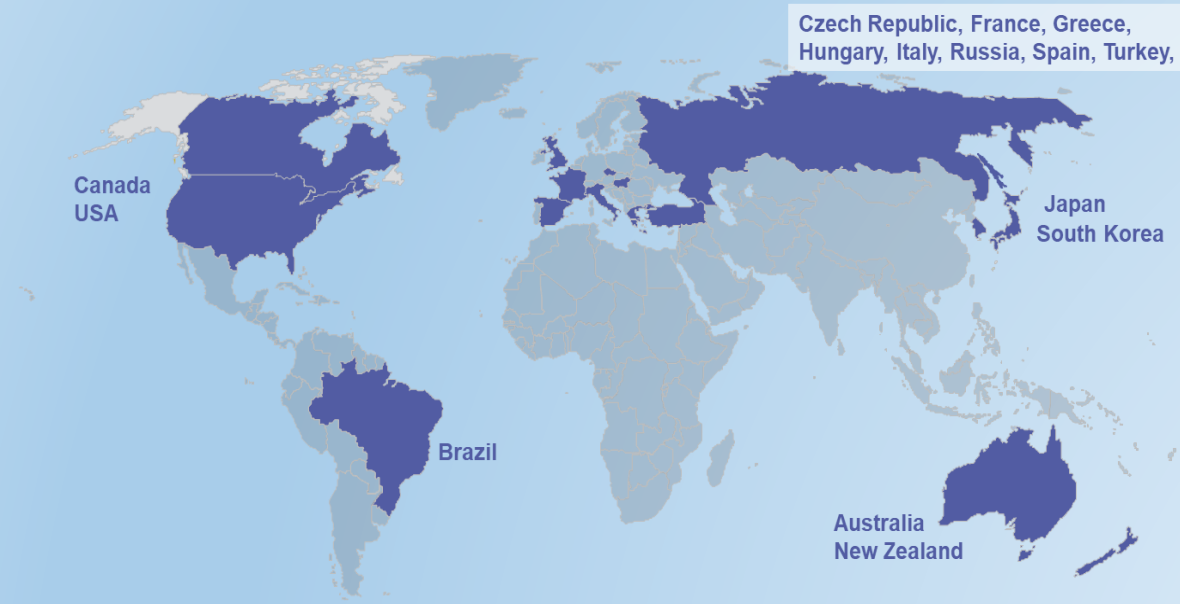
Isatuximab Plus Carfilzomib and Dexamethasone vs Carfilzomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (IKEMA): Interim Analysis of A Phase 3 Randomized, Open-Label Study

Philippe Moreau*,[1], Meletios-Athanasios Dimopoulos[2], Joseph Mikhael[3], Kwee Yong[4], Marcelo Capra[5], Thierry Facon[6], Roman Hajek[7], Ivan Spicka[8], Marie-Laure Risse[9], Gaelle Asset[10], Sandrine Macé[9], Thomas Martin*,[11]

*Co-primary investigators; [1]Department of Hematology, University Hospital Hôtel-Dieu, Nantes, France; [2]The National and Kapodistrian University of Athens, Athens, Greece; [3]Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ, USA; [4]Department of Haematology, University College Hospital, London, UK; [5]Hospital Mãe de Deus, Porto Alegre, Rio Grande do Sul; [6]Lille University Hospital, Lille, France; [7]Department of Hemato-Oncology, University Hospital Ostrava, University of Ostrava, Ostrava, Czech Republic; [8]Clinical Department of Hematology, 1st Medical Department, Charles University in Prague; [9]Sanofi R&D, Vitry/Alfortville, France; [10]Sanofi R&D, Chilly-Mazarin, France; [11]Division of Hematology, University of California, San Francisco, San Francisco, CA, USA

EHA 2020; Final Abstract Code: LB2603

Acknowledgments



16 participating countries

WE WOULD LIKE TO THANK:

The participating patients and their families

Study investigators and staff

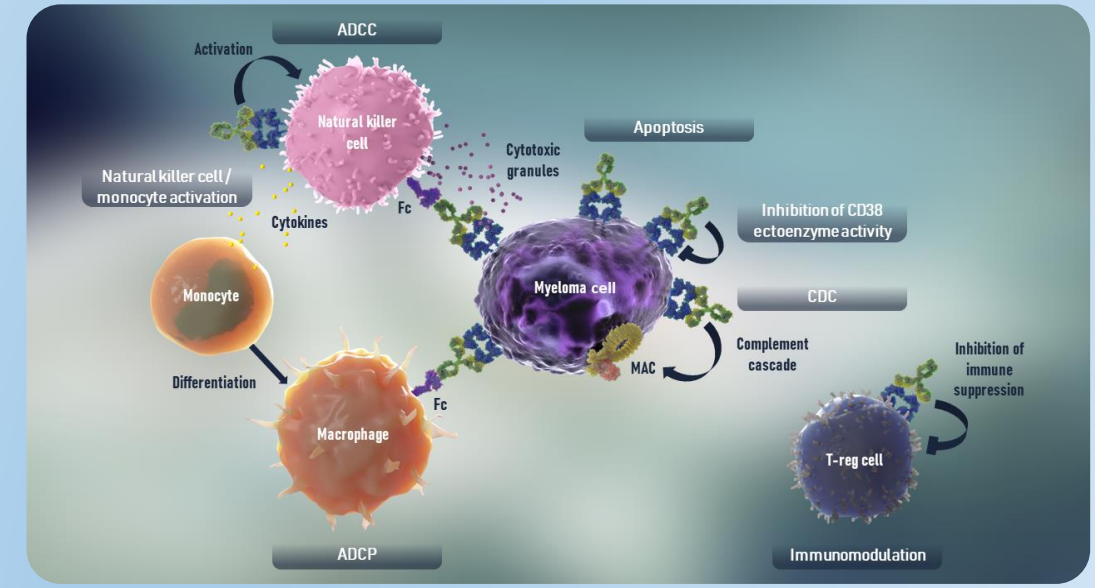
All staff who contributed to data collection and analyses

The Data Monitoring Committee

Study funding: Sanofi

Thank you for your attention

Isatuximab: Targets a specific epitope on CD38



CD38 functions as a receptor and an ectoenzyme, uniformly expressed on multiple myeloma (MM) cells[1–5]

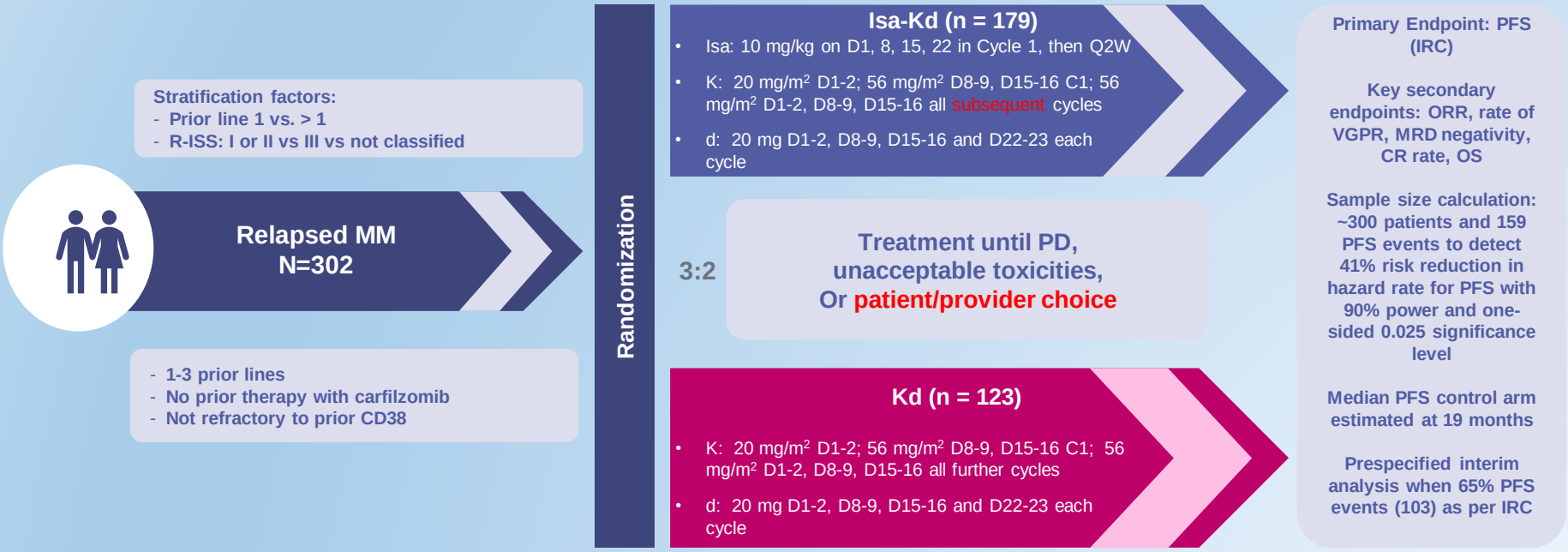
Isatuximab: IgG1 monoclonal antibody targeting a CD38 transmembrane glycoprotein in MM with multiple modes of action:[6]

- ADCC, CDC, and ADCP
- Direct apoptosis
- Immunomodulation
- Inhibition of enzymatic fxn

ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; CDC, complement dependent cytotoxicity; (c)ADPR, (cyclic) adenosine diphosphate–ribose; ER, endoplasmic reticulum; Ig, immunoglobulin; MAC, membrane attack complex; MDSC, myeloid- derived suppressor cells; NAD, nicotinamide adenine dinucleotide

1. Lin P, et al. Am J Clin Pathol. 2004;121:482–8; 2. Angelopoulou MK, et al. Eur J Haematol. 2002;68:12–21; 3. Schwonzen M, et al. Br J Haematol. 1993;83:232–9; 4. Keyhani A, et al. Leukemia Res. 2000;24:153–9; 5. Domingo-Domènech E, et al. Haematologica. 2002;87:1021–7; 6. Jiang H, et al. Leukemia. 2016;30:399–408;

IKEMA
Study design: Isa-Kd vs Kd in Relapsed Multiple Myeloma



CR, complete response; D, day; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ms, months; OR, overall response; OS, overall survival; PFS, progression free survival; R-ISS, revised international staging system; VGPR, very good partial response

Moreau P, et al. Future Oncol 2020;16:4347–58

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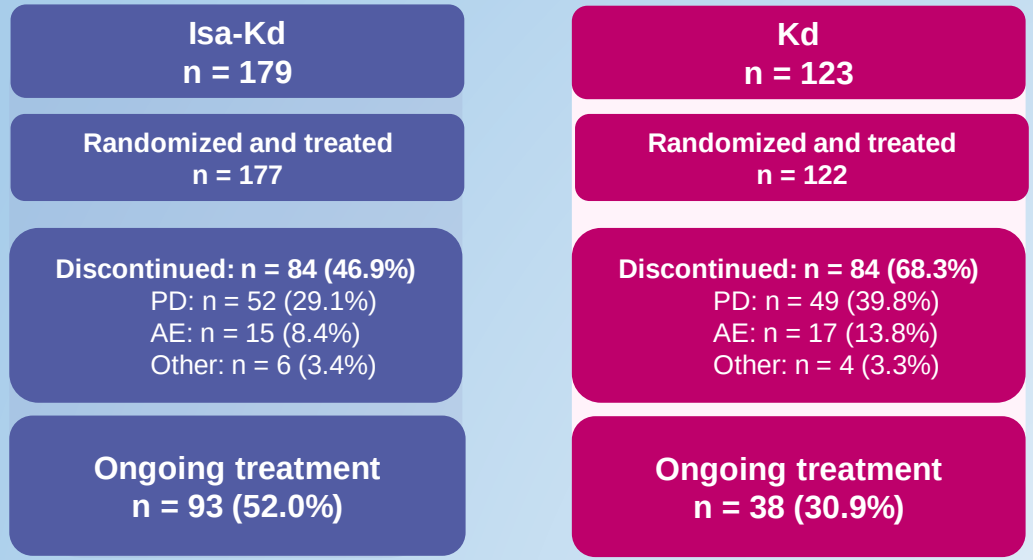
Patient disposition*



Median duration of follow-up: 20.7 months

A higher percentage of patients are still on treatment in the Isa-Kd arm
37.4% discontinued due to PD or due to an AE in the Isa-Kd arm vs 53.7% in the Kd arm

*Data cut-off Feb 7, 2020
AE, adverse event; d, dexamethasone; Isa, isatuximab; K, carfilzomib; PD, progressive disease

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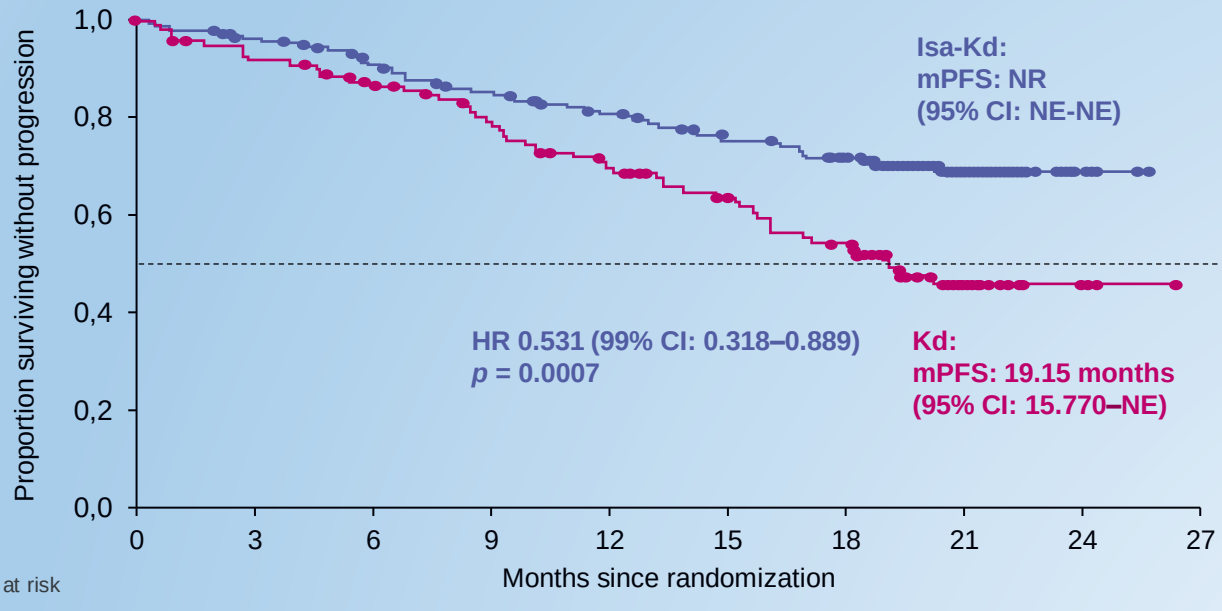
Interim PFS analysis – IRC assessment in ITT population (primary endpoint)



No. at risk										
Isa-Kd	179	164	151	136	124	110	100	36	5	0
Kd	123	108	99	85	72	61	50	19	6	0

One-sided *p* value, level of significance <0.005

Isa-Kd showed a 47% improvement or death vs Kd

CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; NE, not estimable; NR, not reached; PFS, progression-free survival

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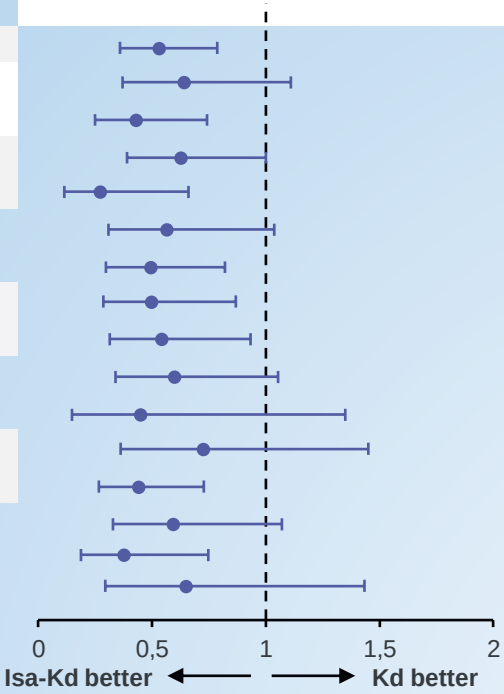
PFS subgroup analyses

Subgroup		Isa-Kd No. of events/total no.	Kd No. of events/total no.	Hazard ratio (95% CI)
All patients		48/179	55/123	0.531 (0.359–0.786)
Age	<65 years	25/88	26/66	0.640 (0.370–1.109)
	≥65 years	23/91	29/57	0.429 (0.248–0.742)
Baseline eGFR (MDRD)	≥60 mL/min/1.73 m²	32/122	38/93	0.625 (0.391–1.001)
	<60 mL/min/1.73 m²	10/43	10/18	0.273 (0.113–0.660)
Prior PI treatment	Yes	22/81	20/47	0.565 (0.308–1.036)
	No	26/98	35/76	0.493 (0.296–0.819)
Prior IMiD treatment	Yes	22/81	29/62	0.498 (0.286–0.869)
	No	26/98	26/61	0.542 (0.314–0.933)
Refractory to Len	Yes	23/57	25/42	0.598 (0.339–1.055)
	No	5/15	9/17	0.448 (0.149–1.349)
High risk cytogenetics	At least one	17/42	15/31	0.724 (0.361–1.451)
	None	27/114	35/77	0.440 (0.266–0.728)
ISS staging at study entry	I	20/89	24/71	0.592 (0.327–1.071)
	II	17/63	16/31	0.375 (0.188–0.748)
	III	11/26	14/20	0.650 (0.295–1.434)



*Cytogenetics by central lab – cut-off 50% for del17, 30% for t(4;14) and t(14;16)

Consistent treatment effect was seen for Isa-Kd across subgroups

CI, confidence interval; d, dexamethasone; eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; MDRD, modified of diet in renal disease; MM, multiple myeloma; PFS, progression-free survival; PI, proteasome inhibitor; ISS, International Staging System

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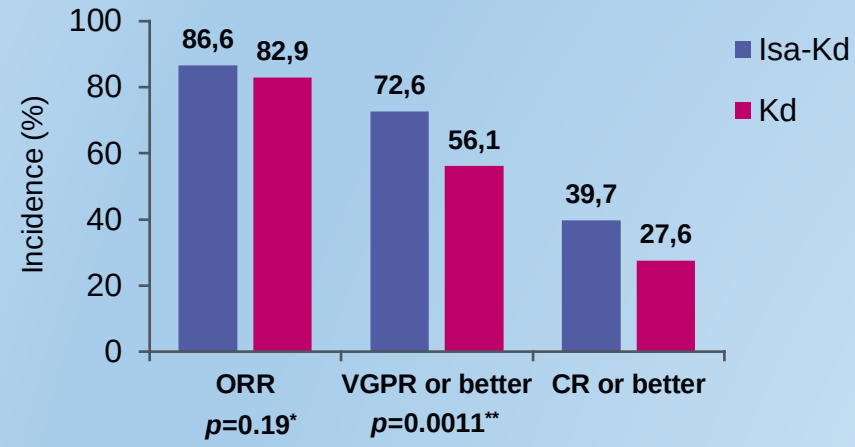
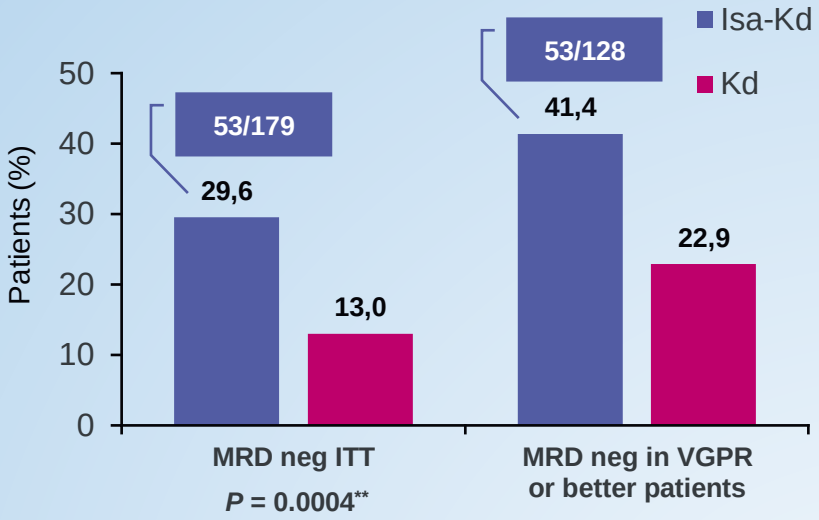
Depth of response

Best overall response



Median time	Isa + Kd (n = 155)	Kd (n = 102)
Time to first response	32 days	33 days
Time to best response	120 days	105 days

MRD rate (Next Generation Sequencing, 10^{-5})



Deeper response was seen with Isa-Kd consistent with striking PFS improvement
MRD negativity rate more than doubled by addition of Isa to Kd

*Stratified Cochran-Mantel_Haenszel test. One sided significant level is 0.025
**Provided for descriptive purposes only
CR, complete response; d, dexamethasone; Dara, daratumumab; Isa, isatuximab; K, carfilzomib;mo, month; NA, not available;
ORR, overall response; VGPR, very good partial response

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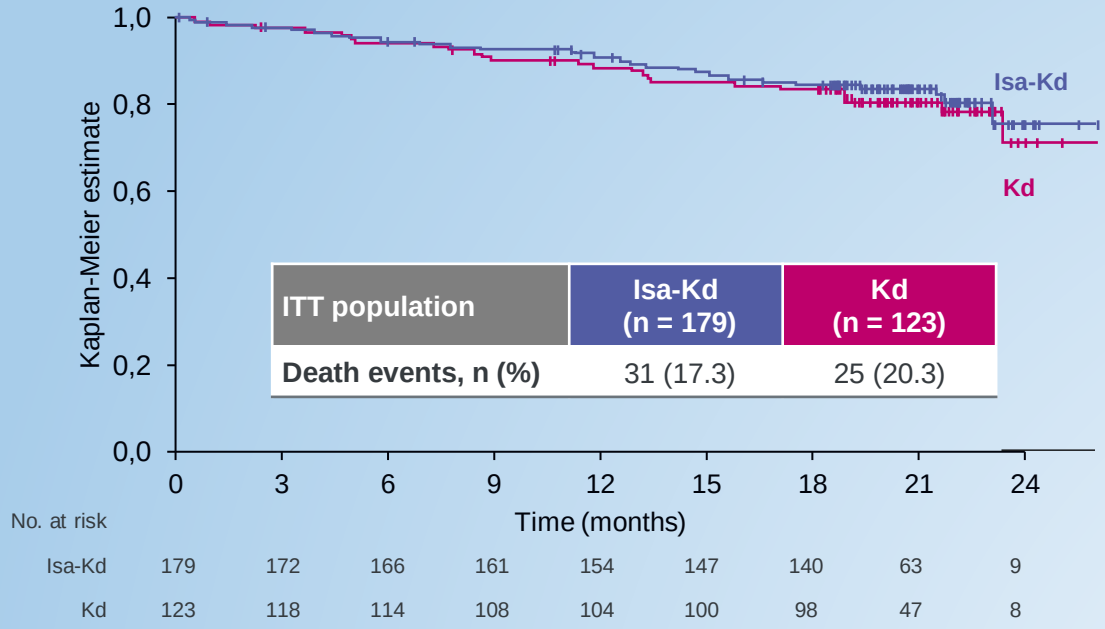
Overall survival



ITT population	Isa-Kd (n = 179)	Kd (n = 123)
Death events, n (%)	31 (17.3)	25 (20.3)

Median follow-up: 20.73 months

Overall survival data at the time of analysis

d, dexamethasone; Isa, isatuximab; ITT, intent to treat; K, carfilzomib

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Safety summary

TEAE overview, %	Isa-Kd (n = 177)	Kd (n = 122)
Any TEAE	172 (97.2)	117 (95.9)
Grade ≥ 3 TEAEs	136 (76.8)	82 (67.2)
Drug-related grade ≥ 3 TEAEs	87 (49.2)	58 (47.5)
Serious TEAEs	105 (59.3)	70 (57.4)
Serious drug-related TEAEs	44 (24.8)	31 (25.4)
Any TEAE leading to definitive discontinuation	15 (8.5)	17 (13.9)
Any TEAE leading to premature discontinuation of Isa	1 (0.6)	–
Any TEAE leading to premature discontinuation of K	26 (14.7)	1 (0.8)
Any TEAE leading to premature discontinuation of d	11 (6.2)	4 (3.3)
Fatal TEAEs	6 (3.4)	4 (3.3)

Despite more grade ≥ 3 TEAEs, addition of Isa to Kd did not increase mortality or events leading to discontinuation

d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event

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Safety summary – continued

Preferred term, n (%) (TEAEs in ≥ 20% of Isa-Kd patients)	Isa-Kd (n = 177)		Kd (n = 122)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Infusion-related reaction	79 (44.6)	1 (0.6)	4 (3.3)	–
Hypertension	65 (36.7)	36 (20.3)	38 (31.1)	24 (19.7)
Diarrhea	64 (36.2)	5 (2.8)	35 (28.7)	3 (2.5)
Upper respiratory tract infection	64 (36.2)	6 (3.4)	29 (23.8)	2 (1.6)
Fatigue	50 (28.2)	6 (3.4)	23 (18.9)	1 (0.8)
Dyspnea	49 (27.7)	9 (5.1)	26 (21.3)	1 (0.8)
Insomnia	42 (23.7)	9 (5.1)	28 (23.0)	3 (2.5)
Pneumonia	42 (23.7)	29 (16.4)	24 (19.7)	15 (12.3)
Bronchitis	40 (22.6)	4 (2.3)	15 (12.3)	1 (0.8)
Back pain	39 (22.0)	3 (1.7)	25 (20.5)	1 (0.8)
Cardiac failure events				
Cardiac failure, any class*	13 (7.3)	7 (4.0)	8 (6.6)	5 (4.1)
Hematologic laboratory abnormalities				
Anemia	176 (99.4)	39 (22.0)	121 (99.2)	24 (19.7)
Neutropenia	97 (54.8)	34 (19.2)	53 (43.4)	9 (7.4)
Thrombocytopenia	167 (94.4)	53 (29.9)	107 (87.7)	29 (23.8)

*Grouping using MedDRA SMQ cardiac failure narrow terms
d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event

Isa-Kd had a manageable safety profile with no new safety signals

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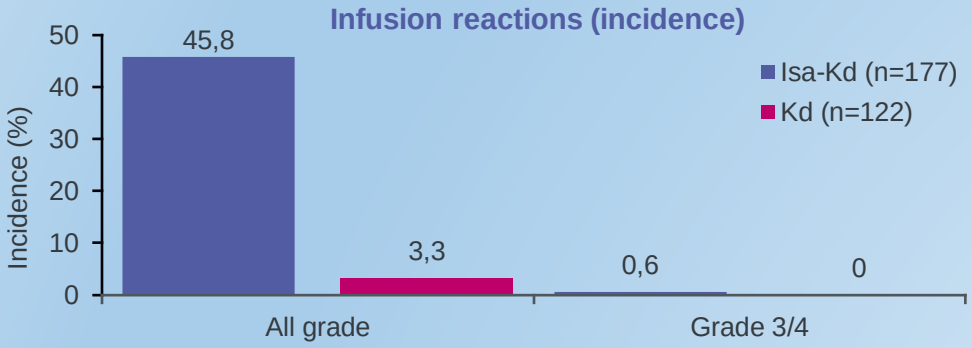
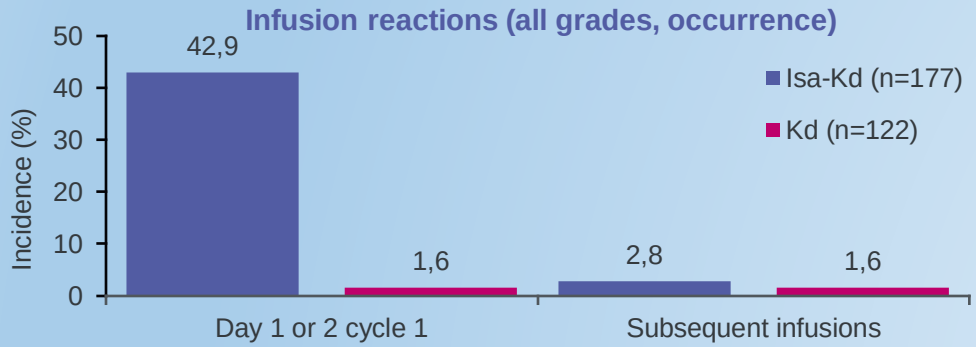
Infusion reactions





- IRs led to infusion interruption in 29.9% of patients in the Isa-Kd arm and to carfilzomib infusion interruption in 0.6% in the Isa-Kd arm and 0.8% of patients in the Kd arm
- IRs resulted in isatuximab discontinuation in 1 patient in the Isa-Kd arm and no discontinuation in the Kd arm
- Similar incidence of IR when isatuximab is combined with K vs isatuximab alone

IRs mainly occurred during the first infusion and were mostly grade 1 or 2

d, dexamethasone; IR, infusion reaction; Isa, isatuximab; K, carfilzomib

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Summary

- **IKEMA recruited a population representative of the highly heterogeneous relapsed MM patient population including those with renal insufficiency, advanced age and high risk cytogenetics**
- **The addition of isatuximab to Kd demonstrated statistically significant improvement in PFS benefit with a 47% reduction in the risk of progression or death**
- **Isa-Kd showed a consistent benefit across multiple subgroups, including those difficult to treat with high unmet medial need**
- **A profound depth of response was seen with Isa-Kd vs Kd with an MRD negativity rate 30% in the ITT**
- **Isa-Kd demonstrated a manageable safety profile and favorable risk/benefit in patients with relapsed MM**

Isa-Kd represents a new potential standard of care for patients with relapsed MM

CR, complete response; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival; SAE, serious adverse event; TEAE, treatment-emergent adverse event; VGPR, very good partial response

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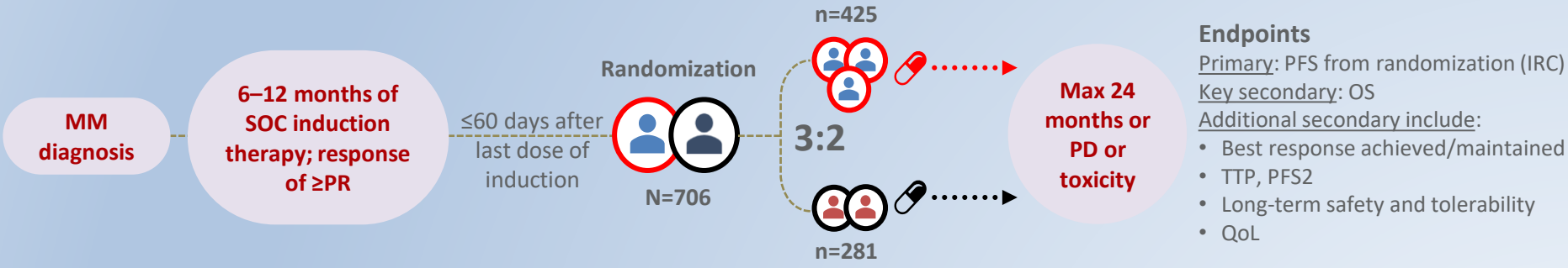
Ixazomib vs placebo maintenance for newly diagnosed multiple myeloma patients not undergoing autologous stem cell transplant: the Phase 3 TOURMALINE-MM4 trial

Meletios A. Dimopoulos,[1] Ivan Špička,[2] Hang Quach,[3] Albert Oriol,[4] Roman Hájek,[5] Mamta Garg,[6] Meral Beksac,[7] Sara Bringhen,[8] Eirini Katodritou,[9] Wee-Joo Chng,[10] Xavier Leleu,[11] Shinsuke Iida,[12] María-Victoria Mateos,[13] Gareth Morgan,[14] Alexander Vorog,[15] Richard Labotka,[15] Bingxia Wang,[15] Antonio Palumbo,[15] Sagar Lonial,[16] on behalf of the TOURMALINE-MM4 study group

[1]Hematology & Medical Oncology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [2]1st Department of Medicine, Department of Hematology, First Faculty of Medicine, Charles University and General Hospital in Prague, Prague, Czech Republic;[3]Department of Haematology, University of Melbourne, St. Vincent's Hospital, Melbourne, Victoria, Australia; [4]Institut d'Investigació contra la Leucèmia Josep Carreras and Institut Català d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [5]Department of Hematooncology, University Hospital Ostrava, University of Ostrava, Ostrava, Czech Republic; [6]Haematology, Leicester Royal Infirmary / University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [7]Department of Hematology, Ankara University, Ankara, Turkey; [8]Division of Hematology, University of Torino, AOU Città della Salute e della Scienza di Torino, Torino, Italy; [9]Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece; [10]Department of Haematology-Oncology, National University Cancer Institute, National University Health System, Singapore, and Cancer Science Institute of Singapore, National University of Singapore, Singapore; [11]Pôle Régional de Cancérologie, Department of Haematology, CHU La Milétrie-Poitiers, Poitiers, France; [12]Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [13]Hematology, Hospital Universitario de Salamanca, University Hospital of Salamanca, CIC, IBMCC (USAL-CSIC), Salamanca, Spain; [14]Perlmutter Cancer Center, NY Langone Health, New York, New York, USA; [15]Millennium Pharmaceuticals Inc., Cambridge, Massachusetts, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [16]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia, USA.

Date: June 13, 2020
Session: New insights in the treatment of newly diagnosed multiple myeloma
Abstract S200

TOURMALINE-MM4 study design



Endpoints

Primary: PFS from randomization (IRC)

Key secondary: OS

Additional secondary include:

- Best response achieved/maintained
- TTP, PFS2
- Long-term safety and tolerability
- QoL

Stratification:

- Induction regimen: PI-containing vs non-PI-containing
- ISS disease stage: I or II vs III*
- Age: <75 vs ≥75* years
- Response to initial therapy: CR or VGPR* vs PR

Ixazomib:	Cycles 1–4: 3 mg on Days 1, 8, and 15 Cycles 5–26: 4 mg: Days 1, 8, and 15 (Dose increased to 4 mg if tolerated during cycles 1–4)
Placebo:	Days 1, 8, and 15

28-day cycles

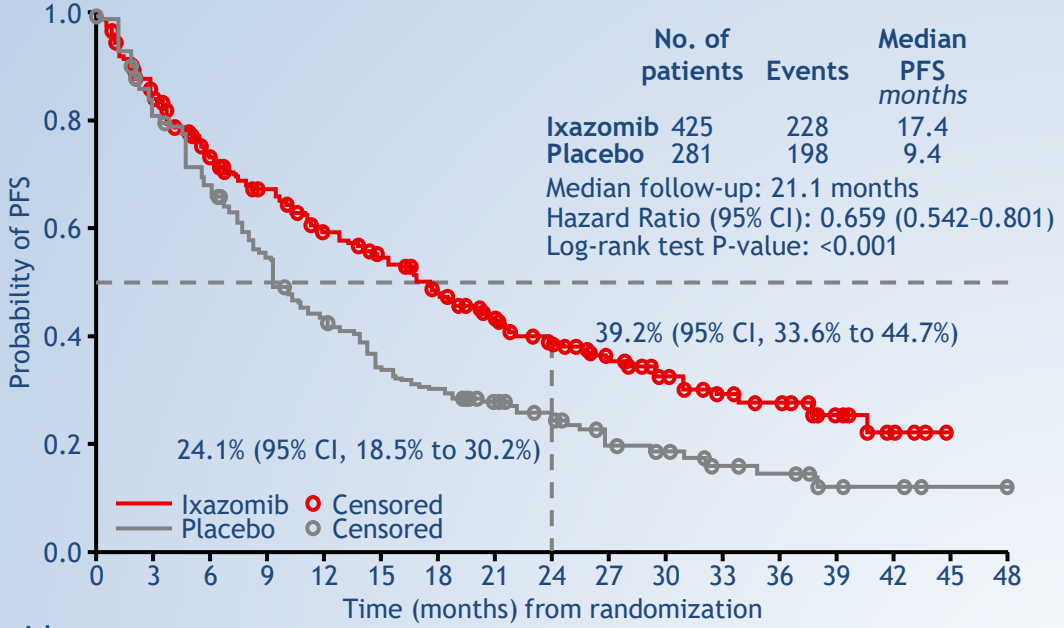
Patients enrolled from April 23, 2015, through October 8, 2018, at 187 sites in 34 countries

*Prespecified subgroups in which the primary endpoint of PFS was tested in parallel (total alpha = 0.01) to the ITT analysis.

CR, complete response; IRC, independent review committee; ISS, International Staging System; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS2, progression-free survival 2; PR, partial response; TTP, time to progression; VGPR, very good partial response.

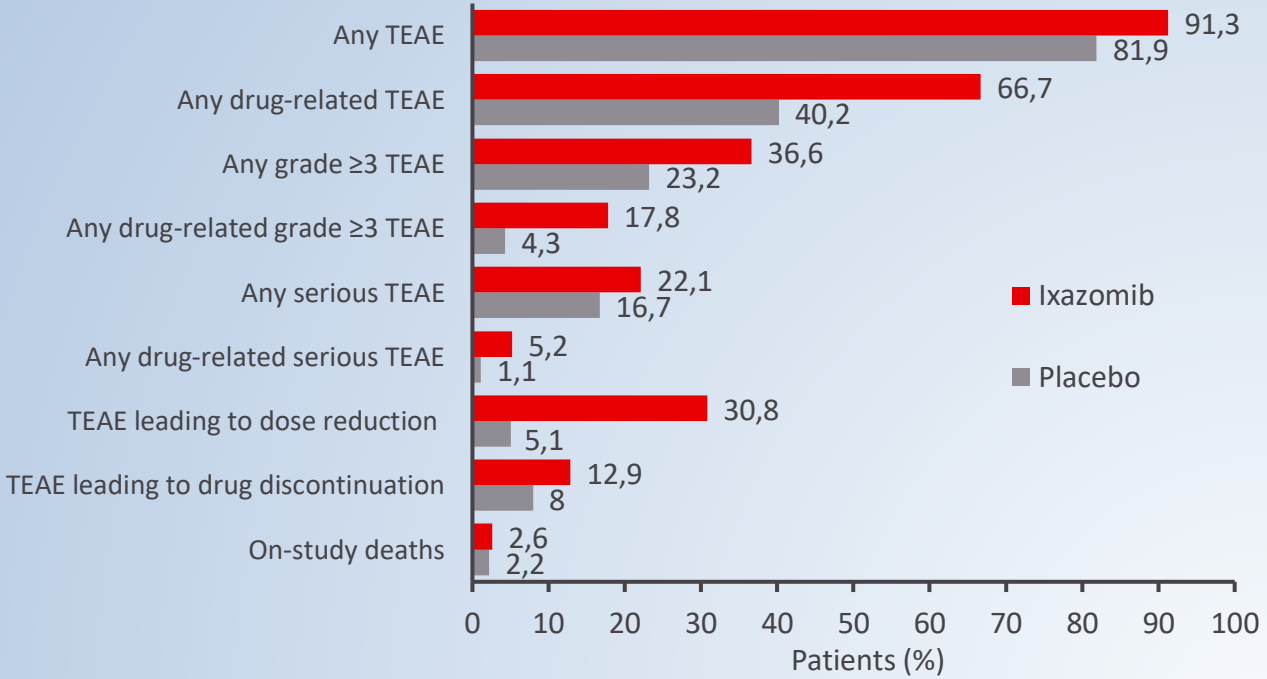
Statistically significant and clinically meaningful improvement in PFS with ixazomib vs placebo

- Data cut-off: August 12, 2019
- Median follow-up for PFS: 21.1 months overall
- Median PFS from randomization: 17.4 vs 9.4 months
- Significant 34.1% reduction in risk of progression or death in the ixazomib vs placebo group



Favorable overall safety profile

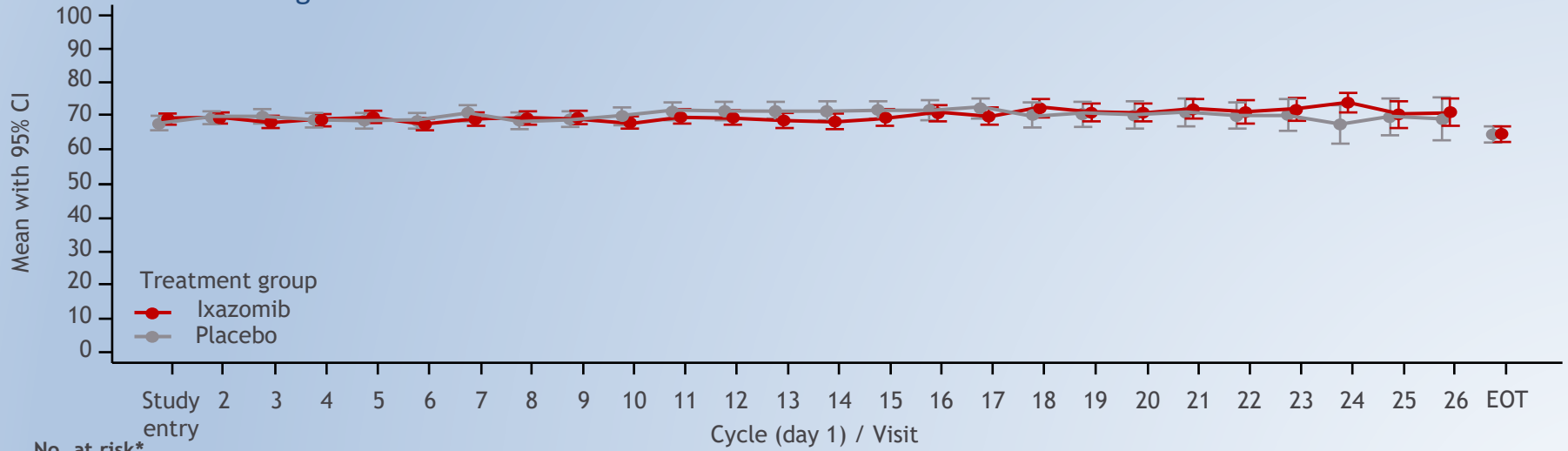
- Overall rates of TEAEs were similar between groups
- Rates of serious TEAEs and discontinuations due to TEAEs appeared slightly higher with ixazomib versus placebo
- The most common TEAEs (with incidence ≥ 5% higher with ixazomib) were nausea, vomiting, diarrhea, rash, PN, and pyrexia
- 5.2% and 6.2% of patients in the ixazomib and placebo groups had new primary malignancies



TEAE, treatment-emergent adverse event.

Quality of life preserved with ixazomib maintenance

– Mean EORTC QLQ-C30 Global Health Status/Quality of Life scores similar between groups at study entry and maintained during treatment



No. at risk*

	Study entry	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	EOT
Ixazomib	407	391	375	361	340	307	291	273	258	245	232	226	208	193	176	167	157	155	141	127	121	108	96	87	79	64	280
Placebo	270	257	257	245	226	213	202	186	173	163	150	141	127	118	107	94	84	75	65	56	52	52	42	42	36	29	211

*Numbers by visit in patients with measurements at study entry and ≥1 measurement after study entry.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EOT, end of treatment.

Conclusions (1)

- Ixazomib maintenance following SOC induction in transplant-ineligible NDMM patients resulted in a statistically significant and clinically meaningful 8-month increase in median PFS, with a 34.1% reduction in the risk of progression or death vs placebo
  - PFS benefits were seen across prespecified patient subgroups, including patients with CR or VGPR to initial therapy, elderly patients, and patients with ISS stage III

- The benefits of ixazomib maintenance were realized in the context of a well-tolerated safety profile and no adverse impact on patients' QoL
  - This is an important consideration in this generally elderly, non-transplant population

Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Total (N=128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	19 (35)	40 (31)
DOR*, median, mo	†	9.9	11.3	10.6
PFS*, median, mo	†	5.8	11.3	8.6
CRS‡				
Overall, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Grade ≥3, n (%)	0	4 (6)	3 (6)	7 (5)
Onset / duration, median, d	7 / 5	2 / 4	1 / 7	1 / 5
NT§				
Overall, n (%)	0	12 (17)	11 (20)	23 (18)
Grade ≥3, n (%)	0	1 (1)	3 (6)	4 (3)
Onset / duration, median, d	NA	3 / 3	2 / 5	2 / 3

CRS, cytokine release syndrome; CR, complete response; DOR, duration of response; NT, investigator identified neurotoxicity; ORR, overall response rate; PFS, progression-free survival; sCR, stringent CR.
*Kaplan-Meier estimate.
†Not reported due to small n.
‡Graded per Lee et al. *Blood* 2014;124:188-195.
§Graded per CTCAE v4.03 criteria.

Table. Summary of responses for CC-93269

Efficacy, n (%)	Pts treated with ≤3 mg (n=7)	Pts treated with 6 mg[a] (n=14)	Pts treated with 10 mg[b] (n=9)
Overall response (PR or better)	0 (0)	5 (36)	8 (89)
VGPR or better	0 (0)	2 (14)	7 (78)
MRD negative[c]	NA	5 (36)	7 (78)
Best response			
sCR/CR	0 (0)	1 (7)	4 (44)
VGPR	0 (0)	1 (7)	3 (33)
PR	0 (0)	3 (21)	1 (11)
MR	0 (0)	0 (0)	0 (0)
SD	4 (57)	1 (7)	0 (0)
PD	2 (29)	5 (36)	0 (0)
Not evaluable	1 (14)	3 (21)	1 (11)

[a] Includes patients who received 6 mg as a fixed dose and pts who received 3 mg on C1D1 and 6 mg from C1D8 onward. [b] Includes patients who received 10 mg as a fixed dose and pts who received 6 mg on C1D1 and 10 mg from C1D8 onward. [c] MRD Euroflow analysis was reported only in the 13 pts who achieved a response and only if a minimum sensitivity of ≤1 tumor cell in 10^5 nucleated cells was achieved.
CR, complete response; MR, minimal response; MRD, minimal residual disease; NA, not applicable; PD, progressive disease; PR, partial response; pt, patient; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.