Dalla teoria alla pratica clinica

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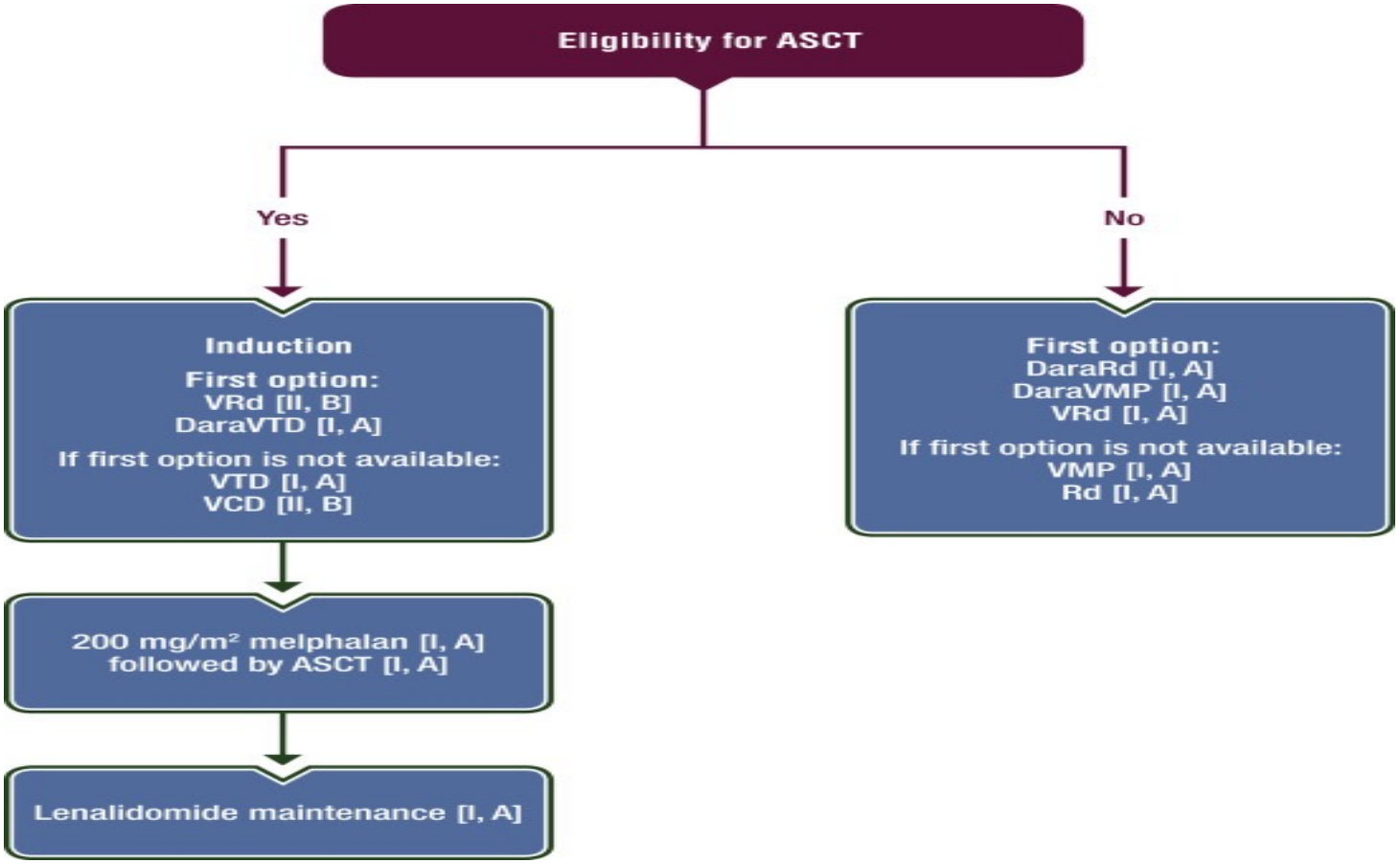
Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



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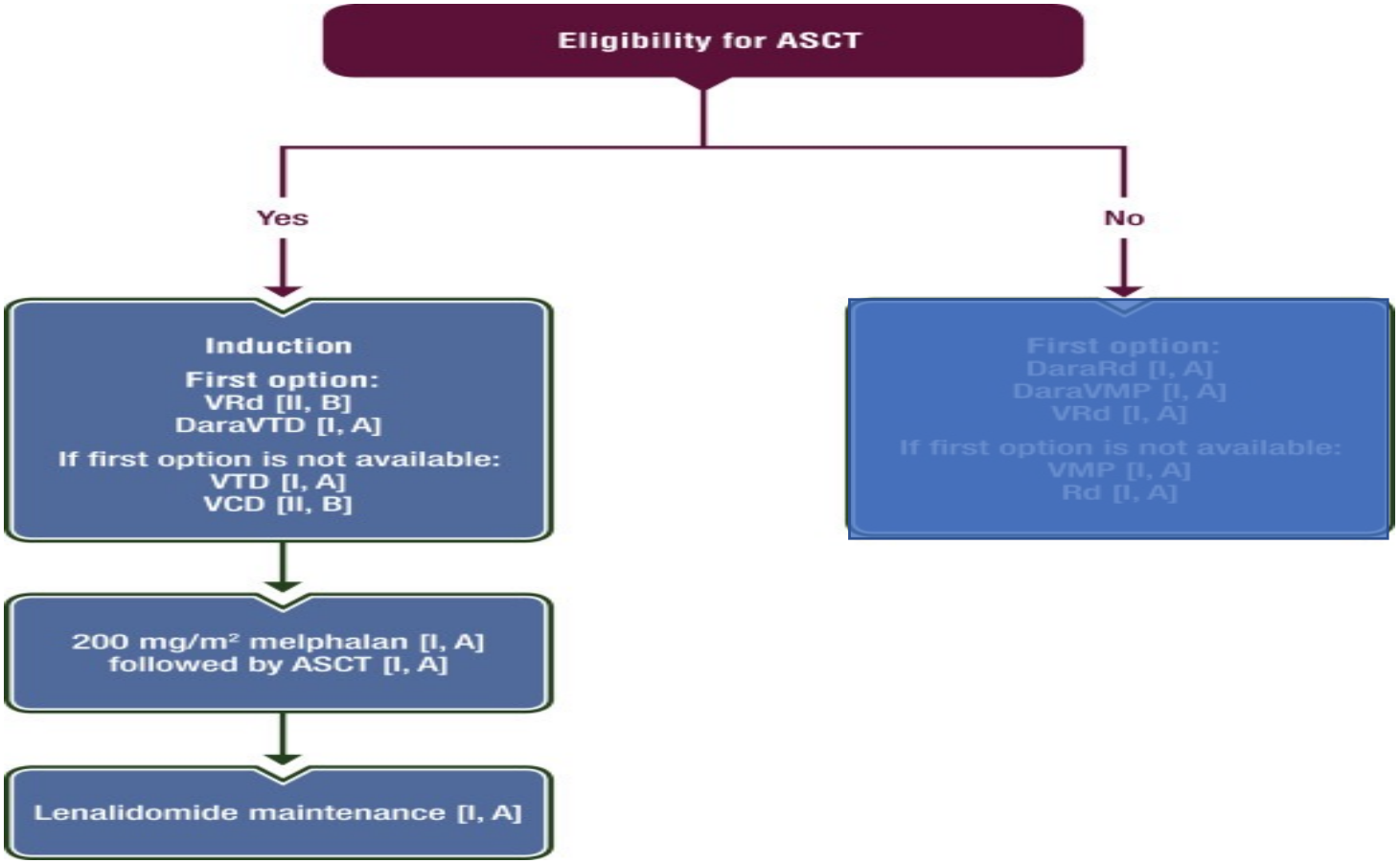

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THE LANCET

Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study

Philippe Moreau, Michel Attal, Cyrille Hulin, Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, Marie C Béné, Annemiek Broijl, Hélène Caillon, Denis Caillot, Jill Corre, Michel Delforge, Thomas Dejoie, Chantal Doyen, Thierry Facon, Cécile Sonntag, Jean Fontan, Laurent Garderet, Kon-Siong Jie, Lionel Karlin, Frédérique Kuhnowski, Jérôme Lambert, Xavier Leleu, Pascal Lenain, Margaret Macro, Claire Mathiot, Frédérique Orsini-Piocelle, Aurore Perrot, Anne-Marie Stoppa, Niels WCJ van de Donk, Soraya Wuilleme, Sonja Zweegman, Brigitte Kolb, Cyrille Touzeau, Murielle Roussel, Mourad Tiab, Jean-Pierre Marolleau, Nathalie Meuleman, Marie-Christiane Vekemans, Matthijs Westerman, Saskia K Klein, Mark-David Levin, Jean Paul Fermand, Martine Escoffre-Barbe, Jean-Richard Eveillard, Reda Garidi, Tahamtan Ahmadi, Sen Zhuang, Christopher Chiu, Lixia Pei, Carla de Boer, Elena Smith, William Deraedt, Tobias Kampfenkel, Jordan Schecter, Jessica Vermeulen, Hervé Avet-Loiseau, Pieter Sonneveld

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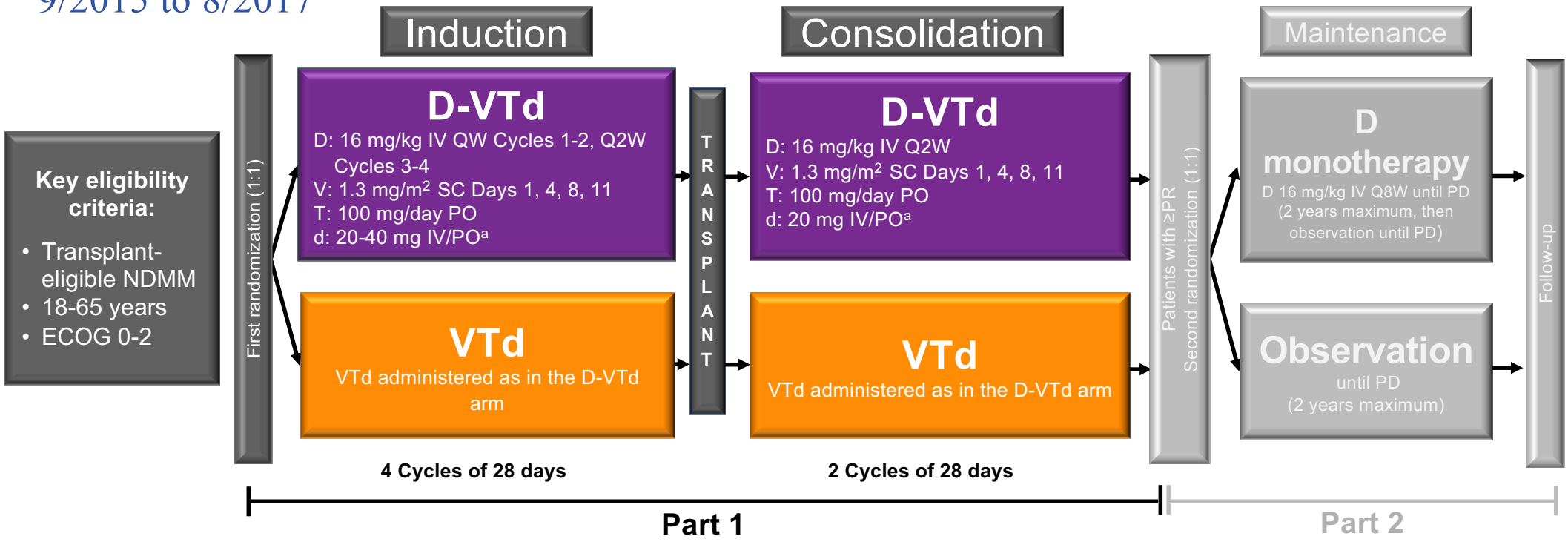
CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.

[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

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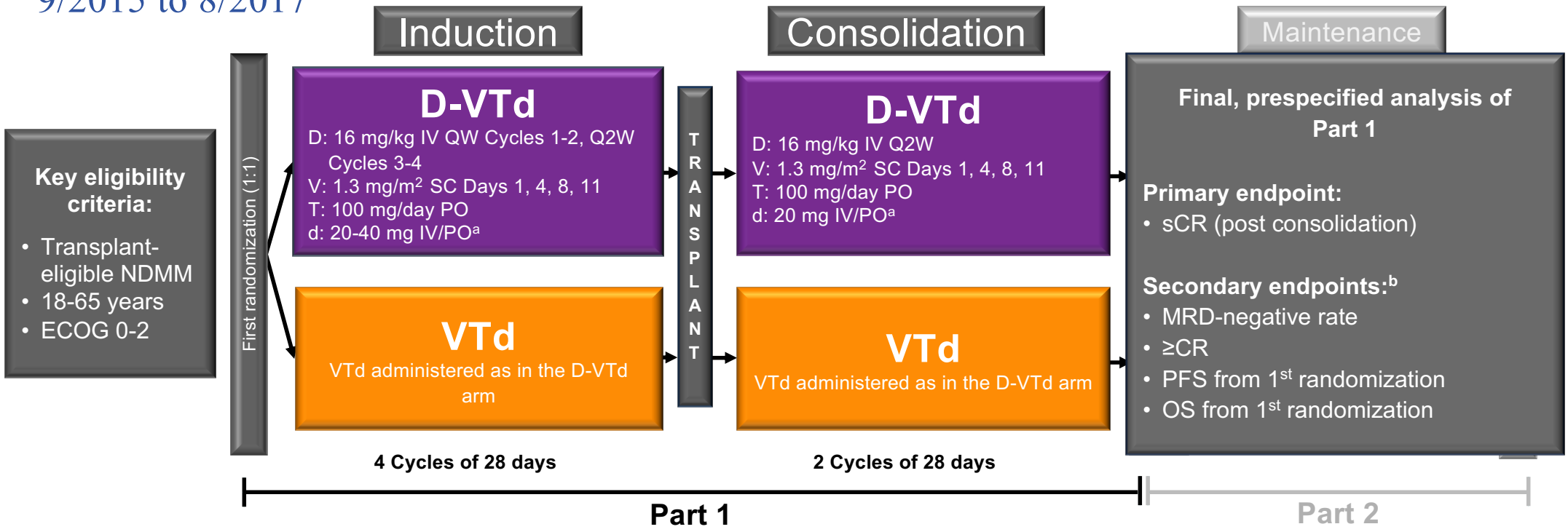

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Baseline Demographic and Clinical Characteristics (ITT)

	D-VTd (n = 543)	VTd (n = 542)
Age		
Median (range), yrs	59 (22-65)	58 (26-65)
Male, n (%)	316 (58)	319 (59)
ECOG status,[a] n (%)		
0	265 (49)	257 (47)
1	225 (41)	230 (42)
2	53 (10)	55 (10)
Type of measurable disease,[b] n (%)		
IgG	331 (61)	314 (58)
IgA	80 (15)	99 (18)

	D-VTd (n = 543)	VTd (n = 542)
ISS stage,[c] n (%)		
I	204 (38)	228 (42)
II	255 (47)	233 (43)
III	84 (16)	81 (15)
Cytogenetic profile[d]		
N	542	540
Standard risk, n (%)	460 (85)	454 (84)
High risk, n (%)	82 (15)	86 (16)

Treatment arms were well balanced

ISS, International Staging System.
[a]ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. [b]Includes patients without measurable disease in serum and urine.
[c]Based on the combination of serum β2-microglobulin and albumin. [d]Based on fluorescence in situ hybridization; high risk was defined as the presence of del17p or t(4;14), as centrally confirmed during screening.
Note: Percentages may not add to 100% due to rounding.

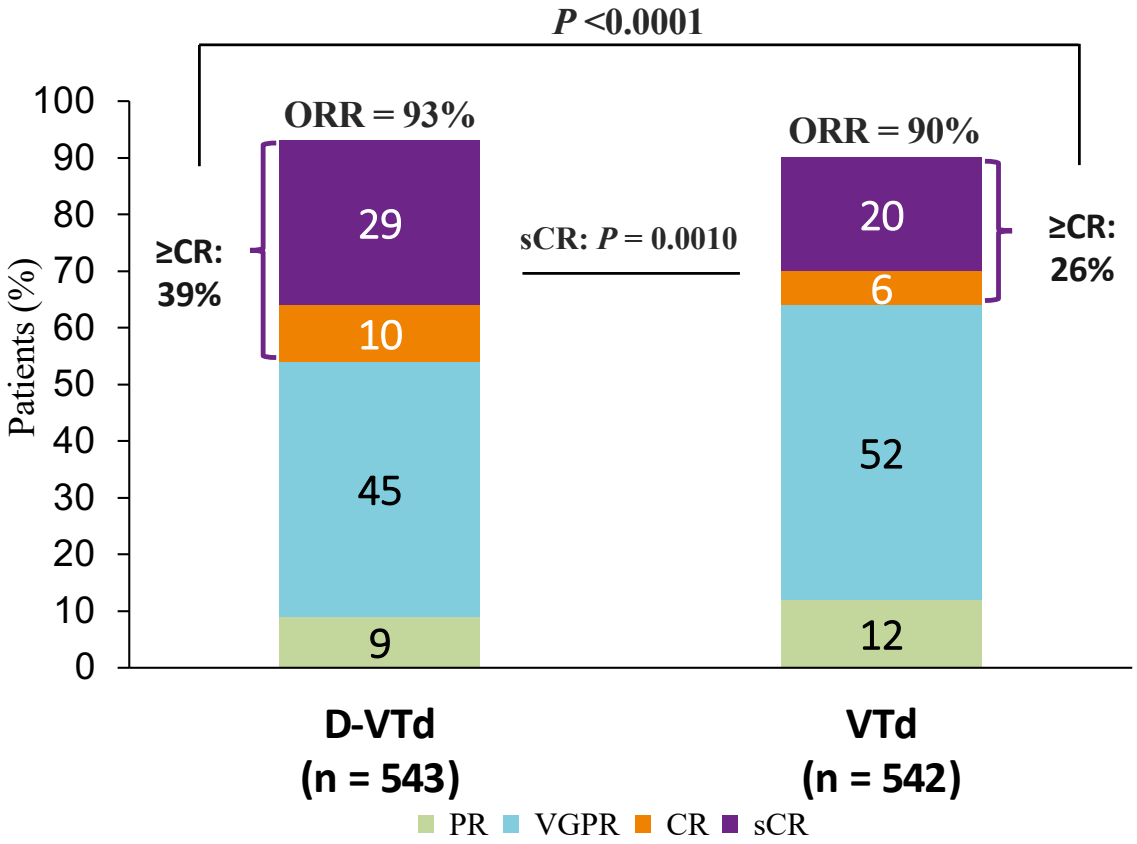
Patient Disposition

- Median follow-up: 18.8 months
- Completed induction and consolidation:
  - **85% D-VTd**
  - **81% VTd**
- Underwent ASCT:
  - **90% D-VTd**
  - **89% VTd**

	D-VTd (n = 543)	VTd (n = 542)
Patients who discontinued study treatment, n (%)	75 (14)	101 (19)
Reason for discontinuation, n (%)[a]		
Adverse event/serious adverse event	49 (9)	55 (10)
Progressive disease	19 (4)	21 (4)
Physician decision	4 (1)	12 (2)
Withdrawal by patient	3 (1)	1 (<1)
Treatment stopped by sponsor	3 (1)	2 (<1)
Lost to follow up	1 (<1)	0
Treatment delay for toxicity (>6 weeks)	2 (<1)	1 (<1)
Patient decision	0	8 (2)
Death	0	7 (1)
Prohibited medication	0	1 (<1)

[a]Patients may have multiple reasons for treatment discontinuation.

Efficacy: Post-consolidation Depth of Response



- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010

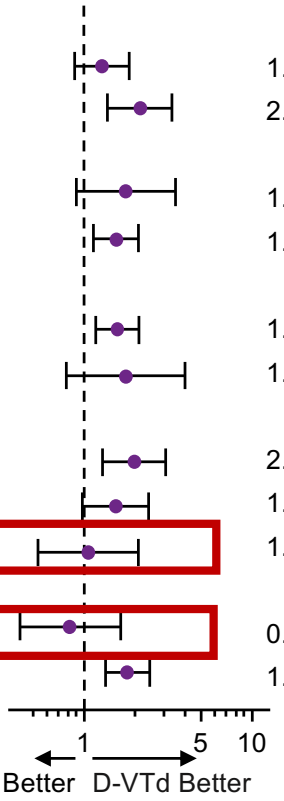
- sCR definition
  - All required:
    - SIFE negative
    - UIFE negative
    - <5% plasma cells in the BM
    - Four-color flow negativity
    - Normal FLC ratio
    - Disappearance of all plasmacytomas

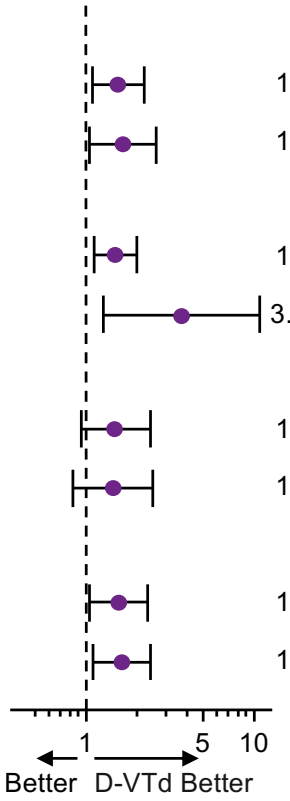
The addition of daratumumab to VTd improved depth of response

ORR, overall response rate; VGPR, very good partial response; CI, confidence interval; SIFE, serum immunofixation; UIFE, urine immunofixation; BM, bone marrow; FLC, free light chain.

Efficacy: sCR in Prespecified Subgroups

Subgroup	VTd stringent complete response, n (%)	D-VTd stringent complete response, n (%)	Odds Ratio (95% CI)
Sex			
Male	70 (22)	84 (27)	1.29 (0.89–1.85)
Female	40 (18)	73 (32)	2.17 (1.40–3.37)
Age			
<50 years	20 (22)	28 (34)	1.78 (0.91–3.50)
≥50 years	90 (20)	129 (28)	1.57 (1.15–2.13)
Site			
IFM	99 (22)	138 (31)	1.59 (1.18–2.14)
HOVON	11 (13)	19 (21)	1.78 (0.79–3.99)
ISS disease stage			
I	48 (21)	71 (35)	2.00 (1.30–3.08)
II	40 (17)	62 (24)	1.55 (0.99–2.42)
III	22 (27)	24 (29)	1.07 (0.54–2.12)
Cytogenetic profile at trial entry[a]			
High risk	24 (28)	20 (24)	0.83 (0.42–1.66)
Standard risk	85 (19)	136 (30)	1.82 (1.34–2.48)
Baseline creatinine clearance			
>90 ml/min	69 (22)	100 (30)	1.55 (1.09–2.21)
≤90 ml/min	41 (18)	57 (27)	1.66 (1.05–2.61)
Baseline hepatic function			
Normal	105 (21)	136 (28)	1.49 (1.11–1.99)
Impaired	5 (12)	21 (33)	3.70 (1.27–10.79)
Type of multiple myeloma[b]			
IgG	32 (10)	48 (15)	1.49 (0.93–2.41)
Non-IgG	50 (41)	47 (51)	1.45 (0.84–2.50)
ECOG performance status			
0	55 (21)	79 (30)	1.56 (1.05–2.32)
1 or 2	55 (19)	78 (28)	1.63 (1.10–2.42)

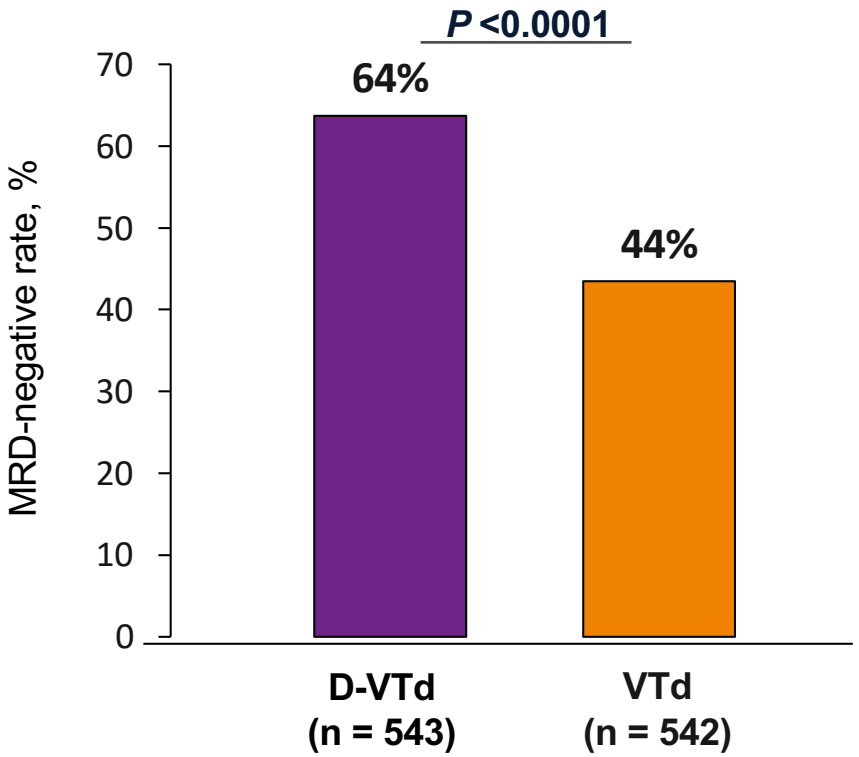




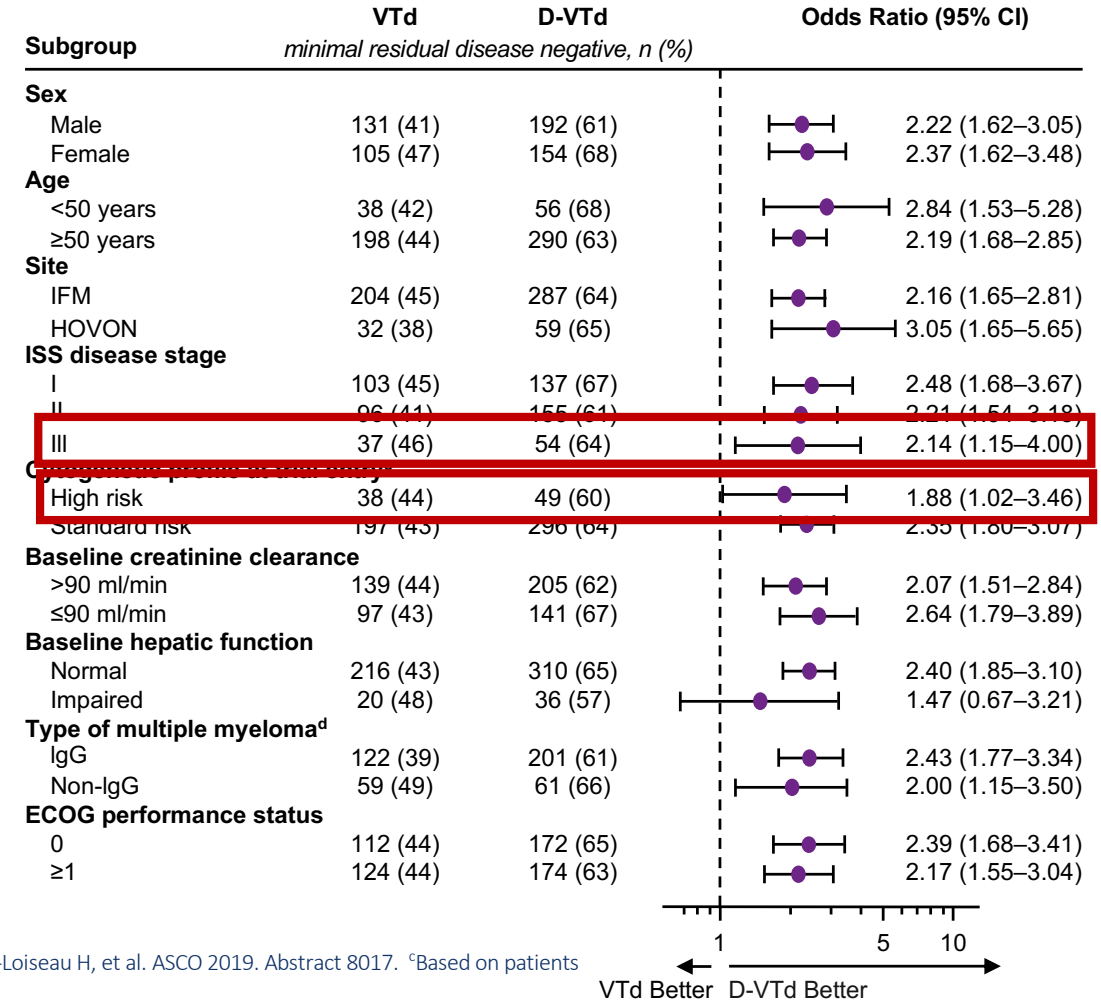
D-VTd was superior to VTd across all subgroups except high-risk cytogenetic profile and ISS disease stage III

[a]Based on patients with available cytogenetics results. [b]Based on patients with available serum heavy chain disease type only.

Efficacy: MRD (Flow Cytometry; 10^{-5})[a,b]

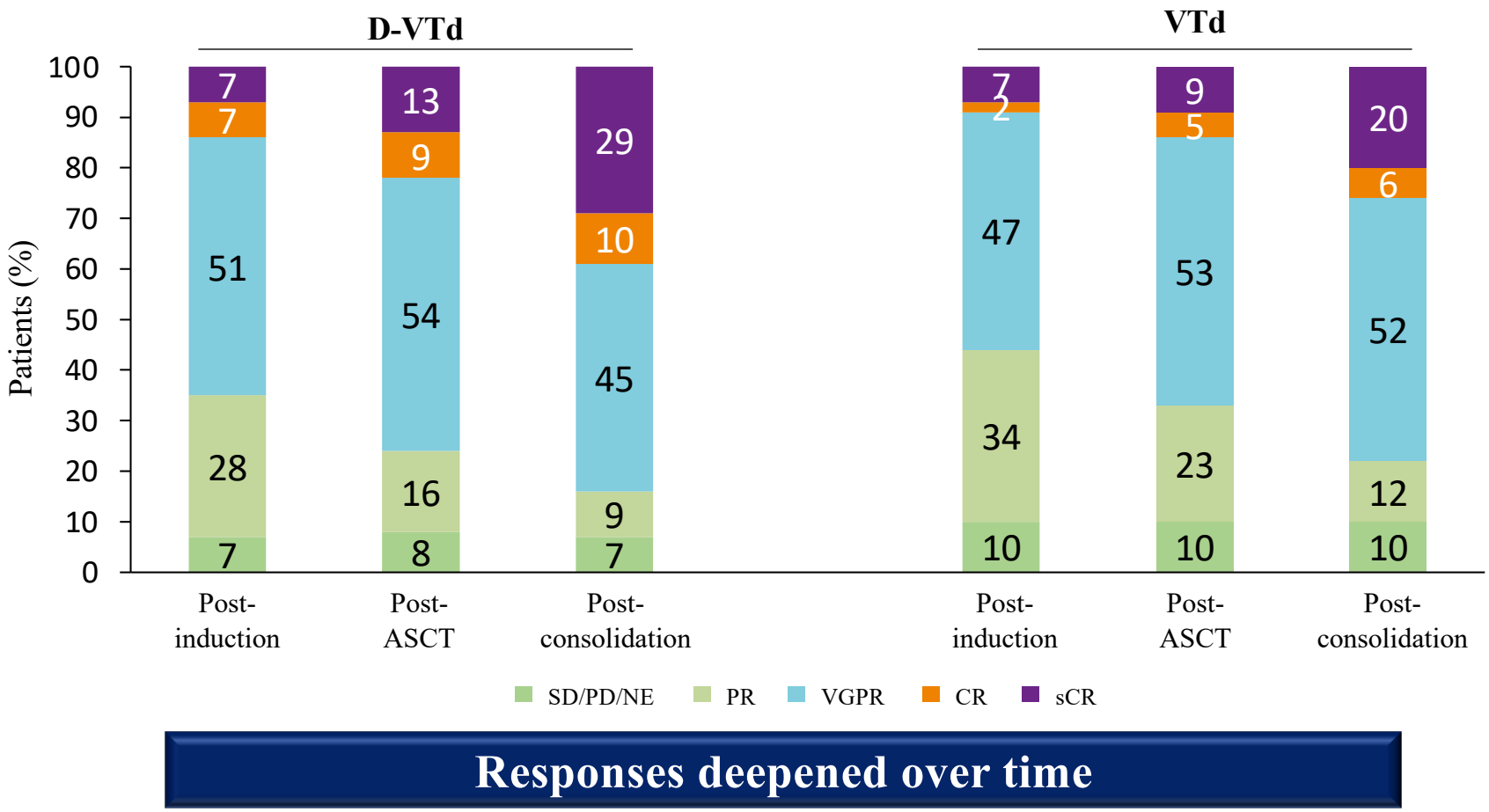


D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III



[a]Post-consolidation. [b]Additional MRD results will be presented during tomorrow's Poster Discussion session: Avet-Loiseau H, et al. ASCO 2019. Abstract 8017. [c]Based on patients with available cytogenetics results. [d]Based on patients with available serum heavy chain disease type only.

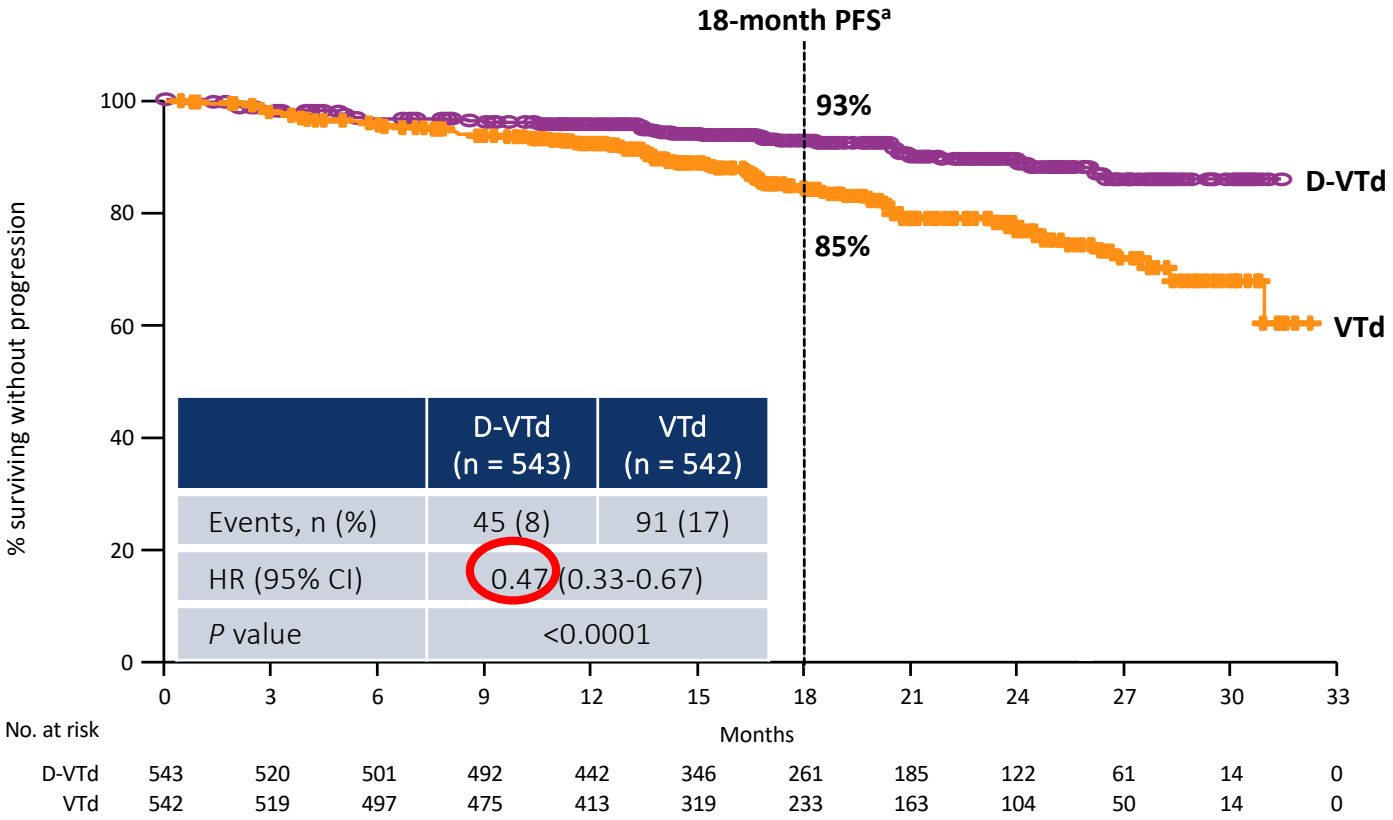
Efficacy: Response Rates Over Time



Responses deepened over time

SD, stable disease; NE, not evaluable.

Efficacy: PFS From First Randomization

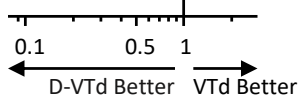


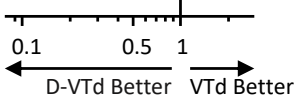
53% reduction in the risk of progression or death in the D-VTd arm

HR, hazard ratio.
[a]Kaplan-Meier estimate.

Efficacy: PFS in Prespecified Subgroups

Subgroup	D-VTd *no. of progression events or deaths/total no.*	VTd *no. of progression events or deaths/total no.*	Hazard Ratio (95% CI)
Sex			
Male	28/316	58/319	0.49 (0.31–0.77)
Female	17/227	33/223	0.44 (0.24–0.79)
Age			
<50 years	5/83	22/90	0.24 (0.09–0.64)
≥50 years	40/460	69/452	0.54 (0.36–0.79)
Site			
IFM	41/452	78/457	0.51 (0.35–0.74)
HOVON	4/91	13/85	0.27 (0.09–0.81)
ISS disease stage			
I	13/204	25/228	0.56 (0.29–1.10)
II	20/255	48/233	0.35 (0.21–0.58)
III	12/84	18/81	0.66 (0.32–1.39)
Cytogenetic profile at trial entry[a]			
High risk	15/82	22/86	0.67 (0.35–1.30)
Standard risk	30/460	69/454	0.41 (0.26–0.62)
Baseline creatinine clearance			
>90 ml/min	29/331	47/316	0.56 (0.35–0.89)
≤90 ml/min	16/212	44/226	0.37 (0.21–0.66)
Baseline hepatic function			
Normal	39/480	81/500	0.48 (0.32–0.70)
Impaired	6/63	10/42	0.39 (0.14–1.07)
Type of multiple myeloma[b]			
IgG	31/331	53/314	0.50 (0.32–0.78)
Non-IgG	6/93	15/121	0.53 (0.21–1.38)
ECOG performance status			
0	18/265	36/257	0.47 (0.27–0.82)
1 or 2	27/278	55/285	0.47 (0.30–0.74)



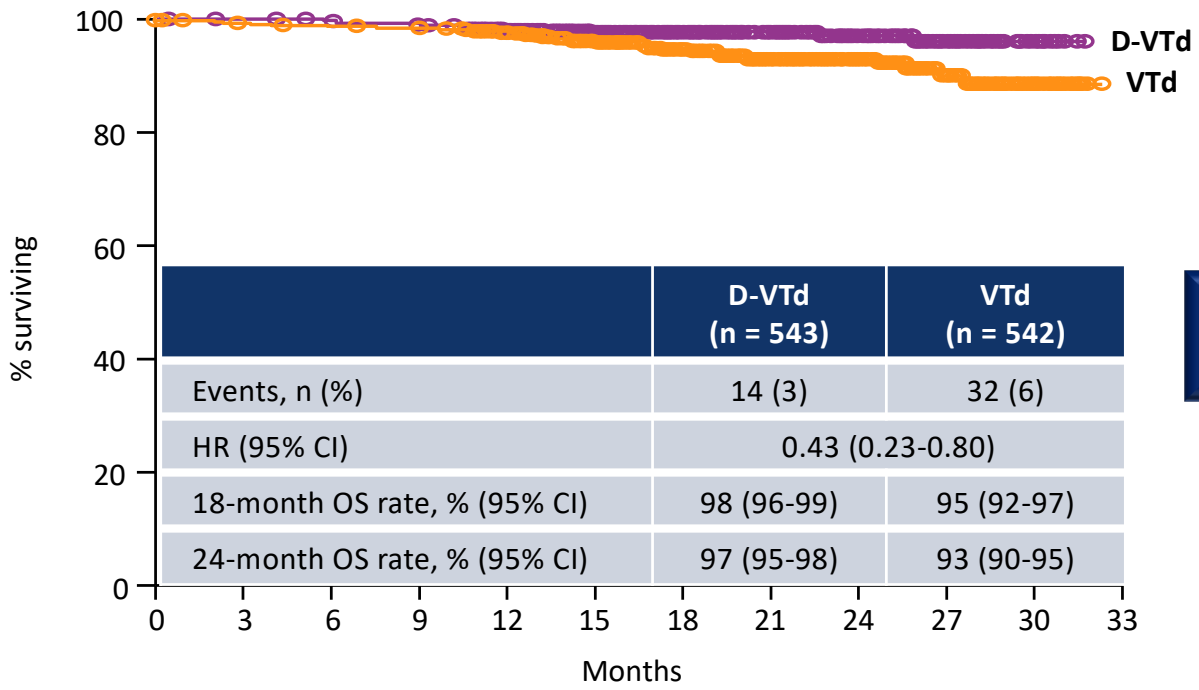


D-VTd reduced the risk of progression or death across all subgroups

[a]Based on patients with available cytogenetics results. [b]Based on patients with available serum heavy chain disease type only.

Efficacy: OS

- Median OS was not reached in either treatment arm



	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	14 (3)	32 (6)
HR (95% CI)	0.43 (0.23-0.80)	
18-month OS rate, % (95% CI)	98 (96-99)	95 (92-97)
24-month OS rate, % (95% CI)	97 (95-98)	93 (90-95)

No. at risk												
VTd	542	535	531	528	480	371	283	206	131	71	17	0
D-VTd	543	539	535	532	485	388	292	212	137	75	17	0

OS data are immature after median follow-up of 18.8 months

Safety: Most Common TEAEs[a,b]

	D-VTd (n = 536)		VTd (n = 538)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	157 (29)	148 (28)	89 (17)	79 (15)
Thrombocytopenia	109 (20)	59 (11)	73 (14)	40 (7)
Lymphopenia	99 (19)	91 (17)	67 (13)	52 (10)
Nonhematologic, n (%)				
Peripheral sensory neuropathy	314 (59)	47 (9)	340 (63)	46 (9)
Constipation	272 (51)	7 (1)	262 (49)	7 (1)
Asthenia	171 (32)	7 (1)	155 (29)	6 (1)
Peripheral edema	162 (30)	3 (1)	148 (28)	7 (1)
Nausea	162 (30)	21 (4)	130 (24)	12 (2)
Pyrexia	140 (26)	14 (3)	114 (21)	12 (2)
Paresthesia	118 (22)	4 (1)	108 (20)	6 (1)
Stomatitis	86 (16)	68 (13)	104 (19)	88 (16)

TEAE, treatment-emergent adverse event.
[a]Any-grade TEAEs reported in ≥20% of patients in either treatment group, and grade 3/4 TEAEs reported in ≥10% of patients in either treatment group.
[b]Safety events were considered until 30 days after end of consolidation.

Safety: Additional Information[a]

TEAEs of Interest

	D-VTd (n = 536)	VTd (n = 538)
Infusion-related reactions, n (%)		
Any grade	190 (35)	–
Grade 3 or 4	19 (4)	–
Infections, n (%)		
Any grade	351 (66)	306 (57)
Grade 3 or 4	118 (22)	105 (20)
Most common serious infection, n (%)		
Pneumonia	19 (4)	9 (2)
Second primary malignancies, n (%)	10 (2)	12 (2)

Stem Cell Collection and Transplantation

	D-VTd	VTd
Patients receiving plerixafor for mobilization, n (%)[b]	110 (22)	39 (8)
$CD34^+$ cells collected, median (10^6/kg)[c]	6.3	8.9
Patients receiving transplant, n (%)[d]	489 (91)	484 (90)
Patients achieving hematopoietic reconstitution, n (%)[e,f]	488 (100)	482 (100)

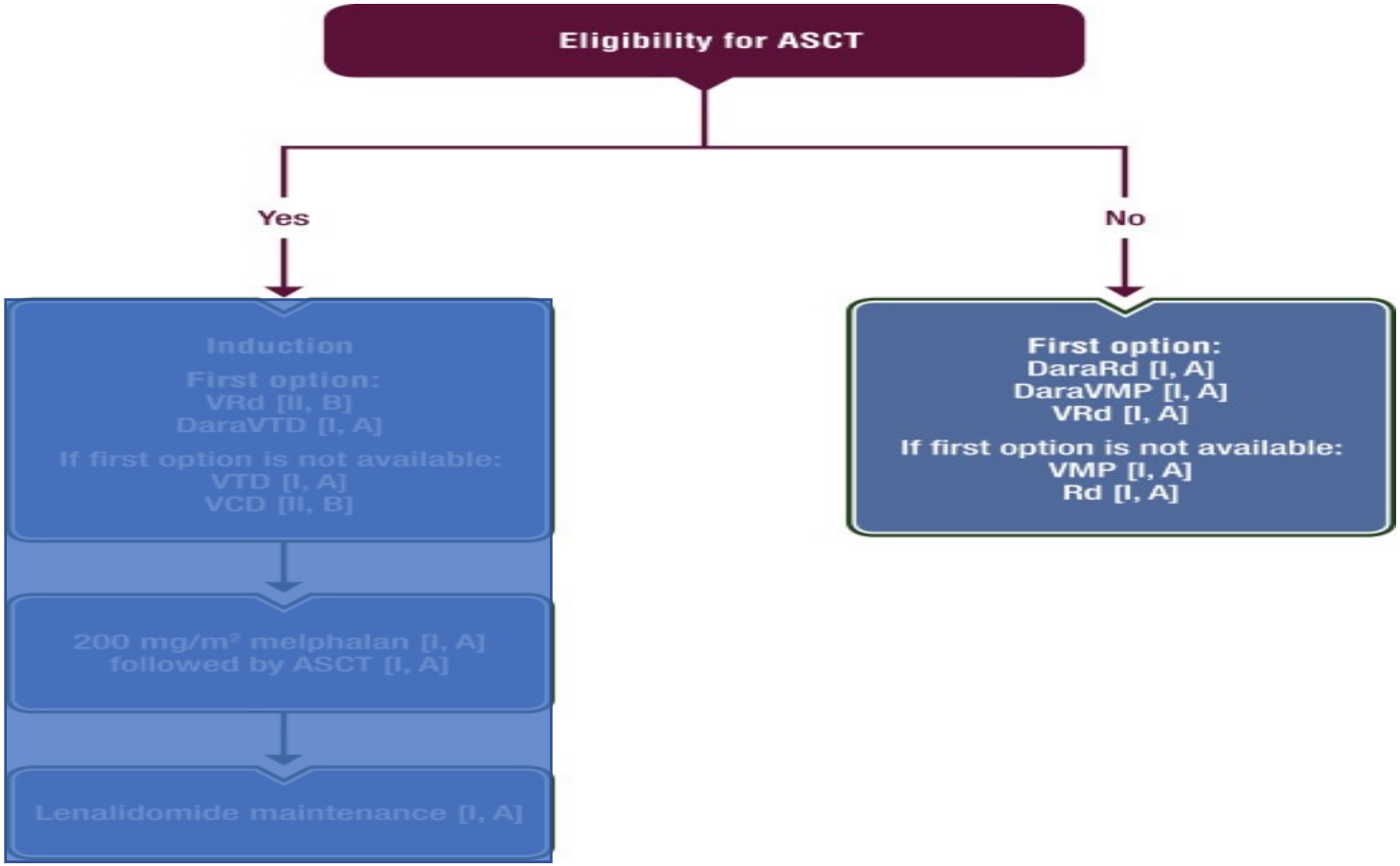
[a]Additional stem cell collection and transplantation results will be presented during tomorrow's Poster session: Hulin C, et al. ASCO 2019. Abstract 8042. [b]Among patients who underwent mobilization (D-VTd, n = 506; VTd, n = 492). [c]Among patients who underwent peripheral blood stem cell apheresis (D-VTd, n = 504; VTd, n = 490). [d]In the safety population (D-VTd, n = 536; VTd, n = 538). [e]Among patients receiving transplant (D-VTd, n = 489; VTd, n = 484). [f]Hematopoietic reconstitution requires: neutrophils >0.5 × 10^9/L, leukocytes >1.0 × 10^9/L, and platelets >50 × 10^9/L (without transfusion).

Conclusions

- D-VTd therapy resulted in a robust clinical benefit that was both statistically significant and clinically meaningful compared with VTd alone
  - Consistently improved post-consolidation responses, including sCR, MRD, and ≥CR
  - 53% reduction in the risk of progression or death
- The combination was well tolerated, consistent with the known safety profiles of daratumumab and VTd

D-VTd should be considered a valid treatment option for NDMM patients who are eligible for ASCT

Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



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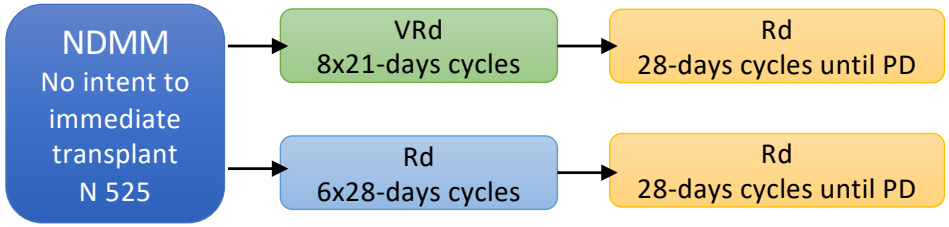
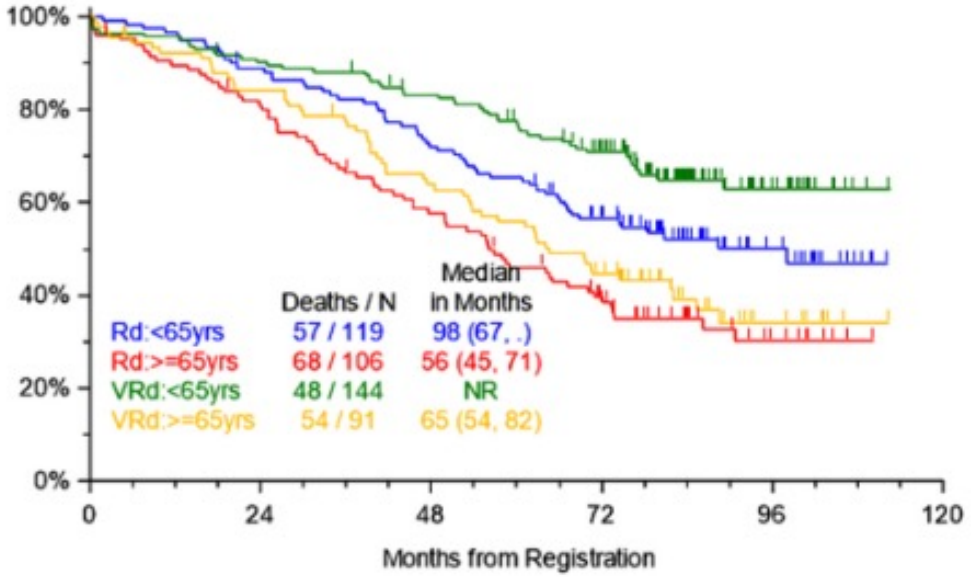
Bortezomib-Rd: SWOG s0777 trial



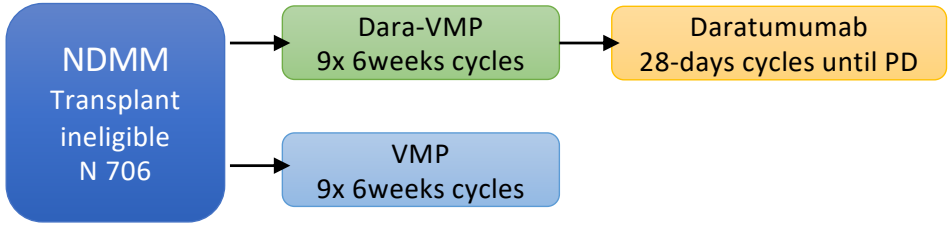
Age (years)	VRd	Rd
< 65	48	34
≥ 65	34	24
> 75	34	17

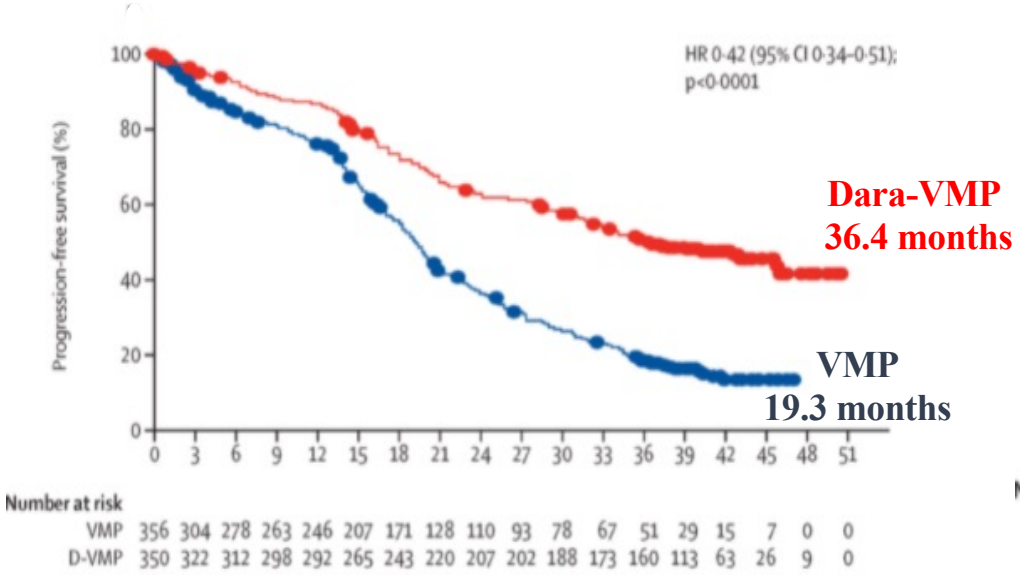


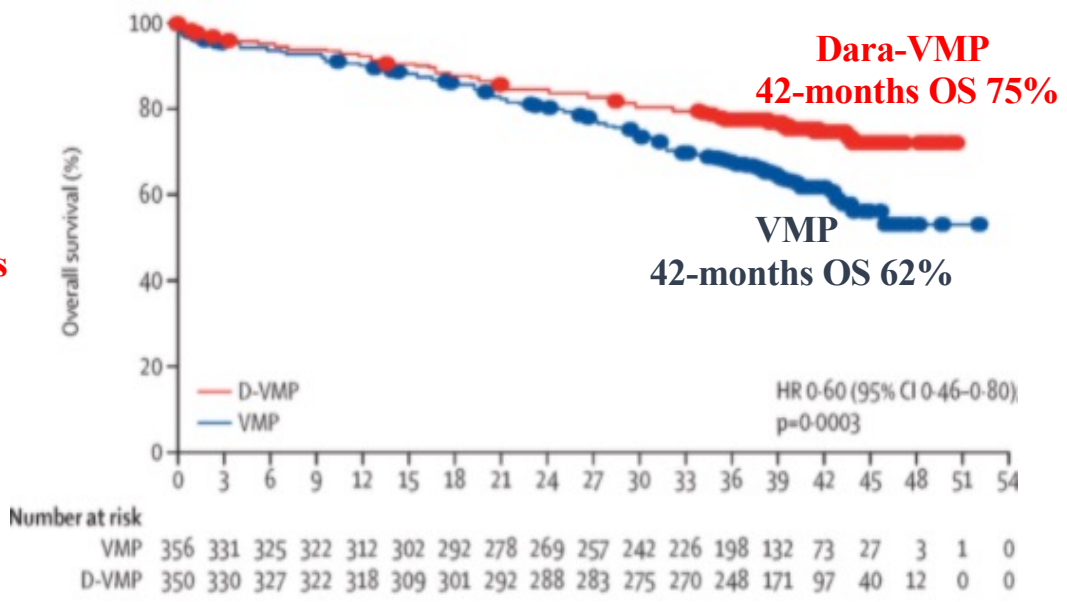
NDMM newly diagnosed multiple myeloma; VRd bortezomib lenalidomide dexamethasone; PD progressive disease; PFS progression free survival

Durie B et al, Blood 2018; 132;1992
Durie et al; Blood Cancer J 2020; 10:53

Daratumumab-VMP: ALCYONE trial

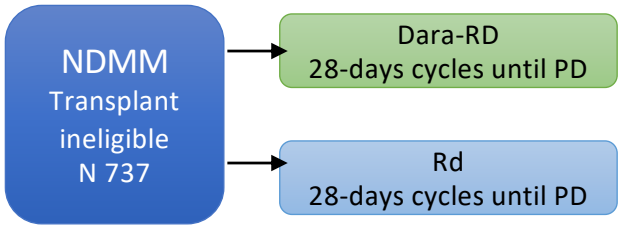


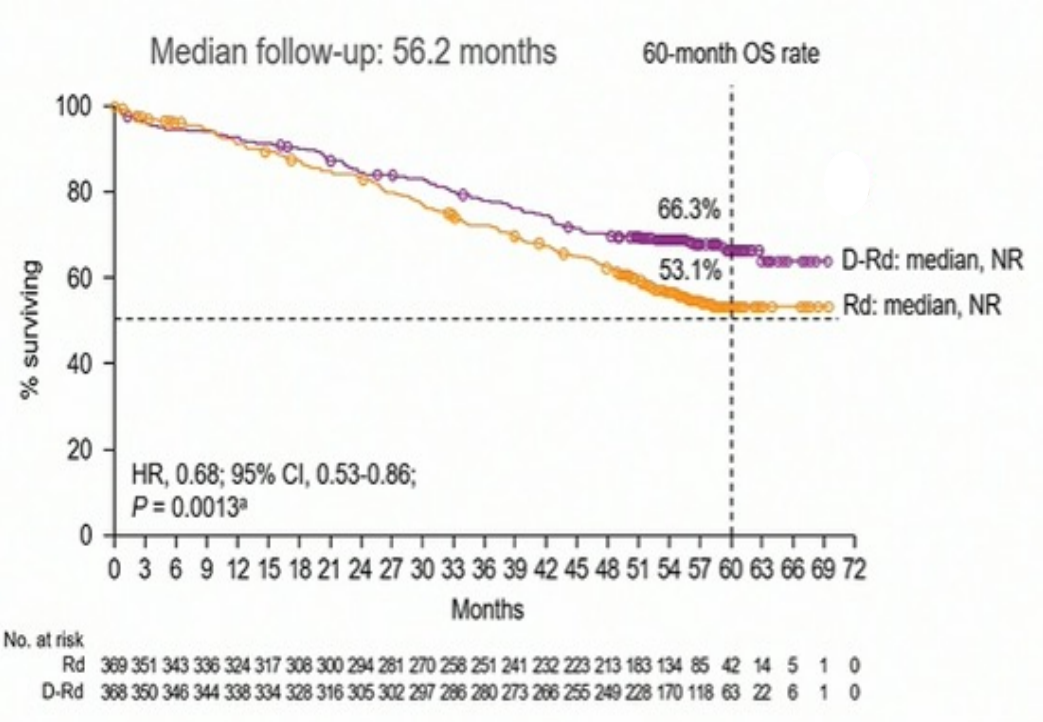




Mateos MV et al, Lancet 2020; 395(10218):132-141

Daratumumab-Rd: MAIA trial

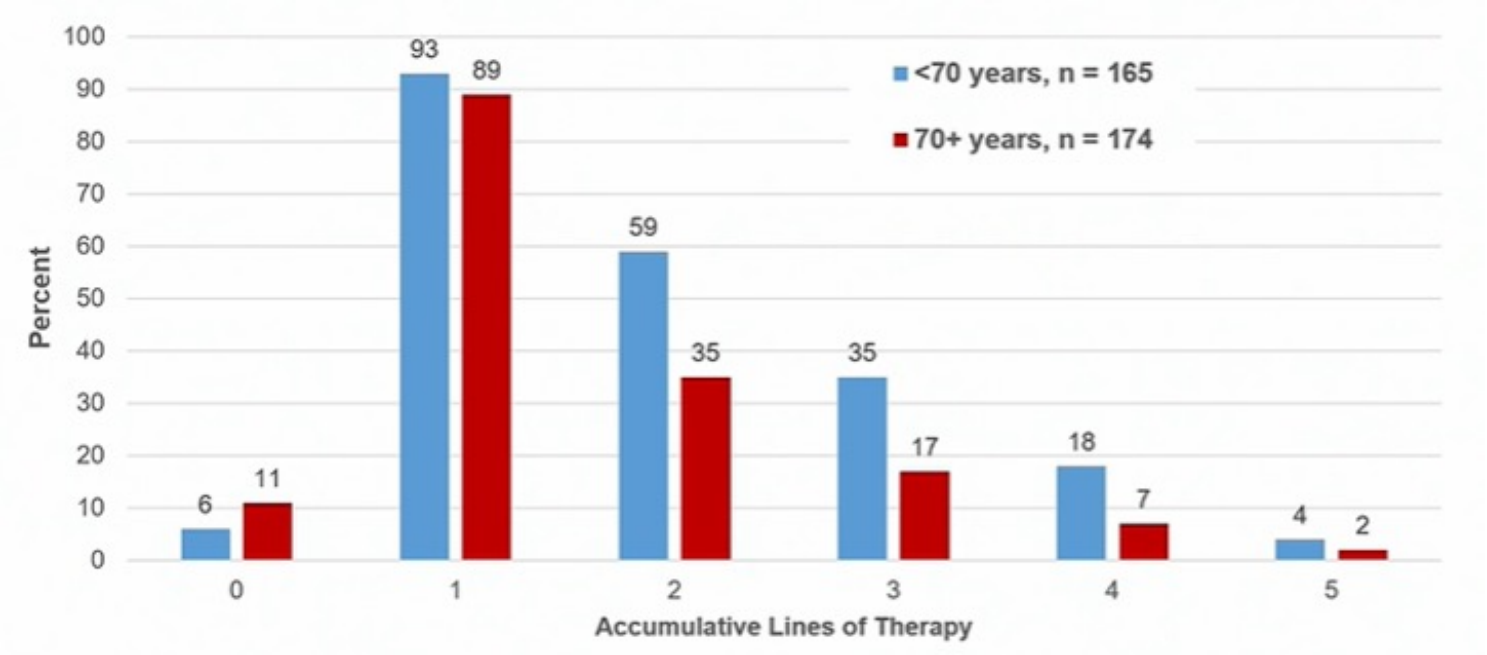




NDMM newly diagnosed multiple myeloma; Dara-Rd daratumumab, lenalidomide, dexamethasone; HR hazard ratio; PFS progression free survival

Moreau P et al, IMW 2021

First line treatment in elderly myeloma patients



Courtesy of Dr A Spencer

CHOOSING BETWEEN THE AVAILABLE REGIMENS

Regimen	Advantages	Disadvantages
Daratumumab -Rd	Survival benefit Subcutaneous daratumumab formulation (lower IRRs, faster drug delivery)	Higher risk of infection Suboptimal if advanced renal failure Risk of daratumumab IRRs Lack of real-life safety data
Daratumumab -VMP	Survival benefit Subcutaneous daratumumab formulation (lower IRRs, faster drug delivery)	Risk of daratumumab IRRs Suboptimal if pre-existing neuropathy Lack of real-life safety data
VRd	Survival benefit Possible benefit in high-risk disease	Suboptimal if pre-existing neuropathy/renal failure
Rd	Fully oral administration, fewer hospital visits High experience with the combination Suitable aslo for frail patients	Suboptimal if advanced renal failure Slower efficacy
VMP	Fixed duration therapy High experience with the combination	Suboptimal if pre-existing neuropathy Similar toxicity of dara-VMP but lower efficacy
Ixazomib-Rd	Fully oral adminisitration, fewer hospital visits Suitable also for frail patients	Not approved frontline
Carfilzomib-Rd	Possible benefit in high-risk disease	Risk of cardiotoxicity Frequent intravenous administration Not approved frontline

Heterogeneity of the aging population

Fit patients ASCT Eligible

Based on
Age
Performance status (PS)
Comorbidities
(R-MCI score, HCT-CI) and organ function

Fit patients No ASCT Eligible

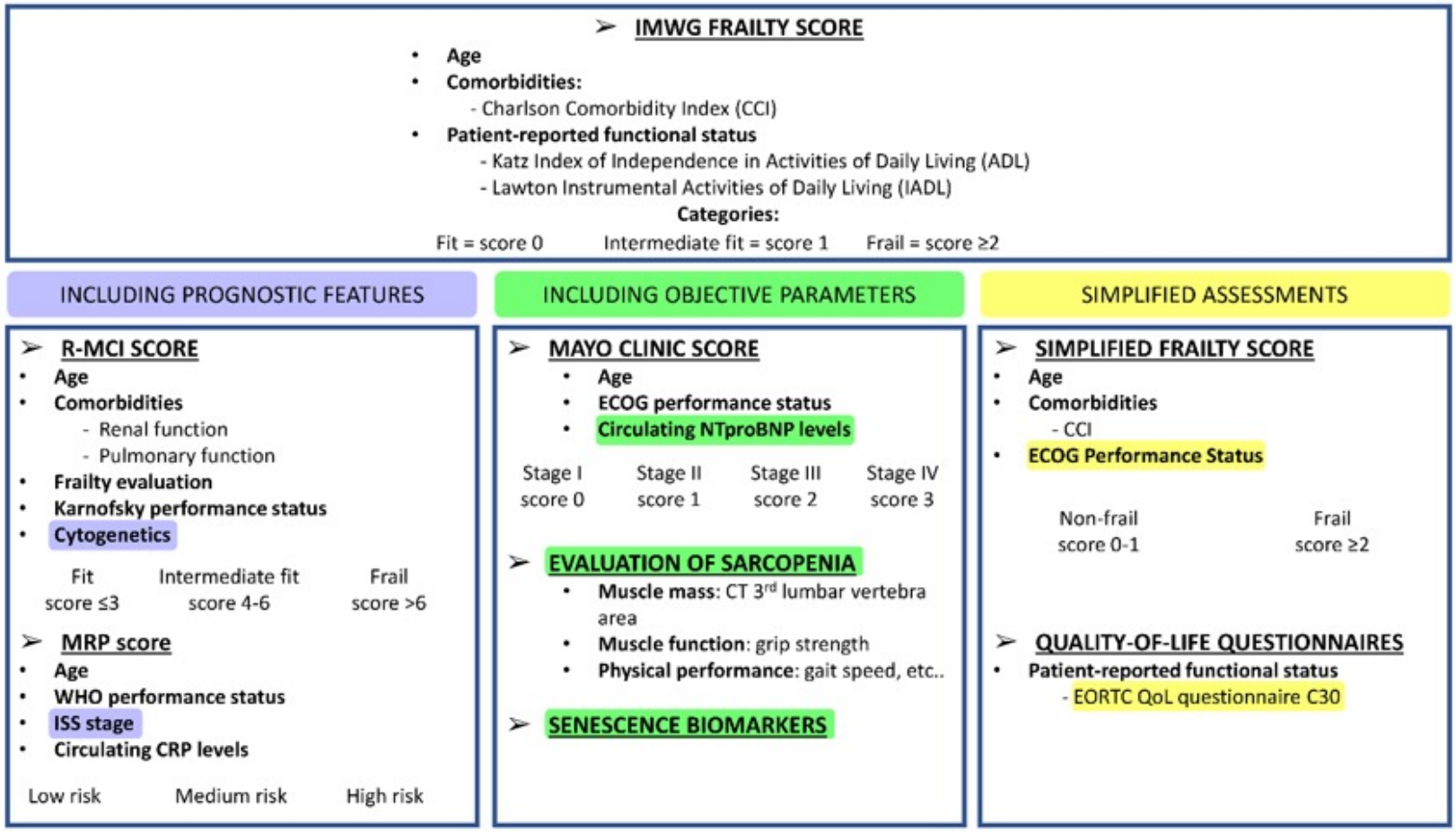
Active, independent, who exercise regularly

Intermediate fit

Can perform limited activities but they don't need any help

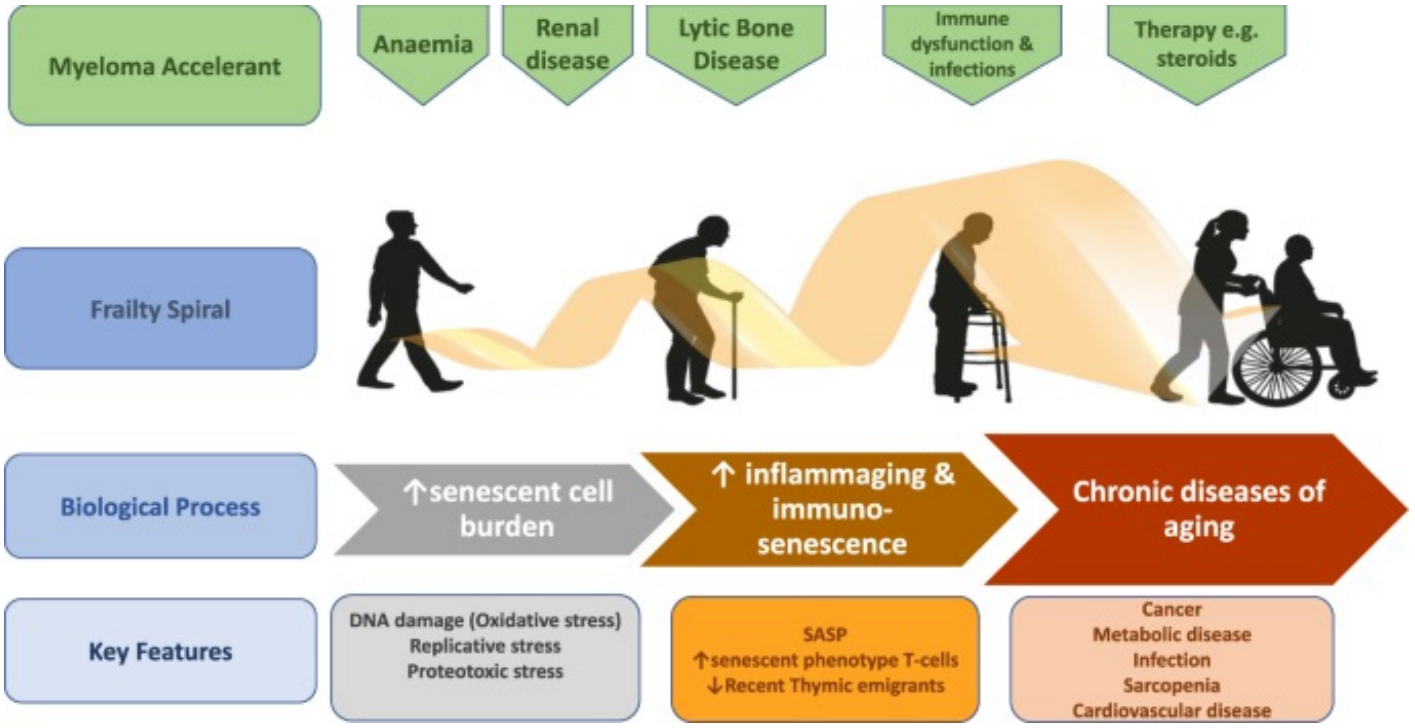
Frail

Help for household tasks
Dependent on other people
Partial help for their personal care



Bonello F et al. Cancers 2021, 12(11):3106

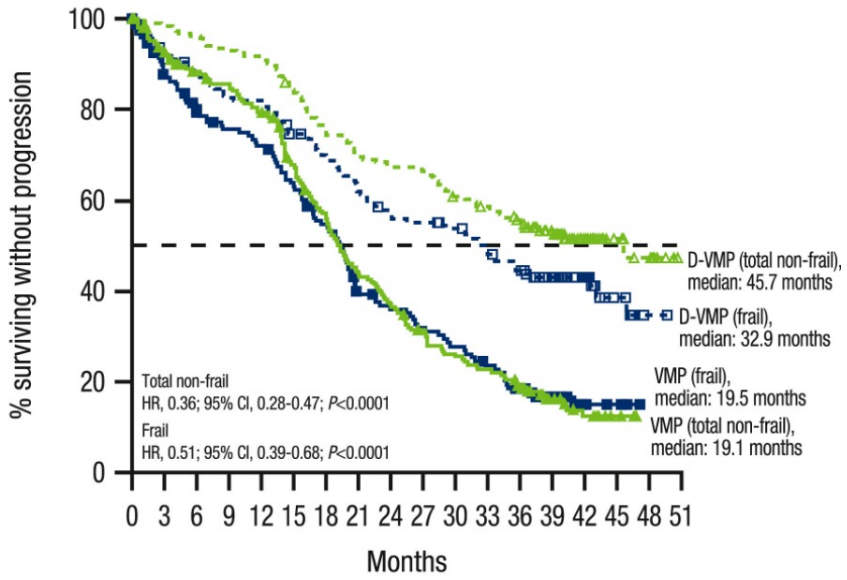
The detection of frailty in elderly patients



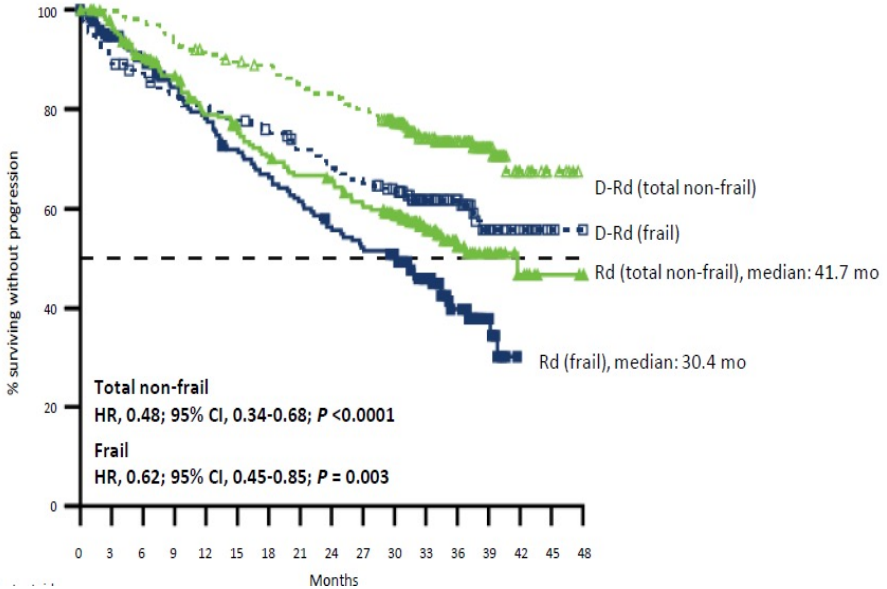
from Cook G et al. Leukemia. 2020;34:2285-2294

Management of frail patients

ALCYONE



MAIA



Mateos MV, et al. Clin Lymphoma Myeloma Leuk. 2021, epub ahead of print; Zweegmann et al, EMN 2021

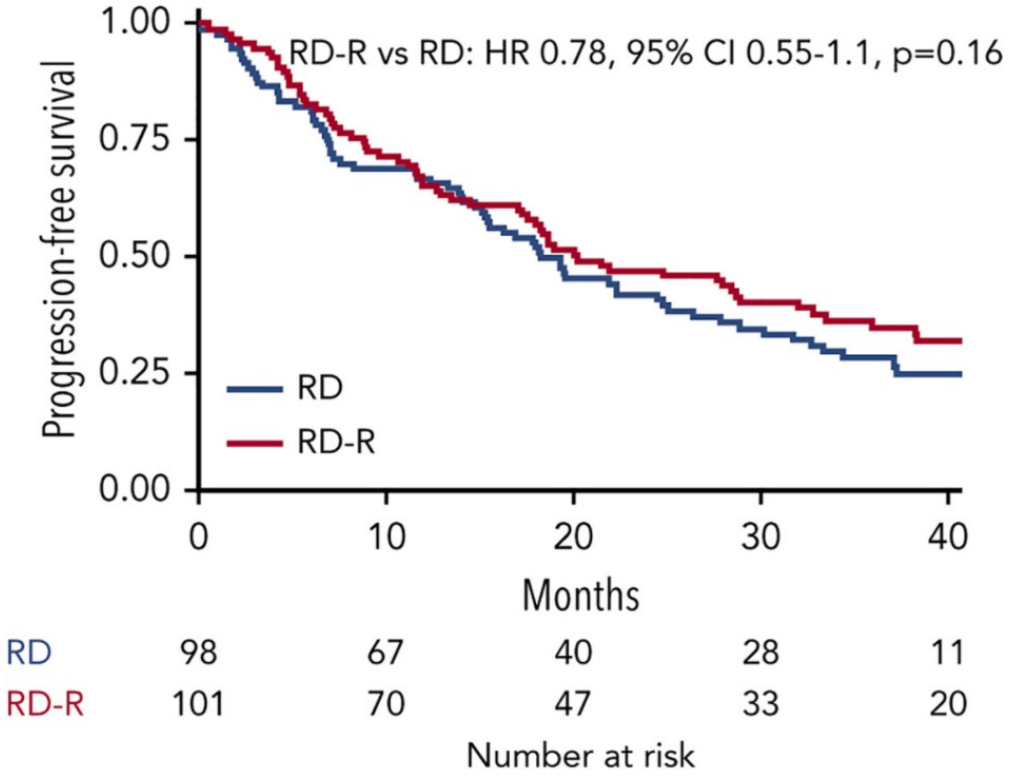
Management of frail patients

Are patients in clinical trial really frail?

	SWOG S0777	ALCYONE	MAIA
Median age (years) ≥ 75 years	63 > 65 43%	71 30%	73 44%
ECOG PS 0-1 2 > 2	 86% 14% 2-3 excluded >3	 75% 25% excluded	 83% 17% excluded
Creatinine clearance 30-60 ml/min < 30 ml/min	 5% creatinine > 2mg/dL excluded	 41% excluded (< 40 ml/min)	 41% excluded
Exclusion criteria	Previous malignancy NYHA III/IV Recent myocardial infarction	AST/ALT > 2.5 ULN Malignancy < 3 years Myocardial infarction < 1 year	AST/ALT > 2.5 ULN Malignancy < 5 years Myocardial infarction < 1 year

Durie B et al, Blood 2018; 132;1992; Durie et al; Blood Cancer J; 10:53; Mateos MV et al, Lancet 2020; 395(10218):132-141; Facon T et al, N Eng J Med 2019 380, 2105-15

Treatment modulation according to fitness: steroid sparing strategies



Outcome in intermediate-fit patients according to IMWG frailty score

	Rd	Rd-r
EFS (median)	6.9	10.4 (HR 0.7, p 0.002)
G≥ 3 non hematol AEs	43%	33%
R dose reduction	62%	45%
Dex dose reduction	31%	17%
Discontinuation	30%	24%

Larocca et al, Blood 2021, 137(22):3027-3036

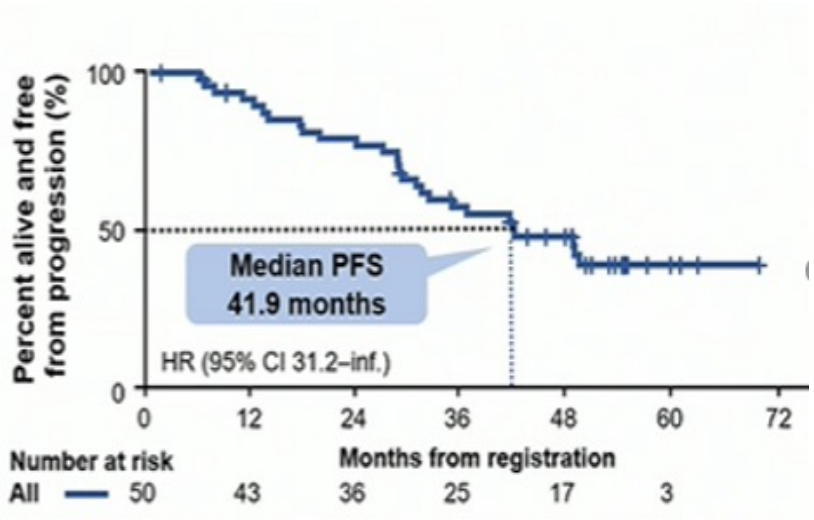
Treatment modulation according to fitness: dose reduced treatment

RVd-lite

9 35-days induction cycles
Lenalidomide 15 mg day 1-21
Bortezomib 1.3 mg/m2 day 1-8-15-22
Dexamethasone 40 mg weekly (20 mg if > 75 years)

→

6 28-days consolidation cycles
Lenalidomide 15 mg day 1-21
Bortezomib 1.3 mg/m2 day 1-15



	RVd-lite
Median age (years)	73
PFS (median)	42 months
ORR	86%
VGPR	66%
Dose reductions	78%
Discontinuation	4%

O'Donnell et al, BJH 2018, 182(2):222-230;
O'Donnell et al, ASH 2019

Conclusions: frailty-tailored treatment

FRAILTY ASSESSMENT IMWG Frailty Score		
FIT PATIENTS **(score 0)**	**INTERMEDIATE-FIT PATIENTS** **(score 1)**	**FRAIL PATIENTS** **(score ≥2)**
		
age ≤75 + ADL >4 + IADL >5 +CCI≤1	age 76-80 or ADL ≤4 or IADL ≤5 +CCI >1	age >80; age 76-80 + ADL ≤4 or IADL ≤5 or CCI >1; age ≤75 + at least 2 ADL ≤4 or IADL ≤5 or CCI >1
APPROVED REGIMENS **with possibile dose-adjustments according to frailty**		
• Daratumumab-VMP • Daratumumab-Rd • VRd • ASCT: Standard of care in ≤70 years old Consider in 71-75 years old* (*possibly with reduced conditioning)	• (Daratumumab)-VMP, consider weekly V • (Daratumumab)-Rd, consider dex discontinuation • Vd • VRd-lite	• Dose-adjusted Rd ± daratumumab • Dose-adjusted Vd • Palliative care
EXPERIMENTAL REGIMENS		
Daratumumab-VRd (NCT03652064) Isatuximab-VRd (NCT03319667) Belantamab-VRd (NCT04091126) KRD (NCT04096066) Ixazomib-RD (NCT018550524)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-VRd lite (NCT04052880) KRD (NCT04096066) Ixazomib-RD (NCT018550524)	Daratumumab-Ixa-dex (NTR6297) Daratumumab-R (NCT03993912) Ixazomib-RD (NCT018550524)

Daratumumab
SubCutaneous formulation

Study overview

PAVO[1]	COLUMBA[2]	PLEIADES[3,4]
Phase 1b	**Phase 3**	**Phase 2**
78 patients	**522 patients**	**265 patients**
Single arm daratumumab monotherapy in RRMM	Randomized, open label, daratumumab monotherapy in RRMM (>2 prior lines)	Open label DVRd (TE-NDMM), DVMP (TIE-NDMM), DRd (RRMM), DKd (RRMM),
Single arm, dose escalation to evaluate appropriate mixed dose of daratumumab and rHuPH20 based on data of safety and PK	Non-inferiority of daratumumab SC monotherapy (1,800 mg) vs. daratumumab IV monotherapy (16 mg/kg) **Endpoints:** ORR and C_{trough}	Investigation to evaluate efficacy & safety of daratumumab SC with SOC **Endpoints:** ORR/VGPR

1. Chari et al. Poster Presentation #1995 ASH 2018
2. Mateos MV, *et al. Lancet Haematol.* 2020;7(5):e370–e380.
3. Chari et al. Br J Haematol. 2021 Mar;192(5):869-878.
4. Moreau et al. Abstract: #1380, 62nd ASH Annual Meeting 2020

COLUMBA study design

Phase 3, randomised, open-label, active-controlled, multicentre non-inferiority study of *daratumumab SC versus daratumumab IV* in patients with heavily pre-treated RRMM (N=522)[1]

Key eligibility criteria:

- RRMM
- ≥3 prior lines, including a PI and an IMiD or
- Refractory to both a PI and IMiD

1:1 RANDOMISATION

DARA SC 1,800 mg (n=263) QW Cycles 1–2, Q2W Cycles 3-6, Q4W Cycles 7+ until PD

DARA IV 16 mg/kg (n=259) QW Cycles 1-2, Q2W Cycles 3-6, Q4W Cycles 7+ until PD

Co-primary endpoints:

- ORR
- Maximum C_{trough}*

Key secondary endpoints:

- IRR rate
- PFS
- Rates of ≥VGPR and ≥CR
- Time to next therapy
- OS
- PROs

- Median patient age 67 years[2]
- Median baseline body weight 73 kg (range: 29–138 kg)[2]
- Patients received a median of 4 lines of therapy and 100% had received both PI and IMiD; 17% had high cytogenetic risk at baseline[2]

Stratification factors:

- Baseline body weight (≤65 kg vs. >65–85 kg vs. >85 kg)
- Prior lines of therapy (≤4 prior lines vs. >4 prior lines)
- Type of myeloma (IgG vs. non-IgG)

Treatment cycle: 28 days

Median follow-up 7.5 months

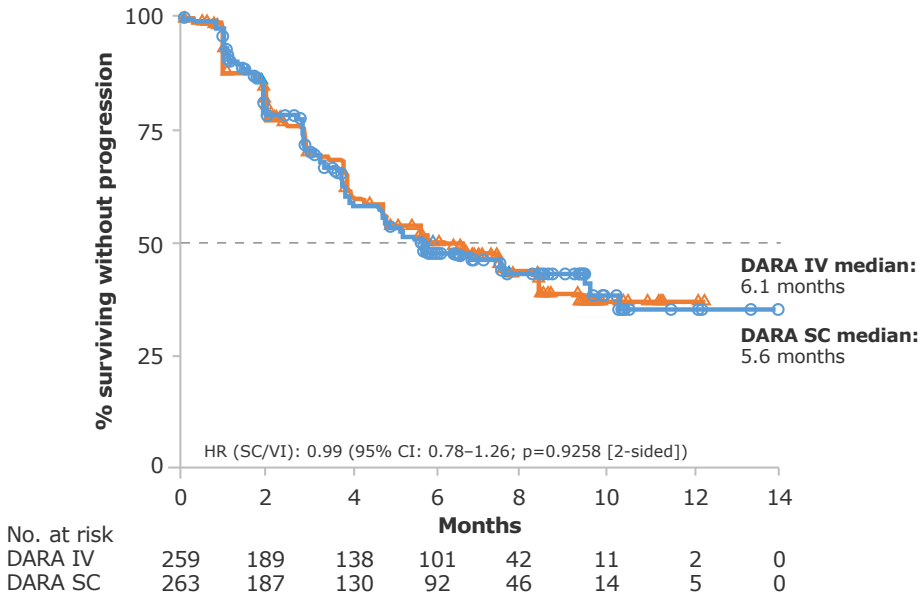
*Serum pre-dose DARA concentration on Cycle 3 Day 1

1.Mateos MV, *et al. Lancet Haematol.* 2020;7(5):e370–e380. 2.Usmani SZ, *et al*. Poster presented at the 61st American Society of Hematology annual meeting; December 7–10, 2019; Orlando, FL; Poster 1865.3. Moreau et al. Abstract: #1380, 62nd ASH 2020

COLUMBA: Key secondary efficacy endpoints (PFS and OS)

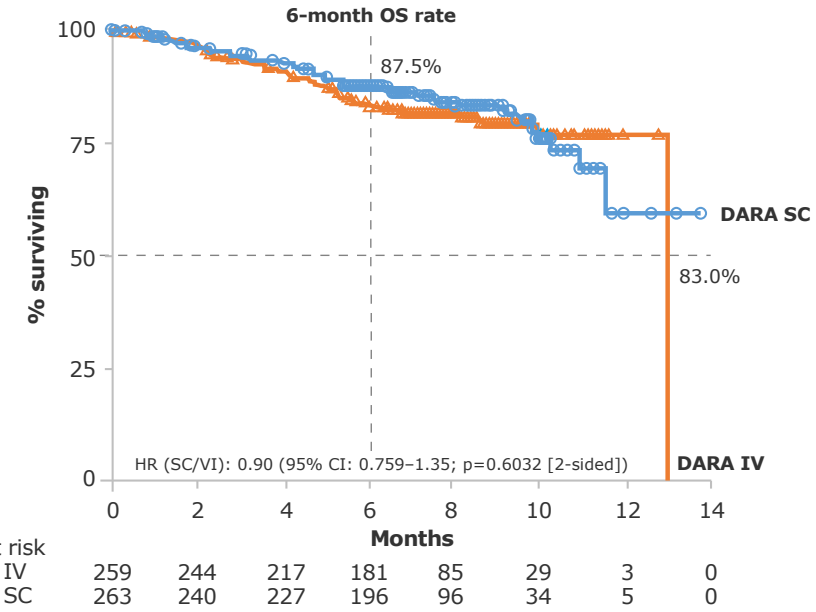
Median (range) follow-up: 7.5 (0.03–13.86) months[1]

PFS (ITT population)



No. at risk								
DARA IV	259	189	138	101	42	11	2	0
DARA SC	263	187	130	92	46	14	5	0

OS (ITT population)



No. at risk								
DARA IV	259	244	217	181	85	29	3	0
DARA SC	263	240	227	196	96	34	5	0

PFS and OS comparable between treatment groups[1]

Mateos MV, *et al. Lancet Haematol.* 2020;7(5):e370–e380.

COLUMBA body weight subgroups: Safety

Median follow-up: 7.5 months (primary analysis)

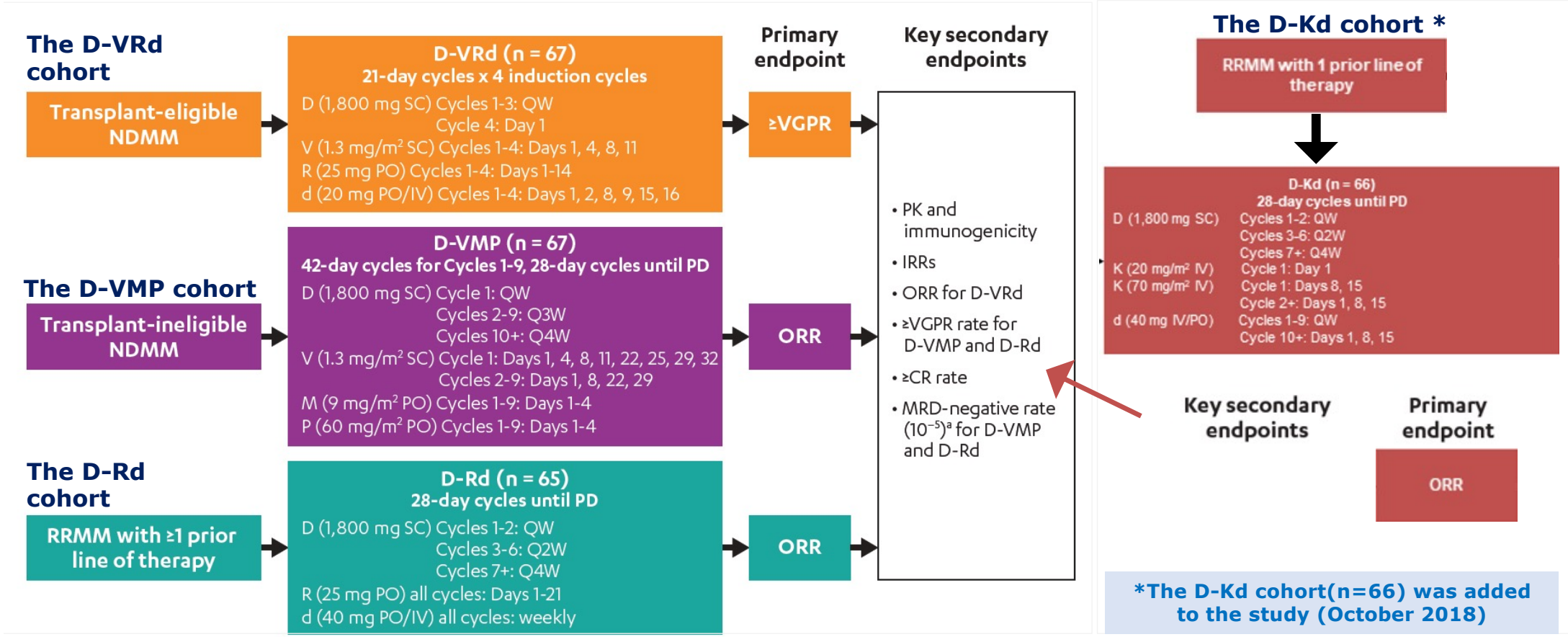
	DARA IV			DARA SC		
	≤65 kg (n=92)	**>65–85 kg** (n=105)	**>85 kg** (n=61)	**≤65 kg** (n=93)	**>65–85 kg** (n=102)	**>85 kg** (n=65)
Any-grade TEAEs, n (%)	82 (89)	94 (90)	54 (89)	88 (95)	89 (87)	51 (79)
Infections	41 (45)	43 (41)	33 (54)	45 (48)	44 (43)	30 (46)
Patients receiving growth factor, n (%)	15 (16)	11 (11)	3 (5)	13 (14)	8 (8)	6 (9)
Grade 3/4 TEAEs, n (%)	47 (51)	51 (49)	28 (46)	46 (49)	46 (45)	26 (40)
Most common (≥10%)						
Anaemia	14 (15)	15 (14)	7 (12)	26 (28)	29 (28)	13 (20)
Thrombocytopenia	17 (18)	18 (17)	13 (21)	21 (23)	19 (19)	8 (12)
Neutropenia	13 (14)	13 (12)	9 (15)	24 (26)	15 (15)	11 (17)
Lymphopenia	7 (8)	7 (7)	3 (5)	10 (11)	5 (5)	4 (6)
Diarrhoea	14 (15)	11 (10)	3 (5)	20 (22)	5 (5)	14 (22)
Upper respiratory tract infection	4 (4)	10 (10)	11 (18)	14 (15)	12 (12)	9 (14)
Pyrexia	14 (15)	10 (10)	9 (15)	15 (16)	12 (12)	7 (11)
Fatigue	8 (9)	13 (12)	6 (10)	9 (10)	7 (7)	12 (19)
Back pain	14 (15)	9 (9)	4 (6)	14 (15)	10 (10)	8 (13)
Nausea	11 (12)	11 (10)	6 (10)	10 (11)	5 (5)	6 (9)
Serious TEAEs, n (%)	28 (30)	33 (31)	15 (25)	22 (24)	29 (28)	17 (26)
TEAEs leading to treatment discontinuation, n (%)	6 (7)	9 (9)	6 (10)	8 (9)	8 (8)	2 (3)
Any-grade IRRs, n (%)	27 (29)	38 (36)	24 (39)	13 (14)	13 (13)	7 (11)

Safety profile comparable between DARA SC and DARA IV when assessed by subgroups[1]

1. Mateos MV, *et al. Lancet Haematol.* 2020;7(5):e370–e380.

PLEIADES study design

Multicentre, open-label, phase 2 study of daratumumab SC in combination with standard of care

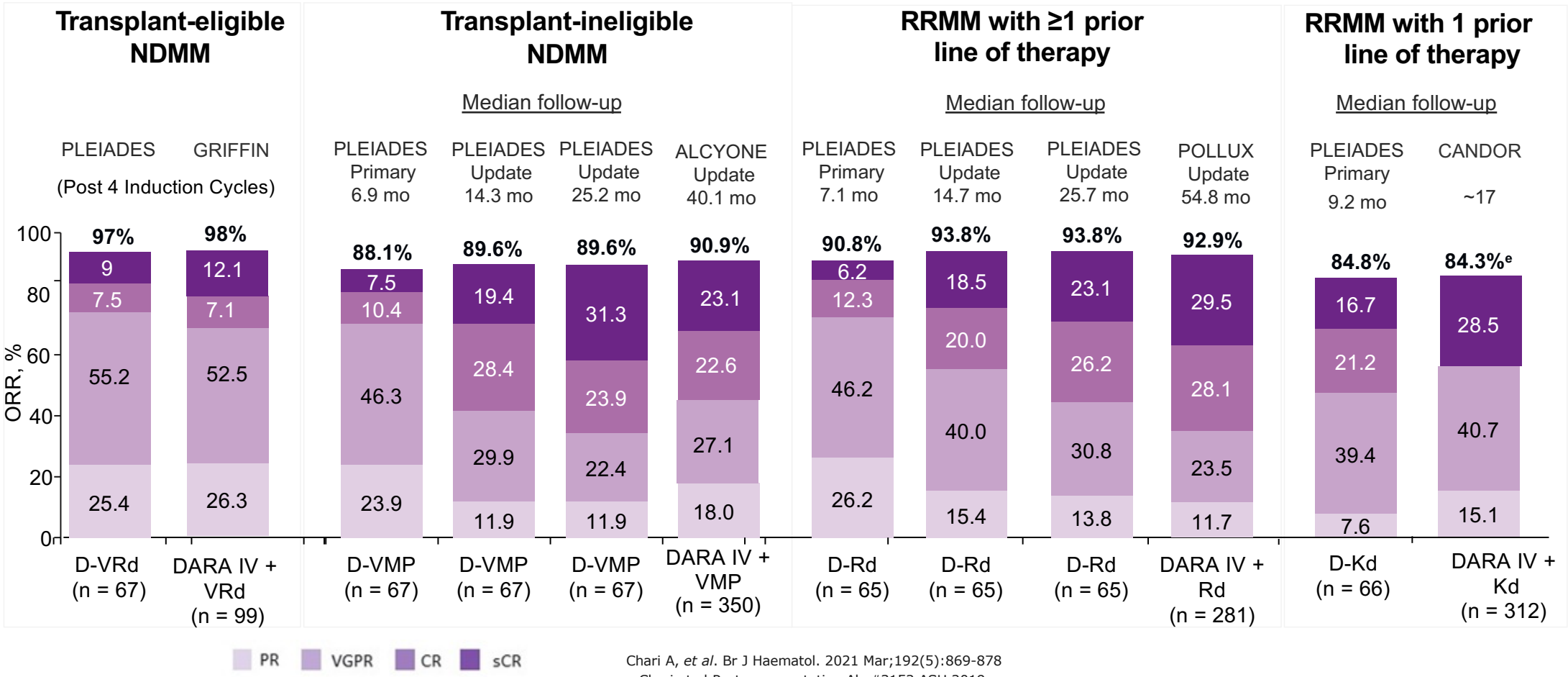


Chari A, *et al*. Br J Haematol. 2021 Mar;192(5):869-878

Moreau et al. Abstract: #1380, 62nd ASH Annual Meeting 2020

PLEIADES: ORR and comparison to Dara IV studies

D-VRd (Griffin), D-VMP (Alcyone), D-Rd (Pollux), DKd (Candor) Cohorts



Chari A, *et al*. Br J Haematol. 2021 Mar;192(5):869-878
Chari et al Poster presentation Abs#3152 ASH 2019
Moreau et al. Abstract: #1380, 62nd ASH Annual Meeting 2020

Daratumumab SC summary

Comparable efficacy for daratumumab SC compared with daratumumab IV demonstrated in COLUMBA and PLEIADES in patients with NDMM & RRMM[1,2,3]

3–5-minute injection time from the first dose vs. 3–7 hours for daratumumab IV[4]

Similar safety profile with **lower and less severe IRRs** vs. daratumumab IV[1,2,3]

- The baseline and treatment-emergent incidence of anti-daratumumab and anti-rHuPH20 antibodies were low overall and consistent with previous reports[1,2,3]

Daratumumab SC patients report **higher satisfaction with treatment than DARA IV** patients[1]

Can be used with **all approved** daratumumab-based regimen[4]

These results support the use of daratumumab SC of 1,800 mg flat dose in combination with standard treatment regimens across lines of therapy in multiple myeloma[1,2]

1. Mateos MV, et al. Lancet Haematol 2020;
2. Chari A, et al. Br J Haematol. 2021 Mar;192(5):869-878
3. Chari A, et al. Poster presentation ABS 3152 ASH 2019
4. Daratumumab SC RCP genn 2022, Daratumumab EV RCP genn 2022

DARATUMUMAB SC® provides comparable efficacy, lower administration-related reactions, reduced administration time and cost predictability

	Administration Time	Dosing	Equivalent Efficacy	Fewer Systemic IRRs
DARATUMUMAB SC®[1,2]	3-5 MINUTES HCP-administered injection	1800 mg fixed dose	41% ORR	13%
DARATUMUMAB IV®[2,3]	180-420 MINUTES HCP-administered infusion	16 mg/kg weight-based	37% ORR	34%

Equivalent efficacy and faster delivery

ARR, administration-related reaction; CTSQ, Cancer Therapy Satisfaction Questionnaire; HCP, healthcare provider; IV, intravenous; ORR, overall response rate; SC, subcutaneous.

1. Daratumumab SC RCP Genn 2022; 2. Mateos et al. Lancet Haematol 2020; 3. Daratumumab EV RCP Genn 2022

Management of IRRs: Prior to daratumumab SC injection

SAME APPROACH AS DARATUMUMAB IV INFUSION

To reduce the risk of IRRs, pre-medications should be administered approximately 1–3 hours before each injection[1]

Corticosteroid (long-acting or intermediate-acting)

- **Monotherapy**
  Methylprednisolone 100 mg, or equivalent. Following the second injection, the dose of corticosteroid may be reduced to methylprednisolone 60 mg
- **Combination therapy**
  Dexamethasone 20 mg (or equivalent), administered prior to every daratumumab SC injection. When dexamethasone is the background-regimen–specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-injection medicinal product on daratumumab SC administration days. Additional background regimen specific corticosteroids (e.g., prednisone) should not be taken on daratumumab SC administration days when patients have received dexamethasone (or equivalent) as a pre-injection medicinal product

Anti-pyretics (paracetamol 650 to 1,000 mg)

Anti-histamine (diphenhydramine 25 to 50 mg or equivalent)

Pre-medications can be given EV or orally[1]

Daratumumab SC should be administered by a healthcare professional, and the **first dose** should be administered in an environment where resuscitation facilities are available[1]

1. Daratumumab SC RCP genn 2022


Thank You !

Back up

Management of frail 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

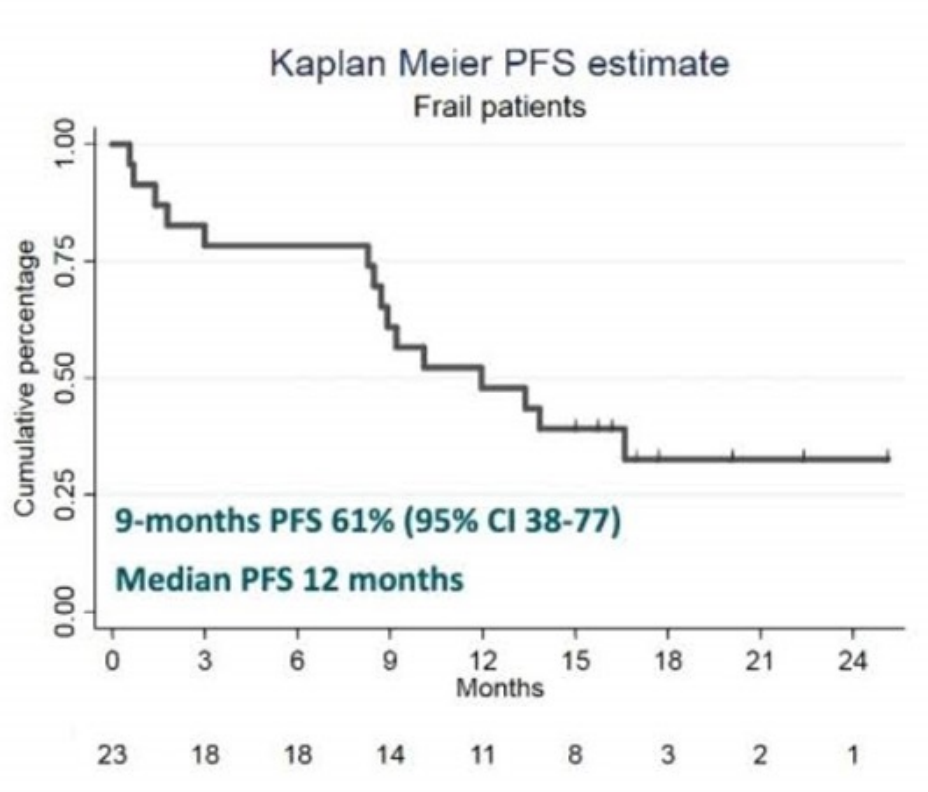
MAINTENANCE

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

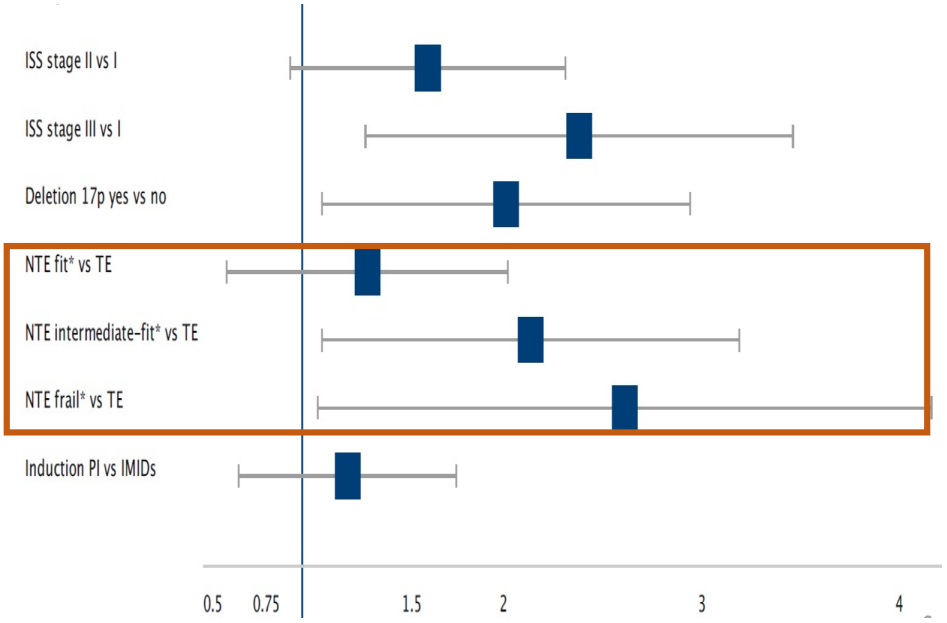
	IRd
PFS (median)	12
OS (1y)	78%
Discontinuation	51%
Toxic deaths	9%



Stege CAM; JCO 2021; 39(25):2758-2767

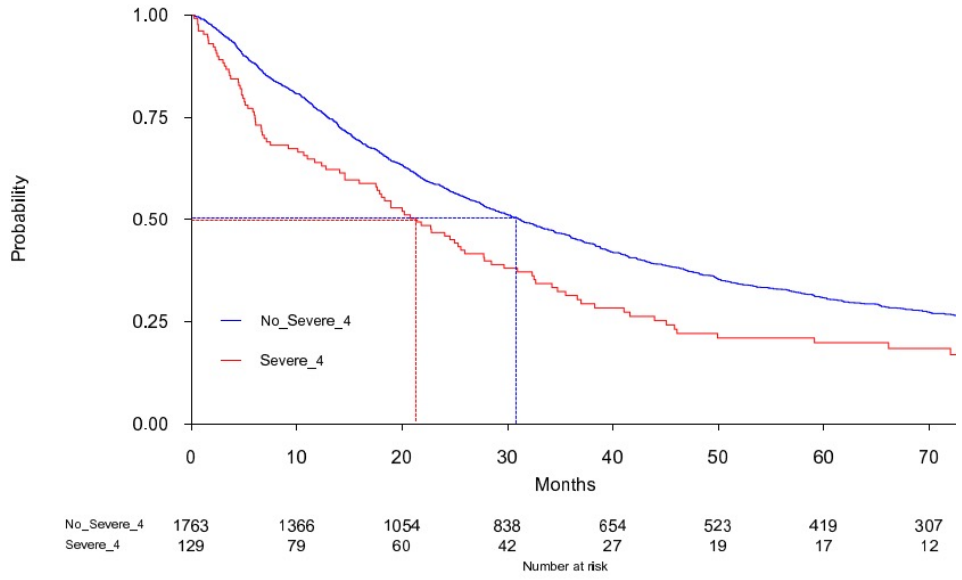
Managing Toxicity In Elderly Patients: Infections

The risk of early severe infections is higher in intermediate fit/frail patients and negatively affects outcome



NO INFECTION **INFECTION**

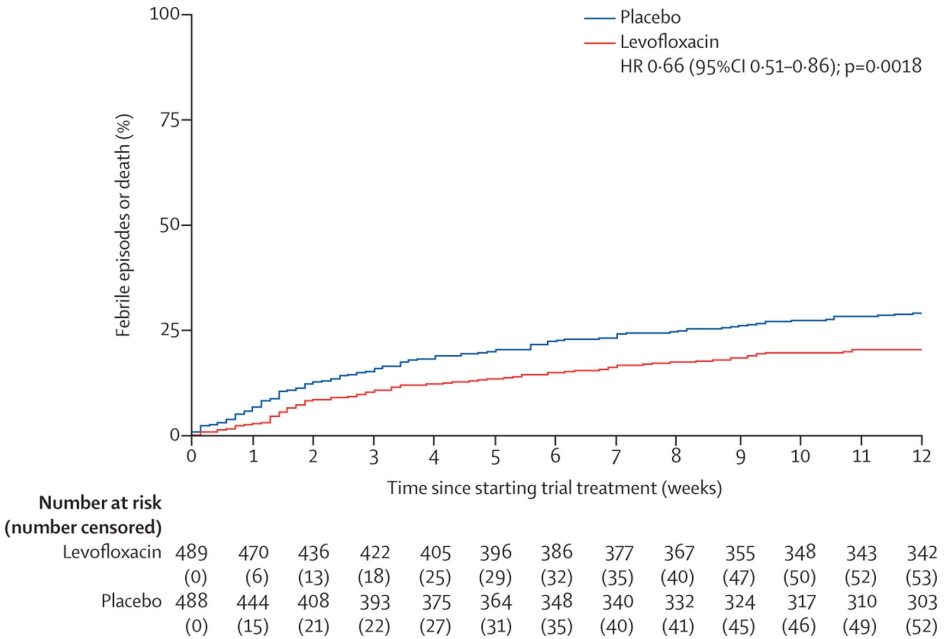
PFS

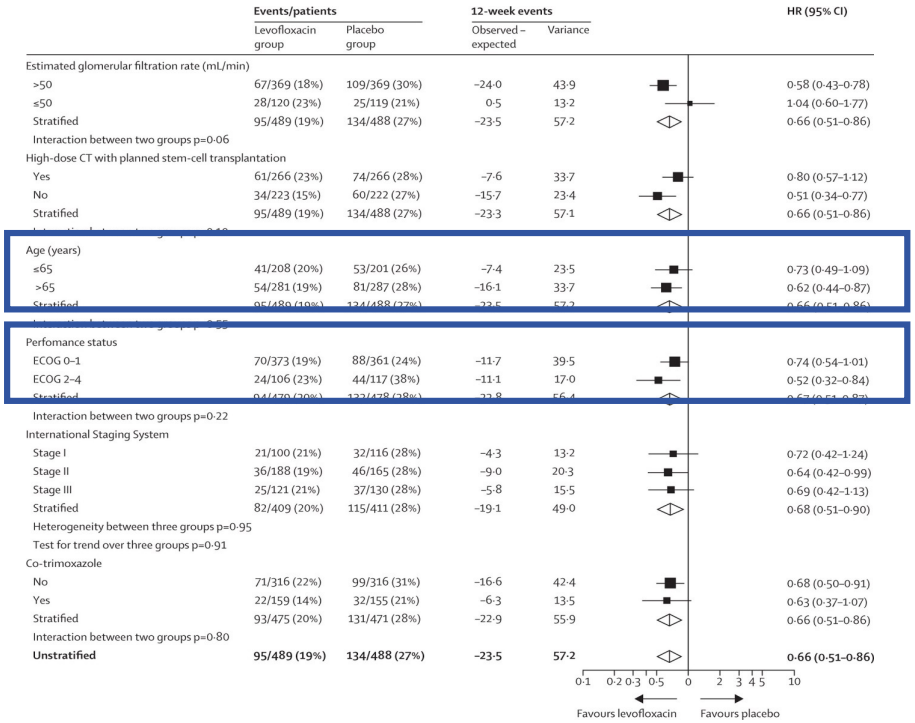


HR* 1.28, 95% CI 1.05-1.58, p 0.02

Bonello F et al, ASH 2020

Managing Toxicity In Elderly Patients: Infections





	Events/patients: Levofloxacin group	Events/patients: Placebo group	12-week events: Observed – expected	12-week events: Variance	HR (95% CI)
Estimated glomerular filtration rate (mL/min)					
>50	67/369 (18%)	109/369 (30%)	−24·0	43·9	0·58 (0·43–0·78)
≤50	28/120 (23%)	25/119 (21%)	0·5	13·2	1·04 (0·60–1·77)
Stratified	95/489 (19%)	134/488 (27%)	−23·5	57·2	0·66 (0·51–0·86)
Interaction between two groups p=0·06					
High-dose CT with planned stem-cell transplantation					
Yes	61/266 (23%)	74/266 (28%)	−7·6	33·7	0·80 (0·57–1·12)
No	34/223 (15%)	60/222 (27%)	−15·7	23·4	0·51 (0·34–0·77)
Stratified	95/489 (19%)	134/488 (27%)	−23·3	57·1	0·66 (0·51–0·86)
Age (years)					
≤65	41/208 (20%)	53/201 (26%)	−7·4	23·5	0·73 (0·49–1·09)
>65	54/281 (19%)	81/287 (28%)	−16·1	33·7	0·62 (0·44–0·87)
Stratified	95/489 (19%)	134/488 (27%)	−23·5	57·2	0·66 (0·51–0·86)
Perfomance status					
ECOG 0–1	70/373 (19%)	88/361 (24%)	−11·7	39·5	0·74 (0·54–1·01)
ECOG 2–4	24/106 (23%)	44/117 (38%)	−11·1	17·0	0·52 (0·32–0·84)
Stratified	94/479 (20%)	132/478 (28%)	−22·8	56·4	0·67 (0·51–0·87)
Interaction between two groups p=0·22					
International Staging System					
Stage I	21/100 (21%)	32/116 (28%)	−4·3	13·2	0·72 (0·42–1·24)
Stage II	36/188 (19%)	46/165 (28%)	−9·0	20·3	0·64 (0·42–0·99)
Stage III	25/121 (21%)	37/130 (28%)	−5·8	15·5	0·69 (0·42–1·13)
Stratified	82/409 (20%)	115/411 (28%)	−19·1	49·0	0·68 (0·51–0·90)
Heterogeneity between three groups p=0·95					
Test for trend over three groups p=0·91					
Co-trimoxazole					
No	71/316 (22%)	99/316 (31%)	−16·6	42·4	0·68 (0·50–0·91)
Yes	22/159 (14%)	32/155 (21%)	−6·3	13·5	0·63 (0·37–1·07)
Stratified	93/475 (20%)	131/471 (28%)	−22·9	55·9	0·66 (0·51–0·86)
Interaction between two groups p=0·80					
Unstratified	**95/489 (19%)**	**134/488 (27%)**	**−23·5**	**57·2**	**0·66 (0·51–0·86)**

0·1 0·2 0·3 0·5 0 2 3 4 5 10

Favours levofloxacin Favours placebo

Dryson et al; The Lancet Oncology 1760-1772

Future directions in the management of elderly ndmm patients

- Frailty-tailored treatment in clinical practice
- Efficacy and safety of antiCD38 monoclonal antibodies plus VRd
- Role of active immunotherapy in elderly patients (CART, BiTEs)
- New IMiDs/cellMODs
- MRD driven treatment: fixed vs continuous treatment
- Improving supportive care: antimicrobial prohylaxis in selected patients

Daratumumab SC storage and handling

Storage conditions[1]:

- Store at **2–8°C** and protected from light
- Do **not freeze**
- For **single use** only – any unused medicinal product or waste material should be disposed of in accordance with local requirements
- Do **not use if opaque particles, discolouration or other foreign particles** are present
- Shelf life of daratumumab SC,Unopened vial:**18 months**

Handling and disposal[1]:

- Formulation compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) SC infusion sets; and stainless-steel transfer and injection needles
- **Before use** remove the daratumumab SC solution for injection vial from refrigerated storage (2–8°C) and equilibrate to **ambient temperature** (15–30°C)
- The unpunctured vial may be stored at **ambient temperature** and ambient light for a maximum of **24 hours** in the original carton to protect from light.
- Once transferred from the vial into the syringe, daratumumab solution for injection can be stored for a **maximum of 4 hours at ambient temperature and ambient light**

1. Daratumumab SC RCP genn 2022