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Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial

Philippe Moreau, Meletios-Athanasios Dimopoulos, Joseph Mikhael, Kwee Yong, Marcelo Capra, Thierry Facon, Roman Hajek, Ivan Špička, Ross Baker, Kihyun Kim, Gracia Martinez, Chang-Ki Min, Ludek Pour, Xavier Leleu, Albert Oriol, Youngil Koh, Kenshi Suzuki, Marie-Laure Risse, Gaelle Asset, Sandrine Macé, Thomas Martin*, on behalf of the IKEMA study group†*

Summary

Background Isatuximab is an anti-CD38 monoclonal antibody approved in combination with pomalidomide–dexamethasone and carfilzomib–dexamethasone for relapsed or refractory multiple myeloma. This phase 3, open-label study compared the efficacy of isatuximab plus carfilzomib–dexamethasone versus carfilzomib–dexamethasone in patients with relapsed multiple myeloma.

Methods This was a prospective, randomised, open-label, parallel-group, phase 3 study done at 69 study centres in 16 countries across North America, South America, Europe, and the Asia-Pacific region. Patients with relapsed or refractory multiple myeloma aged at least 18 years who had received one to three previous lines of therapy and had measurable serum or urine M-protein were eligible. Patients were randomly assigned (3:2) to isatuximab plus carfilzomib–dexamethasone (isatuximab group) or carfilzomib–dexamethasone (control group). Patients in the isatuximab group received isatuximab 10 mg/kg intravenously weekly for the first 4 weeks, then every 2 weeks. Both groups received the approved schedule of intravenous carfilzomib and oral or intravenous dexamethasone. Treatment continued until progression or unacceptable toxicity. The primary endpoint was progression-free survival and was assessed in the intention-to-treat population according to assigned treatment. Safety was assessed in all patients who received at least one dose according to treatment received. The study is registered at ClinicalTrials.gov, NCT03275285.

Findings Between Nov 15, 2017, and March 21, 2019, 302 patients with a median of two previous lines of therapy were enrolled. 179 were randomly assigned to the isatuximab group and 123 to the control group. Median progression-free survival was not reached in the isatuximab group compared with 19·15 months (95% CI 15·77–not reached) in the control group, with a hazard ratio of 0·53 (99% CI 0·32–0·89; one-sided p=0·0007). Treatment-emergent adverse events (TEAEs) of grade 3 or worse occurred in 136 (77%) of 177 patients in the isatuximab group versus 82 (67%) of 122 in the control group, serious TEAEs occurred in 105 (59%) versus 70 (57%) patients, and TEAEs led to discontinuation in 15 (8%) versus 17 (14%) patients. Fatal TEAEs during study treatment occurred in six (3%) versus four (3%) patients.

Interpretation The addition of isatuximab to carfilzomib–dexamethasone significantly improves progression-free survival and depth of response in patients with relapsed multiple myeloma, representing a new standard of care for this patient population.

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Introduction

Multiple myeloma is a cancer of plasma cells and the second most common haematological cancer worldwide.[1] Primary treatment focuses on reducing symptoms and diminishing the morbidity associated with multiple myeloma.[2] Autologous stem-cell transplantation, proteasome inhibitors, and immunomodulatory drugs have extended survival, yet multiple myeloma remains incurable and new therapies are needed.

Isatuximab is an IgG1 monoclonal antibody that binds to a specific epitope of CD38 and acts through a number of mechanisms to kill myeloma cells.[3,4] Preclinical studies with isatuximab showed synergistic action and tumour regression when it was combined with immunomodulatory agents and augmented action when it was combined with proteasome inhibitors.[5,6] The phase 3 ICARIA-MM study led to the approval of isatuximab (also known as Sarclisa) in combination with pomalidomide and dexamethasone in patients with relapsed and refractory multiple myeloma who have received at least two previous therapies, including lenalidomide and a proteasome inhibitor.[7,8]

Based on the IKEMA study results presented here, to date, isatuximab is also approved in combination with carfilzomib and dexamethasone in the USA for relapsed or refractory multiple myeloma after one to three previous lines of therapy and in the EU for multiple myeloma after at least one previous therapy.[7,8]

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Research in context

Evidence before this study

We searched PubMed for clinical trials published from Jan 1, 2012, to Dec 31, 2017, with the terms "relapsed multiple myeloma", "carfilzomib", and "combination treatment". At the time that this study was being designed, there were no studies published with an anti-CD38 monoclonal antibody in combination with the proteasome inhibitor, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma.

Isatuximab is an anti-CD38 monoclonal antibody that has been approved in combination with pomalidomide plus dexamethasone in patients with relapsed and refractory multiple myeloma who have received at least two previous therapies, including lenalidomide and a proteasome inhibitor, and in combination with carfilzomib plus dexamethasone in patients with relapsed or refractory multiple myeloma after one to three previous lines of therapy. In preclinical studies, the antitumour effects of isatuximab are significantly enhanced when combined with immunomodulatory drugs and proteasome inhibitors. Specifically, isatuximab has shown increased direct cytotoxic activity with carfilzomib compared with either agent alone in preclinical studies. Results from a phase 1 study (NCT02332850) showed that the combination of isatuximab with carfilzomib plus dexamethasone was well tolerated and clinically active in heavily pretreated patients with relapsed or refractory multiple myeloma.

Added value of this study

The results of this study indicate that the addition of isatuximab to carfilzomib and dexamethasone provides a significant benefit in progression-free survival over carfilzomib and dexamethasone alone. The addition of isatuximab to carfilzomib and dexamethasone also results in an improved depth and quality of response, with higher rates of very good partial response, complete response, minimal residual disease negativity, and complete response with minimal residual disease negativity.

Implications of all the available evidence

This study provides evidence for the efficacy of isatuximab in combination with the current treatment option of carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma, and it was the basis for the most recent isatuximab approvals. Specifically, the addition of isatuximab to carfilzomib and dexamethasone is a new treatment option for patients with disease progression after an immunomodulatory drug-containing first-line therapy or those who are refractory to immunomodulatory drugs.

Carfilzomib is a next-generation proteasome inhibitor approved in combination with dexamethasone for relapsed or refractory multiple myeloma on the basis of the phase 3 ENDEAVOR study.[9,10] The study, done in patients with relapsed or refractory multiple myeloma after one to three previous lines of treatment, showed the superiority of carfilzomib plus dexamethasone versus bortezomib plus dexamethasone in terms of progression-free survival (median 18·7 months [95% CI 15·6–not evaluable] with carfilzomib *vs* 9·4 months [8·4–10·4] with bortezomib; hazard ratio [HR] 0·53 [95% CI 0·44–0·65], p<0·0001) and overall survival (median 47·6 months [42·5–not evaluable] *vs* 40·0 months [32·6–42·3]; HR 0·79 [0·65–0·96], one-sided p=0·010). These results were the basis for the control treatment used in our trial, the IKEMA study.

The purpose of IKEMA was to investigate the benefit of isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone alone in patients with relapsed multiple myeloma treated with one to three previous lines of therapy.[11]

Methods

Study design

This was a prospective, multinational, randomised, open-label, parallel-group, phase 3 study done at 69 study centres in 16 countries across North America, South America, Europe, and the Asia-Pacific region. An institutional ethics committee or independent review board approved the study protocol for each centre. The study was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients

Patients aged at least 18 years were eligible for enrolment in the study if they had relapsed or refractory multiple myeloma with one to three previous lines of therapy and measurable evidence of disease (serum M-protein ≥0·5 g/dL or urine M-protein ≥200 mg/24 h).

Patients were excluded if they had primary refractory multiple myeloma according to International Myeloma Working Group (IMWG) response criteria, serum-free light chain measurable disease only, or Eastern Cooperative Oncology Group performance status greater than 2. Patients were excluded if they received anti-myeloma treatment within 14 days of randomisation, previous treatment with carfilzomib, were refractory to anti-CD38 antibody therapy, or had a contraindication to dexamethasone. Patients with estimated glomerular filtration rate (eGFR) of less than 15 mL/min per 1·73 m² according to the modification of diet in renal disease formula or left ventricular ejection fraction less than 40% were excluded. Patients with previous pulmonary comorbidities, including chronic obstructive pulmonary disease, could be enrolled.

Randomisation and masking

Patients were randomly assigned in a 3:2 ratio to receive isatuximab plus carfilzomib–dexamethasone (isatuximab

group) or carfilzomib–dexamethasone (control group). Randomisation was stratified by number of previous lines of therapy (one *vs* more than one) and revised International Staging System (R-ISS; stage I or II *vs* III *vs* not classified), at study entry. After confirmation of the eligibility criteria, the study site used the interactive response technology to assign treatment, based on a permuted block randomisation scheme (block size of 5) within each stratum defined by the stratification factors. Treatment assignments were unmasked for study personnel and patients but masked for those analysing the results.

Procedures

Patients in the isatuximab group received isatuximab 10 mg/kg intravenously (days 1, 8, 15, and 22 in the first 28-day cycle; days 1 and 15 in subsequent cycles). In both groups, carfilzomib was administered intravenously at 20 mg/m² on days 1 and 2 of cycle 1; 56 mg/m² on days 8, 9, 15, and 16 of cycle 1; and then 56 mg/m² on days 1, 2, 8, 9, 15, and 16 of subsequent cycles. Dexamethasone 20 mg was administered intravenously or orally on days 1, 2, 8, 9, 15, 16, 22, and 23. Other medication use is outlined in the appendix (p 4). Dexamethasone was administered first, followed by isatuximab, and then carfilzomib. Treatment continued until disease progression, unacceptable adverse event, or other discontinuation criteria (appendix p 4).

Minimal residual disease (MRD) was assessed by next-generation sequencing Adaptive clonoSEQ Assay (Adaptive Biotechnologies, Seattle, WA, USA) with a minimum sensitivity of 1 in 10^5 nucleated cells in patients reaching very good partial response or better. Cytogenetics was assessed by fluorescence in-situ hybridisation during screening by a central laboratory, with a cutoff of 50% for del(17p) and 30% for t(4;14), t(14;16), and gain(1q21). High-risk cytogenetic status was defined as presence of del(17p), t(4;14), or t(14;16).

Efficacy assessments were completed on day 1 of every cycle and when treatment stopped. Quality-of-life assessments included the European Organisation for Research and Treatment of Cancer QLQ-C30 (reported in this manuscript),[12] MY20,[13,14] and EuroQoL EQ-5D-5L (will be reported elsewhere) questionnaires.[15–18] Quality-of-life assessments were completed on day 1 of each cycle before treatment started, at the end of study treatment, and 90 days after the last study treatment. Safety assessments included recording of adverse events, laboratory parameters (both graded per National Cancer Institute Common Terminology Criteria, version 4.03), vital signs, electrocardiograms, and Eastern Cooperative Oncology Group performance status. Safety was regularly reviewed by an independent data monitoring committee.

Endpoints

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to the first documentation of disease progression according to masked independent response committee (IRC) or death from any cause, whichever occurred first. The IRC reviewed disease assessments for response and progression (central radiological assessment, M-protein quantification from central laboratory, and local bone marrow aspiration for plasma cell infiltration when needed).

Key secondary efficacy endpoints were as follows: overall response rate (proportion of patients with stringent complete response, complete response, very good partial response or partial response as best overall response according to IMWG response criteria);[19] rate of very good partial response or better (proportion of patients with stringent complete response, complete response, or very good partial response); MRD negativity rate (proportion of patients for whom MRD was negative at any timepoint after first dose of study treatment);[20–22] complete response rate (proportion of patients who achieved stringent complete response or complete response); and overall survival. Other secondary endpoints were safety, duration of response, time to progression, progression-free survival 2 (time from randomisation to first documentation of progressive disease [as reported by the investigator] after initiation of further anti-myeloma treatment or death from any cause, whichever happens first), time to first

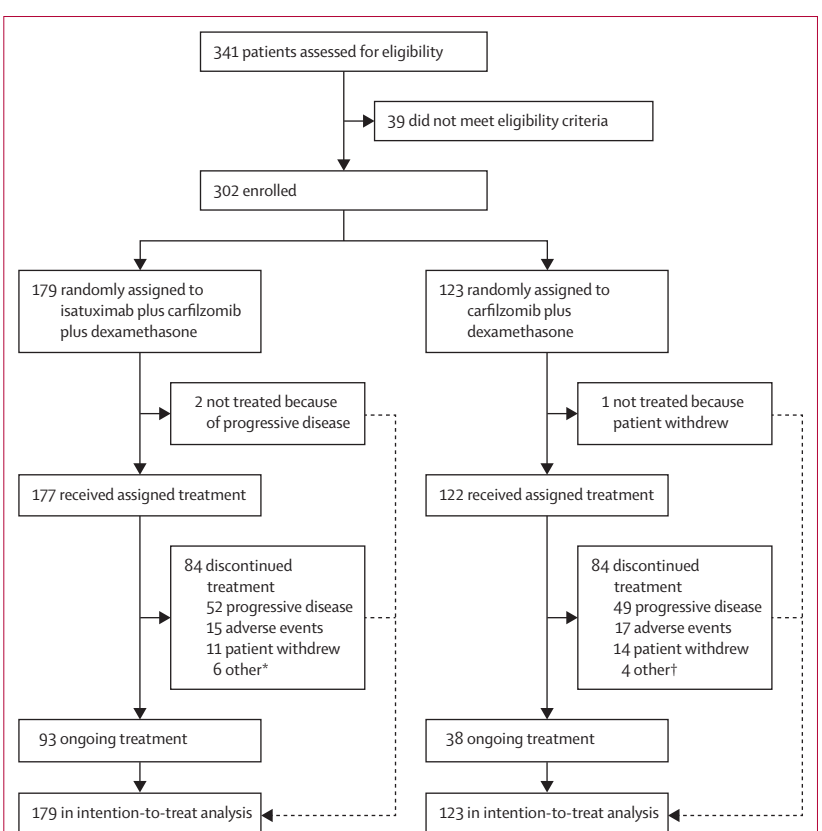


Figure 1: **Trial profile**
*One autologous stem-cell transplant, four unconfirmed progressive disease, and one poor prognosis due to reaching maximum expected response to study treatment. †One autologous stem cell transplant, one achieved maximal effect, one based on serum free light chain increase, and one with no evidence of clinical efficacy.

	Isatuximab group (n=179)	Control group (n=123)
Age, years		
Median (IQR)	65 (55–70)	63 (57–70)
<65	88 (49%)	66 (54%)
≥65 to <75	74 (41%)	47 (38%)
≥75	17 (9%)	10 (8%)
Gender		
Female	78 (44%)	55 (45%)
Male	101 (56%)	68 (55%)
Race		
Asian	26 (15%)	24 (20%)
Black or African American	5 (3%)	4 (3%)
White	131 (73%)	83 (67%)
Other or not reported	17 (9%)	12 (10%)
eGFR, (MDRD)*		
<60 mL/min per 1·73 m²	43 (26%)	18 (16%)
≥60 mL/min per 1·73 m²	122 (74%)	93 (84%)
Eastern Cooperative Oncology Group performance status		
0	95 (53%)	73 (59%)
1	73 (41%)	45 (37%)
2	10 (6%)	5 (4%)
3	1 (1%)	0
Multiple myeloma subtype at study entry		
IgG	126 (70%)	85 (69%)
IgA	38 (21%)	30 (24%)
IgD	4 (2%)	1 (1%)
κ light chain only	5 (3%)	4 (3%)
λ light chain only	6 (3%)	3 (2%)
β2 microglobulin, mg/L		
<3·5	103 (58%)	79 (64%)
≥3·5 to <5·5	50 (28%)	24 (20%)
≥5·5	26 (15%)	20 (16%)
Serum lactate dehydrogenase†, IU/L		
≤ upper limit of normal	132 (75%)	105 (86%)
> upper limit of normal	44 (25%)	17 (14%)
Time from initial diagnosis of multiple myeloma to randomisation, years	3·2 (2·0–5·5)	3·3 (2·1–5·8)
International Staging System stage at study entry		
I	89 (50%)	71 (58%)
II	63 (35%)	31 (25%)
III	26 (15%)	20 (16%)
Unknown	1 (1%)	1 (1%)
(Continued from previous column)		
Cytogenetic risk as defined for Revised International Staging System		
High-risk chromosomal abnormality‡	42 (23%)	31 (25%)
Standard risk chromosomal abnormality	114 (64%)	78 (63%)
Unknown or missing	23 (13%)	14 (11%)
Number of previous lines of therapy		
Median (IQR)	2 (1–2)	2 (1–3)
One	79 (44%)	55 (45%)
Two	64 (36%)	36 (29%)
Three	33 (18%)	30 (24%)
More than three	3 (2%)§	2 (2%)
Autologous transplant	116 (65%)	69 (56%)
Main anti-myeloma therapies by class and agent		
Alkylating agents	169 (94%)	101 (82%)
Proteasome inhibitors	166 (93%)	105 (85%)
Immunomodulators	136 (76%)	100 (81%)
Lenalidomide	72 (40%)	59 (48%)
Corticosteroids	179 (100%)	123 (100%)
Monoclonal antibodies	5 (3%)	1 (1%)
Daratumumab	1 (1%)	0
Refractory to immunomodulatory imide drug	78 (44%)	58 (47%)
Refractory to lenalidomide	57 (32%)	42 (34%)
Refractory to lenalidomide in last previous regimen	36 (20%)	31 (25%)
Refractory to proteasome inhibitor	56 (31%)	44 (36%)
Refractory to immunomodulatory imide drug and proteasome inhibitor	35 (20%)	27 (22%)
Refractory to last regimen	89 (50%)	73 (59%)

Data are median (IQR) or n (%). eGFR=estimated glomerular filtration rate. MDRD=modification of diet in renal disease. *Incidence calculated in patients with race reported in case report form—165 patients in isatuximab group and 111 patients in control group. †Percentages are calculated out of 176 evaluable patients in the isatuximab group and 122 in the control group. ‡High-risk cytogenetic status is defined as the presence of del(17p) or translocation t(4;14) or translocation t(14;16); chromosomal abnormality was considered positive if present in at least 30% of analysed plasma cells, except for del(17p) where the threshold is at least 50%. §For two patients, the number of previous lines was overestimated by the algorithm because of complex specific cases; the number of previous lines was reviewed by a clinician and confirmed to be three.

Table 1: **Demographic, baseline disease, and clinical characteristics (intention-to-treat population)**

response, time to best response, renal response, pharmacokinetic analyses, immunogenicity analyses, and health-related quality of life (appendix p 7). Time to progression, time to best response, and pharmacokinetic analyses are not reported here. Exploratory endpoints are not reported here and are listed in the appendix (p 7).

Statistical analysis

Sample size calculation was based on the primary efficacy endpoint. 159 events were needed to detect a 41% lower risk of disease progression (HR 0·59) using a log-rank test (one-sided significance level of 0·025, 90% power). An interim analysis of progression-free survival was pre-planned when 65% of the 159 progression-free events (103 events) were observed to detect overwhelming efficacy. Comparison between groups was done through a log-rank test procedure stratified by randomisation stratification factors. The nominal significance level at the interim analysis (0·005) was established using α-spending function to control the overall one-sided type 1 error at 2·5%. Median progression-free survival, probabilities

of being progression-free, and corresponding CIs were calculated by the Kaplan-Meier method. Estimates of HRs were established using the stratified Cox proportional hazard model. Prespecified subgroup analyses of progression-free survival were done. Key secondary endpoints were tested using a closed test procedure and the stratified Cochran-Mantel-Haenszel test.

Continuous data were summarised for each treatment group using the number of available observations, mean, median, SD, minimum, and maximum. Categorical and ordinal data were summarised using the number and percentage of patients. Efficacy analyses were performed on the intention-to-treat population and summarised by assigned treatment. Safety analyses and extent of study treatment were assessed and summarised by actual treatment received in patients who received at least one dose of treatment (safety population). Statistical analyses were done using SAS, version 9.4. This study is registered at ClinicalTrials.gov, NCT03275285.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Nov 15, 2017, and March 21, 2019, 302 patients were enrolled and randomly assigned to the isatuximab group (n=179) or the control group (n=123; figure 1). Demographics and clinical characteristics were well balanced at baseline (table 1). Median age was 64 years (IQR 56–70). Median number of previous lines of therapy was two (IQR one to two) and was similar between groups. 134 (44%) had received one, 100 (33%) had received two, and 68 (23%) had received three of more previous lines of therapy. An error in line calculation led to the inclusion of three patients with four previous lines of therapy, one in the isatuximab group and two in the control group. 136 (45%) patients were refractory to immunomodulatory drugs, including 99 (33%) who were lenalidomide refractory. In the isatuximab group, 42 (23%) of 179 patients had high-risk cytogenetics, which was a similar proportion to that in the control group (31 [25%] of 123). At baseline, 43 (26%) of patients were renally impaired (eGFR <60 mL/min per 1·73 m²) in the isatuximab group versus 18 (16%) in the control group.

At data cutoff for the interim analysis, median treatment duration was 80·0 weeks (IQR 40·0–89·0) in the isatuximab group and 61·4 weeks (IQR 28·9–84·0) in the control group. Median relative dose intensity of carfilzomib and dexamethasone were similar in both groups (91·2% [IQR 81·3–97·2] for carfilzomib and 84·8% [67·4–94·6] for dexamethasone in the isatuximab group *vs* 91·3% [78·5–96·3] and 88·4% [73·7–96·2] in the control group). The median relative dose intensity of isatuximab was 94·3% (89·2–97·9). A smaller proportion of patients discontinued treatment in the isatuximab than in the control group (84 [47%] *vs* 84 [68%]; figure 1).

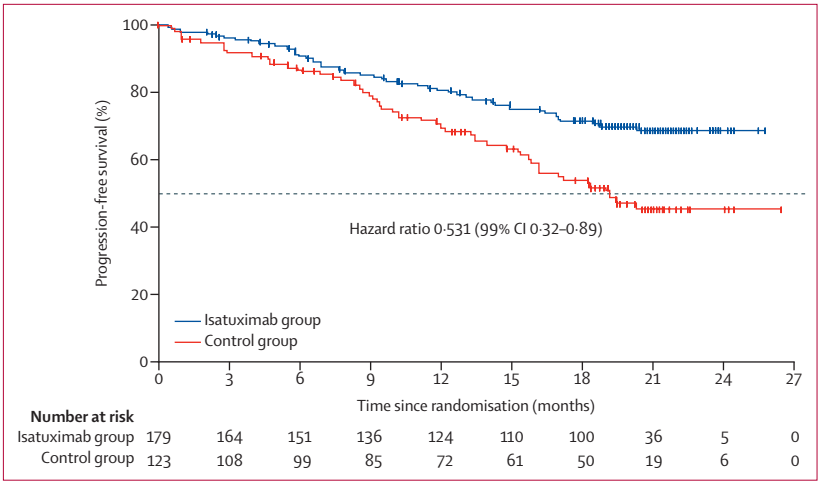


Figure 2: **Progression-free survival**
Kaplan-Meier analysis of progression-free survival among patients in the intention-to-treat population, as assessed by an independent response review committee. Median progression-free survival was not reached (95% CI not estimable) for the isatuximab group and 19·15 months (15·77–not estimable) in the control group. Hazard ratio and 99% CI are derived from Cox proportional hazards model stratified by number of previous lines of therapy and revised International Staging System stage. One sided p value calculated by log-rank test was 0·0007, which was below the nominal significance level at the interim analysis (0·005).

At a median follow-up of 20·7 months (IQR 19·4–22·1), the addition of isatuximab to carfilzomib–dexamethasone showed a significant improvement in progression-free survival (IRC assessment) with an HR of 0·53 (99% CI 0·32–0·89, one-sided p=0·0007). The median progression-free survival of 19·15 months (95% CI 15·77–not reached) in the control group was consistent with the protocol assumption of 19 months (figure 2). At 2 years, estimated progression-free survival was 68·9% (95% CI 60·7–75·8) in the isatuximab group versus 45·7% (35·2–55·6) in the control group. Progression-free survival according to investigator assessment was consistent with the IRC assessment (HR 0·58 [99% CI 0·36–0·92], p=0·0010).

In the intention-to-treat population, 155 (87%) of 179 patients in the isatuximab group versus 102 (83%) of 123 in the control group had an overall response (one-sided p=0·19). The difference between groups was not significant; thus, p values of subsequent key secondary endpoints are provided for descriptive purposes only. Very good partial response or better was reported in 130 (73%) patients in the isatuximab group versus 69 (56%) in the control group (p=0·0011). Complete response occurred in 71 (40%) versus 34 (28%) patients. The MRD negativity rate was more than double in the isatuximab group than in the control group: 53 (30%) in the isatuximab group versus 16 (13%) in the control group (p=0·0004; table 2). 36 (20%) patients in the isatuximab group and 13 (11%) in the control group had a complete response and MRD-negative response. Progression-free survival 2 and overall

	Isatuximab group (n=179)	Control group (n=123)
Best overall response		
Stringent complete response	0	0
Complete response	71 (40%)	34 (28%)
Very good partial response	59 (33%)	35 (28%)
Partial response	25 (14%)	33 (27%)
Minimal response	4 (2%)	5 (4%)
Stable disease	13 (7%)	6 (5%)
Non-progressive disease	1 (1%)	1 (1%)
Progressive disease	2 (1%)	3 (2%)
Unconfirmed progressive disease	0	1 (1%)
Not evaluable or not assessed	4 (2%)	5 (4%)
Overall response		
Responders (stringent complete response, complete response, very good partial response, or partial response)	155 (87%)	102 (83%)
95% CI*	0·81–0·91	0·75–0·89
Stratified Cochran-Mantel-Haenszel test p value† *vs* control group	0·19	..
Stratified OR (95% CI)	1·32 (0·70–2·52)	..
Very good partial response or better	130 (73%)	69 (56%)
95% CI*	0·65–0·79	0·47–0·65
Stratified Cochran-Mantel-Haenszel test p value† *vs* control group	0·0011‡	..
Stratified OR (95% CI)	2·19 (1·32–3·62)	..
Minimal residual disease negativity rate§	53 (30%)	16 (13%)
95% CI*	0·23–0·37	0·08–0·20
Stratified Cochran-Mantel-Haenszel test p value† *vs* control group	0·0004‡	..
Stratified OR (95% CI)	2·81 (1·51–5·23)	..
Complete response (stringent complete response or complete response)	71 (40%)	34 (28%)
95% CI*	0·32–0·47	0·20–0·36
Stratified OR (95% CI)	1·79 (1·07–2·99)	..
Minimal residual disease negativity and complete response (stringent complete response or complete response) rate	36 (20%)	13 (11%)
95% CI*	0·15–0·27	0·06–0·17
Stratified OR (95% CI)	2·11 (1·07–4·19)	..

Data are n (%) unless otherwise specified. *Estimated using Clopper-Pearson method. †Stratified on randomisation factors according to interactive response technology; one-sided significance level is 0·025. ‡For descriptive purposes. §For analysis purposes, patients in the intention-to-treat population but without minimal residual disease assessment were considered as having positive minimal residual disease.

Table 2: **Summary of responses according to independent response committee (intention-to-treat population)**

survival were not mature at the interim analysis and will be reported in a future publication. 39 (22%) in the isatuximab group and 35 (28%) in the control group had progression-free survival 2 events. 31 (17%) patients in the isatuximab group and 25 (20%) in the control group died.

In the prespecified subgroup analyses, clinical benefit in favour of isatuximab with carfilzomib–dexamethasone occurred across almost all groups (figure 3). Median progression-free survival in renally impaired patients was not reached in the isatuximab group versus 13·41 months (95% CI 4·83–not reached) in the control group with an HR of 0·27 (95% CI 0·11–0·66). Complete renal response (improvement in eGFR from <50 mL/min per 1·73 m² at baseline to ≥60 mL/min per 1·73 m² in at least one assessment during the treatment period) occurred in 13 (52%) of 25 patients in the isatuximab group versus four (31%) of 13 patients in the control group and was durable (≥60 days) in eight (32%) of 25 versus one (8%) of 13 patients. Progression-free survival benefit was observed in patients aged 65 years or older, including an HR of 0·24 (95% CI 0·06–1·00) for those aged 75 years or older (data not shown).

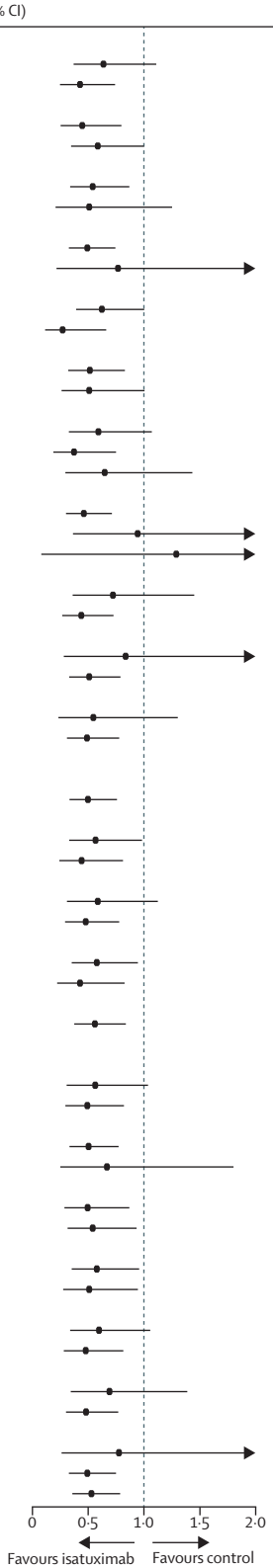
Median time to first response in responders was similar in both groups: 32 days (IQR 30–40) in the isatuximab group and 33 days (30–58) in the control group. Duration of response was longer in the isatuximab group than the control group, with an HR of 0·43 (95% CI 0·27–0·67). Time to next treatment was longer in the isatuximab group than the control group (HR 0·57 [95% CI 0·38–0·84]). 47 (26%) of 179 patients in the isatuximab group received at least one further anti-myeloma therapy versus 53 (43%) of 123 in the control group. Of those who received subsequent treatment, ten (21%) of 47 and 25 (47%) of 53 received daratumumab. Health-related quality of life, as measured by QLQ-C30 Global Health Status score, was maintained with isatuximab plus carfilzomib–dexamethasone (appendix p 9).

A similar incidence of patients with treatment-emergent adverse events (TEAEs) was observed between groups, with 172 (97%) of 177 in the isatuximab group versus 117 (96%) of 122 patients in the control group (table 3). TEAEs of grade 3 or worse occurred in 136 (77%) versus 82 (67%) patients, serious TEAEs occurred in 105 (59%) versus 70 (57%) patients, and TEAEs led to discontinuation in 15 (8%) versus 17 (14%) patients. Fatal TEAEs during study treatment occurred in six (3%) versus four (3%) patients.

The most frequent TEAEs of any grade in the isatuximab group were infusion-related reactions, hypertension, diarrhoea, and upper respiratory tract infection, with higher incidence than in the control group (table 4).

Figure 3: **Subgroup analyses of progression-free survival**
R-ISS stage at study entry and number of previous lines of therapy correspond to the randomisation stratification factors. Interaction test is from the Cox proportional hazards model, including the factor, treatment effect, and the treatment by factor interaction. Individual cytogenetic abnormalities, lenalidomide subgroups, and previous treatment with proteasome inhibitor or immunomodulatory imide drug subgroups other than at last regimen were not prespecified. ECOG=Eastern Cooperative Oncology Group. eGFR=estimated glomerular filtration rate according to modification of diet in renal disease. IMiD=immunomodulatory imide drug. ISS=international staging system. n=number of events. N=total number of patients. NC=not calculated. R-ISS=revised ISS. *Other includes Black or African American, Asian, or mixed race. †High-risk cytogenetic status is defined as the presence of del(17p), translocation t(4;14), or translocation t(14;16); chromosomal abnormality was considered positive if present in at least 30% of analysed plasma cells, except for del(17p), for which the threshold is at least 50%; gain(1q21) is defined as the presence of at least three copies in at least 30% of analysed plasma cells.

	Isatuximab group		Control group		Hazard ratio (95% CI)	$p_{interaction}$
	n/N	Median progression-free survival, months (95% CI)	n/N	Median progression-free survival, months (95% CI)		
Age, years						
<65	25/88	NC (NC–NC)	26/66	NC (14·75–NC)	0·64 (0·37–1·11)	0·37
≥65	23/91	NC (NC–NC)	29/57	17·18 (13·41–NC)	0·43 (0·25–0·74)	
Gender						
Female	21/78	NC (NC–NC)	27/55	16·99 (13·44–NC)	0·45 (0·25–0·80)	0·51
Male	27/101	NC (NC–NC)	28/68	NC (15·24–NC)	0·59 (0·35–1·00)	
Race						
White	34/131	NC (NC–NC)	36/83	19·45 (15·24–NC)	0·54 (0·34–0·87)	0·95
Other*	8/34	NC (NC–NC)	12/28	18·99 (13·24–NC)	0·51 (0·21–1·25)	
Baseline ECOG performance status						
0 or 1	42/168	NC (NC–NC)	51/118	19·45 (16·10–NC)	0·49 (0·33–0·74)	0·49
>1	6/11	13·37 (0·43–NC)	4/5	13·44 (2·79–NC)	0·77 (0·22–2·76)	
Baseline eGFR, mL/min per 1·73 m²						
≥60	32/122	NC (NC–NC)	38/93	NC (16·16–NC)	0·63 (0·39–1·00)	0·11
<60	10/43	NC (NC–NC)	10/18	13·41 (4·83–NC)	0·27 (0·11–0·66)	
Multiple myeloma type at study entry						
IgG	32/126	NC (NC–NC)	37/85	19·45 (16·16–NC)	0·52 (0·32–0·83)	0·92
Non-IgG	16/53	NC (18·46–NC)	18/38	15·70 (8·31–NC)	0·51 (0·26–1·01)	
ISS staging at study entry						
I	20/89	NC (NC–NC)	24/71	NC (18·99–NC)	0·59 (0·33–1·07)	0·60
II	17/63	NC (NC–NC)	16/31	18·20 (11·83–19·45)	0·38 (0·19–0·75)	
III	11/26	12·88 (6·93–NC)	14/20	9·36 (4·99–16·16)	0·65 (0·30–1·43)	
R-ISS stage at study entry						
I or II	38/155	NC (NC–NC)	46/105	19·45 (16·10–NC)	0·46 (0·30–0·71)	0·38
III	9/18	10·28 (5·82–NC)	8/13	9·36 (2·79–NC)	0·95 (0·36–2·46)	
Not classified	1/6	NC (6·93–NC)	1/5	NC (11·99–NC)	1·29 (0·08–20·65)	
Cytogenetic abnormality†						
At least one	17/42	NC (13·08–NC)	15/31	18·20 (8·67–NC)	0·72 (0·36–1·45)	0·27
None	27/114	NC (NC–NC)	35/77	19·45 (15·38–NC)	0·44 (0·27–0·73)	
del(17p)						
Yes	6/18	NC (9·23–NC)	7/16	19·15 (8·67–NC)	0·84 (0·28–2·50)	0·40
No	39/143	NC (NC–NC)	43/96	19·45 (15·38–NC)	0·51 (0·33–0·79)	
t(4;14)						
Yes	10/22	NC (11·43–NC)	11/20	11·14 (4·83–NC)	0·55 (0·23–1·30)	0·80
No	34/137	NC (NC–NC)	39/89	19·45 (15·77–NC)	0·49 (0·31–0·78)	
t(14;16)						
Yes	4/6	7·13 (2·53–NC)	0/0	NC	NC	NC
No	41/153	NC (NC–NC)	50/111	19·15 (15·77–NC)	0·50 (0·33–0·76)	
Gain(1q21)						
Yes	26/75	NC (17·08–NC)	26/52	16·16 (10·19–NC)	0·57 (0·33–0·98)	0·56
No	19/84	NC (NC–NC)	24/55	20·27 (15·77–NC)	0·44 (0·24–0·81)	
Number of previous lines of therapy						
One	18/80	NC (NC–NC)	19/55	NC (15·38–NC)	0·59 (0·31–1·12)	0·68
More than one	30/99	NC (NC–NC)	36/68	16·16 (13·44–19·45)	0·48 (0·29–0·78)	
Previous autologous stem-cell transplant						
Yes	34/116	NC (NC–NC)	30/69	19·15 (15·24–NC)	0·58 (0·35–0·95)	0·45
No	14/63	NC (NC–NC)	25/54	18·99 (13·44–NC)	0·43 (0·22–0·83)	
Previous treatment with proteasome inhibitor						
Yes	48/166	NC (NC–NC)	48/105	19·15 (15·38–NC)	0·56 (0·38–0·84)	0·98
No	0/13	NC (NC–NC)	7/18	NC (12·19–NC)	NC	
Previous proteasome inhibitor treatment at last regimen						
Yes	22/81	NC (NC–NC)	20/47	NC (11·14–NC)	0·57 (0·31–1·04)	0·84
No	26/98	NC (NC–NC)	35/76	19·15 (15·70–NC)	0·49 (0·30–0·82)	
Previous treatment with IMiD						
Yes	39/136	NC (NC–NC)	48/100	17·18 (15·24–NC)	0·51 (0·33–0·77)	0·61
No	9/43	NC (NC–NC)	7/23	NC (11·83–NC)	0·67 (0·25–1·80)	
Previous IMiD treatment at last regimen						
Yes	22/81	NC (NC–NC)	29/62	17·18 (15·24–NC)	0·50 (0·29–0·87)	0·85
No	26/98	NC (NC–NC)	26/61	20·27 (13·44–NC)	0·54 (0·31–0·93	
Previous treatment with lenalidomide						
Yes	28/72	NC (14·92–NC)	34/59	16·10 (11·99–19·15)	0·58 (0·35–0·96)	0·71
No	20/107	NC (NC–NC)	21/64	NC (18·99–NC)	0·51 (0·28–0·95)	
Refractory to lenalidomide						
Yes	23/57	NC (12·88–NC)	25/42	15·70 (9·92–17·18)	0·60 (0·34–1·06)	0·56
No	25/122	NC (NC–NC)	30/81	NC (18·23–NC)	0·48 (0·28–0·82)	
Refractory to lenalidomide at last regimen						
Yes	15/36	NC (11·43–NC)	17/31	16·16 (14·75–19·45)	0·69 (0·35–1·39)	0·34
No	33/143	NC (NC–NC)	38/92	NC (15·77–NC)	0·48 (0·30–0·77)	
Previous proteasome plus IMiD treatment at last regimen						
Yes	7/23	NC (14·29–NC)	6/17	NC (9·92–NC)	0·78 (0·26–2·32)	0·51
No	41/156	NC (NC–NC)	49/106	18·99 (15·70–NC)	0·49 (0·33–0·75)	
All patients	**48/179**	**NC (NC–NC)**	**55/123**	**19·15 (15·77–NC)**	**0·53 (0·36–0·79)**	



	Isatuximab group (n=177)	Control group (n=122)
Any	172 (97%)	117 (96%)
Grade 3 or worse	136 (77%)	82 (67%)
Serious	105 (59%)	70 (57%)
Any leading to definitive discontinuation	15 (8%)	17 (14%)
Any leading to discontinuation of isatuximab	1 (1%)	NA
Any leading to discontinuation of carfilzomib	26 (15%)	1 (1%)
Any leading to discontinuation of dexamethasone	11 (6%)	4 (3%)
Fatal	6 (3%)	4 (3%)

Data are n (%). Premature discontinuation of carfilzomib was mainly because of cardiac failure (five [3%] individuals), congestive cardiac failure (two [1%] individuals), supraventricular tachycardia (two [1%] individuals), and pulmonary hypertension (two [1%] individuals) in the isatuximab group and to haemolysis (one [1%] individual) in the control group. Grade 5 events were penumonia (two [1%]), cardiac failure (one [1%]), cardiac failure with acute kidney injury (one [1%]), atypical pneumonia (one [1%]), and progressive disease (one [1%]) in isatuximab group and were acute myocardial infarction (one [1%]), pneumonia (one [1%]), sudden death (one [1%]), and progressive disease (one [1%]). NA=not applicable.

Table 3: **Treatment-emergent adverse events (safety population)**

	Isatuximab group (n=177)		Control group (n=122)	
	All grades	Grade ≥3	All grades	Grade ≥3
Most common preferred terms in at least 20% of patients in the isatuximab group				
Infusion-related reaction*	81 (46%)	1 (1%)	4 (3%)	0
Hypertension	65 (37%)	36 (20%)	38 (31%)	24 (20%)
Diarrhoea	64 (36%)	5 (3%)	35 (29%)	3 (2%)
Upper respiratory tract infection	64 (36%)	6 (3%)	29 (24%)	2 (2%)
Fatigue	50 (28%)	6 (3%)	23 (19%)	1 (1%)
Dyspnoea	49 (28%)	9 (5%)	26 (21%)	1 (1%)
Insomnia	42 (24%)	9 (5%)	28 (23%)	3 (2%)
Pneumonia†	51 (29%)	37 (21%)	28 (23%)	17 (14%)
Bronchitis	40 (23%)	4 (2%)	15 (12%)	1 (1%)
Back pain	39 (22%)	3 (2%)	25 (20%)	1 (1%)
Selected treatment-emergent adverse events				
Respiratory infection‡	147 (83%)	57 (32%)	90 (74%)	29 (24%)
Thromboembolic events†	27 (15%)	7 (4%)	20 (16%)	7 (6%)
Cardiac failure†	13 (7%)	7 (4%)	8 (7%)	5 (4%)
Ischaemic heart disease†	8 (5%)	2 (1%)	5 (4%)	2 (2%)
Second primary malignancy‡	13 (7%)	4 (2%)	6 (5%)	4 (3%)
Solid skin malignancy	9 (5%)	1 (1%)	3 (2%)	1 (1%)
Solid non-skin malignancy	5 (3%)	3 (2%)	4 (3%)	3 (2%)
Haematological laboratory abnormalities§				
Anaemia	176 (99%)	39 (22%)	121 (99%)	24 (20%)
Neutropenia	97 (55%)	34 (19%)	53 (43%)	9 (7%)
Thrombocytopenia	167 (94%)	53 (30%)	107 (88%)	29 (24%)

Data are n (%). MedDRA=Medical Dictionary for Regulatory Activities. *Reported preferred term was infusion reaction in 83 patients, cytokine release syndrome in one patient (grade 1), and hypersensitivity in one patient (grade 2). †Groupings using standardised MedDRA query (narrow terms). ‡Groupings using customised MedDRA query. §All anaemia events were grade 3; for neutropenia, there were 31 (18%) grade 3 and three (2%) grade 4 in the isatuximab group and eight (7%) grade 3 and one (1%) grade 4 in the control group; and for thrombocytopenia, there were 33 (19%) grade 3 and 20 (11%) grade 4 in the isatuximab group and 19 (16%) grade 3 and ten (8%) grade 4 in the control group.

Table 4: **Treatment-emergent adverse events and haematological laboratory abnormalities (safety population)**

Infusion-related reactions occurred in 81 (46%) patients in the isatuximab group versus four (3%) in the control group. All infusion-related reactions were grade 1 or 2, except for one patient (isatuximab group) with a carfilzomib-induced grade 3 infusion-related reaction. Infusion-related reactions occurred mainly during the first 2 days of study treatment, were reversible, and led to isatuximab discontinuation in one (<1%) patient.

More respiratory infections occurred in the isatuximab group than the control group (table 4). Upper respiratory tract infections, pneumonia (using standardised Medical Dictionary for Regulatory Activities [MedDRA] query infective pneumonia), and bronchitis were all more common in the isatuximab group than the control group. The difference in grade 3 or worse respiratory infections was driven by standardised MedDRA query infective pneumonia.

Laboratory grade 3 neutropenia was more frequent in the isatuximab group than the control group; however, grade 4 neutropenia was similar between the groups (table 4). Complicated neutropenia occurred in five (3%) of 177 patients in the isatuximab group (two [1%] febrile neutropenia and three [2%] neutropenic infection) and no patients in the control group. Cardiac failure events, thromboembolic events, and ischaemic heart disease were reported with similar incidence in both groups.

Second primary malignancies were reported in 13 (7%) of 177 patients in the isatuximab group and six (5%) of 122 in the control group (table 4; appendix p 11). The malignancies included skin cancer in nine (5%) patients in the isatuximab group and three (2%) patients in the control group, none of which led to treatment discontinuation. Solid non-skin cancer was reported in five (3%) patients in the isatuximab group and four (3%) patients in the control group, leading to treatment discontinuation in three (2%) patients in the isatuximab group and one (1%) patient in the control group. Non-skin cancers were diagnosed within the first three cycles in most cases in both groups.

In the isatuximab group, 95 (63%) of 150 patients with a negative test at baseline and at least one test during study treatment had a positive Coombs test during treatment; however, no haemolysis or transfusion-related complications were reported. No antidrug antibodies against isatuximab were detected among the 168 patients tested.

Discussion

The results of this randomised, phase 3 study showed that the addition of isatuximab to carfilzomib–dexamethasone was associated with a significant benefit in progression-free survival in patients with relapsed multiple myeloma versus carfilzomib–dexamethasone alone. The risk of disease progression or death was lower in the isatuximab group, with an HR of 0·53 (99% CI 0·32–0·89). Notably, in this study, the progression-free survival results observed by the IRC and by investigator assessment were consistent. The median progression-free survival of 19·15 months in the control group was consistent with the protocol assumption (19 months) and the ENDEAVOR study

(18·7 months), indicating that superiority of the isatuximab group was not related to a poorly performing control group. Although cross-trial comparisons with phase 3 results of other antiCD38 proteasome inhibitor triplet combinations in this population should be interpreted with caution, the median progression-free survival in the isatuximab group of IKEMA was numerically longer than the median progression-free survival in the CASTOR study (16·7 months for daratumumab–bortezomib–dexamethasone),[23] and the HR in the isatuximab group of IKEMA was also numerically more favourable than in the CANDOR study (0·63 [95% CI 0·46–0·85]; daratumumab–carfilzomib–dexamethasone *vs* carfilzomib–dexamethasone).[24]

A benefit in progression-free survival was seen in almost all subgroups, including patients with high-risk cytogenetics, ISS stage III at study entry, patients aged 65 years or older, patients with renal impairment, patients with at least one previous line of therapy, previous exposure to an immunomodulatory drug (including patients refractory to lenalidomide in last previous regimen), previous exposure to a proteasome inhibitor, and previous exposure to both an immunomodulatory drug and proteasome inhibitor. Patients with del(17p) had a smaller treatment effect. Notably, cytogenetic risk was assessed centrally for all patients using internationally accepted cutoffs for fluorescence in-situ hybridisation positivity and was conclusive for 265 (88%) of 302 patients overall.

The depth and quality of response was better in the isatuximab group than the control group, with higher rates of very good partial response, complete response, MRD negativity, and complete response with MRD negativity. Specifically, the rates of MRD negativity and complete response with MRD negativity in the isatuximab group are very high considering these patients had a median of two previous lines of treatment. Additionally, the rates of complete response and complete response with MRD negativity were probably underestimated because detection of the therapeutic antibody might interfere with the serum immunofixation test required for complete response. On the basis of the previously reported prespecified, exploratory mass spectrometry interference analysis differentiating between therapeutic antibody and myeloma M-protein, the adjusted complete response rate and adjusted complete response with MRD negativity rate were estimated to be 46% and 24% in the isatuximab group.[25] With the same caveat of cross-trial comparisons, depth of response as measured by complete response and MRD negativity was better than phase 3 results of any proteasome inhibitor regimen in this population.[25]

The longer treatment exposure in the isatuximab group might have contributed to the higher frequency of grade 3 or worse adverse events versus the control group. However, the isatuximab group did not have a higher proportion of patients with serious TEAEs, fatal TEAEs, or TEAEs leading to definitive treatment discontinuation. More grade 3 or worse respiratory infections occurred in the isatuximab group, mainly driven by pneumonia, and patients should be monitored to allow timely intervention for respiratory infections. This difference did not lead to more fatal infections or treatment discontinuations.

The overall incidence of grade 3 or worse hypertension, a known and managed side-effect of carfilzomib, was similar in both treatment groups as was the incidence of grade 3 or worse cardiac failure events as per standard MedDRA query grouping. Additionally, the incidence of grade 3 or worse thromboembolic events was similar between groups, indicating that the addition of isatuximab to carfilzomib–dexamethasone did not increase cardiovascular toxic effects. Although the incidence of second primary malignancies was higher in the isatuximab group than the control group, second primary solid non-skin cancers were reported with similar incidence between the two groups and were reported within the first three treatment cycles in most cases, suggesting that these cancers already existed before the initiation of study treatment. These incidences remain within the background incidence range of second primary malignancies, as reported in studies done in patients with multiple myeloma.[26]

To limit the possible bias related to open-label studies, central laboratory assessments not only for M protein, but also for MRD and baseline cytogenetic analysis, ensured homogeneity of laboratory disease assessment across all sites and countries and an IRC (composed of external myeloma specialists independently assessing response and progression on the basis of established IMWG criteria and external radiologists performing central radiology review) ensured a masked, consistent assessment of efficacy in all patients. Another limitation could be the small number of patients refractory to lenalidomide (57 [32%] of 179 in the isatuximab group *vs* 42 [34%] of 123 in the control group). However, this incidence was similar to those reported in studies recently done in patients with at least one previous line of therapy. For CANDOR, 99 (32%) of 312 patients treated with daratumumab, carfilzomib, and dexamethasone and 55 (36%) of 154 treated with carfilzomib and dexamethasone were refractory to lenalidomide.[24] In CASTOR, 60 (24%) of 251 patients in the daratumumab plus bortezomib and dexamethasone group and 81 (33%) of 247 patients in the bortezomib and dexamethasone group were refractory to lenalidomide.[23] Another possible limitation is that the IKEMA study included nine (3%) Black or African American patients, a low percentage that is attributed to the lower recruitment at US sites than non-US sites. However, this proportion is consistent with previous reports from other trials supporting US approval of new anticancer agents between 2011 and 2016, in which an average of 2% of patients were Black or African American (5·4% US and 0·7% ex-US).[27] Furthermore, evidence shows that Black

or African American patients derive similar benefits from proteasome inhibitor treatment as do White patients.[28]

In this study conducted in patients with relapsed multiple myeloma, the addition of isatuximab to carfilzomib–dexamethasone resulted in significantly longer progression-free survival than treatment with carfilzomib–dexamethasone alone. The depth and quality of response was better in the isatuximab group than the control group, including a high complete response with MRD negativity rate, which is a prognostic factor for better progression-free survival and overall survival. The safety profile was manageable and expected, with no differences in cardiovascular events between the groups. Taken together, these results show that isatuximab plus carfilzomib–dexamethasone is a new standard of care for patients with relapsed multiple myeloma.

For **data sharing information and requests** see https://www.clinicalstudydatarequest.com

Contributors

IKEMA Study Steering Committee members (TM, PM, M-AD, JM, and KY) and employees of Sanofi (M-LR, GA, and SM) contributed to the conception and design of the study. All authors contributed to the provision of study material, data collection and analysis, and the final approval of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. PM, TM, M-LR, and GA accessed and verified the data in the study.

Declaration of interests

PM reports honoraria from Amgen, Celgene, Janssen, Novartis, and Takeda; and a consulting or advisory role for Amgen, Celgene, Janssen, Novartis, and Takeda. M-AD reports consulting or advisory role for Amgen, Bristol Myers Squibb (BMS), Celgene, Janssen, and Takeda. JM reports honoraria from Celgene, Takeda, BMS, Janssen, and Amgen; and a consulting or advisory role for Amgen, BMS, Celgene, Janssen-Cilag, and Takeda. KY reports a consulting or advisory role for Amgen, Janssen, and Takeda; speaker's bureau for Amgen and Takeda; and research funding from Amgen and Sanofi. MC reports speaker's bureau for Amgen, Janssen, and Sanofi. TF reports an advisory role for Amgen, BMS, Celgene, Karyopharm, Oncopeptides, Roche, Sanofi, and Takeda; and speaker's bureau for Takeda. RH reports personal fees from AbbVie, Amgen, BMS, Celgene, Pharma Mar, Novartis, and Takeda; and grants from Novartis and Takeda. IS reports a consulting or advisory role for Amgen, BMS, Celgene, Janssen-Cilag, Novartis, and Takeda; and speakers' bureau for Amgen, BMS, Celgene, Janssen-Cilag, Novartis, and Takeda. TM reports research funding from Amgen and Sanofi. M-LR, GA, and SM are employed by Sanofi and may hold shares or stock options in the company. RB reports research funding from AbbVie, Acerta Pharma, Alexion, Amgen, Bayer, BMS, Boehringer Ingelheim, Celgene, CSL Behring, Daiichi Sankyo, Jansen-Cilag, MorphoSys, Pfizer, Portola, Rigel Pharmaceuticals, Roche, Sanofi, Takeda, and Technoclone; and consulting or advisory roles for Jansen-Cilag and Roche. KK reports research funding from BMS and Janssen; and honoraria from Amgen, BMS, Janssen, and Takeda. AO reports honoraria from Amgen, Celgene, and Janssen. KS reports honoraria from AbbVie, Amgen, BMS, Celgene, Jansen, Novartis, ONO, Sanofi, and Takeda; and consulting or advisory roles for AbbVie, BMS, and Celgene. All other authors declare no competing interests.

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Data sharing

Qualified researchers can request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access are available online.

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