ASCO Direct™
Highlights

Multiple Myeloma

Jeffrey A. Zonder, MD
Professor of Oncology
Karmanos Cancer Institute

Disclosure of Conflict(s) of Interest

- Jeffrey A. Zonder, MD reported the following relevant financial relationships or relationships they have with ineligible companies of any amount during the past 24 months:

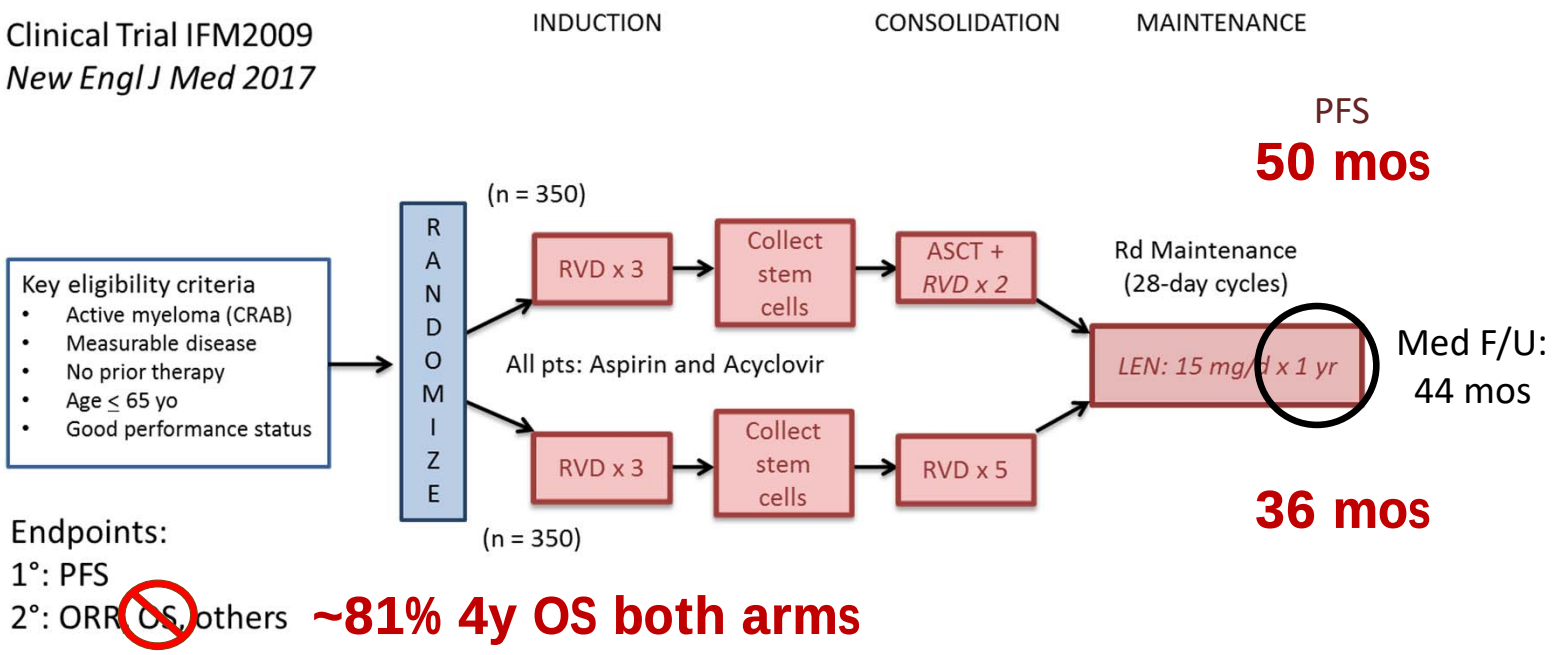
Consultant: Amgen, BMS, Takeda, Janssen, Caelum, Intellia, Regeneron, Alnylam

Research Support: BMS

Objectives

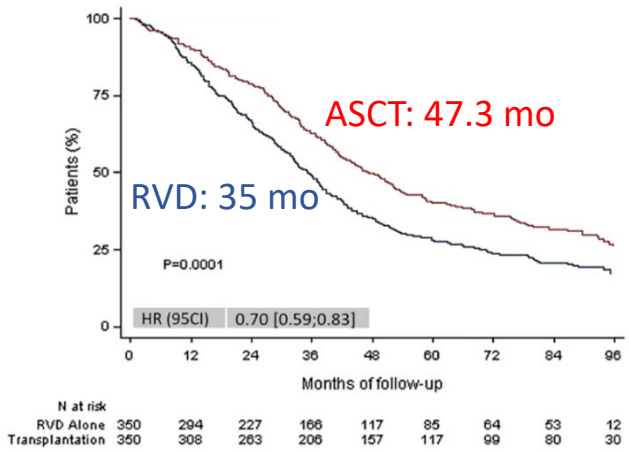
- Review data from ASCO 2021 regarding role of ASCT and emerging maintenance strategies
- Provide update on status of CAR-T cells as therapy for relapsed/refractory multiple myeloma
- Discuss newer immunotherapeutic agents, including bispecific Abs with targets other than BCMA

Initial Therapy for Symptomatic Myeloma

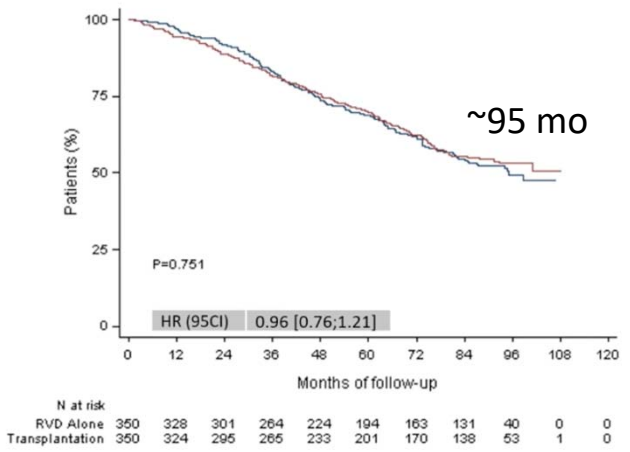


IFM-2009 Update: 89.8 mo F/U[1]

Updated PFS (primary endpoint)



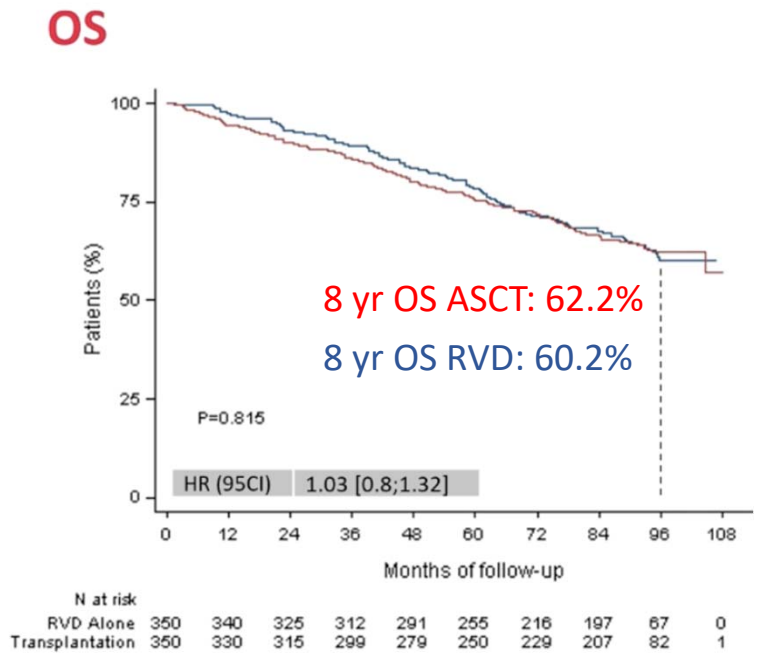
PFS 2



RVD	ASCT
270 with PD	227 with PD
262 second-line Rx	217 second-line Rx
201 ASCT	49 ASCT

Perrot A, et al, ASH 2020, Abstract # 143

IFM-2009 Update: 89.8 mo F/U[1]



Second primary malignancies SPM (8y FU)

	RVd alone N=350	Transplant N=350
Patients with at least one invasive SPM (%)	7.7	9.7
MDS / AML (%)	0.9	1.7
Breast cancer (%)	0.9	1.1
Colon cancer (%)	0.9	1.1
Lung neoplasm (%)	0.9	0.6
Prostate cancer (%)	0.9	0.9
Malignant melanoma (%)	0.9	0

Perrot A, et al, ASH 2020, Abstract # 143

CARDAMON

2021 ASCO ANNUAL MEETING

UPFRONT AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) VERSUS CARFILZOMIB-CYCLOPHOSPHAMIDE-DEXAMETHASONE (KCD) CONSOLIDATION WITH K MAINTENANCE IN TRANSPLANT-ELIGIBLE, NEWLY DIAGNOSED (NDTE) MULTIPLE MYELOMA (MM).

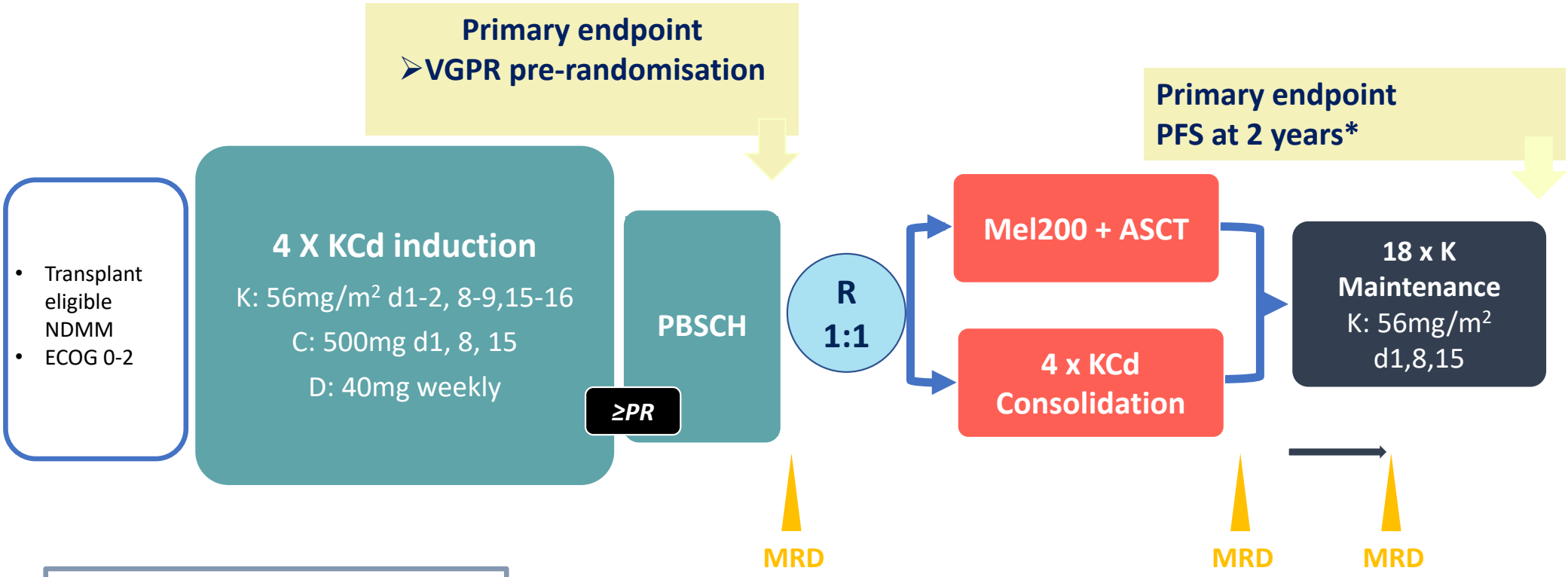
Kwee Yong, Marquita Camilleri, William Willson, Karthik Ramasamy, Matthew J. Streetly, Jonathan Sive, Ceri Bygrave, Michael A Chapman, Ruth De Tute, Selina J. Chavda, Elizabeth Phillips, Maria Cuadrado, Gavin Pang, Richard Jenner, Tushhar Dadaga, Sumaiya Kamora, James D. Cavenagh, Laura Clifton-Hadley, Roger G. Owen, Rakesh Popat

On behalf of the Cardamon investigators, the CR UK & UCL Cancer Trials Centre and the UK Myeloma Research Alliance

NCRI National Cancer Research Institute | CANCER RESEARCH UK | NHS National Institute for Health Research | UK MYELOMA RESEARCH ALLIANCE | Cancer Research UK and UCL Cancer Trials Centre | ASCO Highlights

CARDAMON

CARDAMON Study Design



Last patient enrolled: July 2019
Last patient randomised: Oct 2019

****10% non-inferiority margin, one-sided 15% alpha***

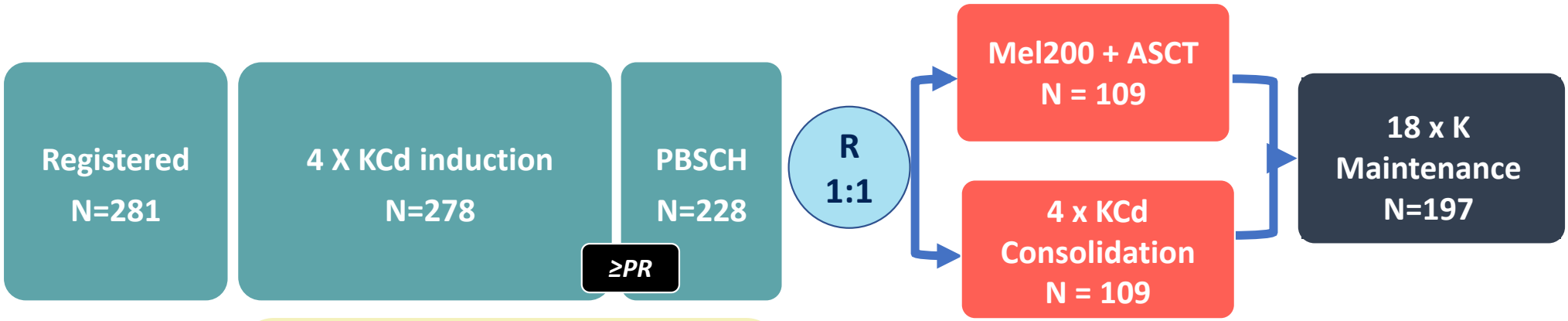
CARDAMON

Patient Characteristics	Induction (N=281)	ASCT (N=109)	KCd Cons (N=109)
Age			
Median (range)	59 (33-74)	58 (34-74)	58 (33-73)
>60yrs	133 (47.3%)	50 (45.9%)	57 (52.3%)
ISS Stage			
I	129 (46%)	53 (48.6%)	54 (49.5%)
II/III	152 (54%)	56 (51.4%)	55 (50.5%)
R-ISS Stage			
I	72 (25.6%)	32 (29.4%)	28 (25.7%)
II	149 (53%)	59 (54.1%)	57 (52.3%)
III	24 (8.5%)	5 (4.6%)	10 (9.2%)
Cytogenetic risk			
High risk*	52 (18.5%)	19 (17.4%)	22 (20.2%)
Standard risk	207 (73.7%)	85 (78%)	79 (72.4%)
Disease Response at Randomisation			
sCR/CR		9 (8.3%)	11 (10.1%)
VGPR or better		72 (66.1%)	72 (66.1%)
MRD negative		31 (28.4%)	30 (27.5%)

***del17p ≥50 threshold, t(4;14), t(14;16), t(14;20)**

CARDAMON

Patient Disposition



Did not complete induction N=23

- Death N=3 (2 infection, 1 Cardiac event)
- Disease progression N=3
- Toxicity N=16
- Other N=1

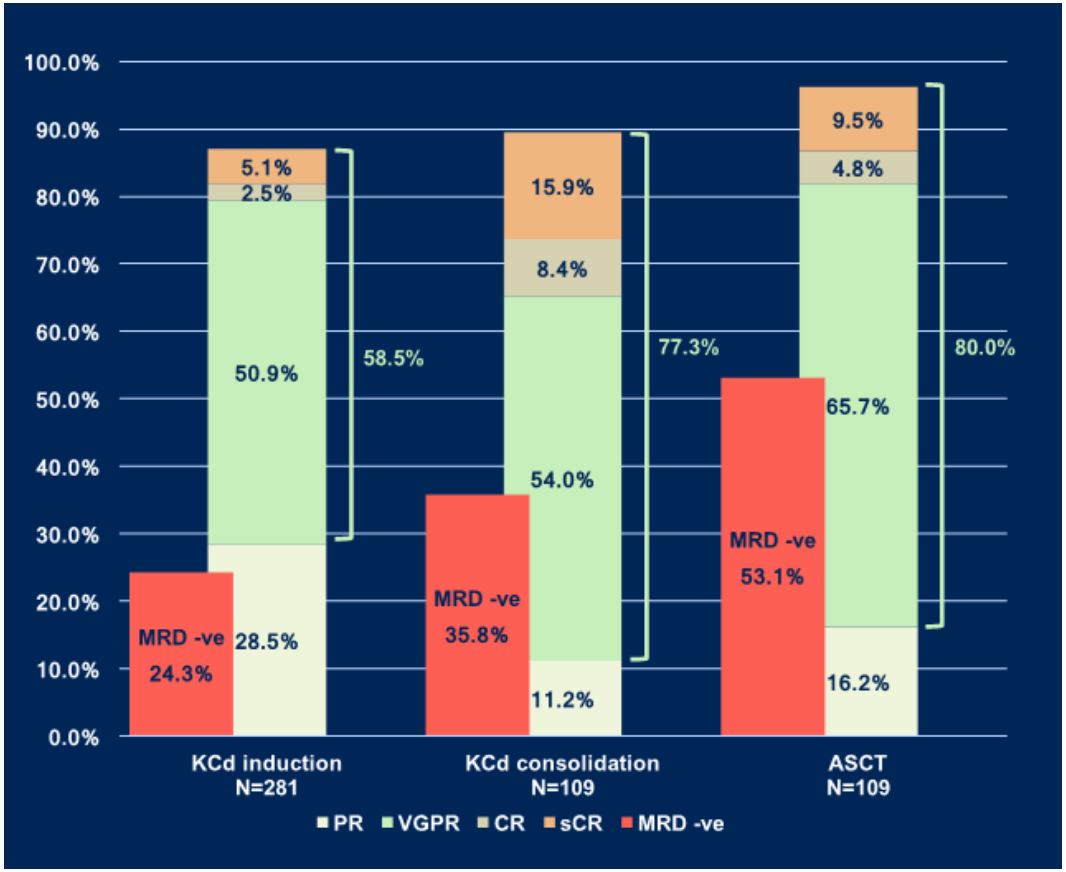
Did not proceed to PBSCH N=27

- Death N=1 (infection)
- Disease progression N=11
- Toxicity N=3
- Inadequate response (MR) N=6
- Other N=6

CARDAMON

Disease Response to Induction and Randomization Arm

KCd cons vs ASCT	OR	P-value
≥PR	0.35	0.08
≥VGPR	0.91	0.8
sCR	1.79	0.2
MRD -ve	0.49	0.02



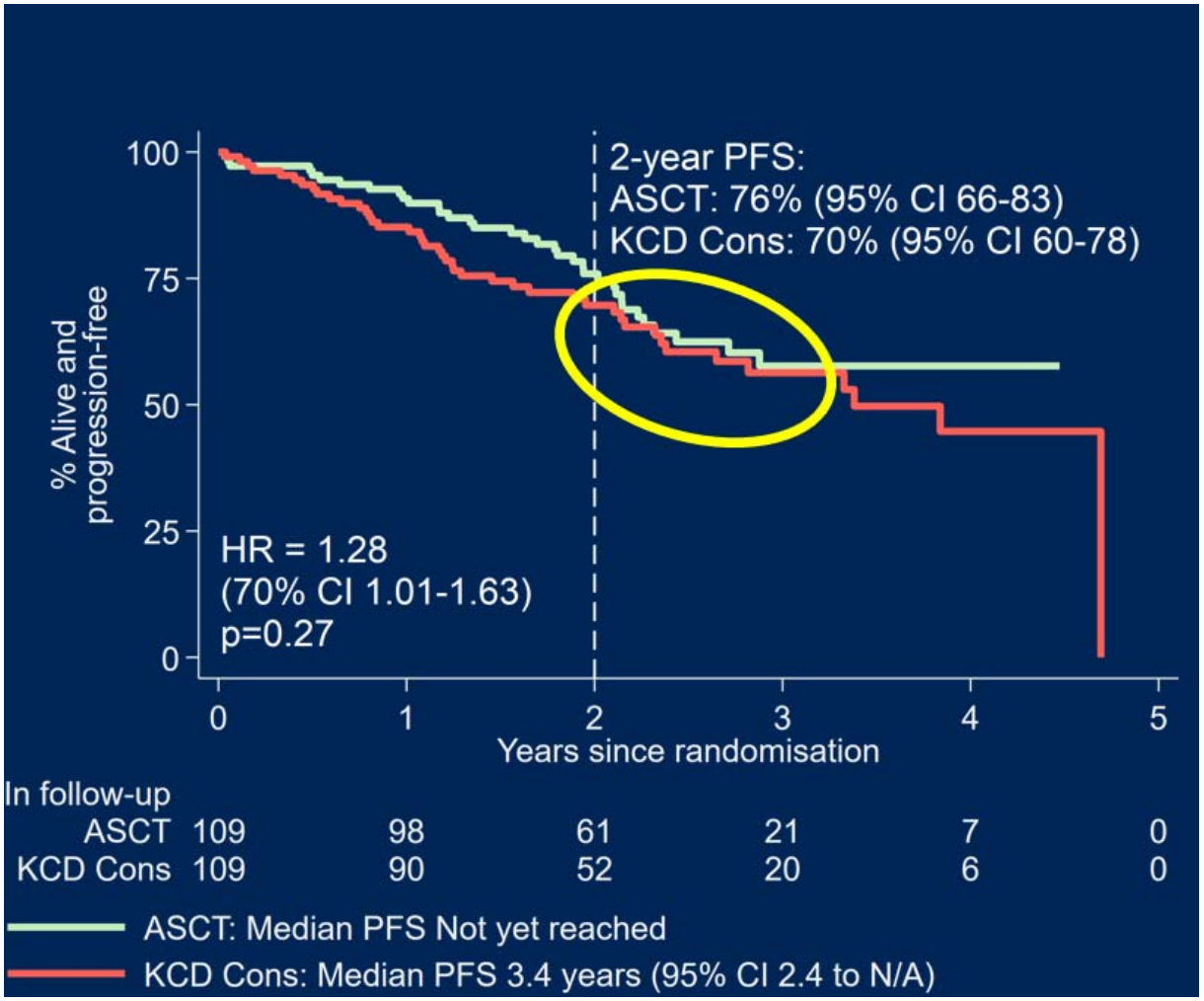
CARDAMON

Progression free survival by randomization arm

Median follow up: 37.5 months (range 0.2-64.5)

2-year PFS for KCd is not non-inferior to ASCT

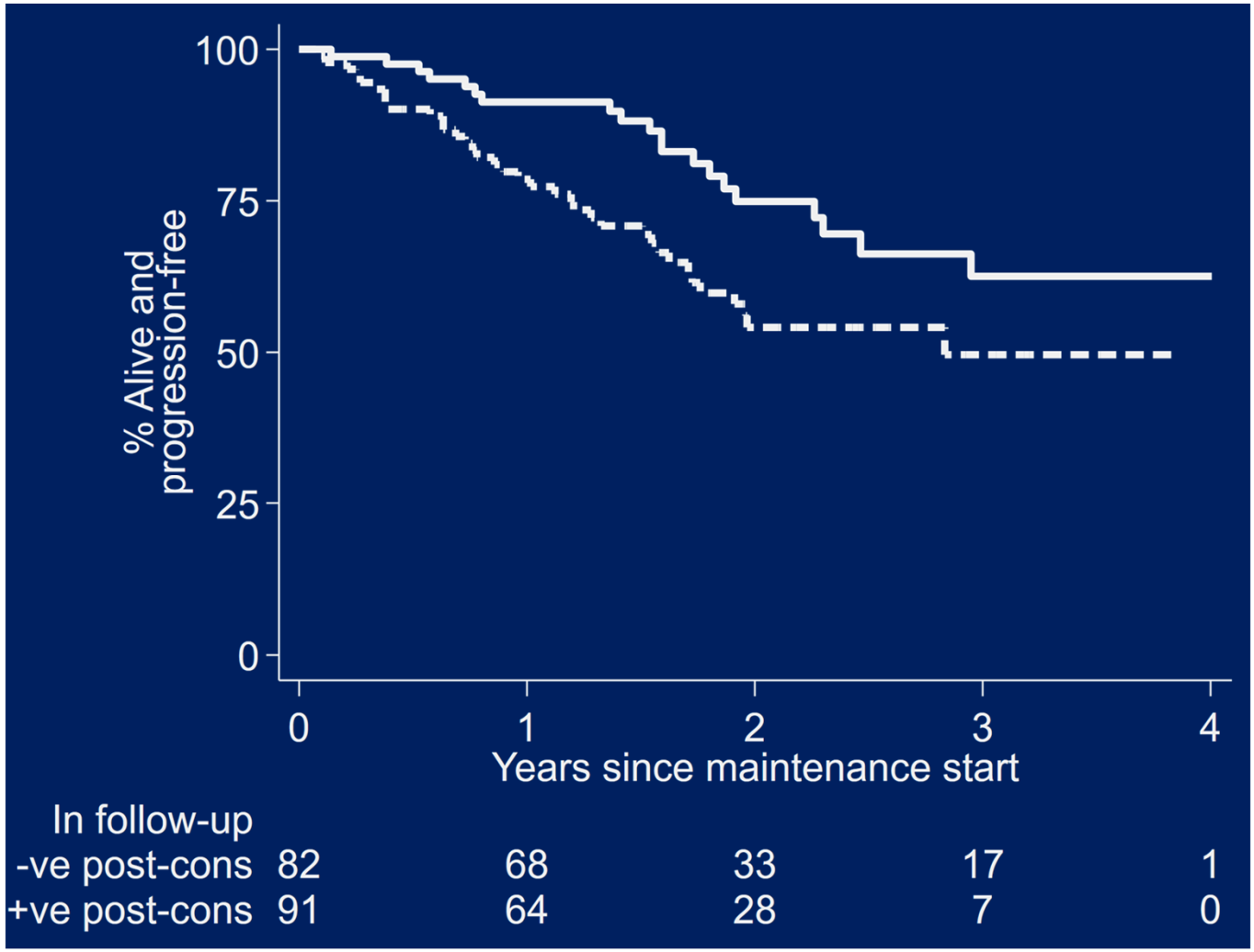
Difference in 2-year PFS KCd Cons vs ASCT -5.8% (-10.4% to -0.3%)



CARDAMON

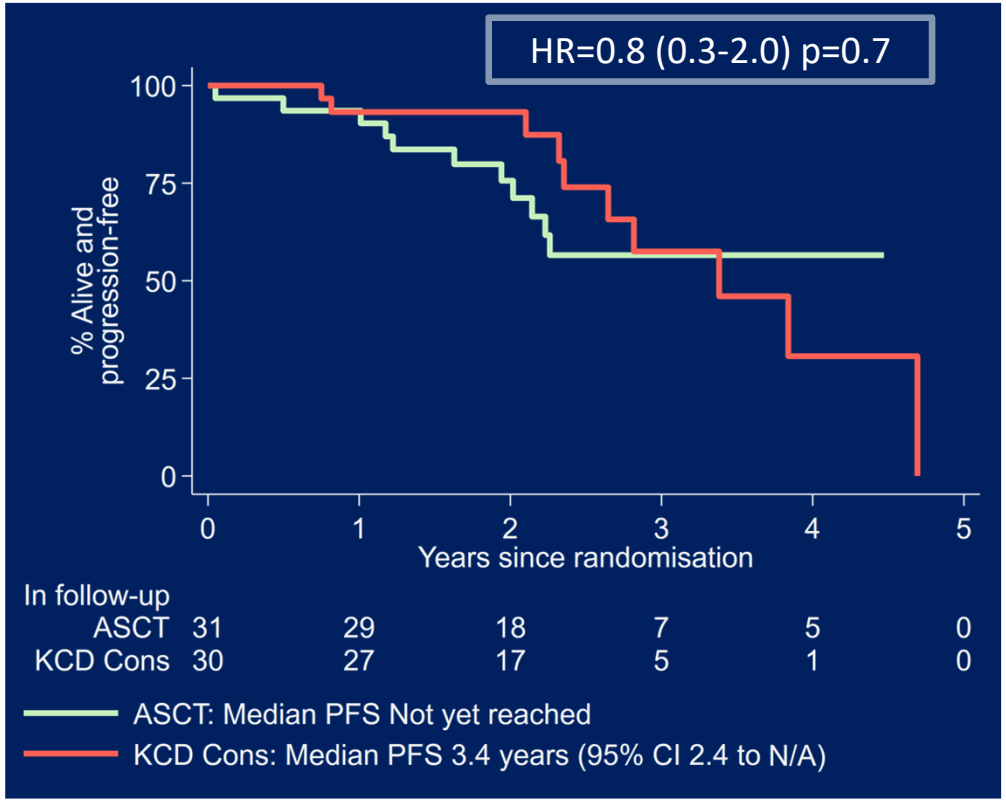
PFS by MRD status pre-maintenance

HR=1.7 (0.9-3.2)
p=0.07

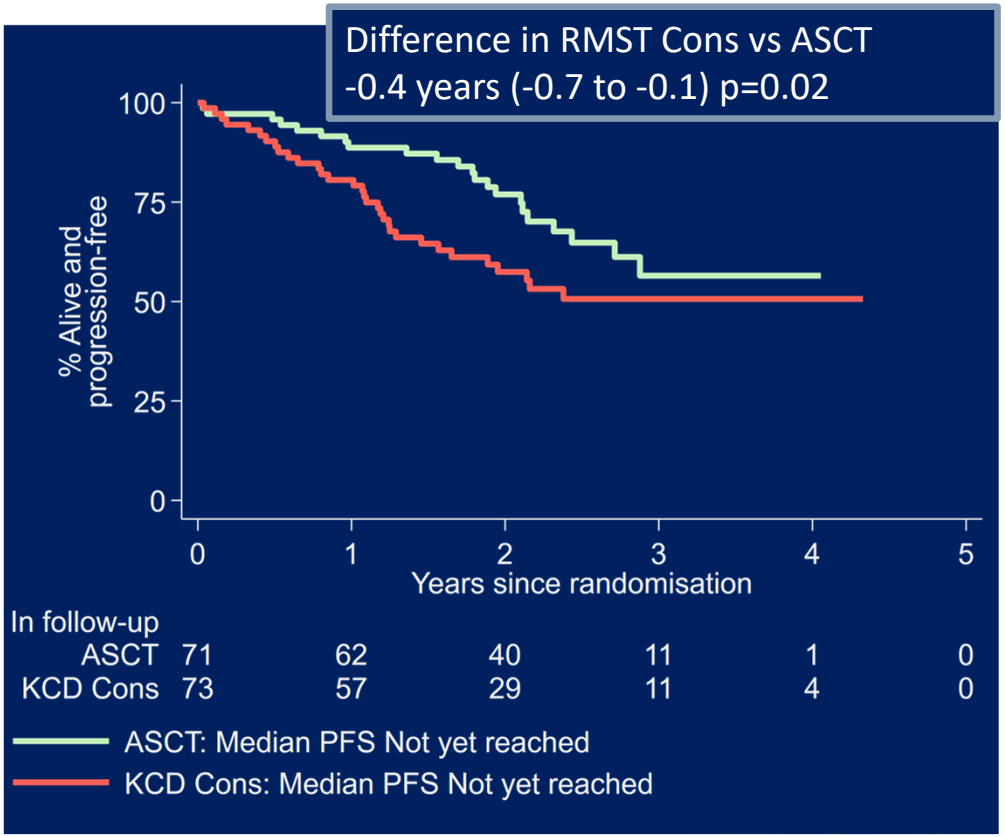


PFS by post-PBSCH MRD status and randomization arm

MRD -ve post-PBSCH



MRD +ve post-PBSCH

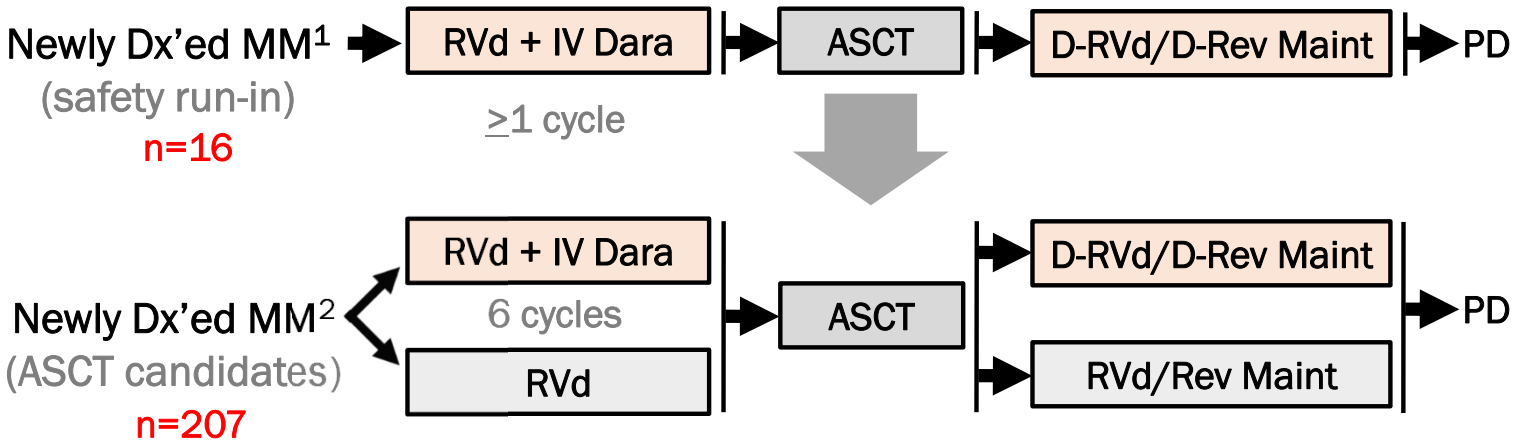


Role of Early ASCT: Conclusions

- ASCT appears to deepen responses relative to non-ASCT Rx
  - May be of more benefit if not MRD(-) at end of induction
- PFS benefit from ASCT greater in IFM-2009 than Cardamon
  - IMiD-containing induction/maintenance (easier to continue?)
  - Neither trial examined indefinite maintenance (better if MRD+?)
- PFS2, OS no different if ASCT available as 2nd-line therapy
- ASCT should remain a part of 1st or 2nd line MM Rx in 2021

Role of Daratumumab in Initial Myeloma Therapy

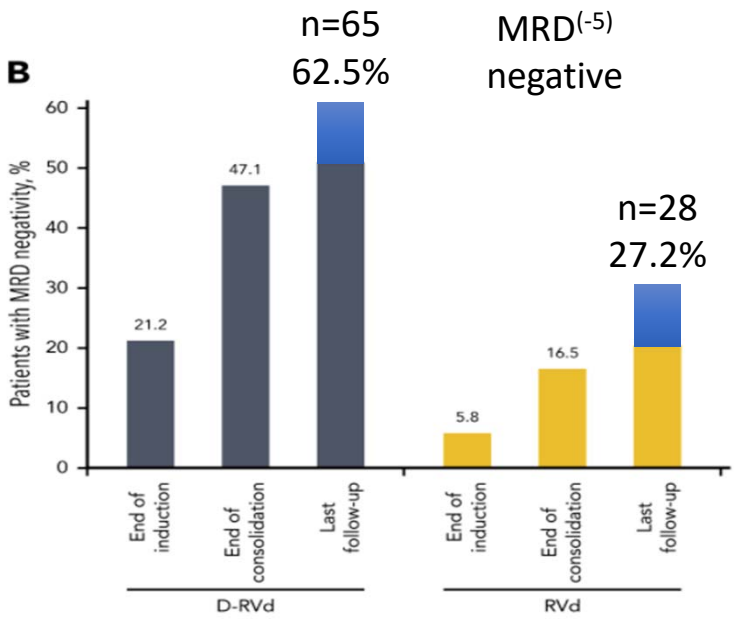
GRIFFIN: RVd +/- Dara (+ASCT) for NDMM



1. Voorhees P, et al. ASH 2018, abstract # 151
2. Voorhees P, et al. *Blood* (2020) 136 (8): 936–945

GRIFFIN: RVd +/- Dara (+ASCT) for NDMM

- 12 m of maintenance
  - VGPR+: 95.9% vs 79.4%
- 12 m sustained MRD(-)
  - D-RVd
    - MRD(-): 30/65 (46.2%)
    - ITT: 30/104 (38.8%)
  - RVd
    - MRD(-): 3/28 (10.7%)
    - ITT: 3/103 (2.9%)



Kaufman J, t al. ASH 2020, abstract # 549

GRIFFIN does not inform us regarding optimal use of Daratumumab during 1st line therapy

Is Dara during induction and maintenance necessary, or can usage be limited?

2021 ASCO
ANNUAL MEETING

DARATUMUMAB MAINTENANCE OR OBSERVATION AFTER TREATMENT WITH BORTEZOMIB, THALIDOMIDE, AND DEXAMETHASONE ± DARATUMUMAB AND AUTOLOGOUS STEM CELL TRANSPLANT IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: CASSIOPEIA PART 2

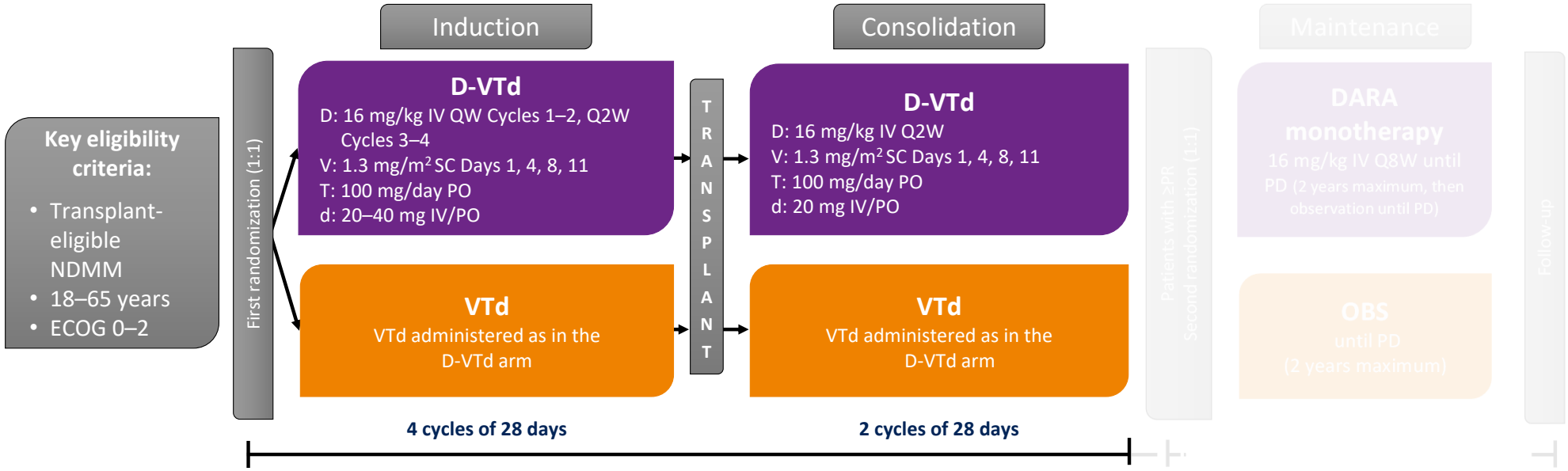
P Moreau[1], C Hulin[2], A Perrot[3], B Arnulf[4], K Belhadj[5], L Benboubker[6], M C Béné[7], S Zweegman[8], H Caillon[9], D Caillot[10], J Corre[11], M Delforge[12], T Dejoie[9], C Doyen[13], T Facon[14], C Sonntag[15], J Fontan[16], L Garderet[17], K-S Jie[18], L Karlin[19], F Kuhnowski[20], J Lambert[21], X Leleu[22], M Macro[23], F Orsini-Piocelle[24], M Roussel[3], A-M Stoppa[25], NWCJ van de Donk[8], S Wuillème[7], A Broijl[26], C Touzeau[1], M Tiab[27], Je-P Marolleau[28], N Meuleman[29], M-C Vekemans[30], M Westerman[31], SK Klein[32], M-D Levin[33], F Offner[34], M Escoffre-Barbe[35], J-R Eveillard[36], R Garidi[37], T Ahmadi[38], M Krevvata[39], K Zhang[40], C de Boer[41], S Vara[42], T Kampfenkel[41], V Vanquickelberghe[43], J Vermeulen[41], H Avet-Loiseau[11], P Sonneveld[26]

[1]University Hospital Hôtel-Dieu, Nantes, France; [2]Bordeaux University Hospital Center, Bordeaux, France; [3]Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France; [4]Hôpital Saint Louis, APHP, Paris, France; [5]Hôpital Henri Mondor, Creteil, France; [6]Tours University Hospital, Hôpital de Bretonneau, Tours, France; [7]Nantes University Hospital, Nantes, France; [8]Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [9]University Hospital, Nantes, France; [10]Dijon University Hospital, Hôpital du Bocage, Dijon, France; [11]IUC-T Oncopole, Toulouse, France; [12]University Hospital Leuven, Leuven, Belgium; [13]Université Catholique de Louvain, CHU UCL Namur, Yvoir, Belgium; [14]Hôpital Claude Huriez, Lille, France; [15]University Hospital, Hôpital Hautepierre, Strasbourg, France; [16]University Hospital Jean Minjoz, Besancon, France; [17]Saint-Antoine Hospital, Sorbonne University, Paris, France; [18]Zuyderland MC, Sittard, Netherlands; [19]Lyon University Hospital, Hematology Centre Hospitalier Lyon-Sud, Pierre–Benite, France; [20]Institut Curie Paris, Paris, France; [21]Hôpital Saint-Louis, Paris, France; [22]Poitiers University Hospital, CHU la Milétrie, Poitiers, France; [23]Caen University Hospital, Caen, France; [24]Centre Hospitalier Annecy Genevois, Pringy, France; [25]Institut Paoli Calmettes, Marseille, France; [26]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [27]Centre Hospitalier Départemental Vendée, La Roche sur Yon, France; [28]Amiens University Hospital, Amiens, France; [29]Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; [30]Université Catholique de Louvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [31]Northwest Clinics, Alkmaar, Netherlands; [32]Meander Medical Centre, Amersfoort, Netherlands; [33]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands; [34]University Hospital Ghent, Ghent, Belgium; [35]Rennes University Hospital, Hôpital de Pontchaillou, Rennes, France; [36]Brest University Hospital, Hôpital A Morvan, Brest, France; [37]Saint-Quentin Hospital Center, Saint Quentin, France; [38]Genmab US, Inc, Princeton, NJ, USA; [39]Janssen Research & Development, Spring House, PA, USA; [40]Janssen Research & Development, LLC, La Jolla, CA, USA; [41]Janssen Research & Development, LLC, Leiden, Netherlands; [42]Janssen Research & Development, LLC, High Wycombe, UK; [43]Janssen Research & Development, Beerse, Belgium

June 8, 2021

CASSIOPEIA Part 1 Study Design

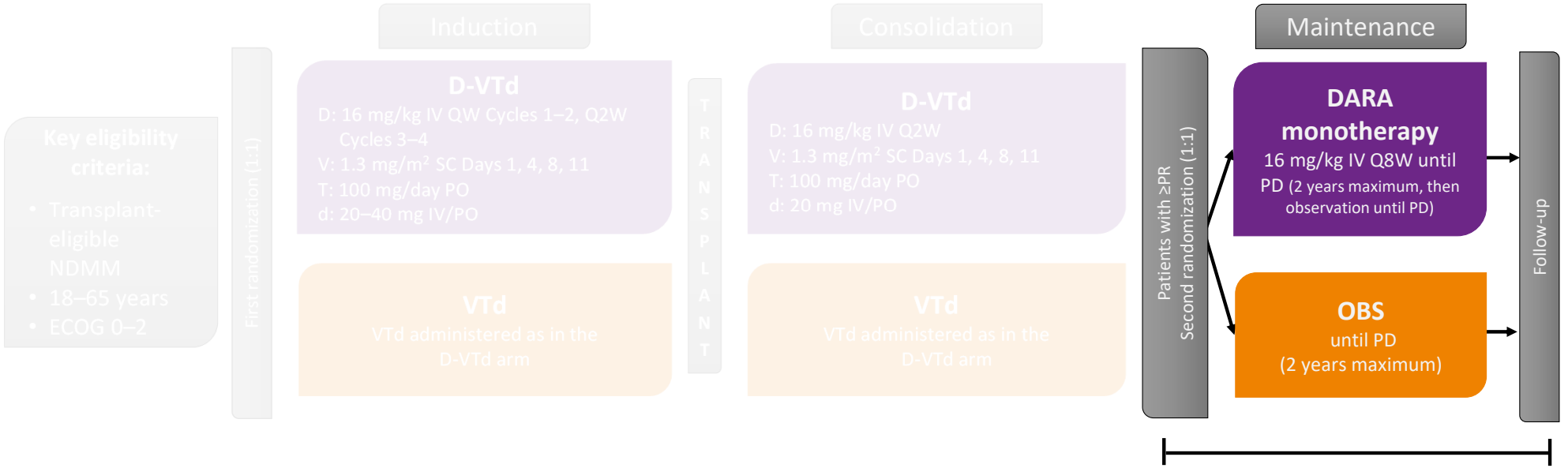
- Part 1 compared D-VTd vs VTd as induction/consolidation



D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; IFM, Intergroupe Francophone du Myélome; ISS, International Staging System; HOVON, the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PO, oral; Q2W, every 2 weeks; QW, every week; SC, subcutaneous; VTd, bortezomib, thalidomide, and dexamethasone.

CASSIOPEIA Part 2 Study Design

- Patients who completed consolidation and achieved ≥PR were re-randomized 1:1 to DARA 16 mg/kg IV every 8 weeks or OBS (no maintenance) for 2 years



≥PR, partial response or better; DARA, daratumumab; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; IV, intravenous; OBS, observation; PD, progressive disease; Q8W, every 8 weeks; VTd, bortezomib, thalidomide, and dexamethasone.

Demographics and Disease Characteristics Were Well Balanced Between Groups

	DARA (n=442)	OBS (n=444)
Median (range) age,* years	59.0 (27–66)	59.0 (36–66)
Male sex,* n (%)	261 (59.0)	254 (57.2)
Baseline ECOG performance status,* n (%)		
0	252 (57.0)	260 (58.6)
1	174 (39.4)	172 (38.7)
≥2	16 (3.6)	12 (2.7)
ISS staging,† n (%)		
I	189 (42.8)	171 (38.5)
II	181 (41.0)	214 (48.2)
III	72 (16.3)	59 (13.3)

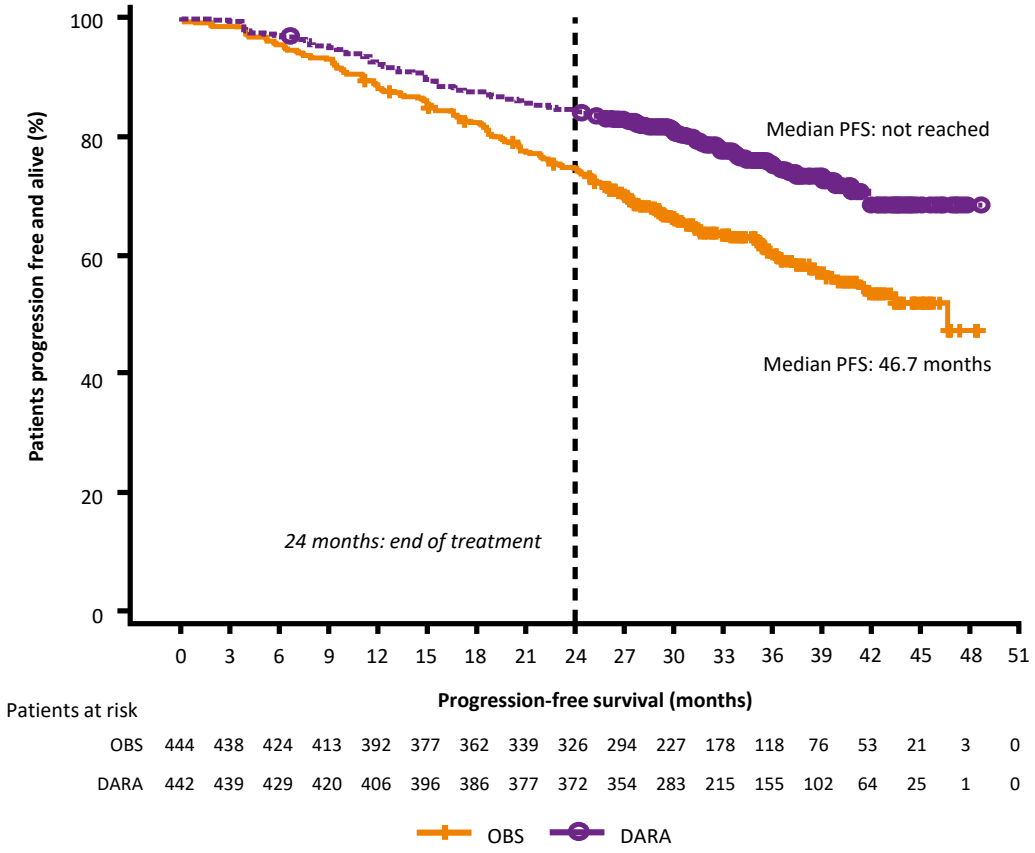
	DARA (n=442)	OBS (n=444)
Cytogenetic profile,† n/N (%)		
Standard risk	383/440 (87.0)	374/444 (84.2)
High risk‡	57/440 (13.0)	70/444 (15.8)
Type of induction/consolidation, n (%)		
D-VTd	229 (51.8)	229 (51.6)
VTd	213 (48.2)	215 (48.4)
Depth of response,§ n (%)		
MRD negative, ≥VGPR	337 (76.2)	337 (75.9)
MRD positive, ≥VGPR	68 (15.4)	69 (15.5)
MRD positive, PR	37 (8.4)	38 (8.6)

*Pre-consolidation; †Pre-induction; ‡Patients with del(17p) or t(11;14); § As determined by MRD measured by multiparametric flow cytometry at 10^{-4} and post-consolidation response per investigator assessment used for stratification.
≥VGPR, very good partial response or better; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; MRD, minimal residual disease; OBS, observation; PR, partial response; VTd, bortezomib, thalidomide, and dexamethasone.

DARA Significantly Improved PFS From Second Randomization vs OBS

Median follow-up: 35.4 months from second randomization

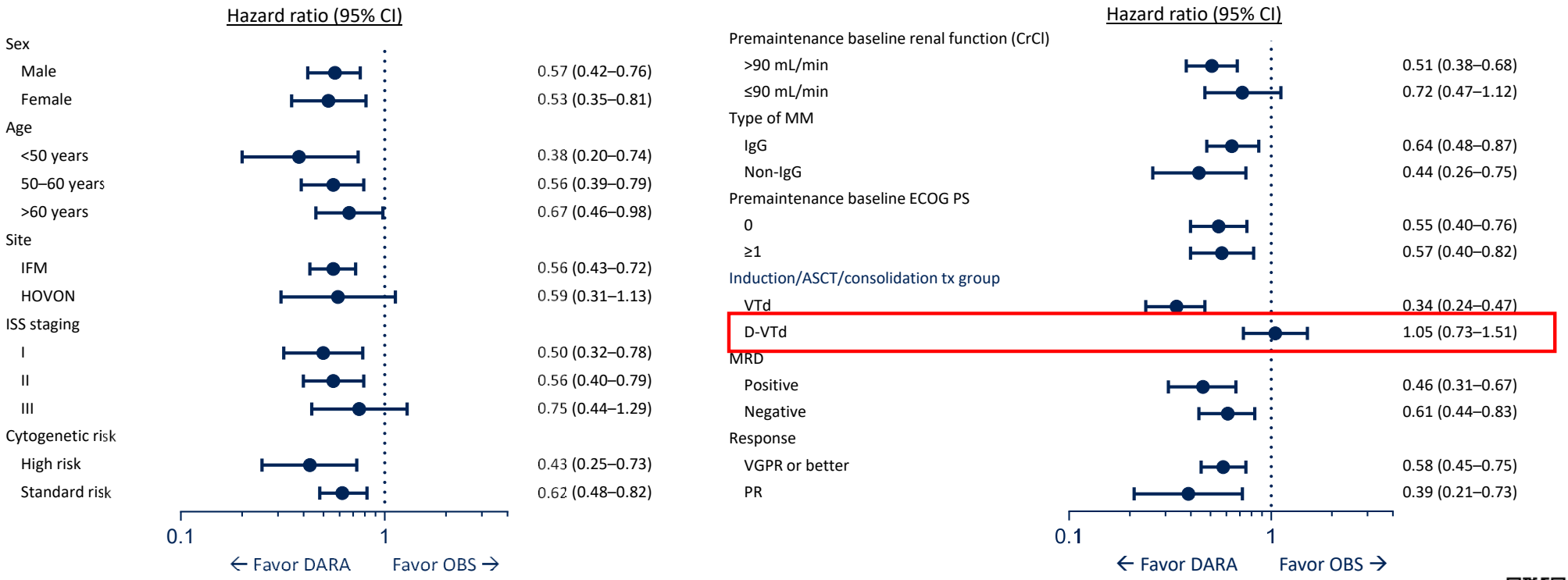
(N = 886 pts)



HR 0.53
(95% CI 0.42–0.68)
P<0.0001

CI, confidence interval; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival.

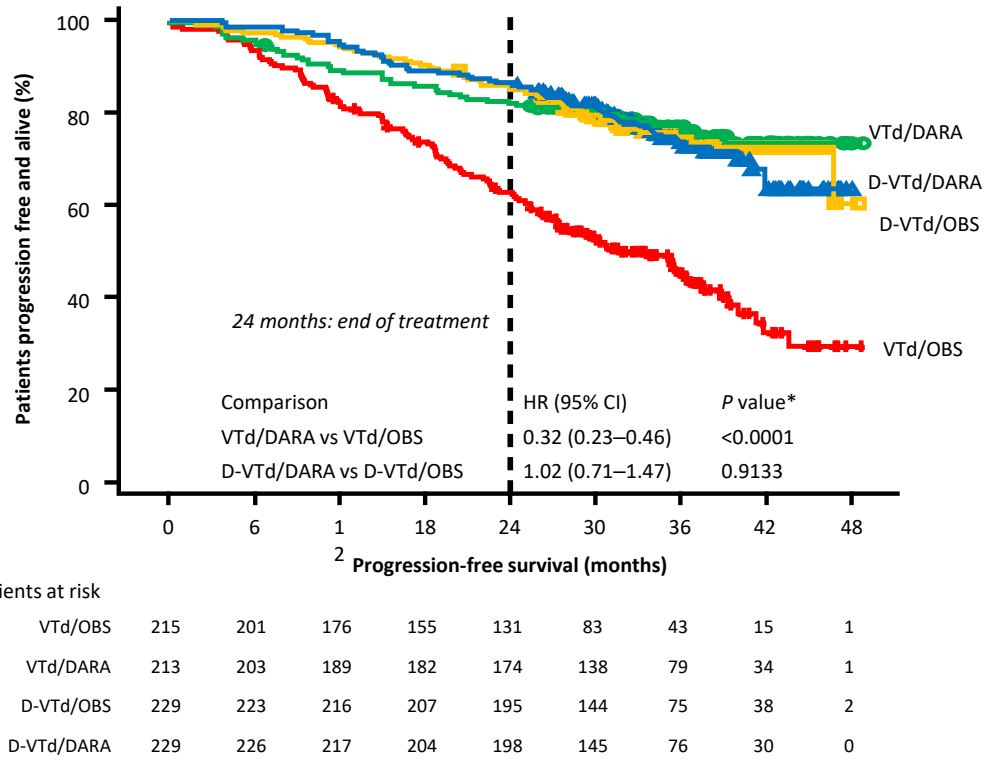
PFS Benefit of DARA Was Consistent Across Most Prespecified Subgroups



ASCT, autologous stem cell transplant; CI, confidence interval; CrCl, creatinine clearance; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; IFM, Intergroupe Francophone du Myélome; IgG, immunoglobulin G; ISS, International Staging System; HOVON, the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology; MM, multiple myeloma; MRD, minimal residual disease; OBS, observation; PFS, progression-free survival; PR, partial response; tx, treatment; VGPR, very good partial response; VTd, bortezomib, thalidomide, and dexamethasone.

DARA Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

- A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy:
- PFS benefit was observed for VTd/DARA vs VTd/OBS
- PFS was not different for D-VTd/DARA vs D-VTd/OBS

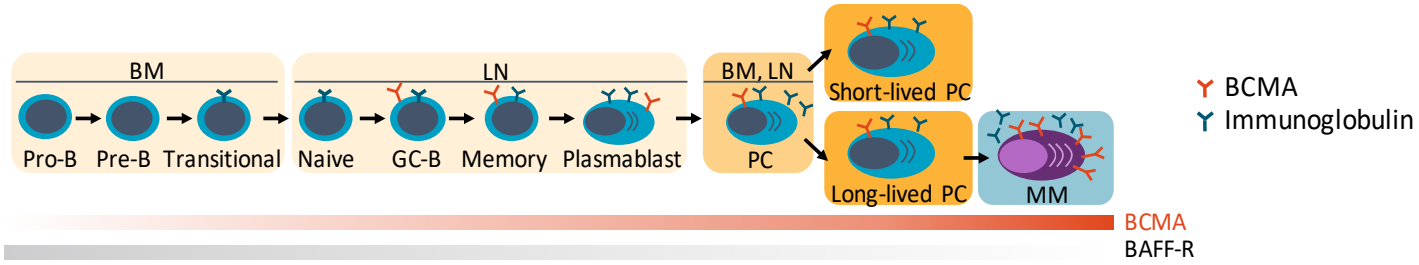


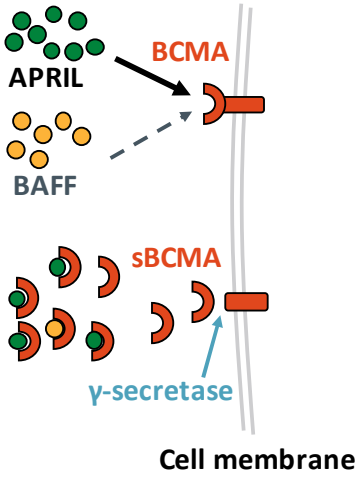
*Nominal *P* value.
CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

Dara as Part of Initial MM Rx: Conclusions

- Daratumumab improves induction response rates, depth
  - GRIFFIN, Cassiopeia, many other trials
- Dara is an effective maintenance option post-ASCT
  - S1803 will help fully define role of dara in combo w Len maintenance
  - AURIGA, PERSEUS, GRIFFIN are other Dara maintenance trials
- Cassiopeia part 2 suggests Dara may not be needed during both induction *and* post-ASCT maintenance

CAR-T Cells in Multiple Myeloma





Cho. Front Immunol. 2018;9:1821. Moreaux. Blood. 2004;103:3148. Sanchez. Br J Haematol. 2012;158:727.

Idecabtagene vicleucel (ABECMA)

- First FDA-approved CAR-T for RRMM (4+ prior Rx)
- KarMMA trial (Phase 2, n=127 pts)
  - ORR: 73% (82% with $450x10^6$ cell dose)
  - MRD(-): 92% of evaluable pts
  - Median PFS: 8.8 mos
  - CRS: 85% (most Gr 1-2; 9% Gr 3; time to onset 1d (1-12 d))
  - ICANS: 17% (most Gr 1-2; 3% Gr 3)
  - HLH/MAS: 4% (1 fatal)

2021 ASCO ANNUAL MEETING

CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN–DIRECTED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED RESULTS FROM CARTITUDE-1

Saad Z Usmani[1], Jesus G Berdeja[2], Deepu Madduri[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], Parameswaran Hari[7], Tzu-Min Yeh[8], Yunsi Olyslager[9], Arnob Banerjee[10], Carolyn C Jackson[8], Alicia Allred[10], Enrique Zudaire[10], William Deraedt[9], Xiaoling Wu[11], Marlene J Carrasco-Alfonso[11], Muhammad Akram[11], Yi Lin[12], Thomas Martin[13], Sundar Jagannath[3]

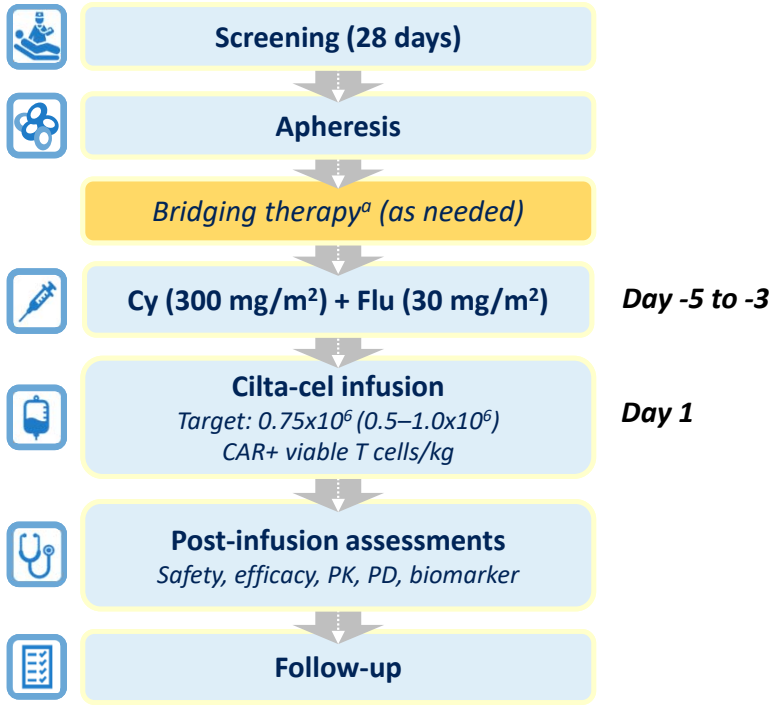
[1]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Janssen R&D, Raritan, NJ, USA; [9]Janssen R&D, Beerse, Belgium; [10]Janssen R&D, Spring House, PA, USA; [11]Legend Biotech USA, Inc, Piscataway, NJ, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

June 8, 2021

CARTITUDE-1: Phase 1b/2 Study Design

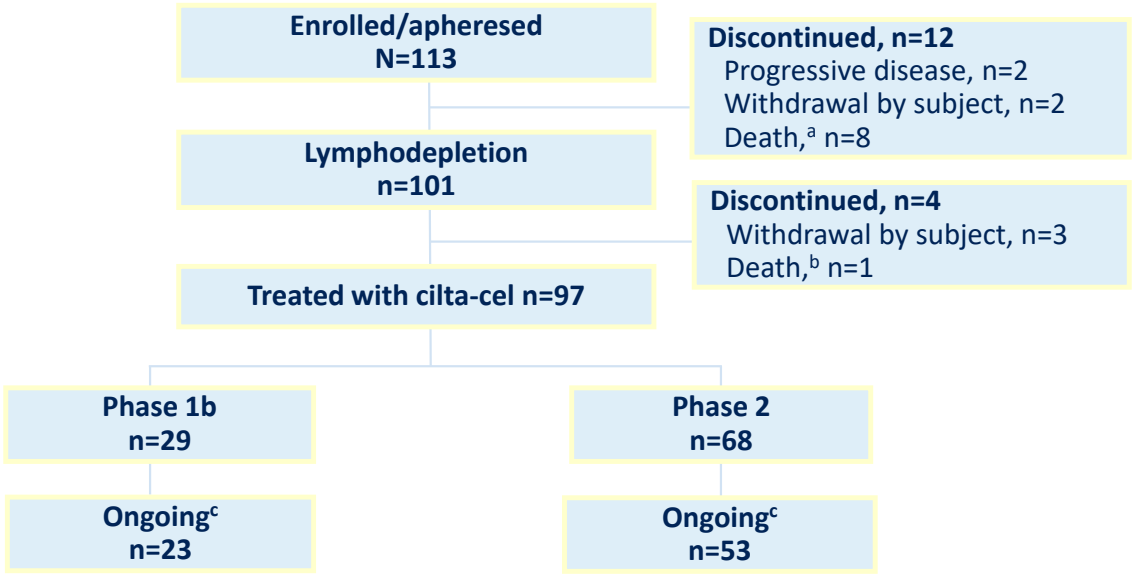
- **Primary Objectives**
  - Phase 1b: Characterize cilta-cel safety and confirm the recommended phase 2 dose
  - Phase 2: Evaluate cilta-cel efficacy
- **Key Eligibility Criteria**
  - Progressive MM per IMWG criteria
  - ≥3 prior therapies or double refractory
  - Prior PI, IMiD, anti-CD38 therapy
  - Measurable disease
  - ECOG PS ≤1

Median administered dose:
0.71x10^6 (0.51–0.95x10^6) CAR+ viable T cells/kg



CAR, chimeric antigen receptor; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics. Feb 11, 2021 data cut-off. [a]Treatment with previously used agent resulting in at least stable disease.

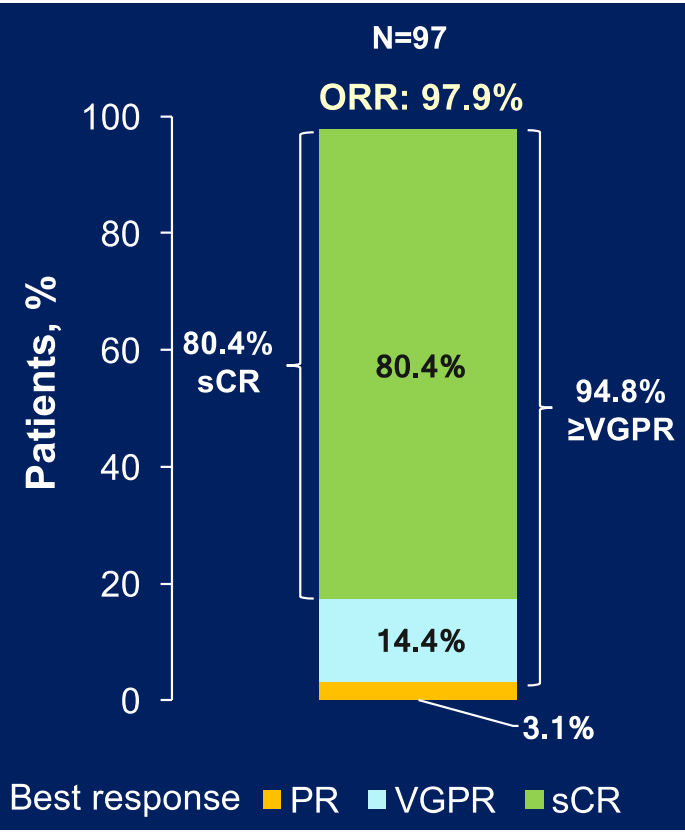
CARTITUDE-1: CONSORT Diagram



A total of 73 patients received bridging therapy[d]
Median turnaround time[e] for cilta-cel: 29 days (range, 23–64)
No patient discontinued due to manufacturing failure
One patient received retreatment with cilta-cel

[a]Due to progressive disease (5), acute cardio-respiratory arrest (1), sepsis (1), and subdural haematoma (1). [b]Due to acute respiratory failure. [c]There were 21 study deaths: 6 were treatment-related as assessed by the investigator, the remaining were due to AEs unrelated to treatment (n=5) and disease progression (n=10). [d]Between apheresis and cilta-cel infusion. [e]Defined as receipt to release, which is calculated from the day after the receipt of leukapheresis material at the manufacturing facility up to and inclusive of the day on which the CAR-T product is released for shipment to the clinical trial site.

CARTITUDE-1: Overall Response Rate

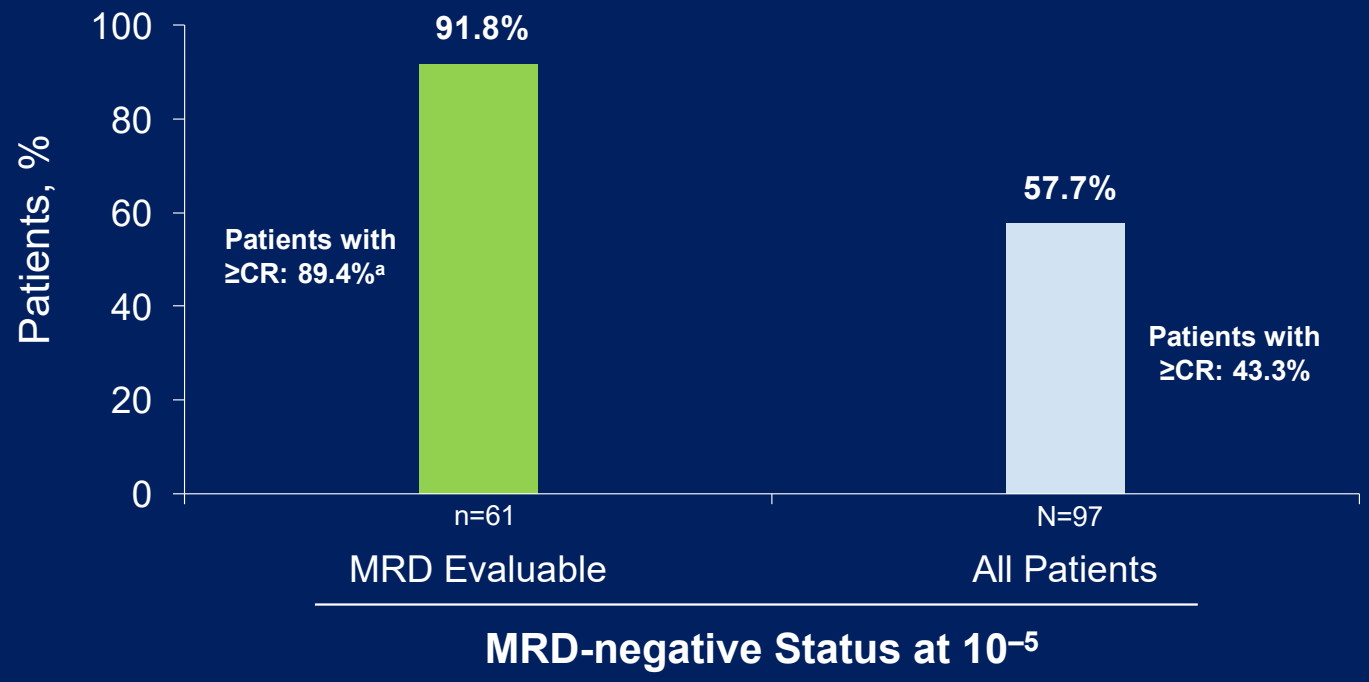


With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: 1 month (range, 0.9–10.7)
- Median time to best response: 2.6 months (range, 0.9–15.2)
- Median time to ≥CR: 2.6 months (range, 0.9–15.2)
- Median duration of response: 21.8 months (95% CI, 21.8–NE)
  - Estimated 73% of responders have not progressed or died at 12 months
  - Median duration of response not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]

CR, complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response. ORR assessed by independent review committee. [a]Subgroups by number of prior lines of therapy (≤4, >4), refractoriness (triple-class, penta-drug), cytogenetic risk (high risk, standard risk), baseline bone marrow plasma cells (≤30%, >30 to <60%, ≥60%), baseline tumor BCMA expression (≥median, <median), and baseline plasmacytomas (including extramedullary and bone-based).

CARTITUDE-1: Minimal Residual Disease 10^{-5}



Almost all (91.8%) evaluable patients were MRD negative

Median time to MRD 10^{-5} negativity: 1 month (range, 0.8–7.7)

MRD, minimal residual disease; sCR, stringent complete response.
MRD was assessed in evaluable samples (ie, patients with identifiable clone at baseline and sufficient cells for testing at 10^{-5} threshold in post treatment samples) by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at Day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine. [a]Denominator n=47; evaluable MRD sample within 3 months of achieving CR/sCR until death/progression/subsequent therapy.

CARTITUDE-1: Safety

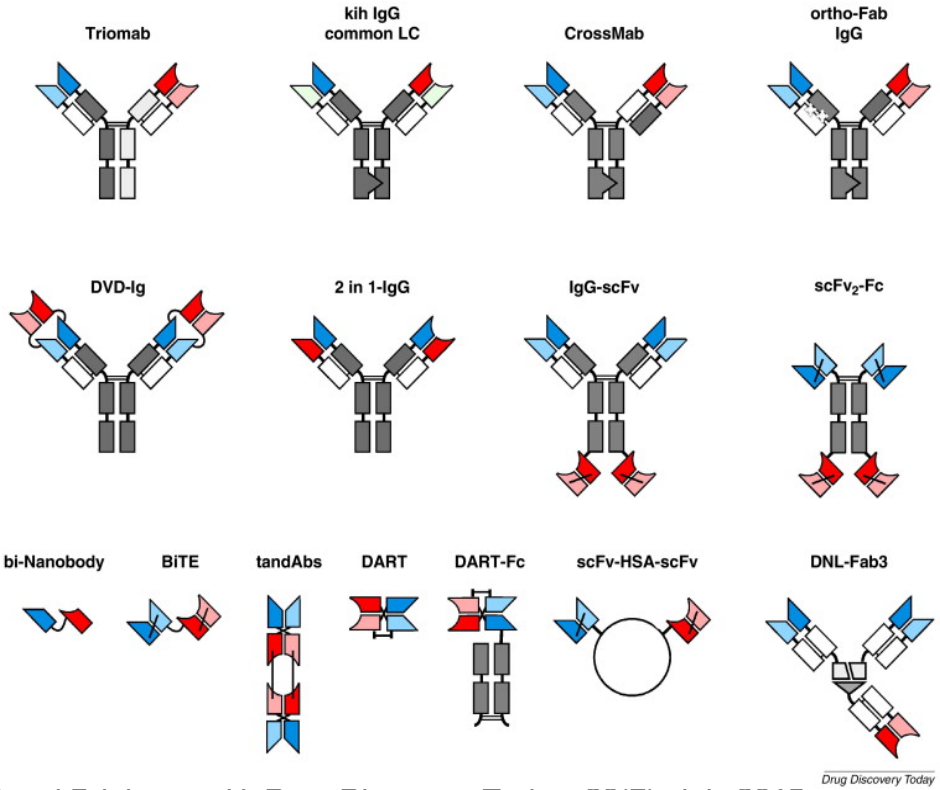
CRS	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]
Of 92 patients with CRS, majority (94.6%) were grades 1/2 **CRS resolved in 91 (98.9%) patients within 14 days of onset**	

Total CAR T-cell neurotoxicities, n (%)	
Any Grade	20 (20.6)
Grade ≥3	10 (10.3)
ICANS, n (%)	
Any Grade	16 (16.5)
Grade ≥3	2 (2.1)

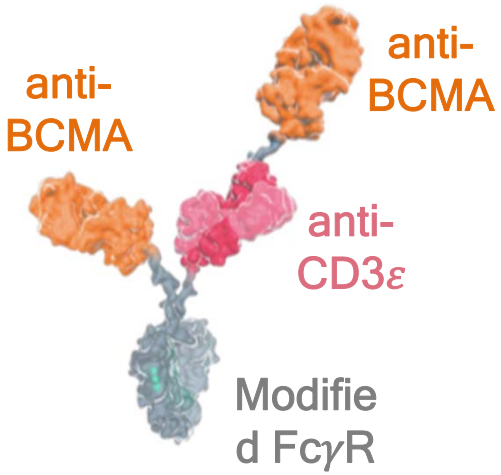
Ciltacabtagene Autoleucel: Conclusions

- Extended Phase 2 results remain promising
- High response rates, with some durability
- Safety profile typical for therapeutic class
  - Vigilance for CRS, ICANS critical in management
- Ongoing Phase 2 and 3 trials
- Granted FDA priority review (PDUFA Nov 29, 2021)

Bispecific Antibody (bsAb) Constructs



CC-93269



1. Kontermann RE and Brinkmann U. Drug Discovery Today, 20(7): July 2015
2. Costa L, et al, ASH meeting 2019, Abstract # 143

BCMA-Targeted ADCs & bsAbs

Report	Agent	Class	n	Sched/Rte	ORR (%)	CRS (%)
ASH19 #143	CC-93269	BsAb	30	qw then q2w IV	89%*	77%
DREAMM2	Bel-Maf	ADC	196	q3w IV	32.7%	
ASH20 #179	MEDI2228	ADC	82	q3w IV	47.6%	
ASH20 #180	Teclistamab	BsAb	149	qw IV (IV 84, SC 65)	62%* (SC)	55%
ASH20 #181	AMG-701	BsAb	85	qw IV	26% (83%*)	65%
ASH20 #291	REGN5458	BsAb	49	qw split then q2w IV	39% (62%*)	39%
ASH20 #293	TNB383B	BsAb	58	q3w IV (no step-up)	47% (80%*)	45%
ASH20 #3206	PF-3135	BsAb	30	qw SC	53% (80%*)	73%

*at highest dose or RP2D

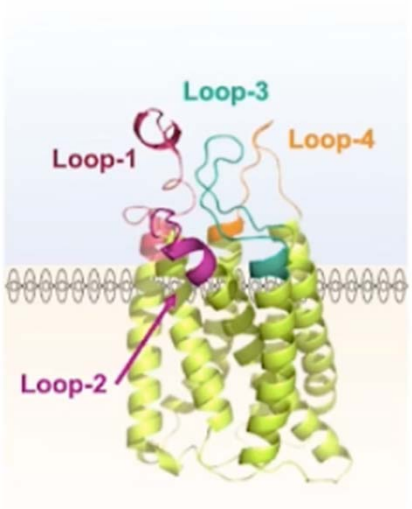
2021 ASCO ANNUAL MEETING

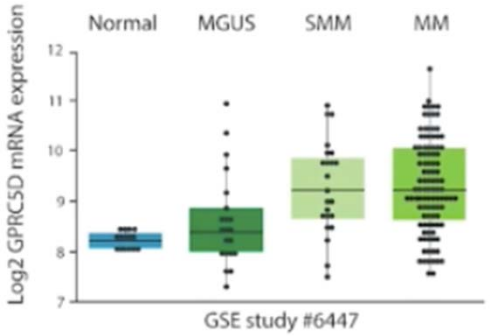
UPDATED RESULTS OF A PHASE 1, FIRST-IN-HUMAN STUDY OF TALQUETAMAB, A G PROTEIN-COUPLED RECEPTOR FAMILY C GROUP 5 MEMBER D × CD3 BISPECIFIC ANTIBODY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

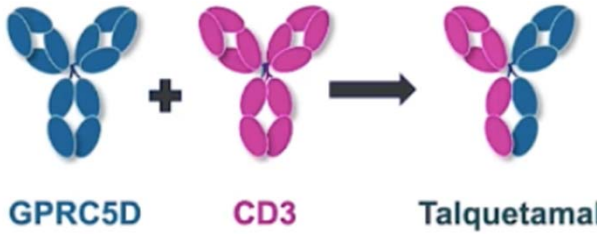
Jesus G Berdeja[1], Amrita Krishnan[2], Albert Oriol[3], Niels WCJ van de Donk[4], Paula Rodríguez-Otero[5], Elham Askari[6], María-Victoria Mateos[7], Monique C Minnema[8], Luciano J Costa[9], Raluca Verona[10], Suzette Girgis[10], Thomas Prior[10], Brandi W Hilder[10], Jeffery Russell[10], Jenna D Goldberg[11], Ajai Chari[12]

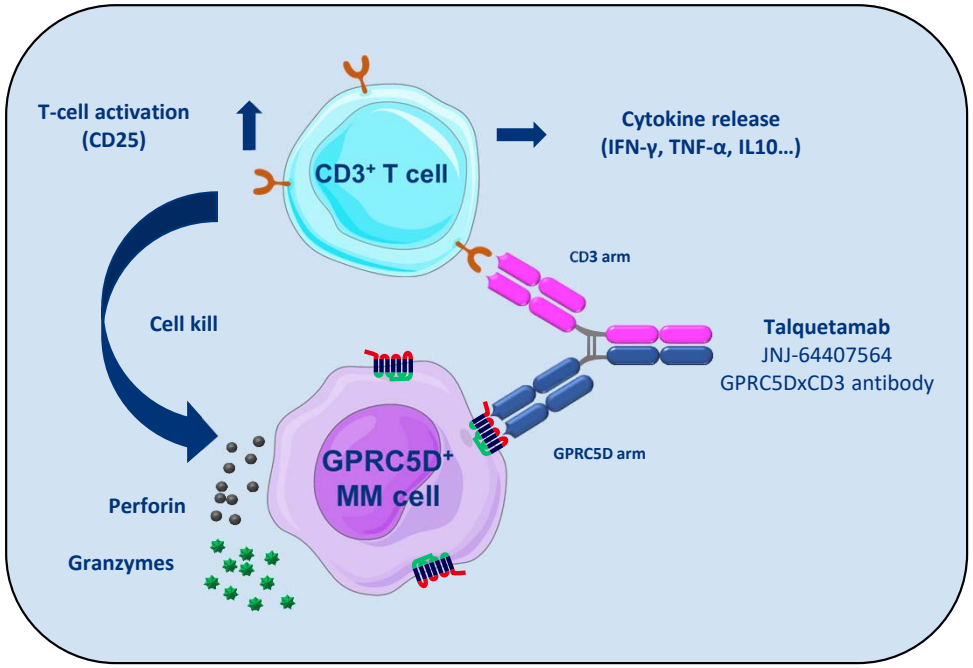
[1]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [2]City of Hope, Duarte, CA, USA; [3]Institut Català d'Oncologia and Institut Josep Carreras; Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [4]Amsterdam University Medical Center, VU University Medical Center, Amsterdam, Netherlands; [5]Clínica Universidad de Navarra, Navarra, Spain; [6]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [7]Hospital Clínico Universitario de Salamanca, Salamanca, Spain; [8]University Medical Center Utrecht, Utrecht, Netherlands; [9]University of Alabama at Birmingham, Birmingham, AL, USA; [10]Janssen R&D, Spring House, PA, USA; [11]Janssen R&D, Raritan, NJ, USA; [12]Mount Sinai School of Medicine, New York, NY, USA

Talquetamab: GPRC5DxCD3 bsAb









Chari A, et al. ASH 2020, Abstract # 290
Berdeja J, et al. ASCO 2021

TALQUETAMAB

MonumenTAL-1 Study Design

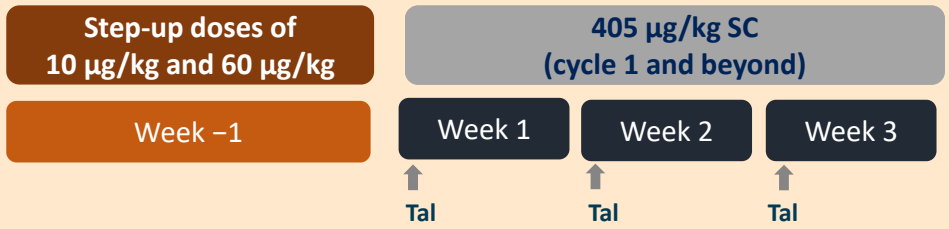
Key Objectives

- Part 1: Identify RP2D
- Part 2: Safety and tolerability at RP2D
- Antitumor activity, pharmacokinetics, pharmacodynamics

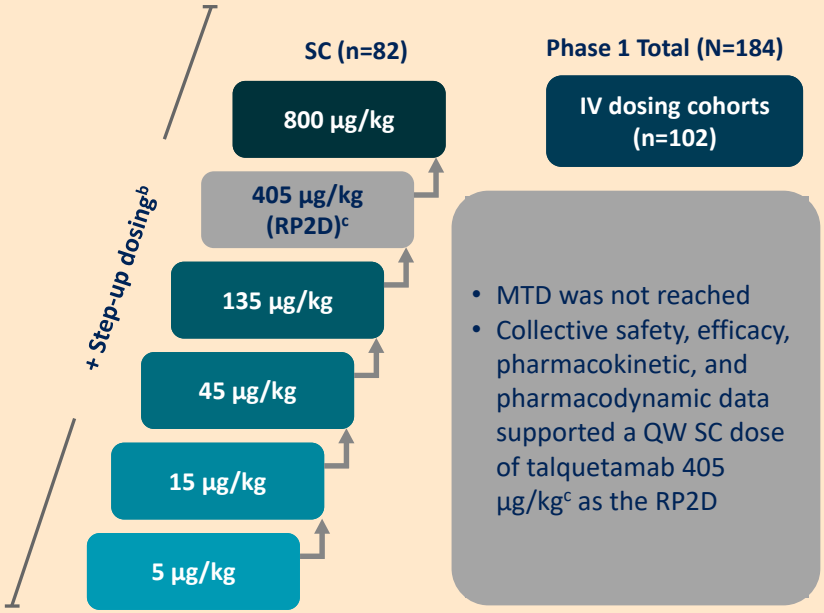
Key Eligibility Criteria

- Adults with measurable MM
- RR or intolerant to established MM therapies
- Hemoglobin ≥8 g/dL, platelets ≥50×10^9/L, ANC ≥1.0×10^9/L
- Prior BCMA-targeted therapy allowed

Dosing Schedule at RP2D



- Premedications[a] were limited to step-up doses and first full dose
  - No steroid requirement after first full dose



- The data cut-off date for these analyses was April 18, 2021

[a]Glucocorticoid, antihistamine, and antipyretic; [b]1-3 step-up doses given within 1 week before a full dose; [c]Step-up doses of 10 and 60 µg/kg.
ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; IV, intravenous; MM, multiple myeloma; MTD, maximum tolerated dose; QW, every week; RP2D, recommended phase 2 dose; RR, relapsed/refractory; SC, subcutaneous.

TALQUETAMAB

Patient Demographics and Disease Characteristics

Characteristic	SC Total n=82	RP2D (405 µg/kg SC QW)[a] n=30
Age, years, median (range)	63.0 (42–80)	61.5 (46–80)
Age ≥70 years, n (%)	22 (27)	7 (23)
Sex, n (%)		
Male	47 (57)	19 (63)
Female	35 (43)	11 (37)
Years since diagnosis, median (range)	5.9 (1–20)	5.6 (2–20)
Extramedullary plasmacytomas ≥1, n (%)[b]	27 (33)	10 (33)
Bone marrow plasma cells ≥60%, n (%)[c]	13 (17)	6 (21)
ISS stage, n (%)[d]		
I	26 (32)	12 (40)
II	36 (44)	13 (43)
III	13 (16)	3 (10)
Prior transplantation, n (%)	71 (87)	27 (90)

Characteristic	SC Total n=82	RP2D (405 µg/kg SC QW)[a] n=30
Prior lines of therapy, n, median (range)	6.0 (2–17)	6.0 (2–14)
Exposure status, n (%)		
Prior BCMA therapy[e]	20 (24)	8 (27)
Triple-class[f]	81 (99)	30 (100)
Penta-drug[g]	64 (78)	24 (80)
Refractory status, n (%)		
Pi[h]	69 (84)	25 (83)
Carfilzomib	54 (66)	19 (63)
IMiD[i]	76 (93)	28 (93)
Pomalidomide	67 (82)	26 (87)
Anti-CD38 mAb[j]	77 (94)	30 (100)
BCMA[e]	14 (17)	5 (16)
Triple-class[f]	62 (76)	23 (77)
Penta-drug[g]	23 (28)	6 (20)
To last line of therapy	69 (84)	26 (87)

[a]Step-up doses of 10 µg/kg and 60 µg/kg; [b]Soft-tissue component of a bone-based plasmacytoma not included; [c]Percentages calculated from n=76 for SC total and n=29 at RP2D; [d]Percentages calculated from n=66 for SC total and n=27 at RP2D; [e]BCMA CAR-T therapy or BCMA non-CAR-T therapy; [f]≥1 PI, ≥1 IMiD, and 1 anti-CD38 mAb; [g]≥2 PI, ≥2 IMiD, and 1 anti-CD38 mAb; [h]Bortezomib, carfilzomib, and/or ixazomib; [i]Thalidomide, lenalidomide, and/or pomalidomide; [j]Daratumumab and/or isatuximab.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

TALQUETAMAB

Safety Profile

AE (≥20% of total SC), n (%)	SC Total n=82		RP2D (405 µg/kg SC QW)[a] n=30	
	Any grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic				
Neutropenia	47 (57)	40 (49)	20 (67)	18 (60)
Anemia	37 (45)	23 (28)	17 (57)	8 (27)
Thrombocytopenia	23 (28)	15 (18)	10 (33)	6 (20)
Leukopenia	21 (26)	16 (20)	11 (37)	8 (27)
Lymphopenia	19 (23)	19 (23)	9 (30)	9 (30)
Nonhematologic				
CRS	55 (67)	1 (1)	22 (73)	1 (2)
Dysgeusia	38 (46)	NA	18 (60)	NA
Fatigue	26 (32)	0	9 (30)	0
Pyrexia	23 (28)	1 (1)	7 (23)	1 (2)
Dry mouth	22 (27)	0	8 (27)	0
Dysphagia	21 (26)	0	11 (37)	0
Headache	19 (23)	1 (1)	7 (23)	0
Diarrhea	18 (22)	0	7 (23)	0
Nausea	18 (22)	0	7 (23)	0

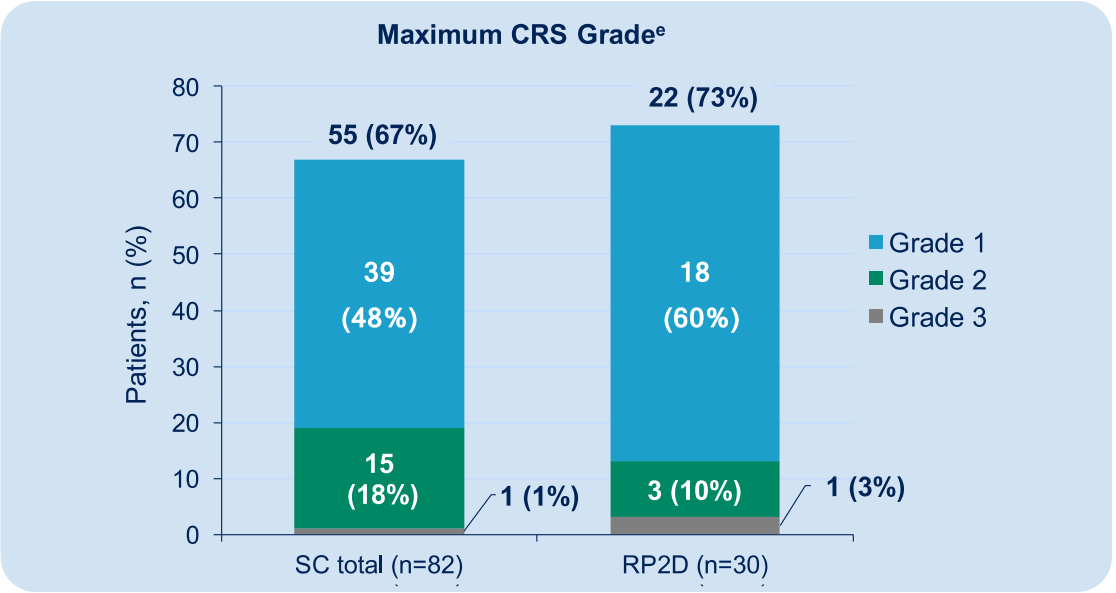
[a]Step-up doses of 10 µg/kg and 60 µg/kg; [b]Includes skin exfoliation, pruritis, rash, and nail disorders; [c]Includes nail disorders, onychomadesis, and nail dystrophy.
AE, adverse event, CRS, cytokine release syndrome; DLT, dose-limiting toxicity; NA, not applicable; RP2D, recommended phase 2 dose; SC, subcutaneous.

- Tolerable safety profile at the RP2D of 405 µg/kg SC
  - No DLTs at the RP2D
  - Cytopenias mostly during step-up doses and cycles 1/2
  - Neutropenia generally < 1 wk and limited to cycles 1/2
- Infections in 37% of SC RP2D patients
  - Grade 3/4: 9% for SC total, 3% for RP2D)
- Neurotoxicities (all grade 1/2)
  - 4 patients with SC dosing; 2 patients (7%) at RP2D
- Injection-site reactions in 17% of SC patients (including RP2D)
  - All grade 1/2
- Skin-related AEs[b] in 67% of SC patients; 77% at RP2D
  - Majority grade 1/2
- Nail disorders[c] in 21% of patients; 27% at RP2D
- No deaths due to AEs at the RP2D

TALQUETAMAB

Cytokine Release Syndrome

Parameter	SC Total n=82	RP2D (405 µg/kg SC QW)[a] n=30
Patients with CRS, n (%)	55 (67)	22 (73)
Time to onset, days,[b] median (range)	2 (1–22)	2 (1–22)
Duration, days, median (range)	2 (1–7)	2 (1–3)
Supportive measures, n (%)[c]	55 (67)	22 (73)
Tocilizumab[d]	43 (52)	18 (60)
Steroids	5 (6)	1 (3)
Low-flow oxygen by nasal cannula	6 (7)	1 (3)
Vasopressor	2 (2)	1 (3)

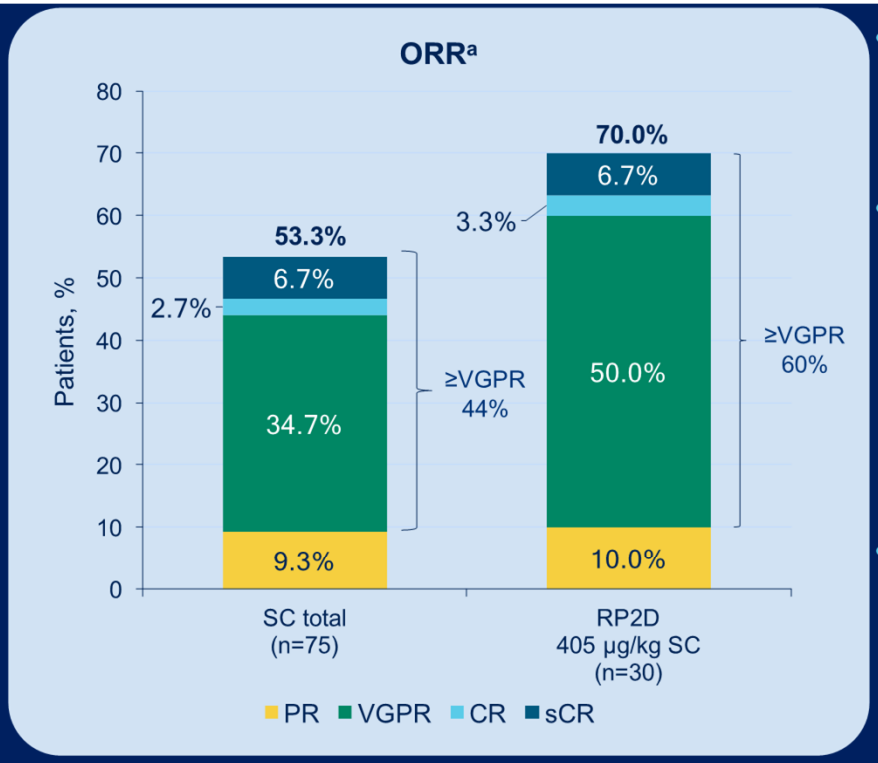


- CRS generally confined to step-up and first full doses
- Across all SC cohorts, CRS wgrade 1/2 in all pts, except1 with grade 3 CRS
- Majority of pats only had 1 dose of tocilizumab for CRS

Step-up doses of 10 µg/kg and 60 µg/kg; [b]Relative to the most recent dose; [c]A patient could receive >1 supportive therapy; [d]Tocilizumab was allowed for all CRS events; [e]Graded according to Lee et al. *Blood* 2014;124:188.
CRS, cytokine release syndrome; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous.

TALQUETAMAB

Overall Response Rate



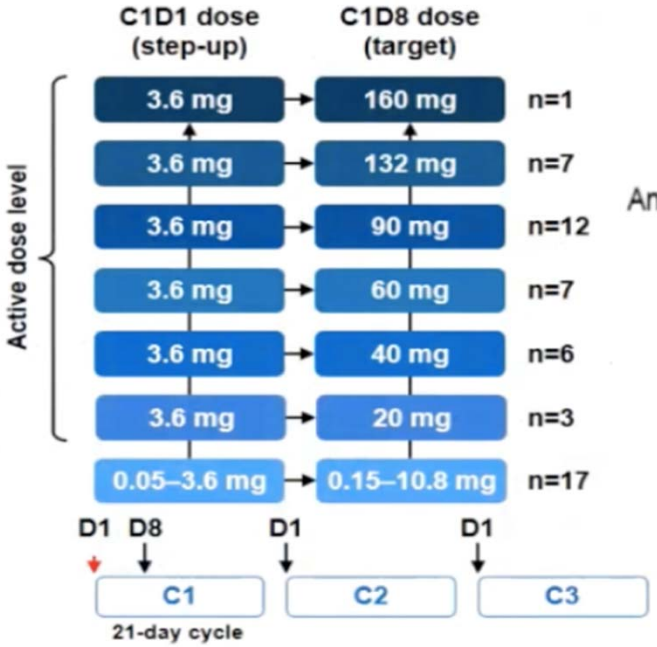
- The RP2D of 405 µg/kg SC QW has been administered to 30 patients with a median follow-up of 6.3 months (range: 1.4–12.0) for responders
- At the RP2D:
  - 70.0% ORR (21/30)
  - Median time to first confirmed response was 1 month (range: 0.2–3.8)
  - 65.2% (15/23) of triple-refractory patients responded
  - 83.3% (5/6) of penta-refractory patients responded
- Of 6 evaluable patients across IV and SC cohorts, 4 had MRD-negative CR/sCR at 10^{-6}, including 1 patient in RP2D cohort
  - MRD negativity was sustained 7 months post CR in 1 evaluable patient

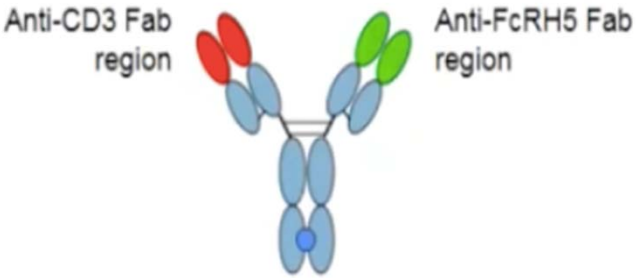
[a]Investigator assessment of evaluable patients who had ≥1 dose of talquetamab and ≥1 postbaseline disease evaluation per 2011 International Myeloma Working Group response criteria; includes unconfirmed response.
CR, complete response; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

Cefostamab: FcRH5xCD3 BsAb

N (%) unless stated	N=53
Number of prior lines of therapy, median (range)	6 (2–15)
Prior PI	53 (100)
Prior IMiD	53 (100)
Prior anti-CD38 antibody	43 (81)
Prior anti-BCMA‡	11 (21)
Triple-class refractory	38 (72)
Penta-drug refractory	24 (45)
Refractory to last prior therapy	50 (94)

‡CAR-T, 6/11; ADC, 5/11



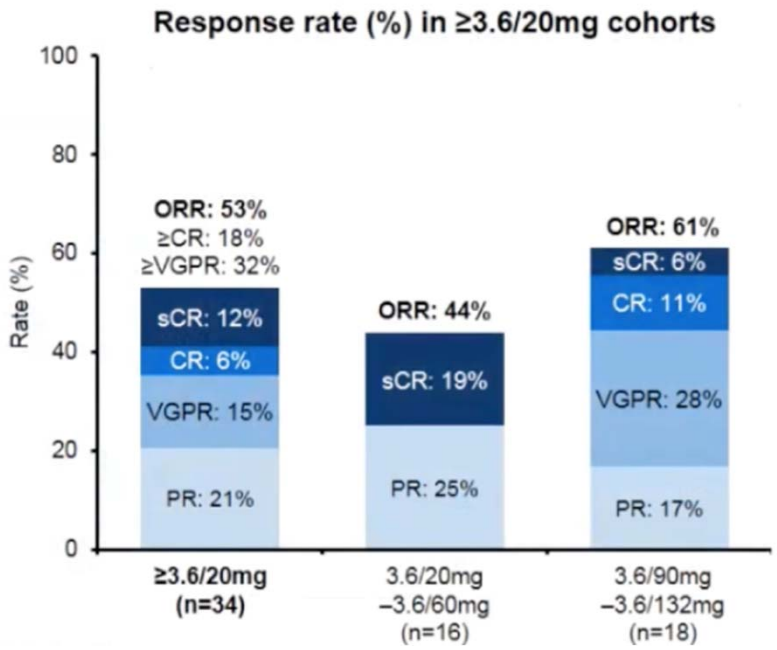


IV Infusion q3wk x 17+ cycles

Cohen A, et al. ASH 2020, Abstract # 292

Cefostamab: FcRH5xCD3 BsAb

N (%)	All Gr (N=53)	All Gr 3–4 (N=53)
Hematologic AEs (≥15%)		
Platelet count decreased*	17 (32)	13 (25)
Anemia	15 (28)	10 (19)
Neutropenia	9 (17)	8 (15)
Lymphocyte count decreased	8 (15)	8 (15)
Non-hematologic AEs (≥15%)		
Cytokine release syndrome	40 (76)	1 (2)
Hypomagnesemia	15 (28)	0
Diarrhea	15 (28)	1 (2)
Infusion-related reaction	12 (23)	0
Hypokalemia	11 (21)	2 (4)
Hypophosphatemia	10 (19)	5 (9)
Nausea	10 (19)	0
Fatigue	9 (17)	2 (4)
AST increased	8 (15)	1 (2)



Cohen A, et al. ASH 2020, Abstract # 292

Novel bsAbs: Conclusions

- GPRC5D & FcRH5 validated as therapeutic targets in RRMM
- High response rates in heavily pre-treated patients
  - Probably higher than ADCs but lower than CAR-T
  - Response data in anti-BCMA treated pts still undefined
  - Durability of responses compared to CAR-T still unclear
- Manageable side effect profile
  - CRS generally mild, requiring modest supportive measures
  - Neurotoxicity much less frequent than with CAR-T

Key Take Home Points

- ASCT improves PFS and depth of responses
  - Most important in pts who remain MRD(+) after induction?
- Daratumumab ought to be “standard” in first-line therapy
  - May not be needed during induction *and* maintenance
- BCMA-targeting therapies are a major breakthrough
  - ADC (Belantamab mafadotin) and CAR-T (ide-cel) approved
  - bsAbs targeting BCMA (*and other targets*) appear promising
    - Talquetamab (GPRC5D) and Cefostamab (FcHRH5)