Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study

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See **Comment** page 2045

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Summary

Background Isatuximab is a monoclonal antibody that binds a specific epitope on the human CD38 receptor and has antitumour activity via multiple mechanisms of action. In a previous phase 1b study, around 65% of patients with relapsed and refractory multiple myeloma achieved an overall response with a combination of isatuximab with pomalidomide and low-dose dexamethasone. The aim of this study was to determine the progression-free survival benefit of isatuximab plus pomalidomide and dexamethasone compared with pomalidomide and dexamethasone in patients with relapsed and refractory multiple myeloma.

Methods We did a randomised, multicentre, open-label, phase 3 study at 102 hospitals in 24 countries in Europe, North America, and the Asia-Pacific regions. Eligible participants were adult patients with relapsed and refractory multiple myeloma who had received at least two previous lines of treatment, including lenalidomide and a proteasome inhibitor. Patients were excluded if they were refractory to previous treatment with an anti-CD38 monoclonal antibody. We randomly assigned patients (1:1) to either isatuximab 10 mg/kg plus pomalidomide 4 mg plus dexamethasone 40 mg (20 mg for patients aged ≥75 years), or pomalidomide 4 mg plus dexamethasone 40 mg. Randomisation was done using interactive response technology and stratified according to the number of previous lines of treatment (2–3 *vs* >3) and age (<75 years *vs* ≥75 years). Treatments were assigned based on a permuted blocked randomisation scheme with a block size of four. The isatuximab–pomalidomide–dexamethasone group received isatuximab intravenously on days 1, 8, 15, and 22 in the first 28-day cycle, then on days 1 and 15 in subsequent cycles. Both groups received oral pomalidomide on days 1 to 21 in each cycle, and oral or intravenous dexamethasone on days 1, 8, 15, and 22 of each cycle. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal. Dose reductions for adverse reactions were permitted for pomalidomide and dexamethasone, but not for isatuximab. The primary endpoint was progression-free survival, determined by an independent response committee and assessed in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of study drug. This study is registered at ClinicalTrials.gov, number NCT02990338.

Findings Between Jan 10, 2017, and Feb 2, 2018, we randomly assigned 307 patients to treatment: 154 to isatuximab–pomalidomide–dexamethasone, and 153 to pomalidomide–dexamethasone. At a median follow-up of 11·6 months (IQR 10·1–13·9), median progression-free survival was 11·5 months (95% CI 8·9–13·9) in the isatuximab–pomalidomide–dexamethasone group versus 6·5 months (4·5–8·3) in the pomalidomide–dexamethasone group; hazard ratio 0·596, 95% CI 0·44–0·81; p=0·001 by stratified log-rank test. The most frequent treatment-emergent adverse events (any grade; isatuximab–pomalidomide–dexamethasone *vs* pomalidomide–dexamethasone) were infusion reactions (56 [38%] *vs* 0), upper respiratory tract infections (43 [28%] *vs* 26 [17%]), and diarrhoea (39 [26%] *vs* 29 [20%]). Adverse events with a fatal outcome were reported in 12 patients (8%) in the isatuximab–pomalidomide–dexamethasone group and 14 (9%) in the pomalidomide–dexamethasone group. Deaths due to treatment-related adverse events were reported for one patient (<1%) in the isatuximab–pomalidomide–dexamethasone group (sepsis) and two (1%) in the pomalidomide–dexamethasone group (pneumonia and urinary tract infection).

Interpretation The addition of isatuximab to pomalidomide–dexamethasone significantly improves progression-free survival in patients with relapsed and refractory multiple myeloma. Isatuximab is an important new treatment option for the management of relapsed and refractory myeloma, particularly for patients who become refractory to lenalidomide and a proteasome inhibitor.

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Introduction

Although several new treatment options for multiple myeloma are now available, there is no cure for this disease. Additionally, despite therapeutic advances, relapse is an inevitable feature of multiple myeloma, resulting in a continued need for new active treatments.[1,2] In particular, patients with relapsed and refractory disease who have had several lines of previous therapy or who are refractory to lenalidomide and proteasome inhibitors, the two more commonly used therapeutic classes for this disease, require new options.[2,3] Almost all patients with myeloma develop disease that is eventually refractory to lenalidomide and to proteasome inhibitors.

Monoclonal antibodies targeting CD38 have emerged as an important new class of drugs against multiple myeloma.[4] Isatuximab is a monoclonal antibody that binds to a specific epitope on the human cell surface antigen CD38, which is widely and uniformly expressed on myeloma cells.[5–7] Isatuximab has antitumour activity via multiple biological mechanisms, including antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and direct induction of apoptosis without crosslinking.[8–12] Additionally, isatuximab directly inhibits CD38 ectoenzyme activity, which is implicated in many cellular functions.[6,9,11]

An in-vitro study[10] showed the combination of isatuximab with pomalidomide (an immunomodulatory drug) resulted in greater direct toxicity and lysis of CD38 multiple myeloma cells by effector cells compared with isatuximab alone. As monotherapy, and in combination with other current standard-of-care therapies, isatuximab has been shown to be an active anti-myeloma treatment in phase 1 and 2 studies.[13–17]

The combination of pomalidomide and low-dose dexamethasone is an approved and established option for the treatment of relapsed and refractory myeloma in patients who have received at least two previous therapies including lenalidomide and a proteasome inhibitor.[18,19] Approval was based on the MM-003 randomised controlled trial,[18] and this combination has subsequently become an established standard of care for patients with relapsed and refractory multiple myeloma. In a single-arm, non-randomised, phase 1 study[20] of 103 patients with daratumumab, another anti-CD38 monoclonal antibody,[20–22] combined with pomalidomide and dexamethasone, the median progression-free survival was 8·8 months and 60% of patients achieved an overall response. In a randomised phase 2 study[23] of 60 patients assigned elotuzumab (a monoclonal antibody targeting signalling lymphocytic activation molecule F7) with pomalidomide and dexamethasone versus 57 assigned pomalidomide and dexamethasone, after a minimium follow-up of 9·1 months the median progression-free survival was 10·3 months in the elotuzumab group versus 4·7 months in the control group (hazard ratio [HR] 0·54, 95% CI 0·34–0·86; p=0·008). In a previous phase 1b dose escalation study, the combination of isatuximab

Research in context

Evidence before this study

We searched PubMed for studies published from Jan 1, 2011, to Dec 31, 2016, with the terms "multiple myeloma", "relapsed and refractory", 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 pomalidomide–dexamethasone. Isatuximab is a monoclonal anti-CD38 antibody which has shown increased direct cytotoxic activity with pomalidomide compared with isatuximab alone in preclinical studies. Preliminary results from a phase 1 study showed that the combination of isatuximab with pomalidomide plus dexamethasone, was well tolerated and clinically active in patients refractory to both lenalidomide and a proteasome inhibitor. These encouraging results led to the design of our phase 3 study using the same combination in patients who have received at least two previous lines with lenalidomide and a proteasome inhibitor.

Added value of this study

To our knowledge, this was the first phase 3 study (ICARIA-MM) of an anti-CD38 antibody in combination with pomalidomide and dexamethasone. The results of this study indicate that the addition of isatuximab to pomalidomide and dexamethasone provides a significant benefit for progression-free survival over pomalidomide and dexamethasone. Patients assessed in the study were more treatment refractory than those included in several previous studies with other combination treatments.

Implications of all the available evidence

This study provides evidence for the efficacy of isatuximab in combination with the current standard-of-care treatment (pomalidomide and dexamethasone) in patients with relapsed and refractory multiple myeloma. If approved, isatuximab will provide a new treatment option for this patient population, particularly those who become refractory to lenalidomide and a proteasome inhibitor. The use of an anti-CD38 antibody after a previous one in different lines of treatment still needs to be assessed.

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See Online for appendix

with pomalidomide and low-dose dexamethasone was assessed in 45 patients with relapsed and refractory multiple myeloma, 82% of whom were refractory to lenalidomide and 84% of whom were refractory to a proteasome inhibitor.[24] At a dose of 10 mg/kg (four weekly doses, then every 2 weeks in 31 patients), 64·5% achieved an overall response with isatuximab and median progression-free survival was 17·6 months (95% CI 6·80–20·5).[24] Based on the results of the phase 1b study, we further assessed the combination of isatuximab with pomalidomide and dexamethasone in a similar population of patients with relapsed and refractory multiple myeloma in the phase 3 ICARIA-MM study.

See Online for video

A video abstract is available online.

Methods

Study design and participants

We did a prospective, randomised, open-label, active-controlled, multicentre, phase 3 study,[25] at 102 hospitals within 24 countries across Europe, North America, and the Asia-Pacific regions (appendix 3). The protocol was approved by institutional review boards and independent ethics committees of all participating institutions.

Eligible patients had relapsed and refractory multiple myeloma, received at least two previous lines of treatment, and had not responded to therapy with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) given alone or in combination.[25] Non-response to therapy included progression on or within 60 days, intolerance to lenalidomide or the proteasome inhibitor, or disease progression within 6 months after achieving at least a partial response. Patients also needed to have measurable disease defined as a serum monoclonal protein concentration of at least 0·5 g/dL, or a urine monoclonal protein concentration of at least 200 mg/24 h, and be refractory to their last line of treatment. Patients were required to have adequate haematological, hepatic, and renal function (estimated glomerular filtration rate [eGFR] ≥30 mL/min per 1·73 m² as per modification of diet in the renal disease study equation).

Patients were excluded if they were refractory to previous therapy with an anti-CD38 monoclonal antibody treatment, had previous treatment with pomalidomide, or an ongoing toxic effect worse than grade 1 from previous antimyeloma therapy. Patients with active primary amyloid-light chain amyloidosis, or concomitant plasma cell leukaemia were also excluded. All patients provided written informed consent.

Randomisation

We randomly assigned eligible patients (1:1) to either isatuximab plus pomalidomide plus dexamethasone, or pomalidomide plus dexamethasone. Randomisation was done using interactive response technology and stratified according to the number of previous lines of treatment (2–3 *vs* >3) and age (<75 years *vs* ≥75 years). After screening was completed and patients were deemed eligible, the study site used the interactive response technology to assign treatment based on a permuted blocked randomisation scheme with a block size of four. Treatment assignments were unmasked for study personnel and patients but masked for those analysing the results until the primary analysis.

Procedures

Patients in the isatuximab–pomalidomide–dexamethasone group received isatuximab 10 mg/kg intravenously (on days 1, 8, 15, and 22 in the first 28-day cycle; and days 1 and 15 in subsequent cycles), in combination with the approved dosing and schedules of pomalidomide 4 mg orally (on days 1 to 21 in each cycle), and dexamethasone 40 mg (20 mg for ≥75 years old) orally or intravenously (on days 1, 8, 15, and 22 in each cycle). All patients in the isatuximab group received premedication before infusions, which consisted of ranitidine (50 mg or equivalent), diphenhydramine (25–50 mg or equivalent), and paracetamol (650–1000 mg); dexamethasone was used both as part of premedication and part of the backbone combination in the isatuximab group. No post-infusion corticosteroid or bronchodilator prophylaxis was required in the isatuximab group. Investigators could reconsider the need for premedication for patients who did not have any infusion-related reactions after the first four administrations of isatuximab. Patients in the pomalidomide–dexamethasone group received pomalidomide and dexamethasone in the same schedule as those in the isatuximab group. All patients received mandatory thromboprophylaxis consisting of aspirin or low-molecular-weight heparin. Therapy continued until disease progression, unacceptable toxicity, or consent withdrawal. Dose adjustments (and reductions for pomalidomide and dexamethasone) were permitted for adverse reactions in both groups, but no dose reductions were permitted for isatuximab. Subsequent therapy after progression was left to investigator discretion. Primary and secondary efficacy assessments were undertaken on day 1 of every treatment cycle. Safety assessments were done at each visit (days 1, 8, 15, and 22 in cycle 1; days 1 and 15 for subsequent cycles; and at 30 and 60 days after last treatment administration). Adverse event reporting occurred throughout the study.

Outcomes

The primary endpoint was progression-free survival, defined as the time from date of randomisation to the date of first documentation of progressive disease (as determined by an independent response committee) or the date of death from any cause, whichever came first. The primary endpoint was centrally assessed and determined by the independent review committee using central laboratory data for M-protein and central review of imaging. Key secondary efficacy endpoints were the number of patients who achieved an objective response and overall survival. Additional secondary endpoints were overall response (ie, very good partial response or better;

complete response; and stringent complete response), time to response, duration of response, time to progression, immunogenicity, pharmacokinetic profile of isatuximab in combination with pomalidomide, quality of life, and safety. Response and disease progression were determined by the independent response committee using the International Myeloma Working Group response criteria,[26] based on monthly central laboratory assessments of monoclonal protein, and central radiology imaging review. Bone marrow samples for minimal residual disease assessment were collected by the investigator for patients with an investigator-assessed complete response or if clinically indicated. The exploratory endpoint of minimal residual disease was assessed by the Adaptive clonoSEQ Assay (version 2.0; Adaptive Biotechnologies, Seattle, WA, USA; further details in the appendix p 4) using bone marrow aspirate samples collected at screening (identification calibration sample), at the time of confirmation of complete response or stringent complete response, and 3 months later in case of minimal residual disease positivity. For analysis purposes, patients in the intention-to-treat population without assessments of minimal residual disease were considered as positive for minimal residual disease.

Cytogenetics were assessed during screening by a central laboratory with a cutoff of 50% for del(17p), and 30% for t(4;14) and t(14;16). High risk was defined as del(17p), t(4;14), or t(14;16) by fluorescence in-situ hybridisation. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, was used to qualify and grade adverse events. Quality of life assessments included the Global Health Status Score of the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire, done on day 1 of each treatment cycle, and at 30 days and 60 days after the last treatment.[27–29]

Statistical analysis

All efficacy analyses were done in the intention-to-treat population. For the primary endpoint of progression-free survival, a total of 162 events were needed to detect an HR of 0·6 using a log-rank test (one-sided α 0·025, 90% power). A total of 220 death events were needed for overall survival to detect an HR of 0·685 using a log-rank test at the one-sided 0·025 level with 80% power. Based on progression-free survival and overall survival assumptions, the study design needed 300 patients (150 in each group) to achieve the targeted number of events. An interim overall survival analysis was done at the time of the progression-free survival analysis. Sensitivity analyses for progression-free survival included progression-free survival based on independent response committee assessment without censoring for further anti-myeloma treatment or considering initiation of further anti-myeloma treatment as a progression-free survival event, and progression-free survival based on investigator's assessment (considering or not symptomatic deterioration as a progression-free survival event). Progression-free survival and overall survival were analysed using the Kaplan-Meier method; HRs were estimated using the stratified Cox proportional hazards model, and both groups were compared using a one-sided log-rank test stratified by previous lines of treatment and age. The numbers of patients achieving a response were compared using the stratified Cochran-Mantel-Haenszel test. Analyses of other secondary endpoints were descriptive only.

The consistency of the results from the primary analysis was evaluated across subgroups of patients with available results. For each subgroup, the treatment-effect HR and 95% CI was estimated, and progression-free survival was analysed using a Cox proportional hazards model with terms for the factor, treatment, and their interaction. The test for the interaction was performed at the 10% α level. Unmasked safety data were periodically reviewed by an independent data monitoring committee. SAS 9.4 was used for all statistical analyses. This study is registered at ClinicalTrials.gov, number NCT02990338.

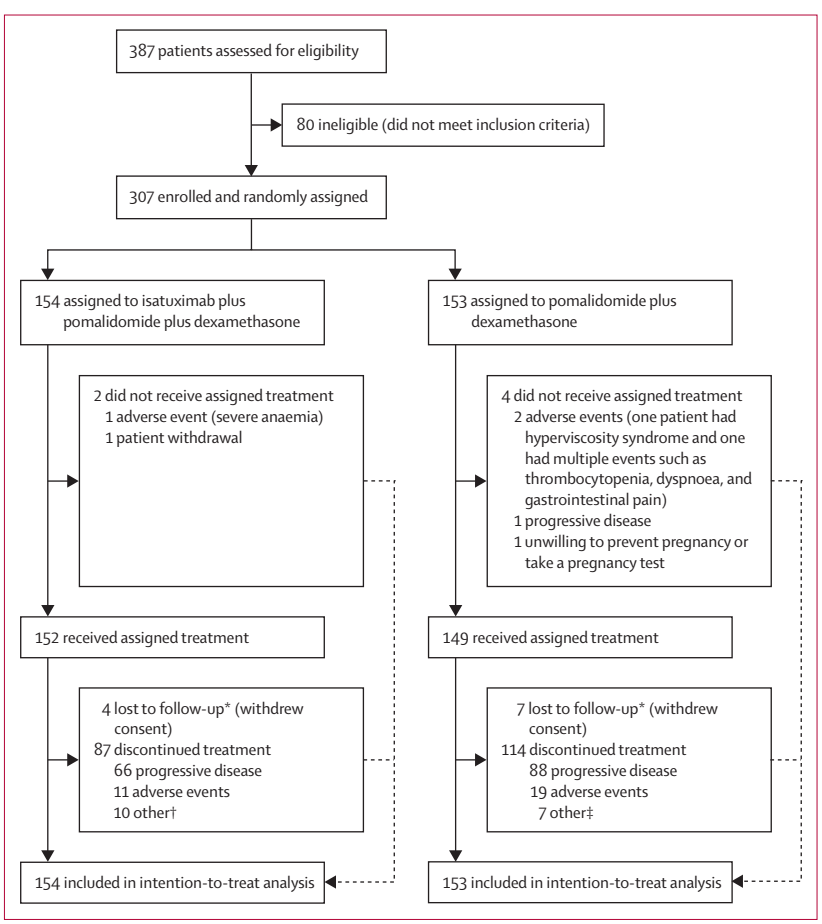

Figure 1: **Trial profile**
*Greater than 8 weeks between last contact and analysis cutoff date. †Five patient decision to withdraw; one poor compliance to protocol; four principal investigator decision (one to switch treatment to daratumumab plus pomalidomide plus dexamethasone; three discontinued because of increase in serum free light chain concentrations). ‡Six patient decision to withdraw; one physician decision to withdraw the patient.

Role of the funding source

The funder of the study, together with the investigator steering committee, had a role in study design. The funder of the study had a role in data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Isatuximab plus pomalidomide plus dexamethasone (n=154)	Pomalidomide plus dexamethasone (n=153)
Age (years)	68 (60–74)	66 (59–71)
<65	54 (35%)	70 (46%)
65–74	68 (44%)	54 (35%)
≥75	32 (21%)	29 (19%)
Sex		
Female	65 (42%)	83 (54%)
Male	89 (58%)	70 (46%)
Previous history of asthma or COPD	16 (10%)	17 (11%)
eGFR*		
<60 mL/min per 1·73 m²	55/142 (39%)	49/145 (34%)
≥30 and <60 mL/min per 1·73 m²	54/142 (38%)	48/145 (33%)
Previous autologous stem-cell transplantation	83 (54%)	90 (59%)
Years since initial diagnosis	4·46 (2·6–7·2)	4·09 (2·9–7·0)
Type of myeloma at diagnosis		
IgA	34 (22%)	41 (27%)
IgG	102 (66%)	100 (65%)
Light chain (κ plus λ)	15 (10%)	11 (7%)
Other†	3 (<1%)	1 (<1%)
ISS stage at diagnosis		
I	36 (23%)	41 (27%)
II	49 (32%)	48 (31%)
III	42 (27%)	44 (29%)
Unknown	27 (18%)	20 (13%)
ISS stage at study entry		
I	64 (42%)	51 (33%)
II	53 (34%)	56 (37%)
III	34 (22%)	43 (28%)
Cytogenetic risk at study entry		
High	24 (16%)	36 (24%)
Standard	103 (67%)	78 (51%)
Missing	27 (18%)	39 (26%)
Previous lines of therapy	3 (2–4)	3 (2–4)
Previous alkylating drug	139 (90%)	148 (97%)
Previous proteasome inhibitors	154 (100%)	153 (100%)
Previous lenalidomide	154 (100%)	153 (100%)
Patients refractory to previous therapy		
Last line of therapy	150 (97%)	151 (99%)
Immunomodulatory drug	147 (96%)	144 (94%)
Lenalidomide	144 (94%)	140 (92%)
Proteasome inhibitor	118 (77%)	115 (75%)
Lenalidomide and proteasome inhibitor	111 (72%)	107 (70%)
Lenalidomide last line	93 (60%)	88 (58%)

Data are median (IQR) or n (%). ISS stage at study entry, not at diagnosis, was used for efficacy assessments. COPD=chronic obstructive pulmonary disease. eGFR=estimated glomerular filtration rate. ISS=International Staging System, derived based on the combination of serum β2, macroglobulin, and albumin. *Information on race could not be collected in some countries, hence not all values were available. †IgM unknown or undetected.

Table 1: **Baseline demographic and patient characteristics of the intention-to-treat population**

Results

Between Jan 10, 2017, and Feb 2, 2018, we randomly assigned 307 patients to treatment: 154 to isatuximab–pomalidomide–dexamethasone and 153 to pomalidomide–dexamethasone; figure 1). Data cutoff was Oct 11, 2018.

Patient characteristics were generally balanced across the groups (table 1). Median age was 67 years (IQR 60–73), and the median number of previous lines of treatment was 3 (IQR 2–4). More than half of the patients had received a previous transplantation, and all were previously treated with lenalidomide and proteasome inhibitors. At study entry, 284 (93%) were refractory to lenalidomide, 181 (59%) were refractory to lenalidomide at the last line before study entry, and 233 (76%) to at least one proteasome inhibitor. One patient in the isatuximab–pomalidomide–dexamethasone group was previously treated with daratumumab. High-risk cytogenetics were present in 60 (20%) patients and 104 (36%) had renal function impairment (eGFR <60 mL/min per 1·73 m²). There were 16 patients in the isatuximab–pomalidomide–dexamethasone group and 17 in the pomalidomide–dexamethasone group with a history of chronic obstructive pulmonary disease or asthma. Median treatment duration was 41 weeks (IQR 19·1–52·3) in the isatuximab–pomalidomide–dexamethasone group and 24 weeks (11·1–48·0) in the pomalidomide–dexamethasone group (table 2). Median infusion duration for isatuximab was 3·3 h (IQR 3·0–4·5) for the first infusion, and 2·8 h (2·5–3·1) for subsequent infusions. At the primary analysis cutoff date, 65 (42%) patients in the isatuximab–pomalidomide–dexamethasone group versus 35 (23%) in the pomalidomide–dexamethasone group were continuing to receive study treatment (figure 1). The primary reason for treatment discontinuation was progressive disease in 66 patients (43%) in the isatuximab–pomalidomide–dexamethasone group and 88 (58%) in the pomalidomide–dexamethasone group.

At a median follow-up of 11·6 months (IQR 10·1–13·9), median progression-free survival (by independent response committee assessment) was significantly longer in the isatuximab–pomalidomide–dexamethasone group compared with the pomalidomide–dexamethasone group (11·5 months [95% CI 8·9–13·9] *vs* 6·5 months [4·5–8·3]; HR 0·596, 95% CI 0·44–0·81; p=0·001 by stratified log-rank test; figure 2), consistent with the prespecified statistical hypothesis. The sensitivity analyses were consistent with the primary progression-free survival analysis, showing consistent HRs ranging from 0·568 to 0·602. Median progression-free survival per investigator assessment using local laboratory and imaging data was 11·1 months in the isatuximab–pomalidomide–dexamethasone group (95% CI 7·5–14·8) versus 6·5 months

	Isatuximab plus pomalidomide plus dexamethasone (n=152)	Pomalidomide plus dexamethasone (n=149)
Treatment duration (weeks)	41·00 (19·1–52·3)	24·00 (11·1–48·0)
Relative dose intensity (%)		
Isatuximab	92·3% (19·7–111·1)	NA
Pomalidomide	85·1% (22·9–103·7)	93·3% (37·2–118·5)
Dexamethasone	87·8% (15·9–130·0)	96·3% (30·3–300·0)
Pomalidomide dose reductions	65 (43%)	36 (24%)
Dexamethasone dose reductions	50 (33%)	38 (26%)

Data are median (IQR) or n (%). NA=not applicable.

Table 2: **Exposure to study treatments**

in the pomalidomide–dexamethasone group (4·7–7·9; HR 0·602, 95% CI 0·444–0·816; p=0·0009; appendix p 8), consistent with the independent response committee assessment.

The progression-free survival benefit with isatuximab occurred in all prespecified subgroups, including patients with poor prognosis; refractory to lenalidomide, a proteasome inhibitor, both lenalidomide and a proteasome inhibitor, or to lenalidomide at the last line previous to study entry (figure 3). Results showed a positive treatment effect in all subgroups consistent with the overall treatment effect, with HRs within the range of 0·5 to 0·6.

Significantly more patients in the isatuximab–pomalidomide–dexamethasone group achieved a partial response (60% in the isatuximab–pomalidomide–dexamethasone group *vs* 35% in the pomalidomide–dexamethasone group; p<0·0001) or a very good partial response or better (32% in the isatuximab–pomalidomide–dexamethasone group *vs* 9% in the pomalidomide–dexamethasone group; p<0·0001) by independent response committee assessment (table 3). Numerically more patients in the isatuximab–pomalidomide–dexamethasone group achieved a complete response or stringent complete response (table 3). Per investigator assessment and local laboratory results, the number of patients achieving an overall response was 97 (63%) in the isatuximab–pomalidomide–dexamethasone group versus 49 (32%) in the pomalidomide–dexamethasone group; and the number of patients achieving a very good partial response or better was 52 (34%) in the isatuximab–pomalidomide–dexamethasone group versus 11 (7%) in the pomalidomide–dexamethasone group (appendix p 13), consistent with the independent response committee assessment. Responses occurred faster and were more durable in the isatuximab–pomalidomide–dexamethasone group compared with the pomalidomide–dexamethasone group, with a median time to first response in patients with a partial response or better of 35 days (IQR 32–60) versus 58 days (32–87),

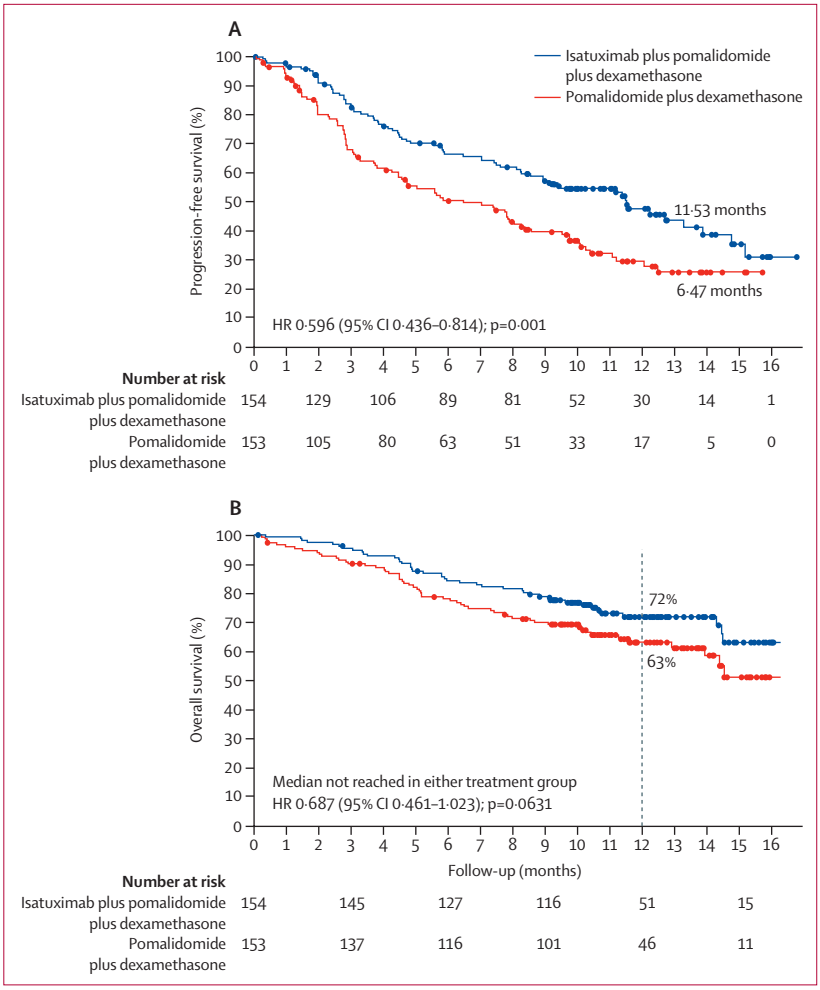

Figure 2: **Progression-free survival and overall survival**
(A) Kaplan-Meier analysis of progression-free survival in the intention-to-treat population (ie, all patients who were randomly assigned to treatment (regardless of treatment received), as assessed by an independent response review committee. Hazard ratio (HR) and corresponding 95% CIs are from a Cox proportional hazard model stratified by age and number of previous lines of therapy. One-sided p value was derived from a log-rank test. (B) Overall survival was compared using a one-sided log-rank test in the intention-to-treat population at the time of the primary analysis on progression-free survival. Patients remaining alive at their last contact were censored at the last date known to be alive or the cutoff date, whichever was earlier.

respectively; median duration of response was 13·3 months (95% CI 10·6–not calculable) in the isatuximab–pomalidomide–dexamethasone group versus 11·1 months (8·5–not calculable) in the pomalidomide–dexamethasone group. Numerically higher numbers of patients achieved an overall response in all subgroups (appendix p 9). In patients with two or three previous lines of treatment, an overall response was achieved by 58 (57%) in the isatuximab–pomalidomide–dexamethasone group versus 39 (39%) in the pomalidomide–dexamethasone group. In patients with more than three previous lines of treatment, 35 (67%) versus 15 (29%) achieved an overall response; appendix p 9).

18 samples from 16 patients were analysed for minimal residual disease, including all patients with a confirmed complete response or stringent complete response

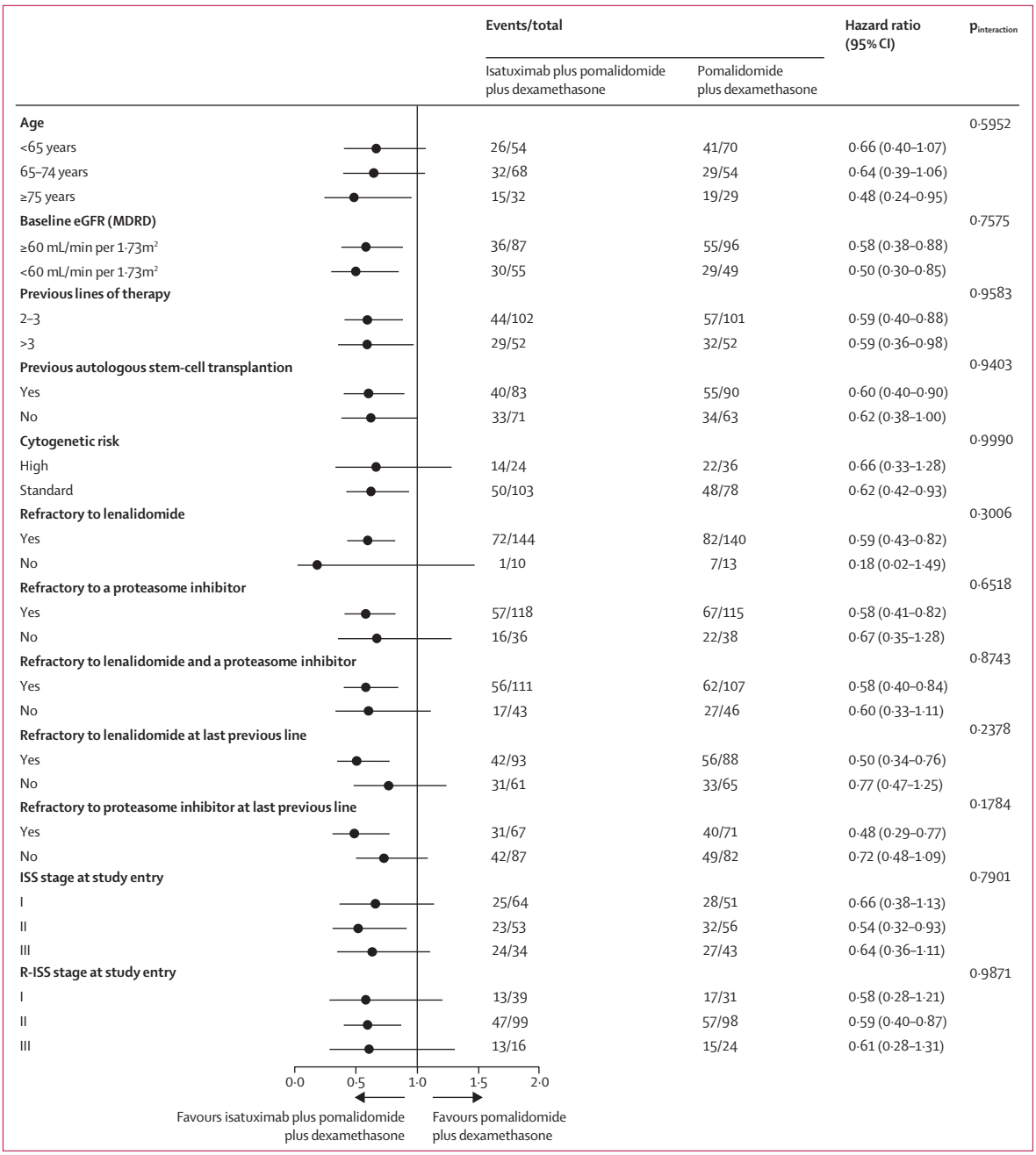

Figure 3: **Subgroup analyses of progression-free survival**

Analyses were prespecified and done in the intention-to-treat population. Results are from a prespecified subgroup analysis of progression-free survival in the intention-to-treat population. Cytogenetics by central laboratory cutoff 50% for del(17p), 30% for t(4;14) and t(14;16). eGFR=estimated glomerular filtration rate. MDRD=modification of diet in renal disease. ISS=International Staging System. R-ISS=revised International Staging System.

according to investigator assessment. A response other than a complete response might have been attributed by the independent response committee because the investigators based their assessments on concentrations of monoclonal protein from local laboratory results, whereas assessments from the independent response committee were based on centrally obtained results. Minimal residual disease negativity (in the intention-to-treat population) was observed in eight (5%) patients at 10^{-5} in the isatuximab–pomalidomide–dexamethasone group, but none in the pomalidomide–dexamethasone group (at the sensitivity levels tested of 10^{-4}, 10^{-5}, and 10^{-6}; appendix p 5).

At the progression-free survival cutoff date, 99 deaths had occurred (43 in the isatuximab–pomalidomide–dexamethasone group and 56 in the pomalidomide–dexamethasone group). As planned per the protocol,

	Isatuximab plus pomalidomide plus dexamethasone (n=154)	Pomalidomide plus dexamethasone (n=153)
Best overall response (n [%])		
Complete response	7 (5%)	2 (1%)
Stringent complete response	0	1 (<1%)
Very good partial response	42 (27%)	10 (7%)
Partial response	44 (29%)	41 (27%)
Minimal response	10 (7%)	17 (11%)
Stable disease	33 (21%)	45 (29%)
Non-progressive disease	4 (3%)	2 (2%)
Progressive disease	6 (4%)	14 (9%)
Unconfirmed progressive disease	1 (<1%)	4 (3%)
Not evaluable or not assessed	7 (5%)	16 (11%)
Overall response		
Responders*	93 (60%; 95% CI† 0·522–0·682)	54 (35%; 95% CI† 0·278–0·434)
Odds ratio	2·795 (95% CI 1·75–4·56)	NA
Stratified Cochran-Mantel-Haenszel test p value† versus control	<0·0001	NA
Very good partial response or better	49 (32%; 95% CI* 0·246–0·398)	13 (9%; 95% CI 0·046–0·141)
Odds ratio	5·026 (95% CI 2·514–10·586)	NA
Stratified Cochran-Mantel-Haenszel test p value‡ versus control	<0·0001	NA

Responses were assessed by an independent response review committee in the intention-to-treat population. NA=not applicable. *Stringent complete response, complete response, very good partial response, or partial response. †Estimated using the Clopper-Pearson method. ‡Stratified by age (<75 years *vs* ≥75 years) and number of previous lines of treatment (2 or 3 *vs* >3). One-sided significance level was 0·025.

Table 3: **Response to therapy**

	Isatuximab plus pomalidomide plus dexamethasone (n=152)			Pomalidomide plus dexamethasone (n=149)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Most common adverse events (in ≥15% of patients with isatuximab, worst grade)						
Infusion reaction*	56 (38%)	2 (1%)	2 (1%)	0	0	0
Upper respiratory tract infection	43 (28%)	5 (3%)	0	26 (17%)	1 (<1%)	0
Diarrhoea	39 (26%)	3 (2%)	0	29 (20%)	1 (<1%)	0
Bronchitis	36 (24%)	5 (3%)	0	13 (9%)	1 (<1%)	0
Pneumonia	31 (20%)	23 (15%)	2 (1%)	26 (17%)	20 (13%)	2 (1%)
Fatigue	26 (17%)	6 (4%)	0	32 (22%)	0	0
Back pain	25 (16%)	3 (2%)	0	22 (15%)	2 (1%)	0
Constipation	24 (16%)	0	0	26 (17%)	0	0
Asthenia	23 (15%)	5 (3%)	0	27 (18%)	4 (3%)	0
Dyspnoea	23 (15%)	6 (4%)	0	15 (10%)	2 (1%)	0
Nausea	23 (15%)	0	0	14 (9%)	0	0
Other adverse events of interest						
Second primary malignancy†	6 (4%)	..	..	1 (<1%)	..	..
Haematological laboratory abnormalities (worst grade in evaluable patients)						
Neutropenia	146/152 (96%)	37/152 (24%)	92/152 (61%)	137/147 (93%)	57/147 (39%)	46/147 (31%)
Thrombocytopenia	127/152 (84%)	22/152 (15%)	25/152 (16%)	118/147 (80%)	14/147 (10%)	22/147 (15%)
Anaemia	151/152 (99%)	48/152 (32%)	0	145/147 (99%)	41/147 (28%)	0

Data are n (%). Analysis was done in the safety population. *As reported by the investigator in the specific form of an adverse event, including infusion-related reaction, cytokine release syndrome, and drug hypersensitivity. †Isatuximab plus pomalidomide plus dexamethasone group: one patient with myelodysplastic syndrome, one patient with post-radiation angiosarcoma, and four patients with squamous cell carcinoma of the skin. Pomalidomide plus dexamethasone group: one patient with squamous cell carcinoma of the skin. All patients continued treatment after complete surgical excision except the patient with myelodysplastic syndrome.

Table 4: **Treatment-emergent adverse events and haematological laboratory abnormalities**

an interim analysis of overall survival was done at that time (HR 0·687, 95% CI 0·461–1·023; p=0·0631, one-sided α 0·0008, with separation of the curves from the beginning of the observation; median not reached in either group; figure 2). The stratified HR from the inverse probability of censoring weights analysis was

0·708 (95% CI 0·451–1·111), which was consistent with the intention-to-treat estimate of 0·687 (0·461–1·023; appendix p 7).

Median time to progression was 12·7 months (95% CI 11·2–15·2) in the isatuximab–pomalidomide–dexamethasone group versus 7·75 months (5·0–9·8) in the pomalidomide–dexamethasone group. At the time of analysis (Nov 22, 2018), 60 (39%) patients in the isatuximab–pomalidomide–dexamethasone group and 83 (54%) in the pomalidomide–dexamethasone group had started subsequent therapy. Of these, six (10%) in the isatuximab–pomalidomide–dexamethasone group and 45 (54%) in the pomalidomide–dexamethasone group received daratumumab. The time to next treatment was longer in the isatuximab–pomalidomide–dexamethasone group (median not reached) than in the pomalidomide–dexamethasone group (9·1 months; HR 0·538, 95% CI 0·382–0·758; appendix p 10). The addition of isatuximab to pomalidomide and dexamethasone did not result in a change from baseline in the Global Health score of the QLQ-C30 over time (appendix p 11).

The overall safety summary is in the appendix (p 14). Infusion reactions and respiratory infections were the most frequent adverse events reported in the isatuximab–pomalidomide–dexamethasone group (table 4). Infusion reactions were only reported in the isatuximab–pomalidomide–dexamethasone group; these were reversible and most occurred with the first infusion. Four patients (3%) had grade 3 or 4 infusion reactions. No delayed infusion reactions were reported. Occurrences of anaemia and thrombocytopenia were similar in both groups. Granulocyte-colony stimulating factor was used in 105 patients (69%) in the isatuximab–pomalidomide–dexamethasone group and 79 (53%) in the pomalidomide–dexamethasone group. Of 99 patients (65%) in the isatuximab–pomalidomide–dexamethasone group tested for indirect antiglobulin (by indirect Coombs test), 67 (68%) were positive. There were no differences between the treatment groups in the number of platelet transfusions or haemorrhages (isatuximab–pomalidomide–dexamethasone *vs* pomalidomide–dexamethasone: 22 [15%] *vs* 23 [15%] and 13 [9%] *vs* 17 [11%], respectively). Of patients who received a blood transfusion (46 [30%] in the isatuximab–pomalidomide–dexamethasone group, 51 [34%] in the pomalidomide–dexamethasone group), none had haemolysis. Grade 3 or higher adverse events occurred in 132 (87%) in the isatuximab–pomalidomide–dexamethasone group versus 105 (71%) in the pomalidomide–dexamethasone group (table 4). The overall incidence of serious adverse events was 94 (62%) in the isatuximab–pomalidomide–dexamethasone group, and 80 (54%) in the pomalidomide–dexamethasone group; when adjusted for difference in exposure, the event rate per patient year was 1·36 in the isatuximab–pomalidomide–dexamethasone group and 1·30 in the pomalidomide–dexamethasone group.

Adverse events with a fatal outcome were reported in 12 patients (8%) in the isatuximab–pomalidomide–dexamethasone group and 14 (9%) in the pomalidomide–dexamethasone group. Deaths due to treatment-related adverse events were reported for one patient (<1%) in the isatuximab–pomalidomide–dexamethasone group (sepsis) and two (1%) in the pomalidomide–dexamethasone group (pneumonia and urinary tract infection; appendix p 14). No anti-drug antibodies against isatuximab were detected in the 151 patients tested. The pharmacokinetics of isatuximab were not affected by the concomitant administration of pomalidomide. Dose reductions for pomalidomide and dexamethasone were numerically more frequent in the isatuximab–pomalidomide–dexamethasone group than in the pomalidomide–dexamethasone group (pomalidomide reductions in 65 patients [43%] *vs* 36 [24%]; dexamethasone reductions in 50 patients [33%] *vs* 38 [26%]; table 2), and were mainly due to neutropenia and infections.

Discussion

In this study, the addition of isatuximab to pomalidomide and dexamethasone was associated with a significant and clinically meaningful benefit in progression-free survival in heavily treated patients with relapsed and refractory multiple myeloma with results from both the investigators and an independent response committee being consistent. Specifically, the Kaplan-Meier curves showed an early and sustained separation that translated into a 40% decrease in risk of death or progression for patients in the group that received isatuximab. The benefit in progression-free survival occurred in all subgroups, including patients with high-risk cytogenetics; aged older than 75 years; renal function impaired; and who received more than three previous lines of treatment, were refractory to lenalidomide and a proteasome inhibitor, and were refractory to lenalidomide in last line. Importantly, the progression-free survival HR for patients with high-risk cytogenetics was 0·66, similar to the HR for patients with standard-risk cytogenetics (0·62). Median progression-free survival in the pomalidomide–dexamethasone group (6·47 months) was longer than that reported in the original pomalidomide-dexamethasone MM-003 study (4·0 months).[18] In other trials with pomalidomide–dexamethasone as a control group, median progression-free survival ranged from 4·7 months[23] to 8·4 months.[30] In our study, the progression-free survival results observed by the independent review committee and by the investigator assessment were consistent, indicating the robustness of these data. Additionally, the longer progression-free survival in our control pomalidomide–dexamethasone group also indicates that the improvement observed with addition of isatuximab in this open-label trial was not inflated by early treatment discontinuation in the pomalidomide–dexamethasone group. Patients in the pomalidomide–dexamethasone group appeared to have received the full treatment benefit in this study.

ICARIA-MM is the first positive randomised, phase 3 study adding an anti-CD38 antibody, isatuximab, to a pomalidomide–dexamethasone backbone therapy for relapsed and refractory multiple myeloma. The patient population studied with at least two previous lines of therapy and mandatory previous lenalidomide and proteasome-inhibitor exposure, was similar to that in other reported trials[23,31] with a pomalidomide–dexamethasone backbone. For example, the combination of daratumumab with pomalidomide and dexamethasone was approved in the USA for the treatment of relapsed and refractory multiple myeloma on the basis of a phase 1 study (EQUULEUS; MMY1001)[20] in which 89% of patients were refractory to lenalidomide (although the percentage of patients refractory to lenalidomide at last line was not reported and the median number of previous treatment lines was four). 90% of the patient population in the phase 2 ELOQUENT-3 study,[23] which assessed the combination of elotuzumab with pomalidomide and dexamethasone, were refractory to lenalidomide (median number of previous lines was three). Other combination studies have assessed earlier lines of treatment. For example, in the OPTIMISMM trial[31] of pomalidomide, bortezomib, and dexamethasone, 63% of patients were refractory to lenalidomide in the last line (median number of previous lines was two). The POLLUX study,[21] which assessed daratumumab with lenalidomide and dexamethasone excluded patients refractory to lenalidomide and had 28% of patients refractory to the last line (median number of previous lines was one). The CASTOR study,[22] which assessed daratumumab with bortezomib and dexamethasone, excluded patients refractory to bortezomib but 32·9% of patients included were refractory to immunomodulatory drugs (30·3% of patients were refractory to the last line; median number of previous lines was two). By contrast, in our ICARIA-MM study, patients received a median number of three previous treatment lines and, overall, most patients were refractory to lenalidomide (more than half were refractory to lenalidomide at last line), and around three-quarters were refractory to proteasome inhibitors. Therefore, the results of this study cannot be directly compared with the results of POLLUX, CASTOR, and other triplet combination studies done in patients with early relapse who were either largely lenalidomide-naive or lenalidomide-sensitive,[30] or were in less advanced relapse, and such cross-trial comparisons can potentially be both uninformative and misleading.

In our study, isatuximab in combination with pomalidomide and dexamethasone increased the number of patients achieving a response, and improved the depth of response compared with pomalidomide and dexamethasone alone. The depth of response, particularly complete response, and as a result, minimal residual disease assessment, might have been underestimated because of the potential interference of isatuximab with the assessment of monoclonal protein by immunofixation. In this context, a specific interference assay is being developed for isatuximab, and exploratory additional analyses to characterise the effect of this interference on response assessment are ongoing. The overall response benefit occurred in all subgroups and was consistent with results for progression-free survival. The number of patients who achieved an overall response was also consistent with results of the phase 1b study with the same treatment combination.[24,32]

Minimal residual disease-negative status at the 10^{-5} level was obtained in 5% of patients in the isatuximab–pomalidomide–dexamethasone group and in none of the patients in the pomalidomide–dexamethasone group (intention to treat) using next-generation sequencing. Although this number is relatively small, it is similar to that previously reported for the daratumumab, pomalidomide, and dexamethasone combination (6%) in the same population.[20]

An interim analysis of overall survival showed an HR consistent with the prespecified study hypothesis. Of patients who received further anti-myeloma treatment, about half in the pomalidomide–dexamethasone group versus 10% in the isatuximab–pomalidomide–dexamethasone group received daratumumab, and use of daratumumab did not appear to affect the overall survival analysis. The stratified HR from the inverse probability of censoring weights analysis was consistent with the intention-to-treat estimate.

The addition of isatuximab to pomalidomide and dexamethasone was well tolerated with no increase in treatment discontinuations or incidence of fatal events compared with that in the pomalidomide and dexamethasone group. Reversible infusion reactions occurred in 38% of patients treated with isatuximab plus pomalidomide and dexamethasone. Despite the absence of mandatory post-infusion corticosteroid prophylaxis, no delayed infusion reactions were reported. Overall, the safety profile was similar to that in the phase 1b study[24] and a subsequent expansion cohort with a shorter isatuximab infusion time.[31]

A limitation of this study was its open-label design that presents a possibility of bias in the primary outcome reporting; however, an independent review committee, who were masked to treatment assignment, was implemented to ensure consistency in the assessment of disease response and without the bias of knowledge of the assigned treatment. Additionally, an interference assay was not available, which might have discouraged some investigators from obtaining bone marrow samples, thereby potentially underestimating the number of patients achieving a complete response and minimal residual disease. Another limitation was that this study did not enrol patients refractory to another anti-CD38 antibody, precluding any activity assessment of this regimen in anti-CD38-refractory patients.

In conclusion, the results of this large international, multicentre study showed that the combination of

isatuximab, pomalidomide, and dexamethasone is an effective and well tolerated treatment option in patients with relapsed and refractory multiple myeloma. Although data from other ongoing combination studies of isatuximab are awaited, the findings of this first phase 3 study of an anti-CD38 antibody with pomalidomide and dexamethasone represent an important advance in the management of relapsed and refractory myeloma, and so provide an active new treatment regimen for these patients who represent an otherwise unmet medical need.

Contributors

FC, the funder's clinical study director, was responsible for study oversight. The manuscript was written by the lead authors SVR, FC, PGR, and MA. MA, PGR, SVR, JS-M, KCA, FC, and SL-G designed the study. MA, PGR, JS-M, MB, IS, XL, PM, MAD, JS-YH, JM, MC, and HMP were investigators in the study, and MA, PGR, SVR, JS-M, KCA, FC, and SL-G analysed the data. MA and PGR were coprimary investigators of this study. All authors interpreted the data and assume responsibility for data integrity and the decision to submit this manuscript for publication; had full access to the study data; and edited, and reviewed manuscript drafts, and approved the final version for submission. The full list of ICARIA-MM investigators is in the appendix (p 3).

Declaration of interests

PGR reports a consulting or advisory role for Karyopharm, Oncopeptides, Celgene, Janssen, Takeda, and Sanofi; and research funding from Oncopeptides, Celgene, Takeda, and Bristol-Myers Squibb (BMS). MA reports research funding from Sanofi. SVR reports patents, royalties, and other intellectual property from UpToDate. JS-M reports a consulting or advisory role for Amgen, BMS, Celgene, Janssen, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda. MB reports a consulting or advisory role for Amgen, Celgene, Janssen-Cilag, and Takeda; and speakers' bureau fees for Amgen, BMS, Celgene, and Janssen-Cilag. IS reports a consulting or advisory role and speakers' bureau for Amgen, BMS, Celgene, Janssen-Cilag, Novartis, and Takeda. XL reports honoraria from AbbVie, Amgen, BMS, Carsgen Therapeutics, Celgene, Janssen-Cilag, Karyopharm Therapeutics, Merck, Mundipharma, Novartis, Oncopeptides, Pierre Fabre, Roche, Sanofi and Takeda; a consulting or advisory role for AbbVie, Amgen, BMS, Carsgen Therapeutics, Celgene, Gilead Sciences, Janssen-Cilag, Karyopharm Therapeutics, Merck, Mundipharma, Novartis, Oncopeptides, Roche, and Takeda; and travel and accommodation expenses from Takeda. FS reports honoraria from AbbVie, Amgen, Celgene, Janssen China R&D, Novartis, and Takeda; a consulting or advisory role for Adaptive Biotechnologies, Amgen, Bayer, BMS, Celgene, Janssen China R&D, Oncopeptides, and Takeda; and research funding from Amgen and Janssen China R&D. PM reports honoraria from Amgen, Celgene, Janssen-Cilag, Novartis, and Takeda; and a consulting or advisory role for Amgen, Celgene, Janssen, Novartis, and Takeda. MAD reports honoraria from Celgene, Takeda, BMS, Janssen, and Amgen; and a consulting or advisory role for Amgen, BMS, Celgene, Janssen-Cilag, and Takeda. JS-YH reports research funding from Sanofi. JM reports consultancy and honoraria from Amgen, BMS, Celgene, Janssen, and Takeda; and is a clinical trials investigator for Amgen, Janssen, Karyopharm, Oncopeptides, and Sanofi. MC reports honoraria from AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GlaxoSmithKline, Janssen-Cilag, and Takeda; and a consulting or advisory role for AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GlaxoSmithKline, Janssen-Cilag, and Takeda. HMP reports honoraria and a consulting or advisory role from Amgen, Celgene, Janssen China R&D, Novartis, and Takeda; and research funding from Sanofi and Takeda. KCA reports stock and other ownership interests, and patents, royalties, and other intellectual property in C4 Therapeutics and OncoPep; and a consulting or advisory role for BMS, Celgene, Gilead Sciences, Janssen Oncology, Millennium, and Sanofi. SM, KPC, FC, SL-G, and FD are employees of Sanofi.

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 at: https://www.clinicalstudydatarequest.com.

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