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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Moreau P, Dimopoulos M-A, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet* 2021; published online June 4. http://dx.doi.org/10.1016/S0140-6736(21)00592-4.

Supplementary Appendix

This appendix provides additional information about the isatuximab IKEMA phase 3 study.
Supplement to: Moreau P, Dimopoulos MA, Mikhael J, et al.
Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: a randomised phase 3 study

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List of IKEMA Investigators

Steering Committee: Thomas Martin (Co-Principal Investigator), Philippe Moreau (Co-Principal Investigator), Meletios-Athanasios Dimopoulos, Joseph Mikhael, Kwee Yong

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Additional Methods

Please see published IKEMA protocol manuscript[1] for further details on methodology:
Moreau P, Dimopoulos MA, Yong K, et al. Isatuximab plus carfilzomib/dexamethasone versus carfilzomib/dexamethasone in patients with relapsed/refractory multiple myeloma: IKEMA Phase III study design. *Future Oncol* 2020; **16:** 4347–58.

Treatment discontinuation
The study treatment was to continue whenever possible until progression, unacceptable adverse event, patient wish, or any other reason. Patients could ask to stop the study treatment, if they decided to do so, at any time and irrespective of the reason.
Definitive treatment discontinuation is discontinuation of all study treatments. Isatuximab, carfilzomib, and/or dexamethasone could be discontinued prematurely (meaning that at least one of the study treatments is continued). The reasons for definitive and premature discontinuation were captured in the electronic case report form.

Other medications
Other medication was considered any treatment received by the patient concomitantly to any study treatment(s). Other medications were allowed if not listed as prohibited medications and if they were considered necessary for the patient's welfare and unlikely to interfere with the investigational product. Other medications were given at the discretion of the investigator and recorded in the electronic case report form. Antiviral prophylaxis, antibacterial prophylaxis, and thromboprophylaxis were given according to site/investigator practice and local labelling of carfilzomib. For patients who are Hepatitis B virus carriers, prophylaxis with antivirals were to be considered. Co-treatment of dexamethasone with CYP3A inhibitors was avoided unless the benefit outweighed the increased risk of systemic corticosteroid side-effects, in which case patients were monitored for systemic corticosteroid side-effects (please refer to dexamethasone package insert).
Prophylactic administration of granulocyte colony stimulating factors in a patient experiencing recurrent neutropenia, or therapeutic use in patients with serious neutropenic complications (such as tissue infection, sepsis syndrome, or fungal infection) was considered at the investigator's discretion, consistent with American Society of Clinical Oncology guidelines (2006) in order to decrease the risk of neutropenia especially in patients with baseline extensive bone marrow involvement and/or low neutrophil count.

Prohibited concomitant therapy
Concurrent treatment with any other anti-myeloma therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy, biological therapies, other investigational drug, or curative radiotherapy. However, palliative radiotherapy was permitted to be given to control pain. In these instances, the irradiated area was required to be as small as possible and not involve more than 20% of the bone marrow in any given 3-week period. In all such cases, the possibility of tumour progression was required to be ruled out by physical, biochemical, and radiological assessments of the tumour. The irradiated area could not be used as a parameter for response assessment.
Concomitant systemic corticosteroids, other than as part of the protocol-specified therapeutic regimen or for treatment of hypersensitivity reaction, were prohibited. Additional glucocorticoids, antihistamines, and analgesics for the management of infusion-associated reactions were permitted. Inhaled glucocorticosteroids could be used whenever indicated.
Live vaccines were to be avoided; however, given the increased risk of infection, routine vaccinations were recommended for the patients and their contacts. Prophylactic vaccination was recommended for influenza A and B virus, pneumococci, and *haemophilus influenzae*.

Premedications and prevention of infusion-associated reactions
Patients allocated to the isatuximab-carfilzomib-dexamethasone arm received premedication prior to isatuximab infusion to reduce the risk and severity of infusion reactions commonly observed with monoclonal antibodies. The recommended premedication agents were diphenhydramine 25 mg to 50 mg intravenously (or equivalent), dexamethasone intravenously/orally (dose defined below), ranitidine 50 mg intravenously (or equivalent), and acetaminophen 650 mg to 1000 mg orally, 15 to 30 minutes (but no longer than 60 minutes) prior to isatuximab infusion. Dexamethasone was used as part of the carfilzomib-dexamethasone backbone, and as premedication for infusion reaction. Once the premedication regimen was completed, the isatuximab infusion was started immediately.
On the day of isatuximab administration, the following order was recommended:

1. Acetaminophen (paracetamol) 650 mg to 1000 mg orally.
2. Ranitidine 50 mg intravenously (or equivalent).
3. Diphenhydramine 25 mg to 50 mg intravenously (or equivalent).

4. Dexamethasone 20 mg intravenously (which is also part of study treatment).

In countries where there was no intravenous formulation of diphenhydramine or equivalent, per os formulation was allowed from the first isatuximab infusion. In these cases, it was taken 1–2 hours prior to isatuximab infusion start.

When carfilzomib was administered without isatuximab (patients allocated to the carfilzomib-dexamethasone arm and on days 2, 8, and 16 for patients allocated to the isatuximab-carfilzomib-dexamethasone arm), dexamethasone was to be administered at least 30 minutes prior to carfilzomib infusion.

In case of dexamethasone being prematurely stopped and other study treatment being continued, steroid premedication could be considered with methylprednisolone 100 mg intravenously if infusion-associated reaction premedication was still needed for isatuximab and/or carfilzomib according to investigator judgement.

For the patients who did not experience an infusion reaction upon four consecutive administrations of isatuximab, the investigator could reconsider the need for specific isatuximab premedication for infusion reactions.

Health-related quality of life

Quality of life assessments were completed on day 1 of each cycle before treatment was started, and at end of study treatment visit and 90 days after the last study treatment.

Definitions

Progression-free survival (PFS): The time from randomisation to the first documented date of disease progression, or the date of death from any cause, whichever came first.

Overall response rate (ORR): The proportion of patients with stringent complete response, complete response, very good partial response, and partial response as best overall response, according to International Myeloma Working Group (IMWG) response criteria.

Very good partial response rate (VGPR) or better: The percentage of patients with stringent complete response, complete response, or very good partial response.

Complete response rate (CR): Patients who achieved a stringent complete response or complete response.

Minimal residual disease (MRD) negativity rate: The proportion of patients for whom MRD was negative at any time point after first dose of study treatment.

Complete renal response (CrR): Improvement in estimated glomerular filtration rate from <50 mL/min/1.73 m^2 at baseline to ≥60 mL/min/1.73 m^2 in at least one post-baseline assessment.

Other Secondary Endpoints and Exploratory Endpoints

Other secondary endpoints included safety (adverse events and laboratory graded according to NCIC-CTC version 4.03), time to progression, progression-free survival 2, defined as time from the date of randomisation to the date of first documentation of progressive disease (as reported by the investigator) after initiation of further anti-myeloma treatment or death from any cause, duration of response, time to first response and time to best response defined as time from randomisation to first response and time to best response, respectively, renal response, pharmacokinetics, immunogenicity, and health-related quality of life.

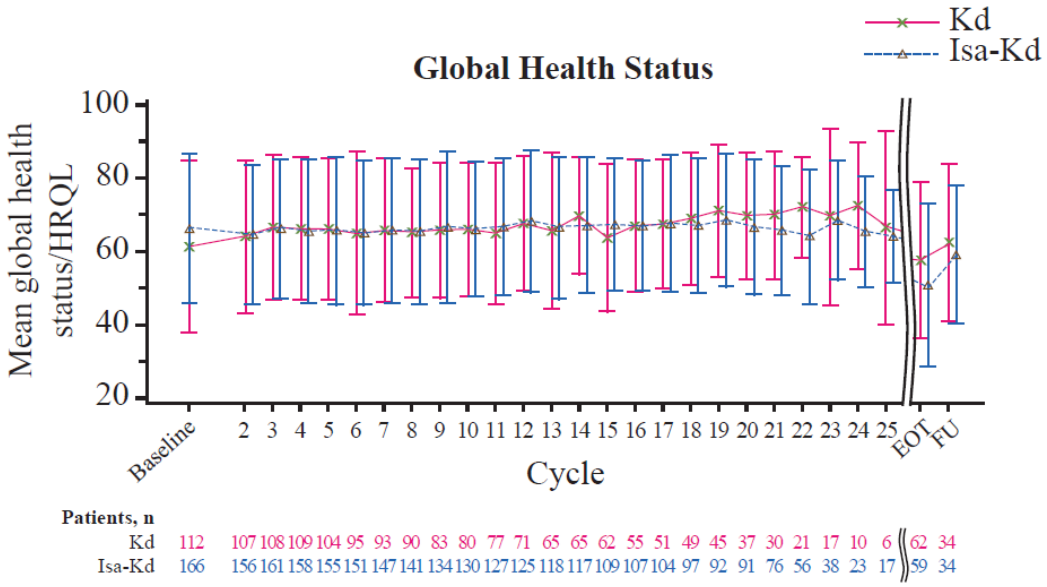
Exploratory endpoints were pharmacokinetic and pharmacodynamic relationships; relationship between immune genetic determinants and efficacy endpoints; relationship between cytogenetics abnormalities not part of R-ISS including but not limited to del(1p) and gain(1q) and efficacy endpoints; and impact of M-protein measurement without isatuximab interference on best overall response assessment.

Statistical Analyses

Continuous data were summarised for each treatment group using the number of available observations, mean, median, standard deviation, minimum, and maximum. Categorical and ordinal data were summarised using the number and percentage of patients.

[[Supplementary Figure]]

Figure S1: **Global Health Status Quality of Life Score Over Time (EORTC-QLQ-C30, intent-to-treat population)**



EOT=end of treatment; FU=follow-up; HRQL=health-related quality of life; Kd=carfilzomib-dexamethasone; IKd=isatuximab-carfilzomib-dexamethasone.

A higher score represents a better level of global health status.

End of treatment: 30 days after last study treatment administration or before further anti-myeloma therapy initiation, whichever comes first. Follow-up: 90 days after last study treatment administration.

Cycles with less than 20 patients overall are not presented.

[[Supplementary Tables]]

Table S1: **Haematologic treatment-emergent adverse events (safety population)**

	Isa-Kd (n=177)		Kd (n=122)	
Preferred term [n (%)]	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Neutropenia	8 (4·5)	7 (4·0)	1 (0·8)	0
Anaemia	7 (4·0)	6 (3·4)	4 (3·3)	1 (0·8)
Thrombocytopenia	5 (2·8)	4 (2·3)	12 (9·8)	10 (8·2)
Platelet count decreased	1 (0·6)	1 (0·6)	0	0
Neutrophil count decreased	2 (1·1)	2 (1·1)	0	0

d=dexamethasone; Isa=isatuximab; K=carfilzomib.
Laboratory abnormalities were to be reported as adverse events (in addition of laboratory results reported in the case report form) when they led to action taken on study treatment (dose modification or drug withdrawn) and/or when they were serious. Reported preferred terms included complete blood count, neutrophil count, platelet count, and haemoglobin values.

Table S2: **Second primary malignancies**

SMQ Preferred term [n (%)]	Isa-Kd (n=177)		Kd (n=122)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any class	13 (7·3)	4 (2·3)	6 (4·9)	4 (3·3)
Second primary malignancies (solid, non-skin)	5 (2·8)	3 (1·7)	4 (3·3)	3 (2·5)
Adenocarcinoma of appendix	1 (0·6)	0	0	0
Colon cancer	1 (0·6)	1 (0·6)	1 (0·8)	1 (0·8)
Pancreatic carcinoma metastatic	1 (0·6)	1 (0·6)	0	0
Squamous cell carcinoma	1 (0·6)	0	0	0
Uterine cancer	1 (0·6)	1 (0·6)	0	0
Bladder neoplasm	0	0	1 (0·8)	0
Large cell lung cancer	0	0	1 (0·8)	1 (0·8)
Lung neoplasm malignant	0	0	1 (0·8)	1 (0·8)
Second primary malignancies (skin)	9 (5·1)	1 (0·6)	3 (2·5)	1 (0·8)
Basal cell carcinoma	6 (3·4)	1 (0·6)	2 (1·6)	0
Squamous cell carcinoma of skin	3 (1·7)	0	1 (0·8)	1 (0·8)
Malignant melanoma in situ	1 (0·6)	0	0	0
Skin cancer	1 (0·6)	0	0	0
Second primary malignancies (haematological)	0	0	0	0

d=dexamethasone; Isa=isatuximab; K=carfilzomib; SMQ=standardised MedDRA query.
n (%) = number and percentage of patients with ≥1 treatment-emergent adverse event.

Reference

1. Moreau P, Dimopoulos MA, Yong K, et al. Isatuximab plus carfilzomib/dexamethasone versus carfilzomib/dexamethasone in patients with relapsed/refractory multiple myeloma: IKEMA Phase III study design. *Future Oncol* 2020; **16:** 4347–58.