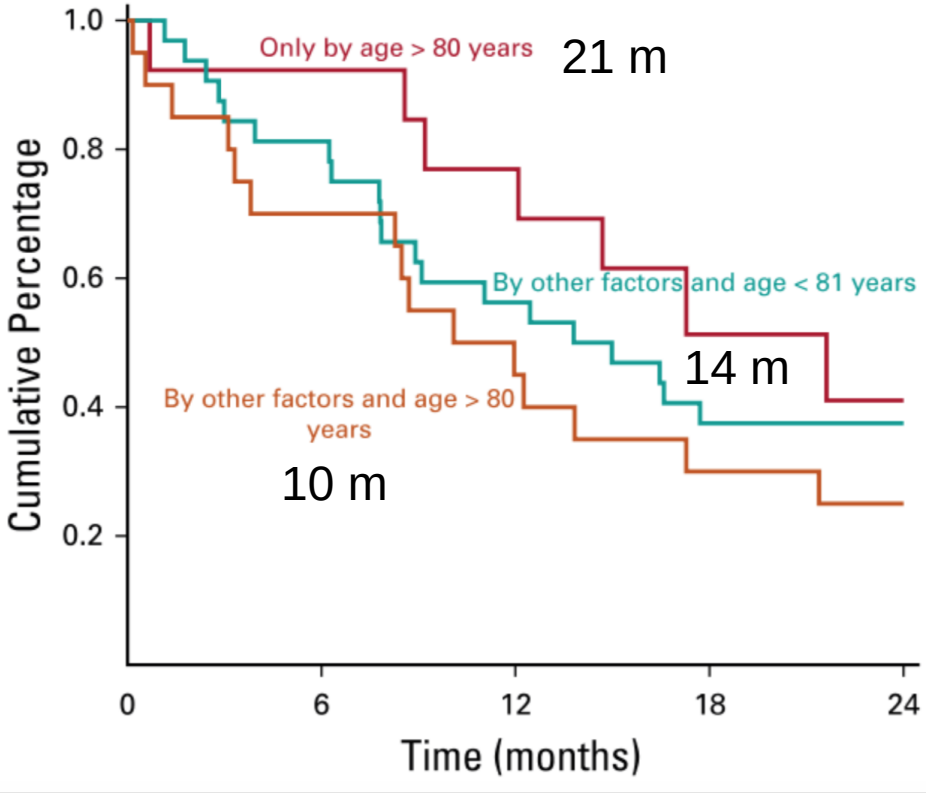
Effective and feasible treatment, however better identification and support of frail patients needed

Antibiotic and -viral prophylaxis: Cotrimoxazole 480 mg/day, Valaciclovir 500 mg tid Vaccinations

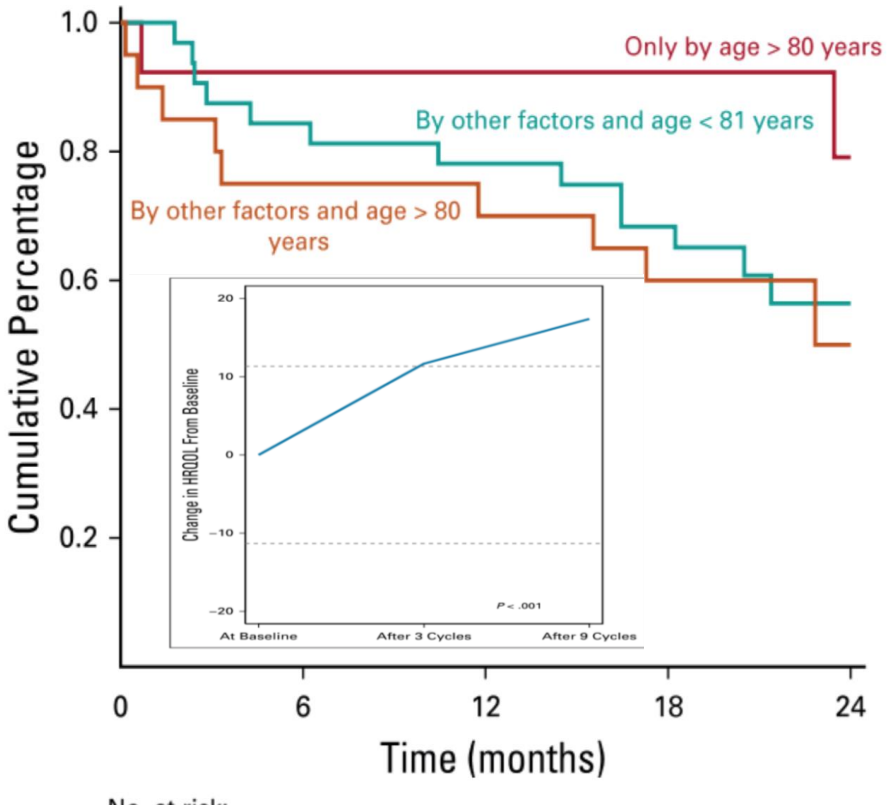
Zweegman et al., ASH 2019; abstract 695

Ixa, Dara and Low dose Dexa

PFS



OS



5% relapse mortality
15% nonrelapse mortality

49% started maintenance

Stege CAM, JCO 2021

Ixazomib, daratumumab and low-dose dexamethasone in intermediate-fit patients

INDUCTION

9 cycles of 4 weeks

Ixazomib 4 mg	day 1, 8, 15
Daratumumab 16 mg/kg	
cycle 1-2	day 1, 8, 15, 22
cycle 3-6	day 1, 15
cycle 7-9	day 1
Dexamethasone	
cycle 1-2 20 mg	day 1, 8, 15, 22
cycle 3-6 10 mg	day 1, 15
cycle 7-9 10 mg	day 1

MAINTENANCE

8-week cycles (until progression for a maximum of 2 years)

Ixazomib 4 mg	day 1, 8, 15, 29, 36, 43
Daratumumab 16 mg/kg	day 1
Dexamethasone 10 mg	day 1

Antibiotic and -viral prophylaxis: Cotrimoxazole 480 mg/day, Valaciclovir 500 mg twice daily
Vaccinations according to local policy

- High-risk cytogenetics (**t(4;14), del(17p), t(14;16)**: 14%

BASELINE CHARACTERISTICS

	n=65 (%)
Male	35 (54)
Median age (years) [range]	76 [65-80]
≤75 years	28 (43)
76-80 years	37 (57)
WHO performance status (%)	
0	25 (38)
1	28 (43)
2	6 (9)
3	3 (5)
unknown	3 (5)

	n=65 (%)
Activity of Daily Living (ADL)	
≥5	65 (100)
≤4	-
Instrumental ADL (IADL)	
≥6	56 (86)
≤5	9 (14)
Charlson Comorbidity Index (CCI)	
≤1	46 (71)
≥2	19 (29)

Groen K, et al. Blood 2021;138 (Suppl 1):81 (oral presentation).

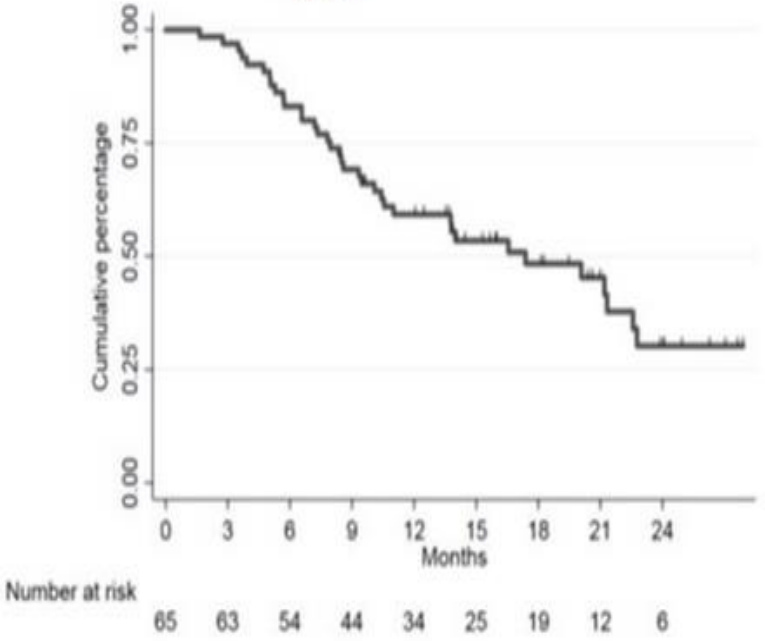
Ixazomib, daratumumab and low-dose dexamethasone in intermediate-fit patients

RESPONSES

Response rate (%)	INT-FIT n=65 (%)
ORR	46 (71)
(s)CR	1 (2)
VGPR	23 (35)
PR	22 (34)
MR	11 (17)
SD	7 (11)
Not evaluable	1 (2)

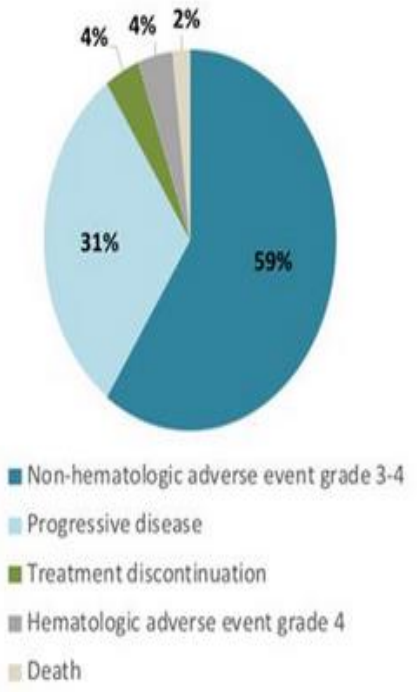
46% did not proceed to maintenance and 11% discontinued ixazomib only

EFS



- **Median follow-up**: 18.1 months
- **Event-free survival**: 5.3 months
- **Progression-free survival:** 17.4 months
- Clinically significant neuropathy:
- Grade 2, 15%; Grade 3 8%

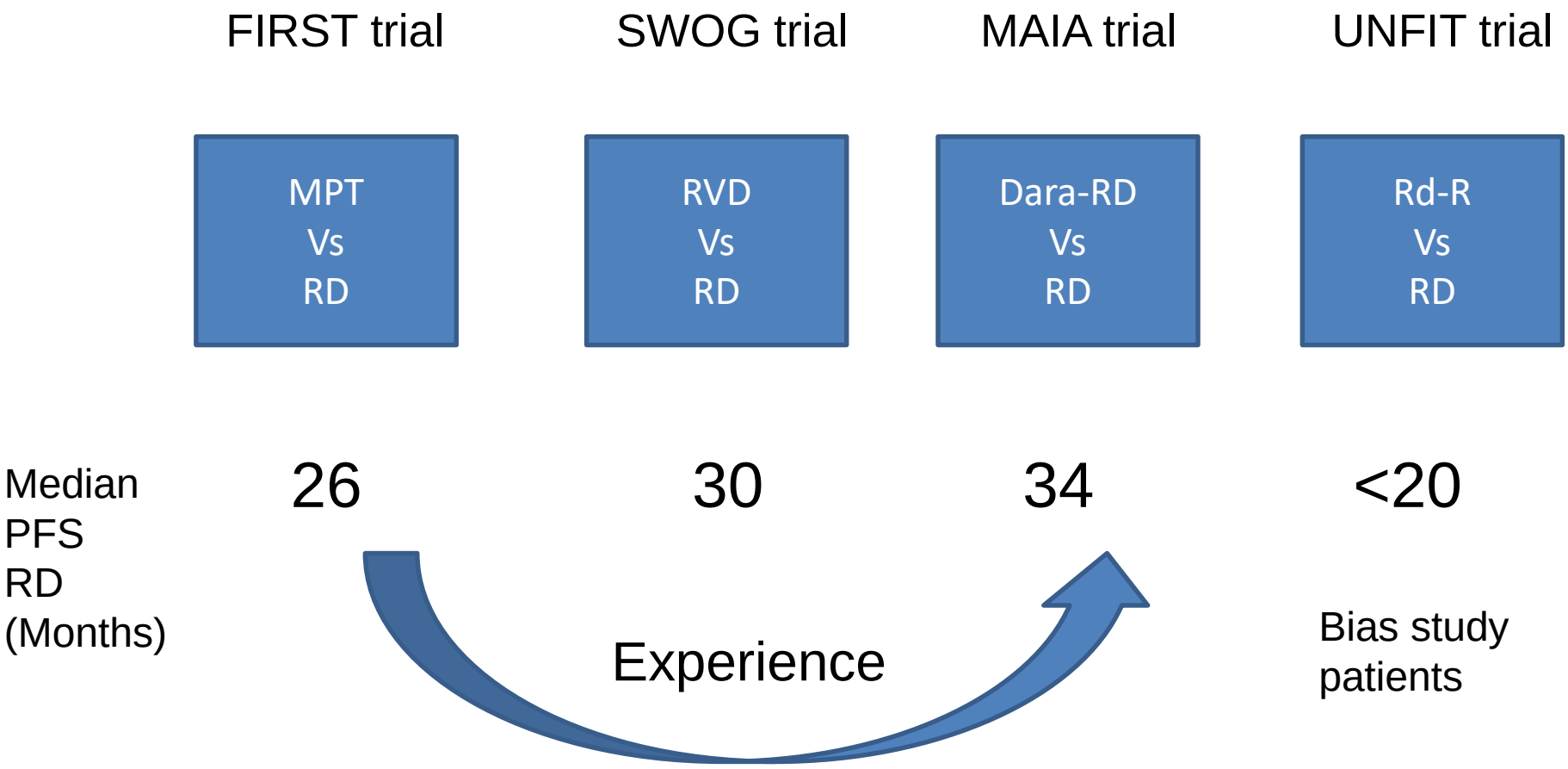
PFS



CR, complete response; EFS, event-free survival; MR, minimal response; ORR, overall response rate; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good partial response

Groen K, et al. Blood 2021;138 (Suppl 1):81 (oral presentation).

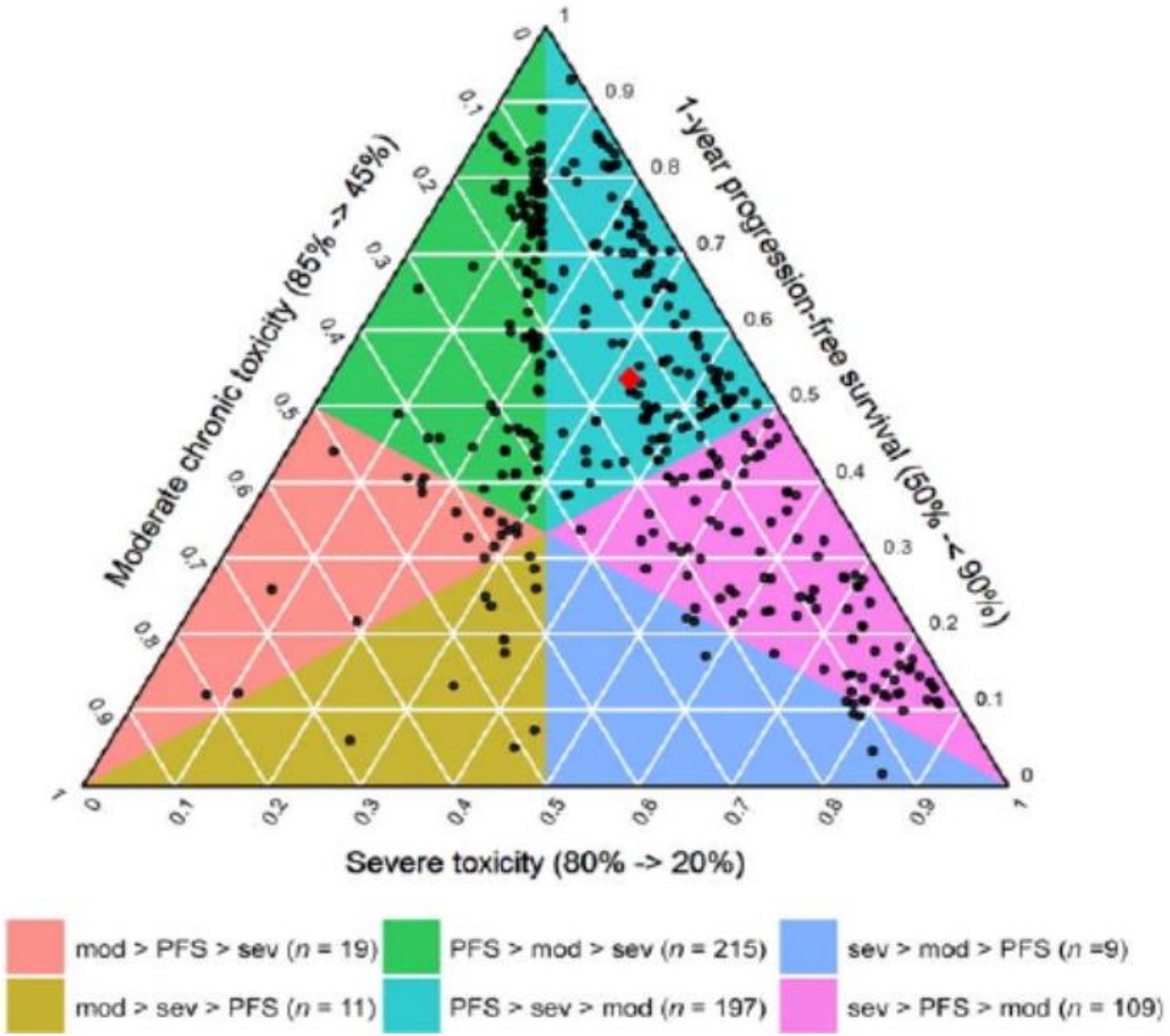
La stessa terapia non sempre produce gli stessi risultati



Strategie terapeutiche e intensità di cura basate su valutazione geriatrica

	Score geriatrico	Obiettivo terapeutico	Opzioni terapeutiche
 **FIT**	IMWG frailty score 0 R-MCI 0-3 ECOG frailty 0-1	Efficacia massima: risposte profonde	ASCT* Dara-VMP Dara-Rd VrD
 **UNFIT**	IMWG frailty score 1 R-MCI 4-6	Bilancio efficacia-tossicità	VMP settimanale Rd (o Rd-R) VRd light Vd
 **FRAIL**	IMWG frailty score ≥2 R-MCI 7-9 ECOG frailty ≥2	Tossicità minima: approccio conservativo	Rd a intensità ridotta Vd a intensità ridotta Terapia di supporto

Patient preference



0.54 for PFS

0.32 for severe or life-threatening toxicity

0.14 for mild or moderate chronic toxicity

Postmus D, The Oncologist 2018