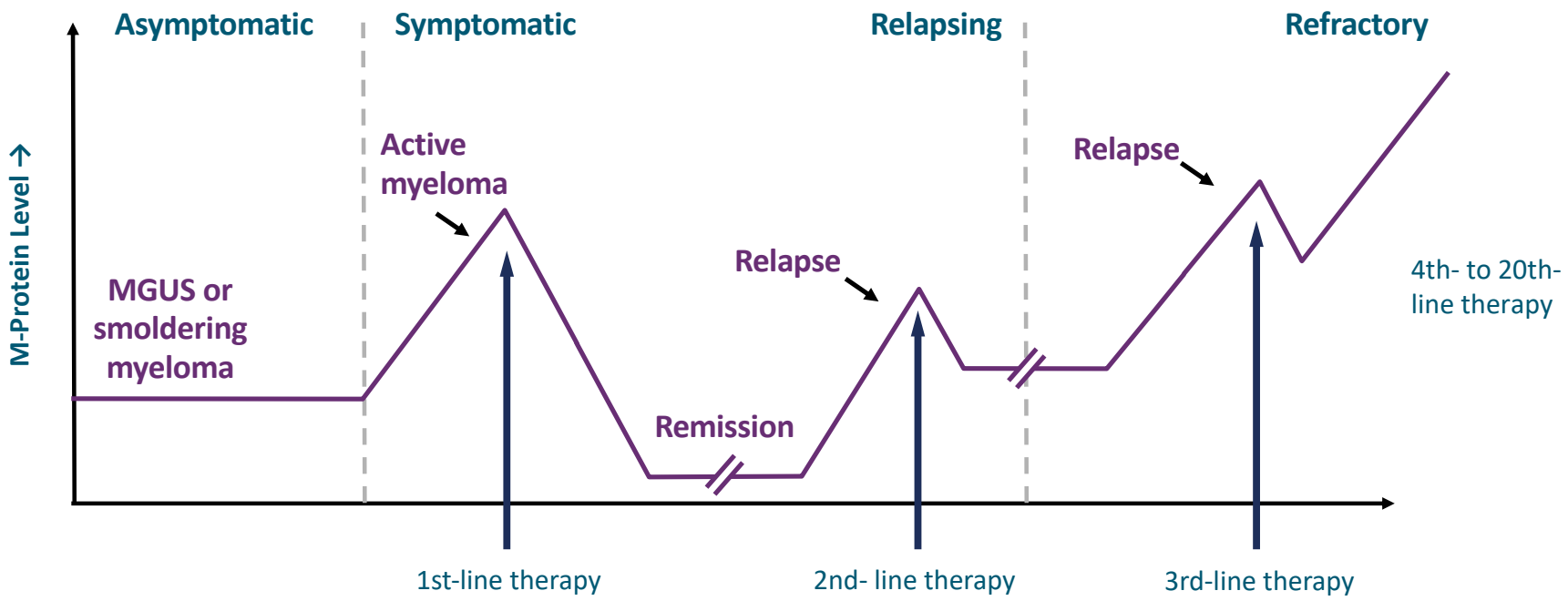
Treating Multiple Myeloma Is a Marathon, Not a Sprint!

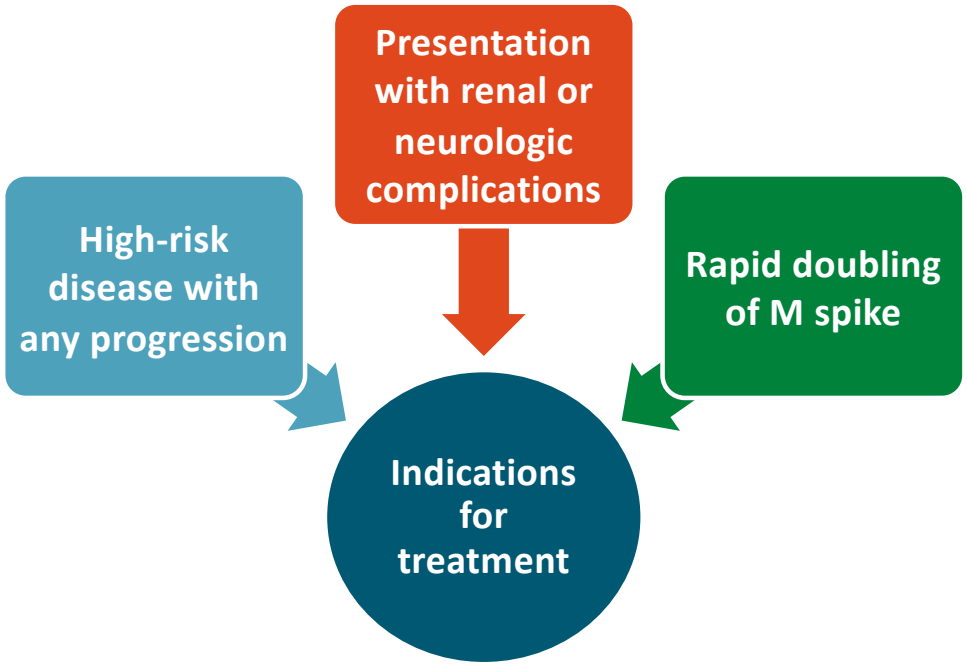
- Strategic vs tactical considerations: tolerability AND efficacy key with combination regimens



Adapted from Borrello. Leuk Res. 2012;36:S3.
Richardson. Blood Cancer J. 2018;8:109.

When Should We Start Treatment for Relapse?

- Patients with clinical progression/CRAB symptoms clearly need treatment
- Those with biochemical progression (no symptoms) may not need immediate treatment, or can consider a rational addition to current therapy
  - Standard-risk disease with slow trend upward

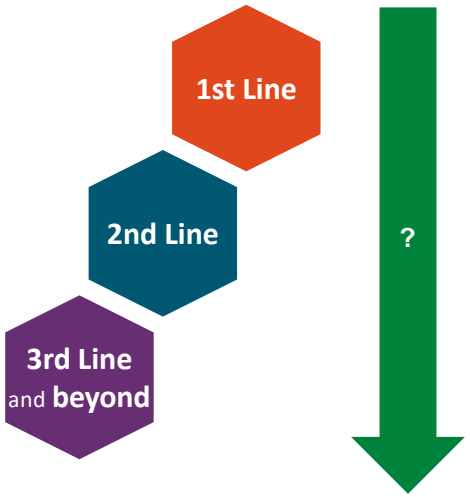


Adapted from Laubach. Leukemia. 2016;30:1005. Moreau. Lancet Oncol. 2021;22:e105.

Multiple Novel Agents Now Available to Treat Newly Diagnosed and Relapsed/Refractory Myeloma in 2021

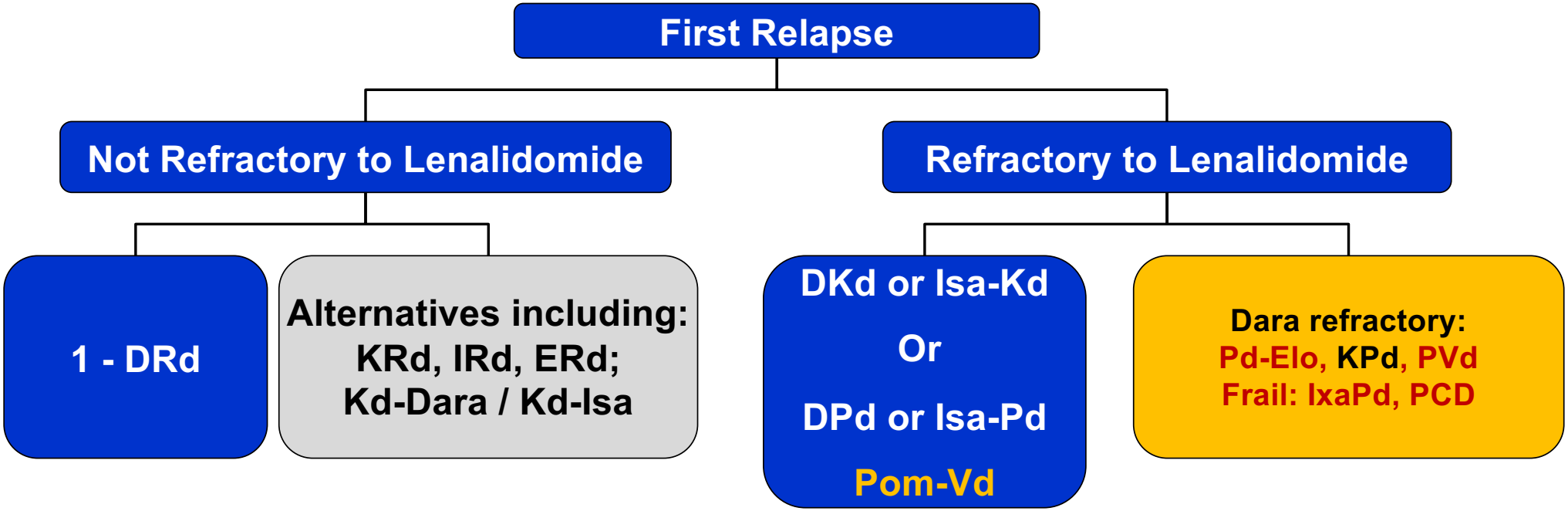
15 Approved Novel Agents in MM . . . and more coming!

How do we sequence and strategize therapies to ensure the best outcomes for our patients?



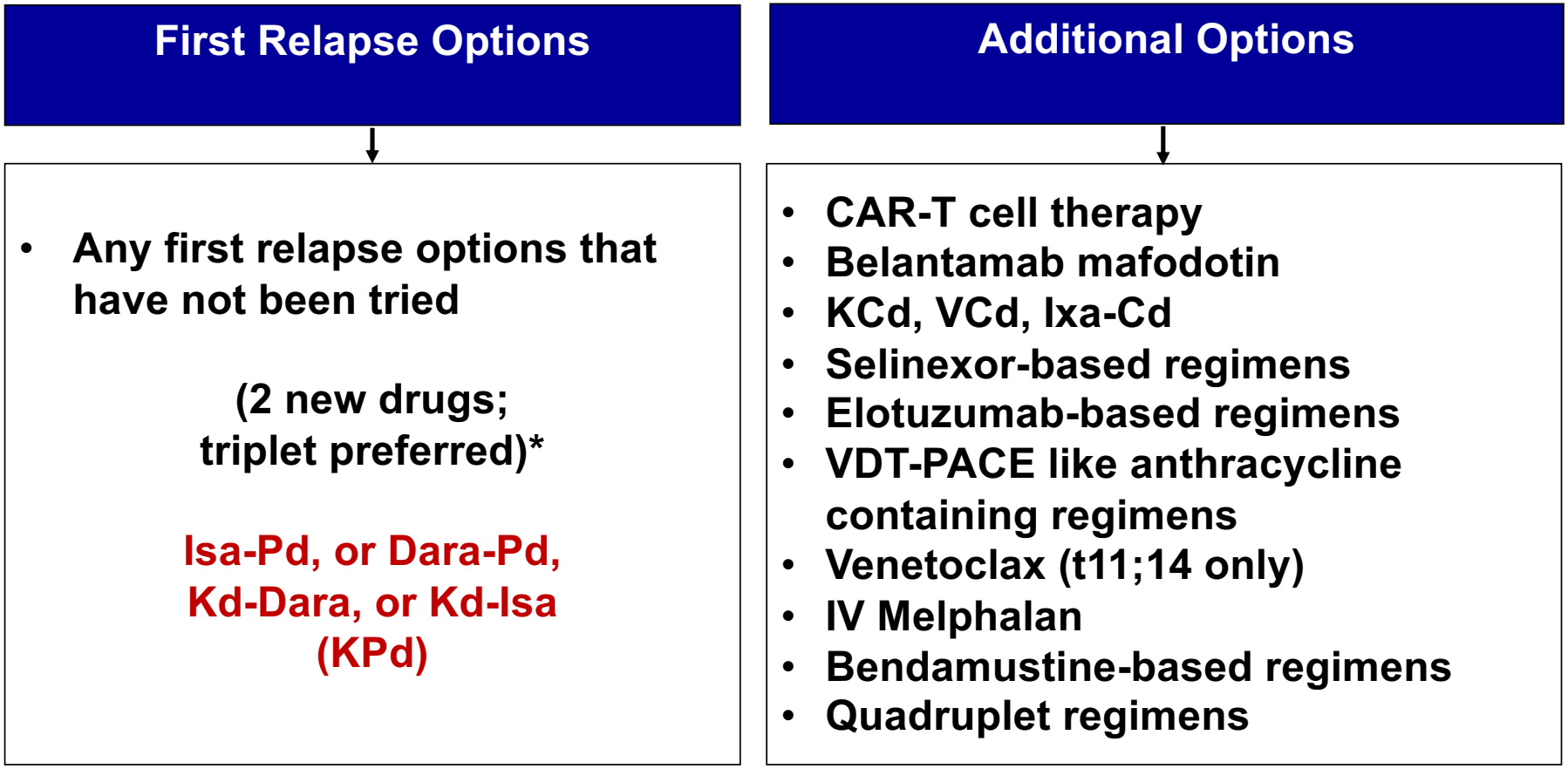
Adapted from Laubach. Leukemia. 2016;30:1005. Moreau. Lancet Oncol. 2021;22:e105.

Myeloma: First Relapse

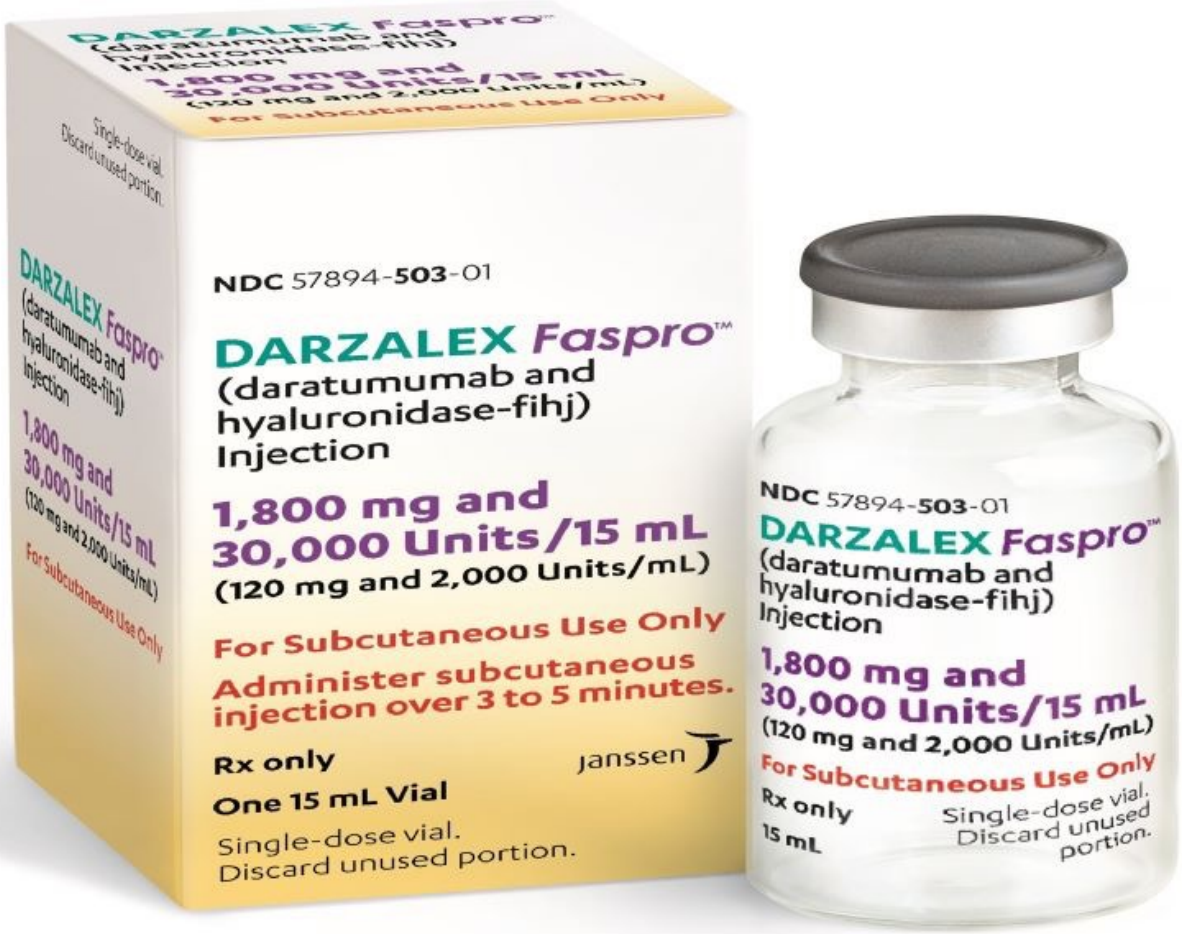


P. Moreau

Myeloma: Second or Higher Relapse



*Consider ixazomib instead of carfilzomib or bortezomib if an all-oral regimen is needed


DARZALEX Faspro™
(daratumumab and hyaluronidase-fihj) injection
1,800 mg and 30,000 Units/15 mL
(120 mg and 2,000 Units/mL)
For Subcutaneous Use Only
Single-dose vial. Discard unused portion.
NDC 57894-503-01
DARZALEX Faspro™
(daratumumab and hyaluronidase-fihj) Injection
1,800 mg and 30,000 Units/15 mL
(120 mg and 2,000 Units/mL)
For Subcutaneous Use Only
Administer subcutaneous injection over 3 to 5 minutes.
Rx only
janssen
One 15 mL Vial
Single-dose vial. Discard unused portion.
NDC 57894-503-01
DARZALEX Faspro™
(daratumumab and hyaluronidase-fihj) Injection
1,800 mg and 30,000 Units/15 mL
(120 mg and 2,000 Units/mL)
For Subcutaneous Use Only
Rx only
15 mL
Single-dose vial. Discard unused portion.

INDICATIONS

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with R/R MM:

- In combination with PD or RD in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor

- In combination with KD in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy

- In combination with VD in patients who have received at least one prior therapy

- As monotherapy in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

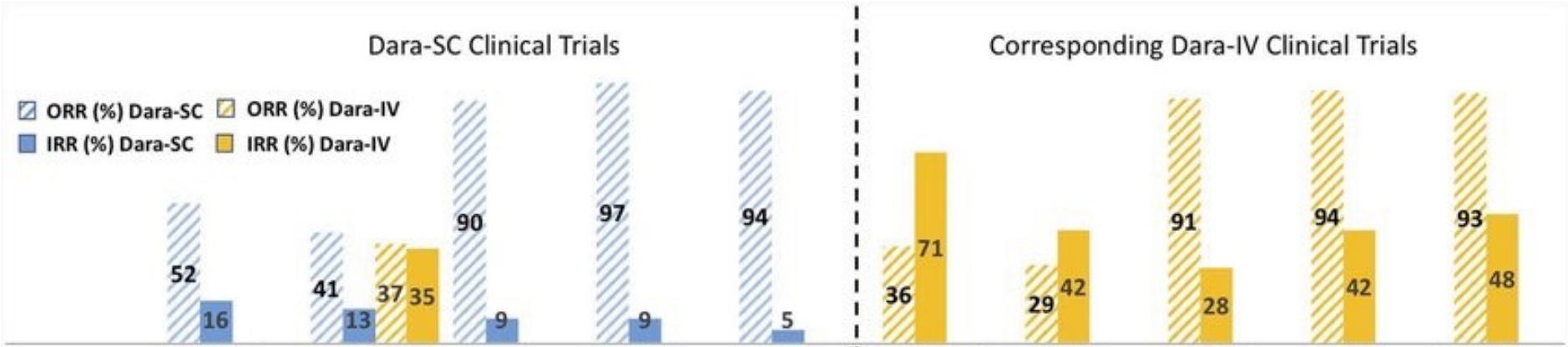
Indicazioni AIFA

- in associazione con lenalidomide e desametasone (DRD), o bortezomib e desametasone (DVD), per il trattamento di pazienti adulti con mieloma multiplo che abbiano ricevuto almeno una precedente terapia.

- in monoterapia per il trattamento di pazienti adulti con mieloma multiplo recidivato e refrattario, le cui terapie precedenti abbiano incluso un inibitore del proteasoma e un immunomodulatore, e che abbiano mostrato progressione della malattia durante l'ultima terapia.

Subcutaneous Daratumumab: Background

- Daratumumab: anti-CD38 antibody approved for R/R MM at 16 mg/kg IV as monotherapy or as triplet therapy with VD, Rd, or Pd
  - Median duration of first, second, third infusions: 7.0, 4.3, 5.0 hrs[1]
  - IRRs manageable, primarily occur during first infusion[2-4]
- Coformulation with rHuPH20, a recombinant human hyaluronidase enzyme, allows SC administration with higher daratumumab concentration, lower injection volume, shorter injection time
  - "DARA-MD": longer SC administration with syringe pump mixed and delivered with rHuPH20
  - "DARA-SC": shorter, manual SC injection of concentrated coformulation of DARA/rHuPH20
  - Low IRR rates observed with SC daratumumab, which requires shorter administration time[5]
- Current analysis sought to determine safety, PK, efficacy of manual injection of SC daratumumab coformulated with rHuPh20 in R/R MM[6]



	PAVO Part 2 (Dara-SC monotherapy) *	COLUMBA (Dara-SC vs IV)	Dara-SC + VMP	PLEAIDES Dara-SC + RVd	Dara-SC + Rd	GEN501 Part 2 (Dara-iV monotherapy)	SIRIUS (Dara-IV monotherapy)	ALCYONE (Dara-IV + VMP)	GRIFFIN (Dara-IV + RVd)	POLLUX (Dara-IV + Rd)
n	25	522	67	67	65	42	106	346	104	286
Median age	68	65 vs 63	75	59	69	64	64	71	59	65
Median prior lines (range)	3 (2-9)	4 (2-12) vs 4 (1-15)	N/A^	N/A^	1 (1-5)	4 (2-12)	5 (2-14)	N/A^	N/A^	1 (1-11)
High risk cytogenetics*	25%	26% vs 17%	20%	25%	36%	-	24%**	17%	16.3%	15%

*del17p, t(4;14), or t(14;16)
**del17p or t(4;14)
^newly diagnosed multiple myeloma

PAVO: Phase Ib Study Design

- Open-label, multicenter, dose-finding, proof-of-concept study

Pts with measurable R/R MM, ≥ 2 lines of therapy, no prior anti-CD38 therapy (N = 53)

Part 1: mix and deliver; sequential enrollment Group 1 and then Group 2

Group 1: DARA-MD
Daratumumab 1200 mg SC +
rHuPH20 30,000 U SC
via syringe pump x 20 min
(n = 8)

→

Group 2: DARA-MD
Daratumumab 1800 mg SC +
rHuPH20 45,000 U SC
via syringe pump x 30 min
(n = 45)

Part 2: concentrated coformulation

Group 3 DARA-SC:
Daratumumab 1800 mg SC +
rHuPH20 30,000 U SC manually x 3-5 min
(n = 25)

- Dosing schedule: QW x 8, then Q2W x 16 wks, then Q4W
- Pre/postadministration medication includes acetaminophen, diphenhydramine, montelukast, and methylprednisolone

- Primary endpoints: C_{trough} of daratumumab at cycle 3/day 1, safety
- Secondary endpoints: ORR, CR, DoR, time to response

Chari A, et al. ASH 2017. Abstract 838. Usmani SZ, et al. ASH 2016

PAVO: Patient Characteristics

Characteristic	DARA-MD 1200 mg (n = 8)	DARA-MD 1800 mg (n = 45*)	DARA-SC 1800 mg (n = 25)
Median age, yrs (range)	66 (49-78)	63 (36-79)	68 (51-85)
▪ ≥ 75 yrs, %	13	9	24
Median weight, kg (range)	75.0 (53.0-82.5)	74.8 (48.0-133.0)	70.9 (52.0-104.8)
ECOG PS 0/1/2, %	25/63/13	24/73/2	44/52/4
ISS stage, %			
▪ I	17	47	54
▪ II	50	33	21
▪ III	33	20	25
Median time from diagnosis, yrs (range)	6.55 (1.9-10.3)	5.94 (1.1-15.2)	5.96 (2.1-13.2)
IgG myeloma, n (%)	3 (38)	30 (67)	13 (54)

Chari A, et al. ASH 2017. Abstract 838.

Slide credit: clinicaloptions.com

PAVO: Patient Characteristics

Characteristic	DARA-MD 1200 mg (n = 8)	DARA-MD 1800 mg (n = 45*)	DARA-SC 1800 mg (n = 25)
Prior lines of therapy, median (range)	5 (2-10)	4 (2-11)	3 (2-9)
▪ ≤ 3 lines, %	38	36	64
▪ > 3 lines, %	63	64	36
Prior ASCT, %	63	82	68
Prior PI, %	100	100	100
▪ Prior bortezomib	100	96	96
Prior IMiD, %	100	100	100
▪ Prior lenalidomide	100	100	92
Refractory, %			
▪ PI only	0	2	12
▪ IMiD only	13	16	8
▪ Both PI and IMiD	63	64	60
▪ Last line of therapy	88	80	76

Chari A, et al. ASH 2017. Abstract 838.

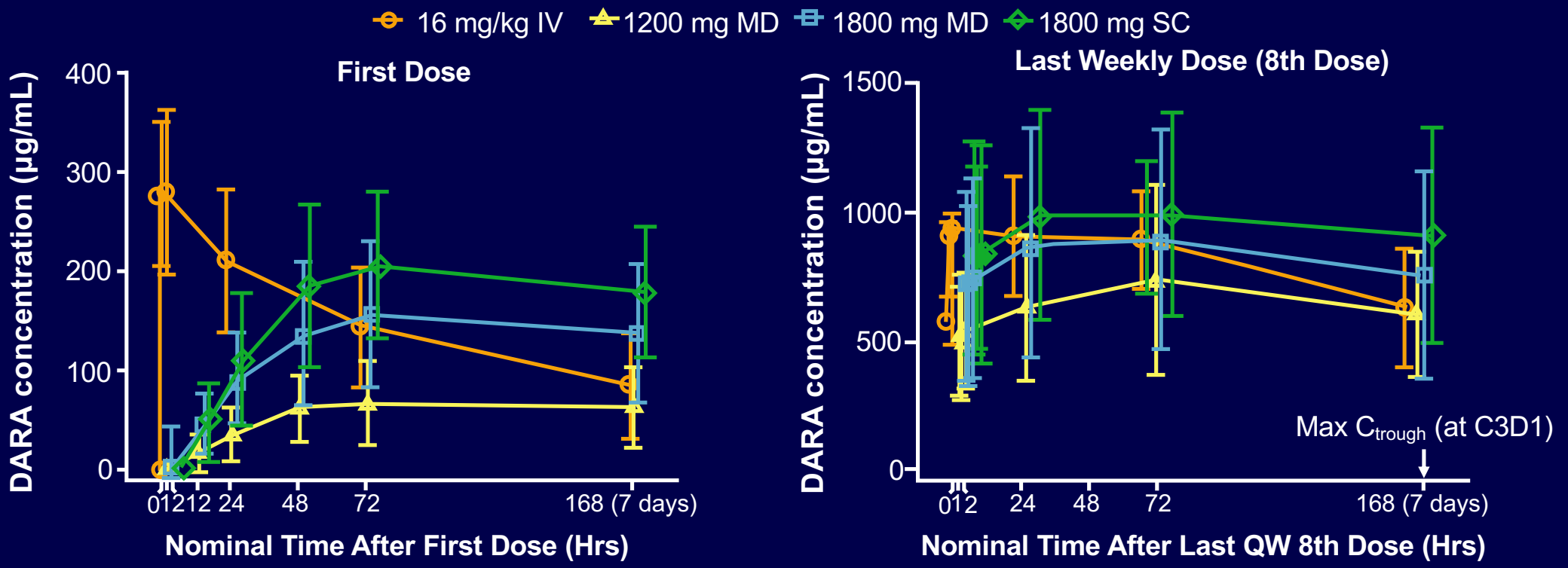
PAVO: Patient Disposition

Characteristic	DARA-MD 1200 mg (n = 8)	DARA-MD 1800 mg (n = 45*)	DARA-SC 1800 mg (n = 25)
Discontinuation, n (%)	8 (100)	35 (78)	5 (20)
▪ Progressive disease	5 (63)	28 (62)	4 (16)
▪ Withdrawal by patient	1 (13)	1 (2)	0 (0)
▪ Physician decision	1 (13)	5 (11)	1 (4)
▪ Death	1 (13)	1 (2)	0 (0)
Median duration of follow up, months (range)	5.2 (1.6-13.9)	8.3 (1.8-19.5)	4.6 (2.4-5.5)

- Clinical cut-off date: Oct 30, 2017

Chari A, et al. ASH 2017. Abstract 838.

PAVO: Mean Daratumumab Serum Concentration Profiles



- SC administration results in slower systemic absorption compared with IV
- Maximum C_{trough} is similar or higher following 1800 mg SC compared with 16 mg/kg IV

Chari A, et al. ASH 2017. Abstract 838.

PAVO: Safety

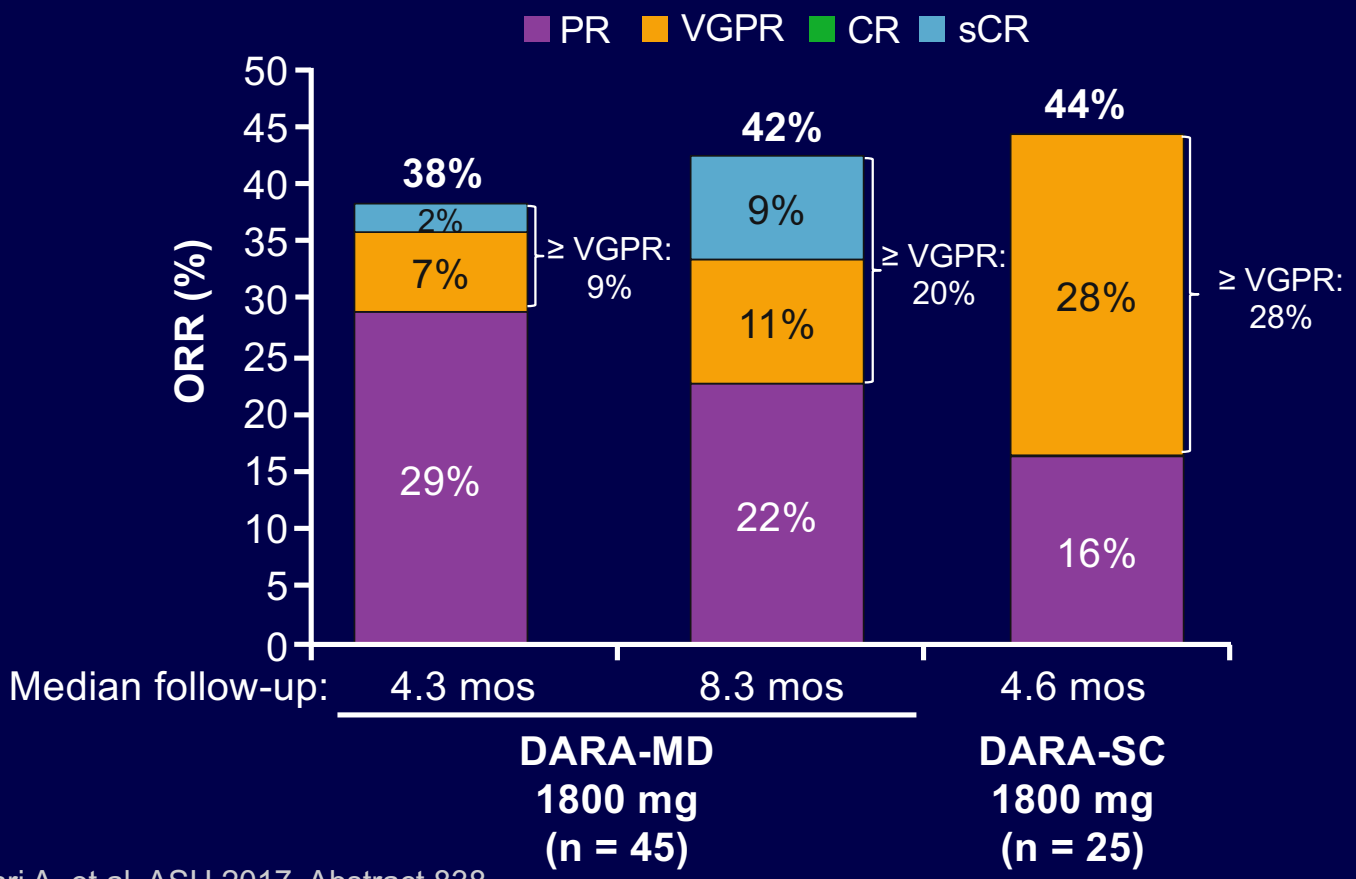
TEAE, n (%)	DARA-MD 1200 mg (n = 8)	DARA-MD 1800 mg (n = 45)	DARA-SC 1800 mg (n = 25)
Drug-related TEAE	5 (63)	31 (69)	12 (48)
▪ Serious drug-related TEAE	1 (13)	3 (7)	0
▪ Grade ≥ 3 TEAE	5 (63)	22 (49)	10 (40)
Hematologic TEAE, n (%)			
Thrombocytopenia	3 (38)	8 (18)	5 (20)
▪ Grade ¾	1 (13)	3 (7)	2 (8)
Anemia	2 (25)	15 (33)	3 (12)
▪ Grade 3/4	1 (13)	7 (16)	1 (4)
Lymphopenia	0	8 (18)	7 (28)
▪ Grade 3/4	0	5 (11)	4 (16)
Grade 3/4 neutropenia	1 (13)	3 (7)	2 (8)

Nonhematologic TEAE, n (%)	DARA-MD 1200 mg (n = 8)	DARA-MD 1800 mg (n = 45)	DARA-SC 1800 mg (n = 25)
URTI	3 (38)	11 (24)	2 (8)
Decreased appetite	3 (38)	3 (7)	2 (8)
Insomnia	3 (38)	5 (11)	4 (16)
Pyrexia	2 (25)	12 (27)	4 (16)
Grade 3/4 fatigue	2 (25)	1 (2)	1 (4)
Grade 3/4 hypertension	2 (25)	2 (4)	1 (4)
Grade 3/4 hyponatremia	0	2 (4)	1 (4)
Grade 3/4 pneumonia	1 (13)	2 (4)	0
Device-related infection	0	2 (4)	0
RSV infection	0	2 (4)	0
Median duration of treatment, mos	**2.6**	**5.4**	**4.6**

No TEAE-related discontinuations
Safety profile similar between SC daratumumab and historical data for IV administration.

Chari A, et al. ASH 2017. Abstract 838.

PAVO: Responses in Dara 1800-mg Groups



- Deepening responses seen in DARA-MD 1800-mg group
- Similar ORR with DARA-MD and DARA-SC

Chari A, et al. ASH 2017. Abstract 838.

PAVO: Injection-Related Reactions

Reaction, n (%)	DARA-SC 1800 mg in 15 mL/3-5 min (n = 25)
Pt-reported IRR	All at first injection (within 6 h)
▪ Pt 1	Grade 3 hypertension, grade 2 chills, grade 2 dyspnea
▪ Pt 2	Grade 1 allergic rhinitis
▪ Pt 3	Grade 1 sneezing
Investigator-reported injection-site TEAEs	
▪ Induration	1 (4)
▪ Erythema	1 (4)
▪ Injection-site discoloration	1 (4)
▪ Hematoma	1(4)
▪ Injection-site measurement of erythema	5 (20)

- Low IRR incidence and severity with DARA-SC
  - No grade 4 IRRs, discontinuations due to IRRs, or delayed IRRs
- Few injection-site TEAEs with DARA-SC
  - Measurable erythema reversible within 1 hr

Chari A, et al. ASH 2017. Abstract 838.

PAVO: Conclusions

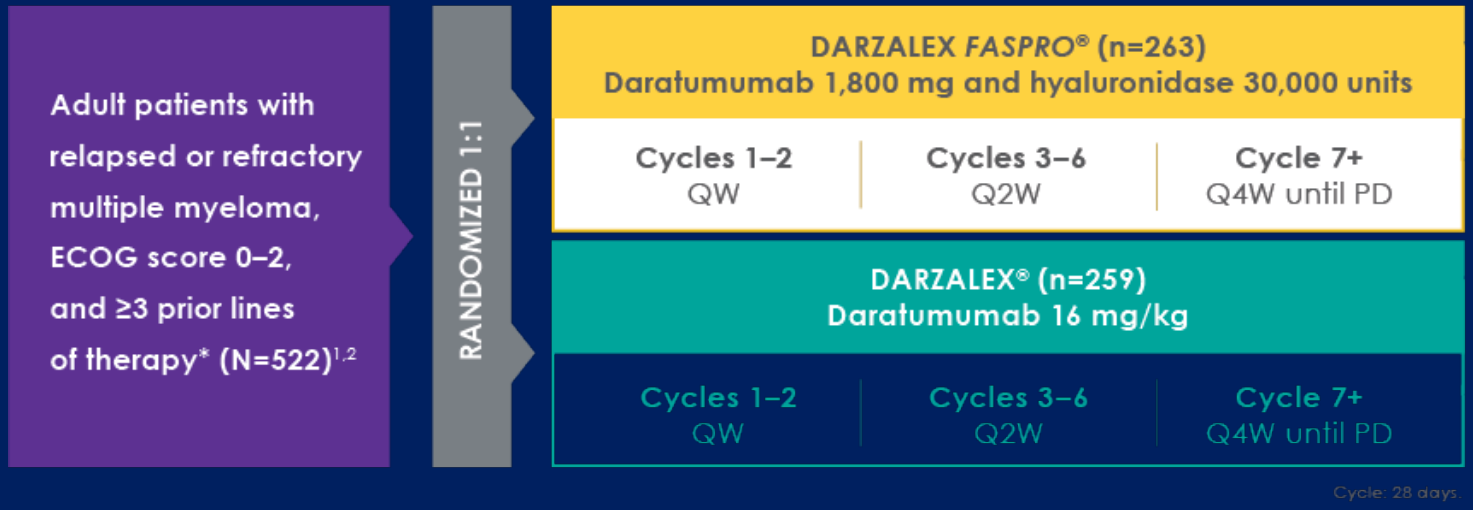
- Daratumumab coformulated with rHuPH20 (DARA-SC) enables SC dosing in 3-5 mins[1]
- DARA-SC achieved greater maximum C_{trough} values vs standard IV daratumumab by cycle 3[1]
- DARA-SC well tolerated[1]
  - IRRs with DARA-SC: 12%
  - IRRs with daratumumab IV in R/R MM: 45% to 56% (historical data)[2-7]
- Responses to DARA-SC observed at similar rates as IV daratumumab[2]
- Results informed 4 ongoing phase III studies of DARA-SC 1800 mg: COLUMBA (dara SC vs IV), AQUILA (dara SC in SMM), APOLLO (dara SC + PomDex), and ANDROMEDA (Dara SC + VCd in amyloidosis)

1. Chari A, et al. ASH 2017. Abstract 838. 2. Usmani S, et al. Blood. 2016;128:37-44. 3. Plesner T, et al. Blood. 2016;128:1821-1828. 4. Chari A, et al. ASH 2016. Abstract 2142. 5. Palumbo A, et al. N Engl J Med. 2016;375:754-766. 6. Dimopoulos MA, et al. N Engl J Med. 2016;375:1319-1331. 7. Chari A, et al. Blood. 2017;130:974-981.

Subcutaneous DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) vs i.v DARZALEX® (daratumumab)

COLUMBA is a phase 3, randomized, open-label, non-inferiority, multicenter trial comparing

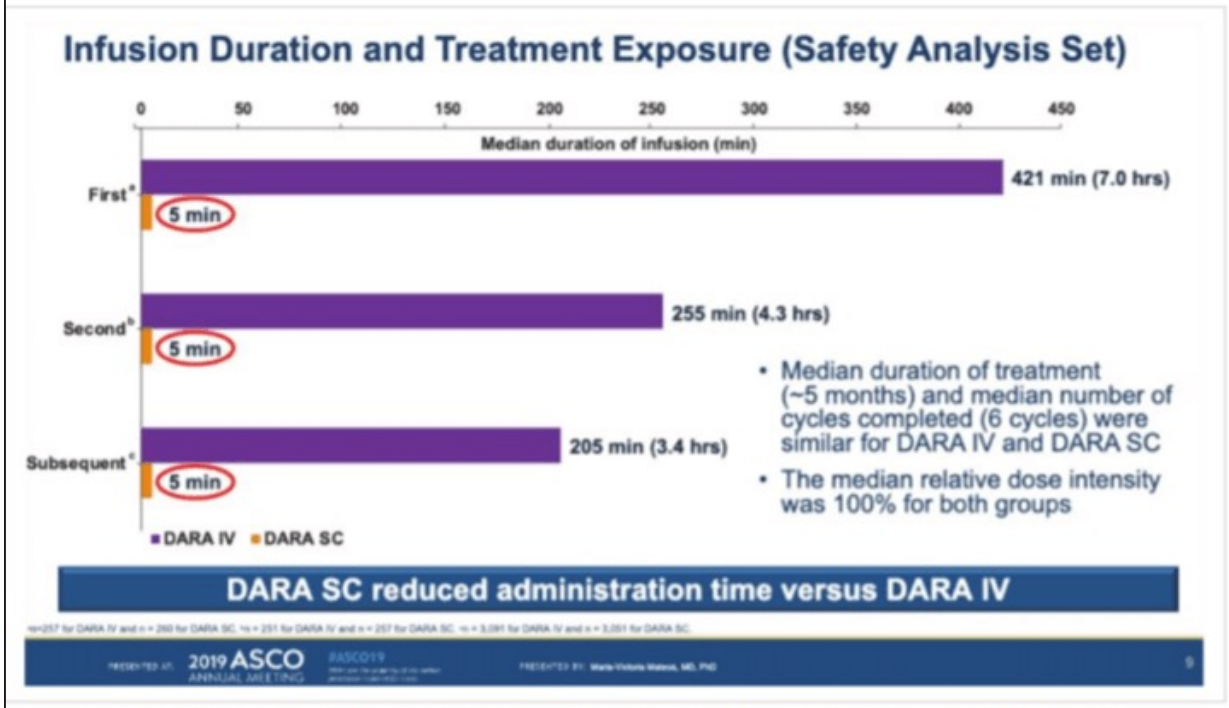
DARZALEX *FASPRO*® monotherapy vs DARZALEX® monotherapy in 522 adult patients with RRMM



Mateos et al. Lancet Hematol, 2020

Potential for Competitive Differentiation for Daratumumab SC

Daratumumab SC: Phase 3 COLUMBA Study



- **Primary endpoints met for SC versus IV**
  - PK non-inferiority
  - Response rate non-inferiority

- **5 minute SC administration time**

Source: ASCO 2019, *COLUMBA trial: intravenous versus subcutaneous daratumumab*. Presentation by Maria-Victoria Mateos, MD, PhD, University Hospital of Salamanca-IBSA at 2019 ASCO Annual Meeting

Mateos et al. Lancet Hematol, 2020

Patient characteristics

- Baseline demographics and disease characteristics were similar between the 2 treatment groups[1]

- The median age was 67 years (range: 33–92). The median weight was 73 kg (range: 29–138). Patients had received a median of 4 prior lines of therapy; 51% had a prior ASCT and 100% had received both a PI and an immunomodulatory agent

Non-inferiority co-primary endpoints

- **Overall response rate[†] (ORR) and a maximum trough (C_{trough}) concentration of daratumumab measured on Day 1 of Cycle 3[1]**

Selected secondary endpoints

- **Percentage of patients with systemic administration-related reactions[‡] (ARRs), very good partial response (VGPR) or better rate, complete response (CR) or better rate, and progression-free survival (PFS)**

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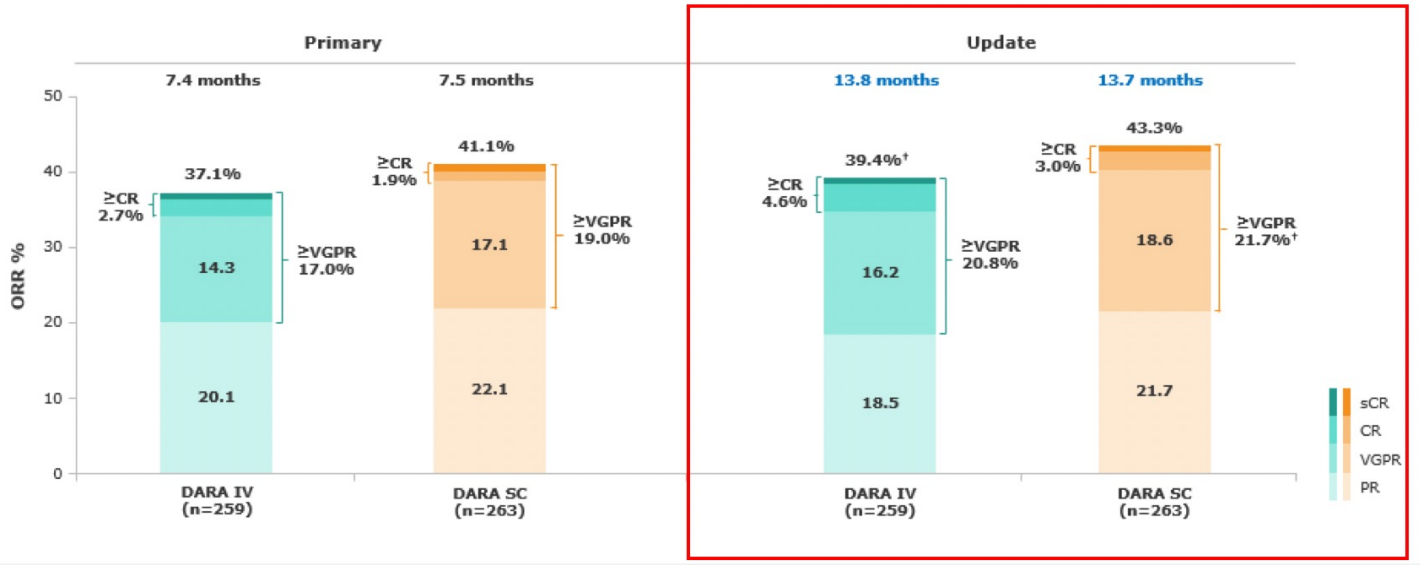
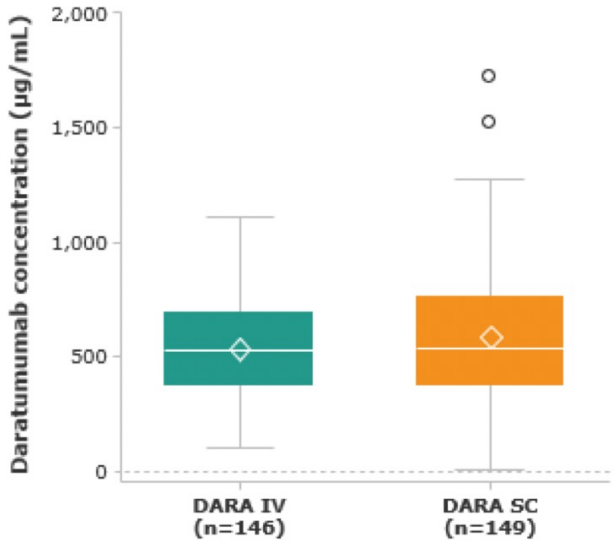
COLUMBA: Co-primary endpoints
(ORR and max C_{trough} at C3D1)

Overall response rate[1]



Maximum C_{trough} at C3D1*[1]



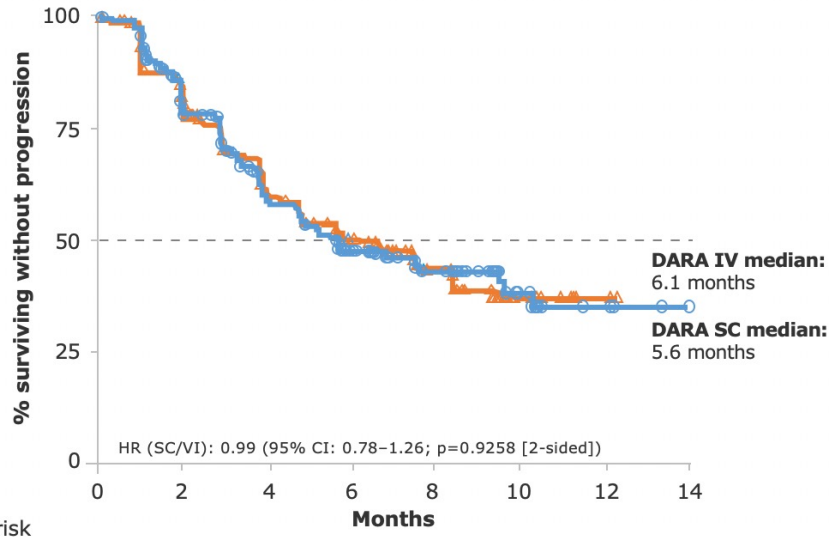
Daratumumab SC was non-inferior to IV[1]

Mateos et al. Lancet Hematol, 2020

COLUMBA: Key secondary efficacy endpoints (PFS and OS)

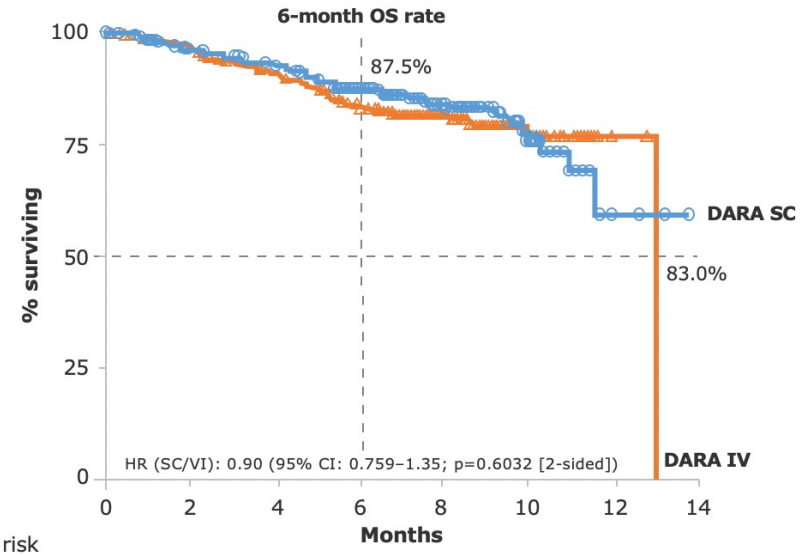
Median (range) follow-up: 7.5 (0.03–13.86) months[1]

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 et al. Lancet Hematol, 2020

Safety: Infusion-related Reactions (IRRs)

	DARA IV (n = 258)	DARA SC (n = 260)	Odds ratio* (95% CI)	*P*- value†
IRR rate	**34.5%**	**12.7%**	0.28 (0.18-0.44)	<0.0001

- IRRs were mild and occurred primarily at first administration in both arms:
  - Grade 1/2 with few grade 3 (1.5% in DARA SC vs 5.4% in DARA IV)
  - no grade 4
  - 2 DARA IV and 1 DARA SC patients had IRRs on non-treatment days (low grade)
- Median time to onset of IRRs was 1.5 hrs for DARA IV and 3.6 hrs for DARA SC with majority occurring on day of first dose
- Injection-site reactions occurred in 6.9% of DARA SC patients (all grade 1/2)

IRR rate was significantly reduced with DARA SC (12.7%) vs Dara IV (34.5%)
IRRs were mainly grade 1 and 2 with no grade 4 IRRs

*Stratified Cochran-Mantel-Haenszel estimate of the common odds ratio of DARA SC over DARA IV is used. The stratification factors included body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG). *P*-value is from Cochran-Mantel-Haenszel Chi-Squared test.

Mateos et al. Lancet Hematol, 2020

COLUMBA safety: Most common any grade (>10%) and grade 3 or 4 (>5%) TEAEs[1]

	DARA IV (n=258)		DARA SC (n=260)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Haematologic, %				
Anaemia	23	14	26	13
Thrombocytopenia	18	13	19	14
Neutropenia	14	8	19	13
Lymphopenia	7	6	7	5
Non-haematologic, %				
Pyrexia	13	1	13	0
Cough	13	0	9	1
Back pain	13	3	11	2
Chills	12	1	5	<1
Dyspnoea	11	1	6	1
Diarrhoea	11	<1	15	1
Nausea	10	<1	9	<1
Fatigue	11	1	11	1
Upper respiratory tract infection	10	1	13	0
Hypertension	8	6	5	3

Grade ≥3 TEAEs[1]:

- DARA IV: 49%
- DARA SC: 45%

TEAEs leading to treatment discontinuation[1]:

- DARA IV: 8%
- DARA SC: 7%

Grade 5 TEAEs were low[1]:

- DARA IV: 7%
- DARA SC: 5%

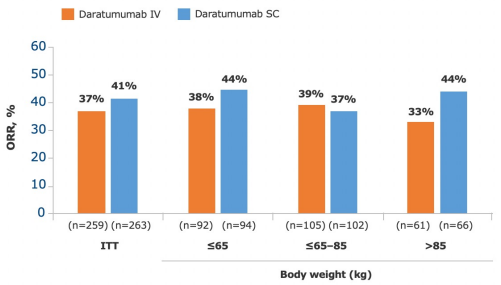
Incidences of DARA and rHuPH20 antibodies were low and consistent with literature reports[1–3]

Safety profile comparable between DARA SC and DARA IV[1]

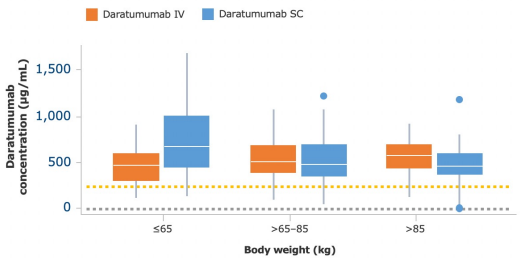
Mateos et al. Lancet Hematol, 2020

COLUMBA: Body weight subgroup analysis

ORRs in the ITT population and across body weight subgroups[1]



Observed maximum C_{trough} (Cycle 3 Day 1 pre-dose) by baseline body weight[1]



- ORRs in the DARA SC and DARA IV body weight subgroups were consistent with the ITT population
- The higher concentration of daratumumab SC in patients ≤65 kg did not have a clinically relevant effect on safety

No dose individualisation of daratumumab SC on the basis of body weight is necessary

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]

Mateos et al. Lancet Hematol, 2020

Subcutaneous daratumumab in Asian patients with heavily pretreated multiple myeloma: subgroup analyses of the noninferiority, phase 3 COLUMBA study

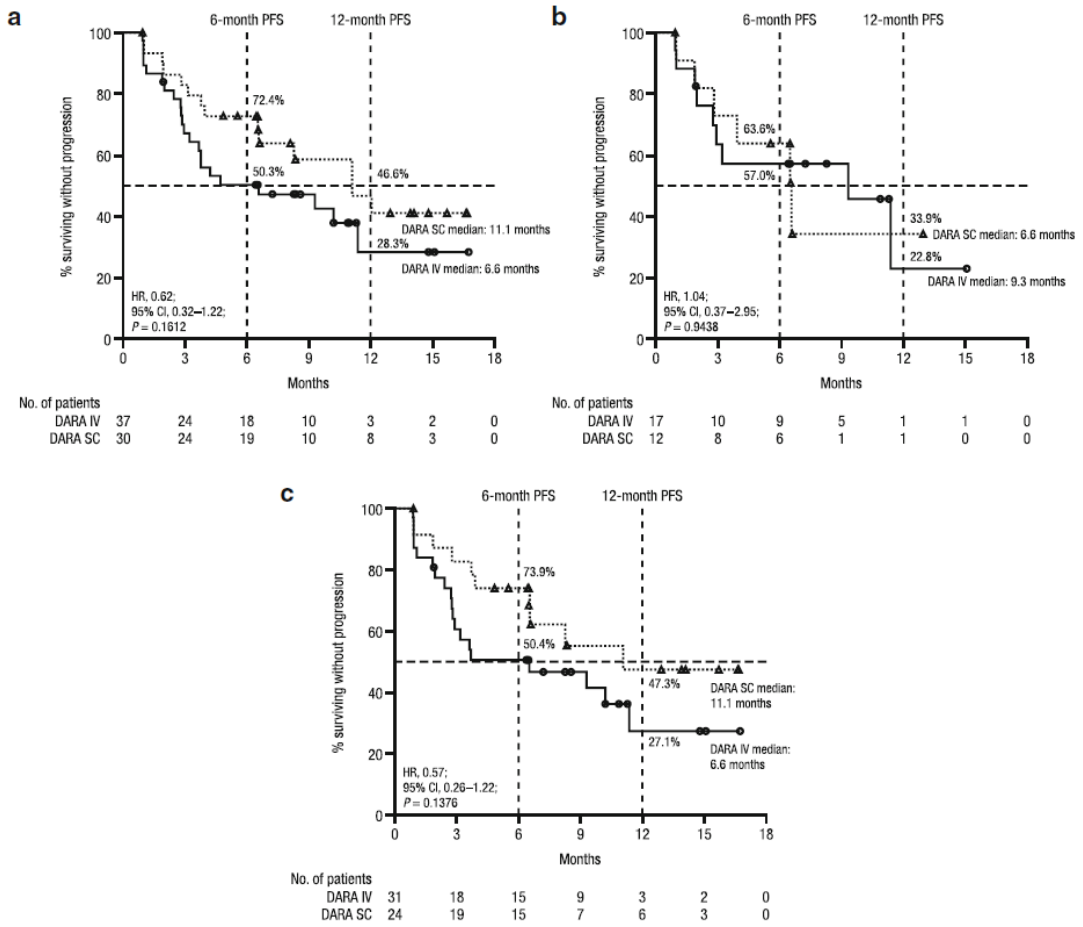
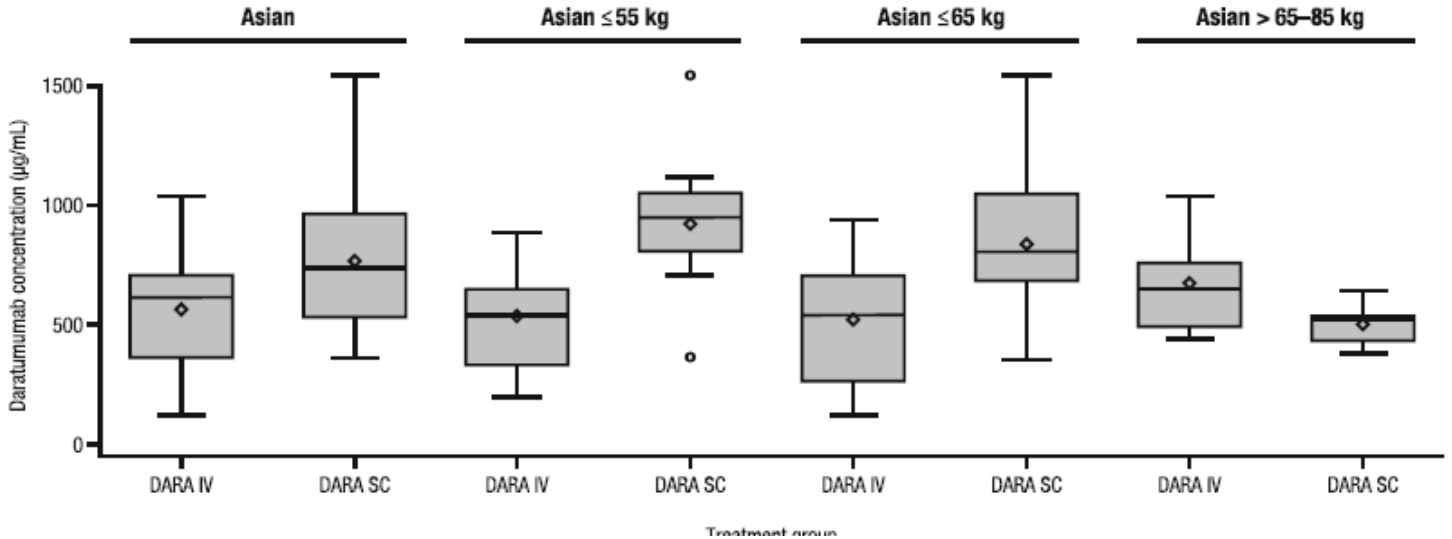
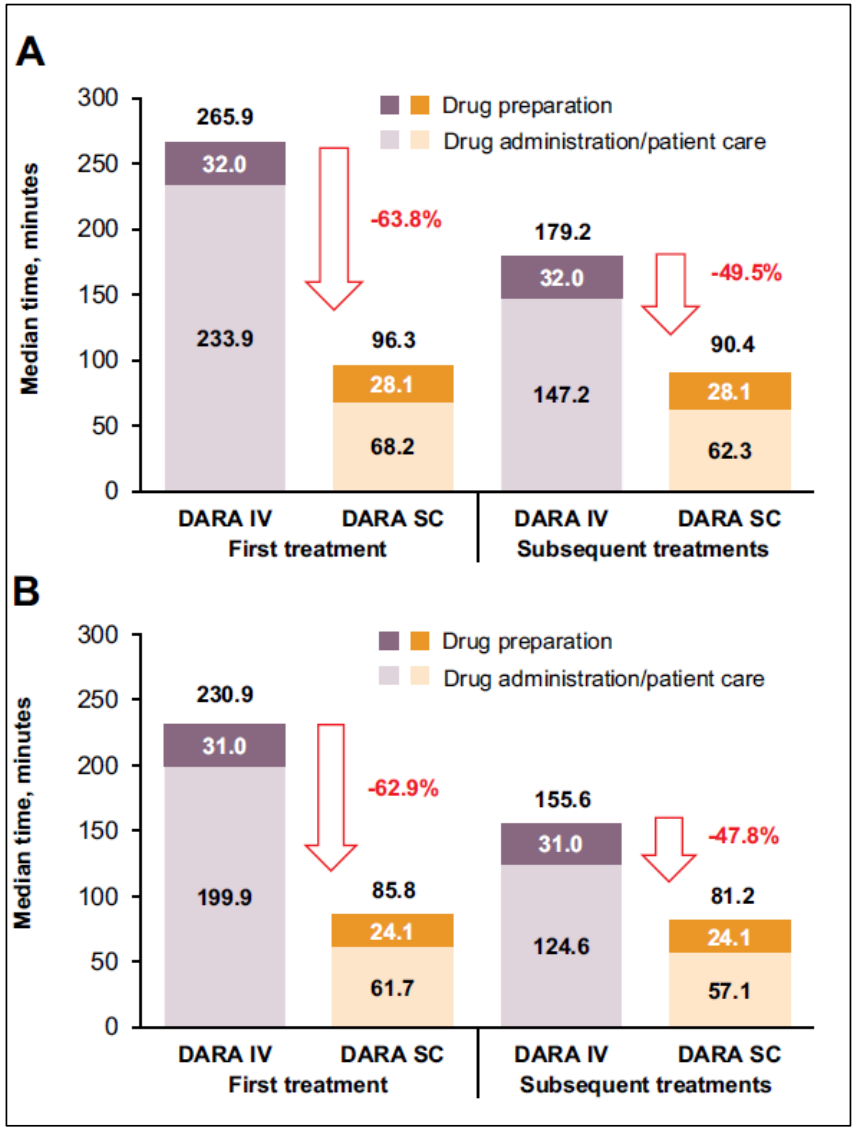


Fig. 1 PFS of (**a**) Asian patients; (**b**) Asian patients with baseline bodyweight ≤ 55 kg; and (**c**) Asian patients with baseline bodyweight ≤ 65 kg. PFS, progression-free survival; DARA, daratumumab; SC, subcutaneous; IV, intravenous; HR, hazard ratio; CI, confidence interval

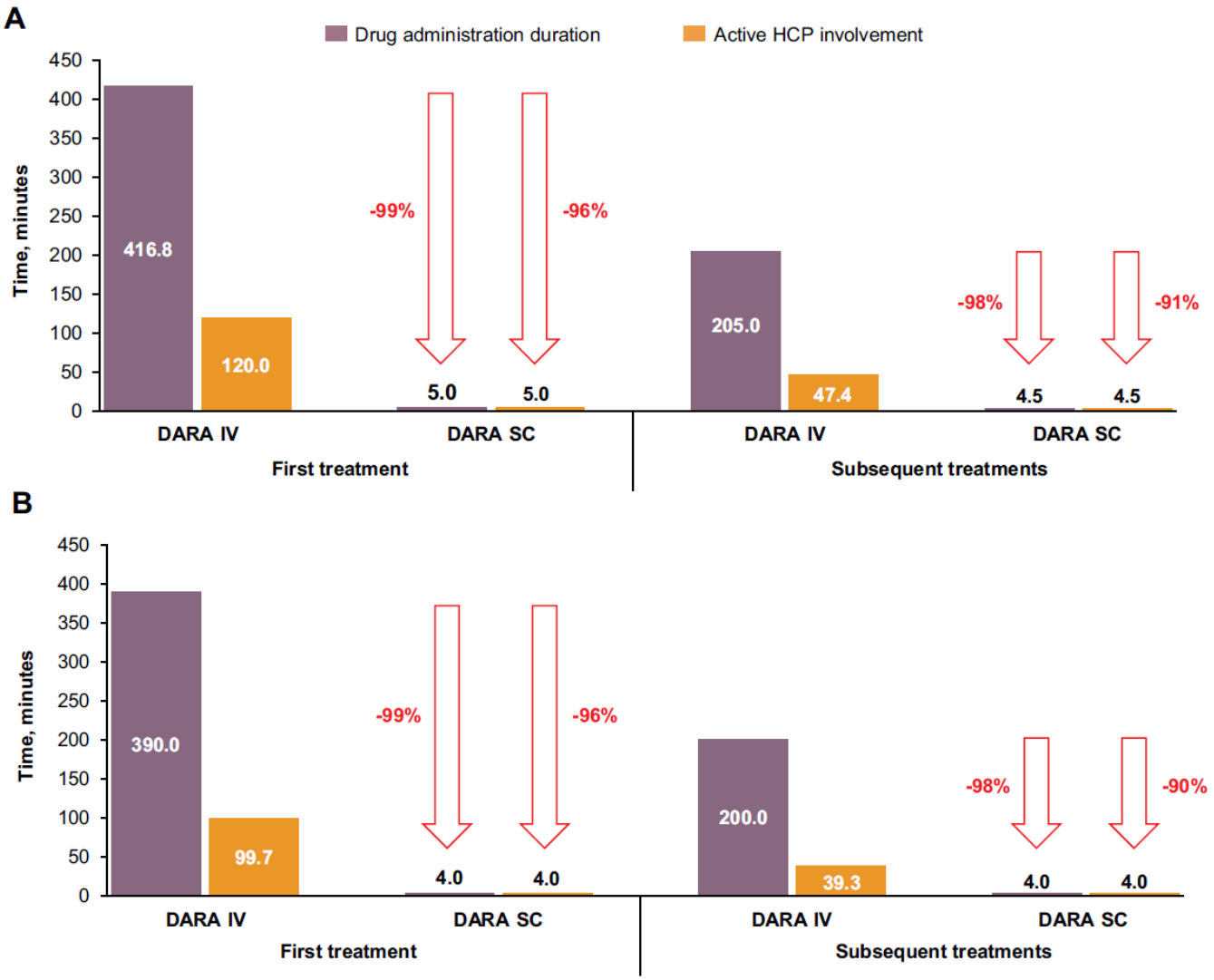
Lida et al, 2021



Lida et al, 2021



Slavcec et al, 2021



Slavcec et al, 2021

Journal of Cancer Research and Clinical Oncology (2021) 147:619–631
https://doi.org/10.1007/s00432-020-03365-w

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Greater treatment satisfaction in patients receiving daratumumab subcutaneous vs. intravenous for relapsed or refractory multiple myeloma: COLUMBA clinical trial results

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Take Home: Conclusions

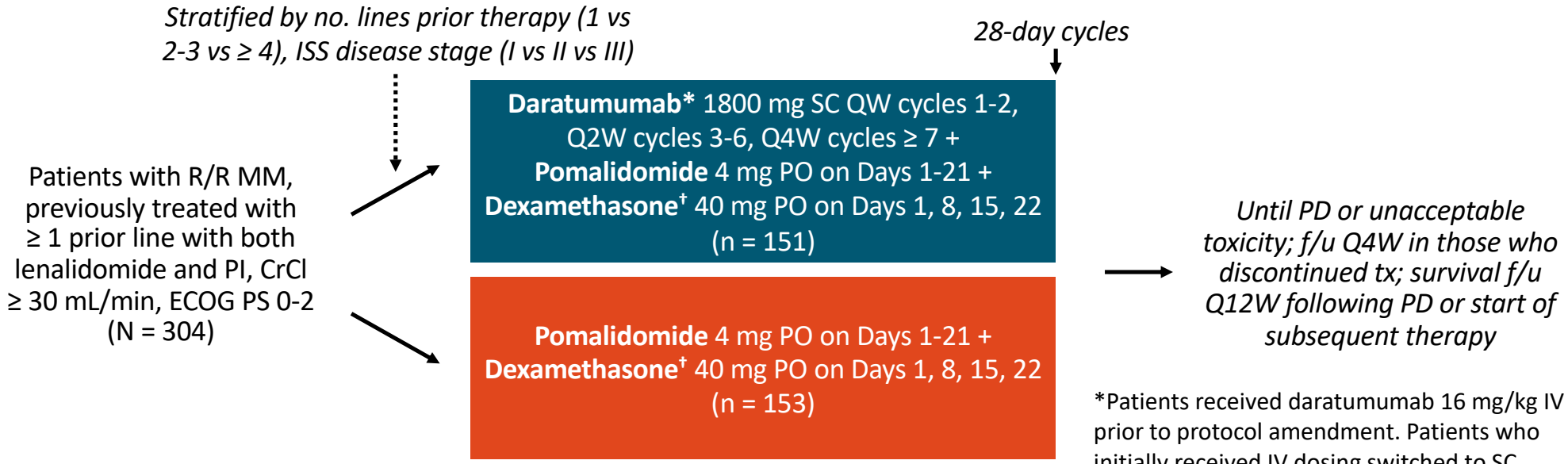
- DARA SC is non-inferior to DARA IV in terms of ORR and maximum C_{trough} (Cycle 3 Day 1)

- DARA SC and DARA IV have similar safety profiles with a statistically significant reduction in IRR rates and a low incidence of injection-site reactions with DARA SC

These results support the use of flat dose 1,800 mg DARA SC, which is comparable to DARA IV and needs investigation in combination

APOLLO: Study Design

- International, randomized, open-label phase III trial (median f/u: 16.9 mos)



*Patients received daratumumab 16 mg/kg IV prior to protocol amendment. Patients who initially received IV dosing switched to SC dosing on Day 1 of any cycle from cycle 3+.
†20 mg wkly in those aged ≥ 75 yrs.

- Primary endpoint: PFS
- Secondary endpoints: response, TTR, DoR, MRD, OS, time to next therapy, safety, HRQoL

Dimopoulos. ASH 2020. Abstr 412. NCT03180736.

APOLLO: Baseline Characteristics

Characteristic	D-Pd (n = 151)	Pd (n = 153)
Median age, yrs (range)	67 (42-86)	68 (35-90)
▪ < 65 yrs, n (%)	63 (42)	60 (39)
▪ 65 to < 75 yrs, n (%)	63 (42)	62 (41)
▪ ≥ 75 yrs, n (%)	25 (17)	31 (20)
ECOG PS, n (%)		
▪ 0	91 (60)	77 (50)
▪ 1	54 (36)	57 (37)
▪ 2	6 (4)	19 (12)
ISS disease stage, n (%)		
▪ I	68 (45)	69 (45)
▪ II	50 (33)	51 (33)
▪ III	33 (22)	33 (22)
MM type, n (%)		
▪ IgG	83 (55)	87 (57)
▪ IgA	34 (23)	30 (20)
▪ Light chain	26 (17)	30 (20)
High cytogenetic risk, n/N (%)	39/103 (38)	35/108 (32)

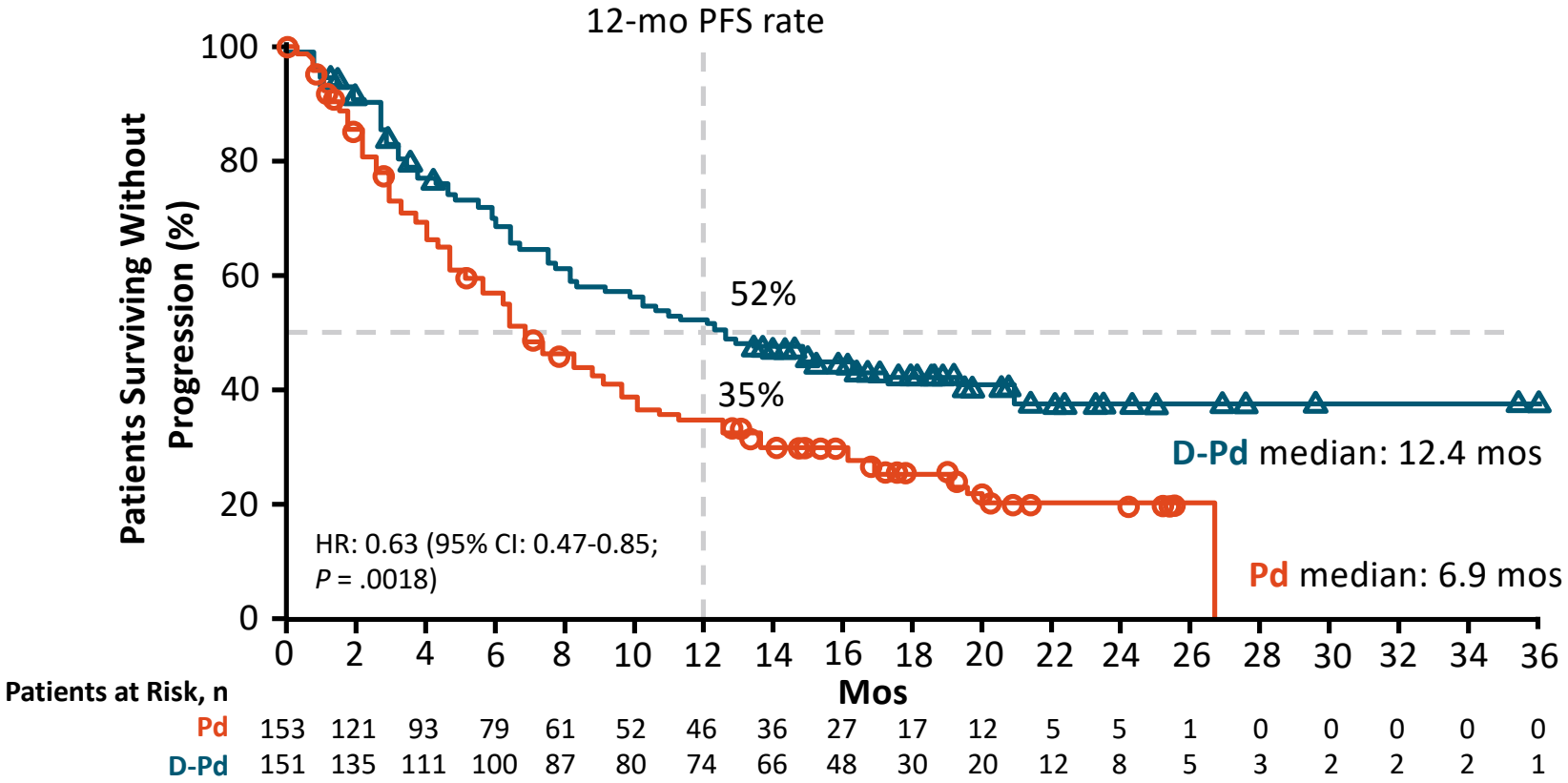
Characteristic, n (%)	D-Pd (n = 151)	Pd (n = 153)
Median time since dx, yrs (range)	4.39 (0.5-20.0)	4.48 (0.6-19.0)
Median no. prior tx, n (range)	2 (1-5)	2 (1-5)
▪ 1, n (%)	16 (11)	18 (12)
▪ 2-3, n (%)	114 (75)	113 (74)
▪ ≥ 4, n (%)	21 (14)	22 (14)
Prior ASCT	90 (60)	81 (53)
Refractory to		
▪ Lenalidomide	120 (79)	122 (80)
▪ PI	71 (47)	75 (49)
▪ Lenalidomide + PI	64 (42)	65 (42)
Refractory to last tx	122 (81)	123 (80)

- All patients had previously received PI and IMiD

*High cytogenetic risk determined with FISH and included those with del(17p), t(4;14), or t(4;16)

Dimopoulos. ASH 2020. Abstr 412.

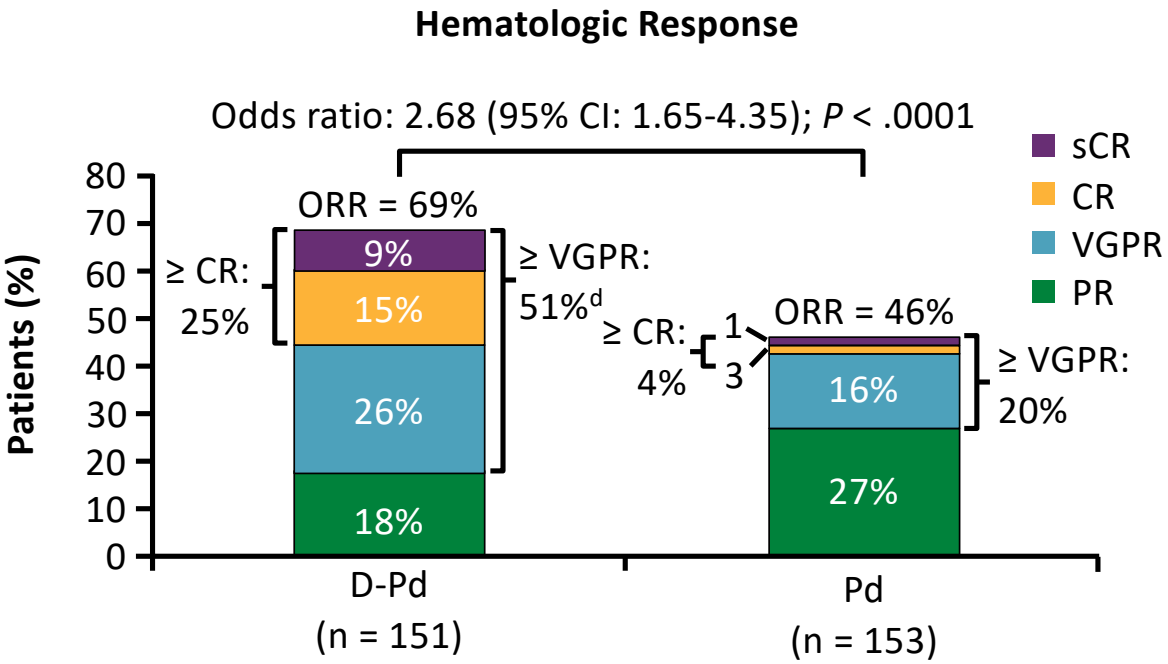
APOLLO: PFS at Median Follow-up of 16.8 Mos (Primary Endpoint)

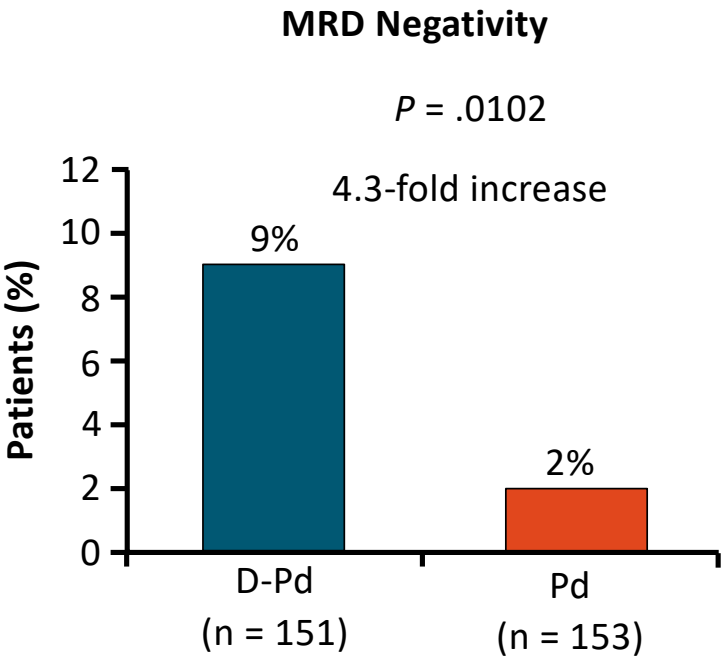


- D-Pd reduced risk of progression or death by 37% vs Pd (*P* = .0018)
- Among those refractory to lenalidomide, mPFS was 9.9 mos with D-Pd vs 6.5 mos with Pd
- PFS benefit generally consistent across prespecified subgroups

Dimopoulos. ASH 2020. Abstr 412. Reproduced with permission.

APOLLO: Response and MRD Negativity





- D-Pd significantly improved ORR and rates of ≥ VGPR, ≥ CR, and MRD negativity (all $P \leq .0102$)

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APOLLO: Safety Outcomes

Common or High-Grade TEAEs,* n (%)	D-Pd (n = 149)		Pd (n = 150)	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Hematologic				
▪ Neutropenia	105 (70)	101 (68)	80 (53)	76 (51)
▪ Anemia	55 (37)	25 (17)	66 (44)	32 (21)
▪ Thrombocytopenia	48 (32)	26 (17)	50 (33)	27 (18)
▪ Leukopenia	39 (26)	25 (17)	18 (12)	7 (5)
▪ Lymphopenia	22 (15)	18 (12)	12 (8)	5 (3)
▪ Febrile neutropenia	13 (9)	13 (9)	4 (3)	4 (3)
Nonhematologic				
▪ Infections	105 (70)	42 (28)	83 (55)	34 (23)
• Upper RTI	34 (23)	0	24 (16)	3 (2)
• Pneumonia	30 (20)	20 (13)	19 (13)	10 (7)
• Lower RTI	29 (19)	17 (11)	24 (16)	14 (9)
▪ Fatigue	38 (26)	12 (8)	38 (25)	7 (5)
▪ Asthenia	33 (22)	8 (5)	24 (16)	1 (1)
▪ Diarrhea	33 (22)	8 (5)	21 (14)	1 (1)
▪ Pyrexia	29 (19)	0	21 (14)	0
▪ Hyperglycemia	15 (10)	8 (5)	19 (13)	7 (5)

*Any-grade TEAEs in ≥ 15% or grade 3/4 TEAEs in ≥ 5% of either arm.

- Comparable rates of TEAEs leading to death with D-PD vs Pd (both 7%)
- Comparable rates of discontinuation due to TEAEs (D-Pd, 2%; Pd, 3%)
- Most common serious TEAEs with D-Pd vs Pd
  - Pneumonia: 15% vs 8%
  - Lower RTI: 12% vs 9%
- IRRs observed in 5% of patients receiving D-Pd (all grade 1/2)
- Local injection site reactions only occurred with daratumumab SC (2%, all grade 1)
- Secondary primary malignancy occurred in 2% of each treatment arm

Dimopoulos. ASH 2020. Abstr 412.

APOLLO: Investigators Conclusions

- The phase III APOLLO met its primary endpoint of significantly improved PFS with D-Pd vs Pd only in patients with R/R MM
  - 37% reduction in risk of progression or death (median PFS: 12.4 vs 6.9 mos; *P* = .0018)
  - In subgroup refractory to lenalidomide, D-Pd prolonged median PFS (9.9 vs 6.6 mos)
- D-Pd induced significantly deeper responses (≥ CR rate: 25% vs 4% with Pd; *P* < .001) and greater rate of MRD negativity (9% vs 2%; *P* = .0102)
- No new safety signals observed and safety profile comparable to those observed with daratumumab SC only and Pd only
  - Low rate of injection site reactions with D-Pd
- Investigators concluded that D-Pd represents an efficacious treatment option with short administration time for patients with R/R MM previously treated with lenalidomide and PI

Dimopoulos. ASH 2020. Abstr 412.

Daratumumab sc, esperienza Cardarelli (approvazione gennaio 2022)

- **Protocollo PERSEUS: 2 pazienti (in corso mantenimento)**
- **Nuove diagnosi: 4 DVTD* + 5 DRD**
- **Daratumumab già precedentemente iniziato: 64 (100%)**

** In un caso necessario proseguire con Dara ev per ripetuti episodi sincopali con ipotensione*

Table 3. Ongoing clinical trials of subcutaneous daratumumab in multiple myeloma.

NCT number	Title	Phase	*n*	Recruitment
Newly diagnosed multiple myeloma				
NCT03993912	A phase III study comparing lenalidomide and Dara-SC (R-Dara-SC) *versus* lenalidomide and dexamethasone (Rd) in frail subjects with previously untreated multiple myeloma who are ineligible for high dose therapy	III	294	Recruiting
NCT04052880	A phase II study of Dara-SC in combination with dose-attenuated bortezomib, lenalidomide, and dexamethasone in elderly newly diagnosed multiple myeloma patients	II	38	Recruiting
NCT04151667	Phase II study of daratumumab based response adapted therapy for older adults with newly diagnosed multiple myeloma	II	32	Recruiting
NCT03710603	A phase III study comparing daratumumab, VELCADE (bortezomib), lenalidomide, and dexamethasone (D-VRd) *versus* VELCADE, lenalidomide, and dexamethasone (VRd) in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy (PERSEUS)	III	690	Active, not recruiting
NCT03652064	A phase III study comparing daratumumab, VELCADE (bortezomib), lenalidomide, and dexamethasone (D-VRd) with VELCADE, lenalidomide, and dexamethasone (VRd) in subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy	III	395	Active, not recruiting
NCT03901963	A randomized study of daratumumab plus lenalidomide *versus* lenalidomide alone as maintenance treatment in patients with newly diagnosed multiple myeloma who are minimal residual disease positive after frontline autologous stem cell transplant (AURIGA)	III	214	Recruiting
NCT04497961	Daratumumab *versus* lenalidomide maintenance therapy for multiple myeloma: a randomized pilot study comparing patient-reported health related quality of life measures	II	100	Not yet recruiting
Relapsed refractory multiple myeloma				
NCT03180736	A phase III study comparing pomalidomide and dexamethasone with or without daratumumab in subjects with relapsed or refractory multiple myeloma who have received at least one prior line of therapy with both lenalidomide and a proteasome inhibitor (APOLLO)	III	304	Active, not recruiting
NCT03314181	A phase I/II, multicenter, dose-escalation and expansion study of combination therapy with venetoclax, daratumumab and dexamethasone (with and without bortezomib) in subjects with relapsed or refractory multiple myeloma	II	104	Recruiting
NCT03871829	A phase II study of Dara-SC administration in combination with carfilzomib and dexamethasone (DKd) compared with carfilzomib and dexamethasone (Kd) in participants with multiple myeloma who have been previously treated with Dara-IV to evaluate daratumumab retreatment	II	230	Recruiting
Novel combinations				
NCT04108195	A phase Ib study of subcutaneous daratumumab regimens in combination with bispecific T-cell redirection antibodies for the treatment of subjects with multiple myeloma	II	100	Recruiting
NCT03837509	A randomized open-label phase I/II study of INCB001158 combined with Dara-SC, compared with Dara-SC, in participants with relapsed or refractory multiple myeloma	I/II	98	Recruiting
Smoldering myeloma				
NCT03301220	A phase III randomized, multicenter study of subcutaneous daratumumab *versus* active monitoring in subjects with high-risk smoldering multiple myeloma	III	389	Active, not recruiting

Dara-IV, intravenous daratumumab; Dara-SC, subcutaneous daratumumab; NCT, National Clinical Trial.