Isatuximab for relapsed/refractory multiple myeloma: review of key subgroup analyses from the Phase III ICARIA-MM study

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In the Phase III ICARIA-MM study (Trial Registration number: NCT02990338 [ClinicalTrials.gov]), the addition of the anti-CD38 monoclonal antibody isatuximab to pomalidomide and dexamethasone led to increased progression-free survival and improved response rates in patients with relapsed/refractory multiple myeloma. There is an unmet treatment need, particularly among patients with poor prognoses, including those with high-risk cytogenetics, those who have renal impairment, those who are elderly and those who are refractory to prior lines of treatment. In this review, the subgroup analyses from the ICARIA-MM study, representing subpopulations with poor prognostic factors, are discussed. Overall, the addition of isatuximab to pomalidomide and dexamethasone improved progression-free survival and disease response rates across different subgroups, regardless of prognostic factor.

Lay abstract: Currently, the majority of patients with multiple myeloma are not cured, and current treatments may not be helpful for patients with poor prognoses, including those with high-risk chromosomal changes, those who have impaired kidney function, those who are elderly and those who are refractory to prior treatments. In this review, we will discuss the benefits of the combination of isatuximab plus pomalidomide and dexamethasone in these difficult-to-treat patients.

Tweetable abstract: Isatuximab combination improves progression-free survival and disease response rates in difficult-to-treat patients with multiple myeloma.

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Multiple myeloma (MM) is a neoplasm of B-cell lineage characterized by the proliferation of malignant plasma cells in the bone marrow, with consequent anemia and increased bone resorption by osteoclasts, often resulting in bone fractures or hypercalcemia [1]. The malignant plasma cells produce and secrete immunoglobulin (Ig), usually of the IgG class, which is seen as a monoclonal component (M-protein) on serum electrophoresis. M-protein and
free light chains, part of the Ig, accumulate in the bloodstream and urine of patients with MM, and commonly induce renal failure [2].

MM is the second most frequent hematologic malignancy after lymphoma, totaling 1% of all cancers and approximately 10% of all hematologic malignancies [3,4]. In 2020, the global age-adjusted annual incidence of MM was 1.8/100,000, with a mortality rate of 1.1/100,000 [5]. Furthermore, there were approximately 176,404 new cases of MM across the world and more than 117,077 people died from the disease in 2020. MM typically affects elderly patients, with a median age at diagnosis of 70 years; only 37% of patients diagnosed with MM are younger than 65 years of age [6].

Currently, the majority of patients with MM are not cured; however, the use of autologous stem cell transplantation as intensification therapy and the use of consolidation therapy in patients with newly diagnosed MM has prolonged median progression-free survival (PFS) [7,8]. The availability of proteasome inhibitors (PIs; bortezomib, carfilzomib and ixazomib) and immunomodulatory agents (thalidomide, lenalidomide [Len] and pomalidomide) has significantly extended the survival of patients with MM [9–11]. However, patients with MM continually relapse over time, highlighting an urgent need for new therapeutic approaches [12]. Monoclonal antibodies such as daratumumab (anti-CD38) and elotuzumab (antisignaling lymphocytic activation molecule family member 7 [SLAMF7]) were approved for the treatment of relapsed/refractory MM (RRMM) in 2015 [13], and isatuximab (anti-CD38) was approved in 2020 for patients with two prior therapies, including Len and a PI [14].

Historically, in the USA and Europe, the most common first- and second-line therapies for MM include bortezomib and Len-based regimens, respectively [15–17]. These regimens, with or without the glucocorticoid dexamethasone, represented the most common approaches in the earlier 2010s, with expansion into triplet therapy with newer agents (e.g., carfilzomib, ixazomib, daratumumab and elotuzumab) in 2015 [15,16]. Despite the introduction of targeted therapies and combination regimens, patients with MM continue to experience multiple relapses and/or become refractory to treatment [18]. Outcomes, including duration of response and overall survival (OS), worsen with successive lines of therapy [19].

There are several identified factors for MM that can portend prognosis and may be important in terms of determining treatment decisions. Such prognostic factors are categorized by disease burden, host factors, tumor biology and depth of response to therapy [20]. Worse outcomes have been observed in patients with high LDH, increased plasma cell proliferative activity, and in those who have been classified as International Staging System stage III. Additional subgroups of patients with MM and a poor prognosis include those with high-risk cytogenetics, those who have renal impairment, those who are elderly and those who are refractory to prior lines of treatment.

This review summarizes data from the Phase III ICARIA-MM trial (isatuximab in combination with pomalidomide and dexamethasone in RRMM) analyzed by each of these four subgroups that negatively impact prognosis.

**Isatuximab, a monoclonal antibody targeting CD38**

CD38 is a transmembrane glycoprotein involved in the regulation of migration, signal transduction and receptor-mediated adhesion [21–23]. Furthermore, CD38 serves as an ectoenzyme with cyclic ADP-ribose hydrolase activity, catalyzing the metabolism of calcium messengers [23]. CD38 is highly expressed in MM cells and at relatively low levels in other tissues, making this a desirable target for therapeutic antibodies to treat MM [21].

Isatuximab is a monoclonal antibody that binds to a specific epitope of CD38 [24,25]. Isatuximab has anti-MM activity via multiple biological mechanisms (Figure 1). Some mechanisms are mediated by the Fc portion of the antibody, which binds to the Fcγ receptors expressed on effector natural killer cells and macrophages to trigger antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis, or that allows the fixation of the human complement to trigger complement-dependent cytotoxicity [25,26]. Unlike other anti-CD38 antibodies, isatuximab is able to induce direct apoptosis in the absence of cross-linking agents and to inhibit CD38 ectoenzyme activity, which may be specific to the CD38 epitope targeted by isatuximab [24,27]. Increasing CD8+ T-cell responses against NY-ESO-1 were observed in two patients who exhibited an autologous IgG and IgM antibody response against this antigen; these patients also exhibited a newly developed CD8+ T-cell response against CD38 following initiation of isatuximab treatment [28]. Therefore, tumor-specific immune fitness may be associated with clinical responses, and the development of adaptive antitumor immunity in response to isatuximab treatment is clinically relevant.

This review will summarize the data found in the pivotal Phase III ICARIA-MM trial, focusing on the results for specific high-risk patient subgroups, including high-risk cytogenetics, renal impairment, elderly patients and number of prior lines and refractory status.
Figure 1. Mechanisms of action of isatuximab. The CD38 antibody isatuximab was shown to kill multiple myeloma cells by ADCP, ADCC, CDC via the MAC, and direct apoptosis. Isatuximab also inhibits CD38 ectoenzyme activity and the production of immune-suppressive adenosine, which likely alleviate immunosuppressive microenvironment in bone marrow niche of multiple myeloma patients.


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Phase III trial of isatuximab in combination with pomalidomide in RRMM patients (ICARIA-MM)

ICARIA-MM (NCT02990338) was a prospective, randomized, open-label, active-controlled, multicenter Phase III study that compared treatment of isatuximab in combination with pomalidomide and dexamethasone ([Pd], Isa-Pd) with Pd [30,31].

In ICARIA-MM, 307 patients who had received ≥2 prior lines of therapy including Len and a PI were enrolled. Patients in the Isa-Pd arm received 10 mg/kg of isatuximab intravenously weekly for the first 4 weeks, then every other week thereafter. Both arms received approved doses of Pd every 28 days. Treatment continued until disease progression or unacceptable toxicity. The primary end point was PFS. Secondary end points included overall response rate (ORR) and OS.

Randomized patients (154 Isa-Pd and 153 Pd) had a median age of 67 (range: 36–86) years and 19.5% had high-risk cytogenetics. Patients received a median of 3 (range: 2–11) prior lines of therapy, with 92.5% being refractory to Len and 75.9% being refractory to PIs.

At a median follow-up of 11.6 months, PFS was 11.5 months (95% CI: 8.9–13.9) in the Isa-Pd arm versus 6.5 months (95% CI: 4.5–8.3) in the Pd arm, with a hazard ratio (HR) of 0.60 (95% CI: 0.44–0.81); p = 0.001.

The ORR was 60.4% in Isa-Pd versus 35.3% in Pd (p < 0.0001). The proportion of patients who achieved at least a very good partial response (VGPR) rate or better was 31.8% in the Isa-Pd versus 8.5% in the Pd arm. The median time to progression was longer in the Isa-Pd group (12.7 months; 95% CI: 11.2–15.2) than in the control group (7.8 months; 95% CI: 5.0–9.8).

Grade ≥3 adverse events (AEs) were observed in 86.8% of patients in the Isa-Pd arm compared with 70.5% in the Pd arm. However, only 7.2% versus 12.8% of patients discontinued treatment due to AEs in the Isa-Pd and Pd arms, respectively. The most frequent treatment-emergent AEs (TEAEs; any grade) were infusion reactions ([IRs] 38.2% Isa-Pd vs 0% Pd), and respiratory infections (28.3% Isa-Pd vs 17.4% Pd). The most frequent laboratory
abnormality was neutropenia, being reported in 24.3% (grade 3) and 60.5% (grade 4) in the Isa-Pd arm versus 38.8% (grade 3) and 31.3% (grade 4) in the Pd arm.

Overall, the addition of isatuximab to pomalidomide and dexamethasone resulted in a significant and clinically meaningful benefit in PFS and response rate in patients with RRMM, with a manageable safety profile [30,31]. Importantly, the results of ICARIA-MM formed the basis for the approval of isatuximab. Isatuximab (Sarclisa®) is approved in a number of countries in combination with pomalidomide and dexamethasone for the treatment of adult patients with RRMM who have received at least two prior therapies, including Len and a PI. Based on the Phase III IKEMA study, isatuximab in combination with carfilzomib and dexamethasone is approved in the USA for the treatment of adult patients with RRMM who have received one to three prior lines of therapy, and in the European Union for the treatment of adult patients with MM who have received at least one prior therapy [14,32–36].

ICARIA-MM subgroup information

Overall, the ICARIA-MM study population was representative of the global population with RRMM, including important subgroups of patients with characteristics associated with poor prognosis: high-risk cytogenetics defined by the presence of del(17p), translocation t(4;14) and/or translocation t(14;16) (19.5%), renal impairment defined as creatinine clearance <60 ml/min/1.73 m² as determined using the Modification of Diet in Renal Disease (MDRD) equation (36.2%), 75 years of age or older (19.9%), International Staging System stage III (25.1%), Eastern Cooperative Oncology Group performance score of 2 (10.4%) and high levels of LDH (32.2%).

Importantly, all patient subgroups benefited from the addition of isatuximab [31], as shown in Table 1 [31,37–40] and further discussed in the next sections of this review.

ICARIA-MM subgroup: high-risk cytogenetics

A prespecified subgroup analysis of the ICARIA-MM study assessed whether the PFS benefit with isatuximab in addition to pomalidomide and dexamethasone is maintained in patients with high-risk cytogenetics versus standard-risk patients [37,41].

Risk classification based on cytogenetic profiling and careful analysis of risk subgroups is becoming increasingly important in the evaluation of novel MM therapies [42]. Some of the genetic abnormalities that have been associated with MM include the following: high-risk cytogenetics defined by the presence of del(17p), translocation t(4;14) and/or translocation t(14;16) (19.5%), renal impairment defined as creatinine clearance <60 ml/min/1.73 m² as determined using the Modification of Diet in Renal Disease (MDRD) equation (36.2%), 75 years of age or older (19.9%), International Staging System stage III (25.1%), Eastern Cooperative Oncology Group performance score of 2 (10.4%) and high levels of LDH (32.2%).

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<th>Table 1. Summary of safety and efficacy subgroup analyses from ICARIA-MM.</th>
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† Refractory status is a reflection of treatment resistance of the myeloma clone and should not influence systemic safety. TEAE incidence should be interpreted in light of the difference in treatment duration due to longer PFS in the Isa-Pd arm.

d: Dexamethasone; Isa: Isatuximab; Len: Lenalidomide; ORR: Overall response rate; P: Pomalidomide; PFS: Progression-free survival; PI: Proteasome inhibitor; TEAE: Treatment-emergent adverse event.
0.49; 95% CI: 0.19–1.31). The isatuximab treatment effect on PFS was less pronounced in high-risk patients with del(17p) (9.1 vs 7.4 months; HR: 0.76; 95% CI: 0.30–1.92). There was no significant interaction at the 10% level between cytogenetic risk status and treatment groups. There was an observed PFS benefit in both high- and standard-risk patients treated with Isa-Pd, which was less pronounced in patients with del(17p).

Compared with Pd alone, Isa-Pd treatment led to improved ORR from 16.7 to 50.0% in patients with high-risk cytogenetics. A VGPR or better rate was observed in 29.2% of patients in the Isa-Pd cohort versus 2.8% in the Pd cohort, and the treatment benefit was maintained regardless of the high-risk cytogenetic cutoff definition used.

The median time-to-progression benefit observed with isatuximab in the overall ICARIA-MM population was maintained in patients with high-risk cytogenetics. The HRs for del(17p) were 0.62 (95% CI: 0.25–1.53) at 5% cutoff and 0.68 (95% CI: 0.19–2.48) at 60% cutoff. For t(4;14), HRs were 0.34 (95% CI: 0.11–1.04) at 3% cutoff and 0.14 (95% CI: 0.03–0.67) at 60% cutoff. These results indicate that the time-to-progression benefit with isatuximab was maintained in patients with high-risk cytogenetic abnormalities, and the benefit was independent of the cutoff definition used.

Although cross-trial comparisons must be approached with caution due to differences in patient populations, subgroup analyses of other studies investigating anti-CD38 monoclonal antibody combinations in patients with high-risk cytogenetics have demonstrated PFS benefit and increased depth of response. In the Phase III POLLUX study, patients receiving daratumumab plus lenalidomide and dexamethasone exhibited prolonged PFS compared with lenalidomide and dexamethasone alone in both standard- (HR: 0.43; 95% CI: 0.32–0.57) and high-risk (HR: 0.34; 95% CI: 0.16–0.72) patients [47]. Results from a subgroup analysis of the Phase III CASTOR study demonstrated prolonged PFS in patients with standard (HR: 0.26; 95% CI: 0.19–0.37) and high (HR: 0.41; 95% CI: 0.21–0.83) cytogenetic risk treated with daratumumab, bortezomib and dexamethasone compared with bortezomib and dexamethasone alone [48]. In POLLUX and CASTOR, the threshold for positive findings was determined locally and varied by site for each chromosomal abnormality, whereas there were consistent thresholds used by central laboratory analysis in ICARIA-MM, which may contribute to more reliable results. Additionally, POLLUX did not include patients who were refractory to or intolerant of lenalidomide, whereas ICARIA-MM included these patients. Results of an exploratory analysis from the EQUULEUS study investigating the combination of daratumumab, pomalidomide and dexamethasone demonstrated a median PFS of 10.3 months (95% CI: 4.6–NE) for patients with standard cytogenetic risk and 3.9 months (95% CI: 2.3–NE) in those with high cytogenetic risk [49]. This study did not have a control group, so it is difficult to determine the impact of daratumumab on the PFS of patients with standard versus high cytogenetic risk; however, patients with high cytogenetic risk had lower PFS. In the ICARIA-MM study, the benefit of isatuximab in high-risk patients was similar to that observed in standard-risk patients.

**Patients with gain(1q21)**

A retrospective analysis of plasma cells revealed that 128 of 307 (41.7%) patients had gain(1q21) abnormality, with 26.1% having three copies of gain(1q21) and 15.6% having ≥4 copies. Overall, 85 of 307 (27.7%) patients had isolated gain(1q21), which was defined as those patients who had no other high-risk chromosomal abnormalities, including del(17p), t(4;14) or t(14;16), and more patients treated with isatuximab had isolated gain(1q21) (36.4 vs 19.0%). Compared with Pd alone, longer median PFS was observed in patients treated with Isa-Pd who had isolated gain(1q21) (11.2 vs 4.6 months; HR: 0.50; 95% CI: 0.28–0.88) and in patients without gain(1q21) and standard risk (15.2 vs 9.8 months; HR: 0.64; 95% CI: 0.29–1.38). Patients treated with Isa-Pd also exhibited a higher ORR compared with Pd-treated patients, regardless of gain(1q21) status. Compared with patients who received Pd, a higher proportion of patients who received Isa-Pd achieved VGPR or better, including those with isolated gain(1q21) (25.0 vs 3.4%) and those without gain(1q21) with standard risk (34.5 vs 11.4%).

Results from a subgroup analysis of the Phase III ELOQUENT 2 study demonstrated that patients with gain(1q21) treated with the combination of elotuzumab, lenalidomide and dexamethasone exhibited a reduced risk for disease progression or death [50]; however, the combination of elotuzumab, pomalidomide and dexamethasone did not contribute to a PFS benefit in this patient subgroup in the ELOQUENT-3 study [51]. A meta-analysis of daratumumab studies demonstrated a survival benefit with the addition of daratumumab in standard- and high-risk patients; however, the impact of gain(1q21) was not discussed [52]. A recent study investigating the prognostic impact of gain(1q21) in patients who received daratumumab demonstrated shorter PFS and OS among those with gain(1q21) (PFS: 0.5 years [95% CI: 0.3–1.4]; OS: 0.9 years [95% CI: 0.7–2.3]) than patients without gain(1q21) (PFS: 2.1 years [95% CI: 1.9–not reached]; OS: not reached [95% CI: 1.9 years–not reached]). To date, these
findings do not demonstrate a treatment benefit of daratumumab among patients with gain(1q21), whereas the ICARIA-MM study demonstrates improved PFS and ORR with isatuximab treatment in this difficult-to-treat patient subgroup [53].

**Safety**

Isatuximab had a manageable safety profile in both high-risk and standard-risk patients. More grade ≥3 AEs occurred in patients who received Isa-Pd compared with Pd who had high-risk cytogenetics (95.7 vs 67.6%) or standard-risk cytogenetics (85.4 vs 76.3%). The incidence of serious adverse events (SAEs) was also higher following isatuximab treatment compared with Pd alone in the high-risk subgroup (73.9 vs 50.0%), but not in the standard-risk group (58.3 vs 61.8%). The addition of isatuximab to Pd did not increase treatment discontinuations in the high-risk (8.7% Isa-Pd vs 23.5% Pd) or standard-risk subgroups (6.8% Isa-Pd vs 7.9% Pd). Furthermore, treatment-related mortality did not increase in either subgroup following isatuximab treatment compared with the control group.

The most frequent TEAEs in the high-risk Isa-Pd group versus the control group were febrile neutropenia (13 vs 0%) and pneumonia (21.7 vs 17.6%). IRs of grade ≥3 occurred only in the Isa-Pd group, at a frequency of 8.7% in the high-risk population and 1% in the standard-risk population. Among high-risk patients, G-CSF was used in 16 (28.1%) and 21 (36.8%) patients treated with Isa-Pd or Pd, respectively. Among standard-risk patients, G-CSF was used in 70 (39.1%) and 35 (19.6%) patients treated with Isa-Pd or Pd, respectively. Overall, these data demonstrate that the addition of isatuximab to pomalidomide and dexamethasone provides a benefit over pomalidomide and dexamethasone therapy alone in the difficult-to-treat subgroup of patients with RRMM who have high-risk cytogenetics, consistent with the results from the overall ICARIA-MM study population.

**ICARIA-MM subgroup: renal impairment**

Renal impairment affects up to 50% of patients with MM, mainly due to the accumulation and precipitation of Ig free light chains in the distal tubules, resulting in tubule obstruction and cast neuropathy [54]. Moreover, renal impairment is an independent predictor of adverse survival outcomes for MM patients, and is associated with a higher rate of AEs, early mortality and reduced OS [55]. The median survival of patients with renal impairment is approximately half that of patients with no renal impairment [56]. Entry criteria in most clinical trials result in the exclusion of many patients with renal dysfunction; therefore, enrolled candidates may not be representative of the typical patient with MM [50,57–59]. Notably, in the ICARIA-MM, patients were included if they had baseline eGFR ≥30 ml/min/1.73 m², determined using the MDRD equation [31].

An ICARIA-MM subgroup analysis was conducted to examine the efficacy of Isa-Pd in patients with moderate renal impairment (eGFR ≥30 to <60 ml/min/1.73 m²) [38]. In ICARIA-MM, patients were required to have an eGFR ≥30 ml/min/1.73 m² [31]. An eGFR was calculated using the MDRD equation at screening; within 24 h prior to study treatment administration on days 1, 8, 15 and 22 of cycle 1; within 24 h prior to study treatment administration on day 1 of every subsequent cycle; at the end of treatment visits; and as clinically indicated. eGFR results were classified as renal impairment (<60 ml/min/1.73 m²) or no renal impairment (≥60 ml/min/1.73 m²); data were also examined among patients with eGFR <45 ml/min/1.73 m². Complete renal response was defined as an improvement in eGFR less than 50 ml/min/1.73 m² at baseline to ≥60 ml/min/1.73 m² in at least one post-baseline assessment, in accordance with the International Myeloma Working Group recommendations [60]. Responses were considered durable (sustained) when lasting ≥60 days. A minor renal response was defined as an improvement in eGFR from less than 15 ml/min/1.73 m² at baseline to ≥15 to less than 30 ml/min/1.73 m², or from ≥15 to less than 30 ml/min/1.73 m² at baseline to ≥30 ml/min/1.73 m² in at least one assessment during treatment.

In the Isa-Pd arm, the number of patients with renal impairment at baseline was 39% with eGFR less than 60 ml/min/1.73 m² and 38% with eGFR ≥30 to 60 ml/min/1.73 m². In the Pd arm, 34% of patients had eGFR less than 60 ml/min/1.73 m² and 33% had eGFR ≥30 to 60 ml/min/1.73 m². No patients were receiving renal replacement therapy or hemodialysis.

The median PFS for patients with renal impairment was 9.5 months in those receiving Isa-Pd (n = 55) and 3.7 months in those receiving Pd (n = 49; HR: 0.50; 95% CI: 0.30–0.85). Among patients with an eGFR less than 45 ml/min/1.73 m², the median PFS was 7.5 with Isa-Pd (n = 20) and 2.8 months with Pd (n = 17; HR: 0.50; 95% CI: 0.22–1.13). Among patients without renal impairment, median PFS was 12.7 months in the Isa-Pd arm (n = 87) and 7.9 months in the Pd arm (n = 96; HR: 0.58; 95% CI: 0.38–0.88).
At the time of the primary analysis, median OS for patients with renal impairment was not reached in patients receiving Isa-Pd versus 11.6 months in those receiving Pd (HR: 0.53; 95% CI: 0.30–0.96). Among patients with an eGFR less than 45 ml/min/1.73 m², median OS was 10.7 months for the Isa-Pd arm versus 6.6 months for the Pd arm (HR: 0.62; 95% CI: 0.26–1.45). Among patients without renal impairment, median OS was not reached with Isa-Pd or Pd (HR: 0.62; 95% CI: 0.33–1.19).

A higher ORR was achieved with Isa-Pd versus Pd treatment, regardless of renal impairment status. The ORR was 56.4% (Isa-Pd) and 24.5% (Pd) for patients with renal impairment (odds ratio [OR]: 3.98; 95% CI: 1.60–10.17). Among those with renal impairment, a VGPR or better was achieved by more patients treated with Isa-Pd (32.7%) than Pd (4.1%). A total of eight patients receiving Isa-Pd achieved MRD negativity (sensitivity level: 10⁻⁵); of these, three had an eGFR less than 60 ml/min/1.73 m². No patients receiving Pd achieved MRD negativity. Among patients with eGFR less than 45 ml/min/1.73 m², the ORR was 35.0 and 23.5% in the Isa-Pd and Pd arms, respectively (OR 1.75; 95% CI: 0.34–10.11). Among patients without renal impairment, the ORR was 67.8% in the Isa-Pd arm and 42.7% in the Pd arm (OR: 2.83; 95% CI: 1.48–5.42). Among patients with mild renal impairment (eGFR ≥45 to <60 ml/min/1.73 m²), the ORR was 68.6% in those treated with Isa-Pd (n = 35), which was similar to the ORR in patients without renal impairment. For patients with mild renal impairment in the Pd arm (n = 32), the ORR was 25.0%.

Complete renal responses were observed in 71.9% (23/32) of patients receiving Isa-Pd and 38.1% (8/21) of those receiving Pd (OR: 4.15; 95% CI: 1.12–15.78). More frequent durable complete renal responses were achieved with Isa-Pd (31.3%) versus Pd (19.0%; OR: 1.93; 95% CI: 0.45–9.82). A minor renal response was observed in one patient receiving Isa-Pd. Among responders, the median time to renal response was 3.4 weeks for patients treated with Isa-Pd and 7.3 weeks for patients treated with Pd.

Fewer patients progressed to end-stage renal disease (eGFR <15 ml/min/1.73 m²) during treatment with Isa-Pd compared with Pd (2.9 vs 7.9%). Among patients with moderate renal impairment at baseline, renal function worsened to severe renal impairment or end-stage renal disease in 22.6% of patients treated with Isa-Pd and 34.8% of patients treated with Pd (OR: 0.55; 95% CI: 0.20–1.45).

All patients with renal impairment experienced AEs, whereas 98.8 and 96.8% of patients without renal impairment experienced AEs in the Isa-Pd and Pd arms, respectively. There was a ≥10% higher incidence of cardiac disorders and infections in patients with versus without renal impairment in the Isa-Pd arm. The incidence of grade ≥3 AEs was similar for all patients treated with Isa-Pd, regardless of renal impairment status (90.7% with renal impairment vs 86% without renal impairment). IRs were more common in patients receiving Isa-Pd than in patients receiving Pd, affecting around a third of patients both with and without renal impairment. The incidence of AEs leading to definitive treatment discontinuation was higher in patients with renal impairment who received either Isa-Pd or Pd.

The pharmacokinetics of isatuximab were comparable between the renal subgroups, which was expected because monoclonal antibodies are not renally excreted. Therefore, there is no pharmacokinetics-based need for dose adjustment in patients with renal impairment. The results of this ICARIA-MM subgroup analysis provide evidence of improvement in renal function with Isa-Pd treatment. Results from the EQUULEUS study investigating the combination of daratumumab, pomalidomide and dexamethasone demonstrated that patients with and without renal impairment exhibited a similar ORR (58.1 and 61.1%, respectively), which was also comparable with that observed in the entire cohort (60.2%) [49]. To be included, patients needed a calculated creatinine clearance ≥45 ml/min/1.73 m²; therefore, these patients had less renal impairment compared with those included in the ICARIA-MM. There are currently no studies reporting renal response in patients with MM treated with daratumumab.

**ICARIA-MM subgroup: elderly patients**

MM is a neoplastic disease which typically affects elderly patients. MM is most frequently diagnosed in people aged 65–74 years, with a median age at diagnosis of 69 years [61,62]. Elderly patients comprise a heterogeneous population with the potential for various co-morbidities, reduced functional status and increased risk of frailty. Furthermore, due to restrictive trial entry criteria in most clinical trials, the majority of very elderly patients are excluded, and the candidates enrolled in trials aged ≥75 years tend to be unusually fit and are not representative of the typical elderly patient [63].

Due to its prognostic relevance, age (<75 vs ≥75 years) was one of the stratification factors of ICARIA-MM. A prespecified subgroup analysis comparing efficacy and safety in patients aged ≥75 years, 65–74 years and less than
65 years was conducted [39,64]. The median age of patients was 68.0 years in the Isa-Pd arm and 66.0 years in the Pd arm. In the Isa-Pd and Pd arms, there were 54 (35.1%) and 70 (45.8%) patients younger than 65 years of age, 68 (44.2%) and 54 (35.3%) patients 65–74 years of age, and 32 (20.8%) and 29 (19.0%) patients ≥75 years of age, respectively.

PFS was significantly improved with Isa-Pd versus Pd in all age groups; patients ≥75 years of age had a median PFS of 11.4 versus 4.5 months, respectively (HR: 0.48; 95% CI: 0.24–0.95). Similarly, in the Isa-Pd and Pd groups, patients 65–74 years of age had a PFS of 11.6 and 8.6 months (HR: 0.64; 95% CI: 0.39–1.06); in patients younger than 65 years of age, PFS was 11.5 versus 5.0 months, respectively (HR: 0.66; 95% CI: 0.40–1.07).

The ORRs in patients receiving Isa-Pd versus Pd by age group were as follows: 53.1 and 31.0% in patients aged ≥75 years (OR: 2.52; 95% CI: 0.79–8.26); 64.7 and 38.9% in patients aged 65–74 years (OR: 2.88; 95% CI: 1.29–6.46); and 59.3 and 34.3% in patients aged younger than 65 years (OR: 2.79; 95% CI: 1.26–6.20). The proportion of patients achieving at least a VGPR or better by age in patients receiving Isa-Pd versus Pd was 31.3 versus 0% in those aged ≥75 years (OR not calculated); 32.4 versus 13.0% in those aged 65–74 years (OR: 3.21; 95% CI: 1.17–9.70); and 31.5 versus 8.6% in those aged younger than 65 years (OR: 4.90; 95% CI: 1.64–16.35).

Of eight patients with negative MRD at 10−5 in the Isa-Pd arm, two patients were ≥75 years of age, PFS was 11.5 versus 5.0 months, respectively (HR: 0.66; 95% CI: 0.40–1.07).

In the Isa-Pd arm, nearly all patients reported AEs of any grade, with an incidence of 100% among patients aged ≥75 years, 100% among those aged 65–74 years and 98.1% among those aged younger than 65 years. There were more grade ≥3 AEs with Isa-Pd in patients aged ≥75 years (93.8%) compared with patients younger than 65 years of age (85.2%), with a similar trend observed in the Pd arm (75.0 and 64.7%, respectively). There were also more treatment discontinuations due to AEs in patients ≥75 versus <65 years of age who received Isa-Pd (15.6 and 7.4%, respectively) and Pd (14.3 and 10.3%, respectively).

There was a higher incidence of SAEs in patients ≥75 versus less than 65 years of age in both arms (Isa-Pd, 68.8 and 57.4%; Pd, 57.1 and 47.1%, respectively). The incidence of AEs with fatal outcome was lower in patients aged ≥75 years who received Isa-Pd (6.3%) than in patients aged less than 65 years (11.1%), whereas the opposite trend was observed with Pd (14.3 vs 5.9%). TEAEs were reported in 98.1 versus 97.1% of patients aged less than 65 years who received Isa-Pd versus Pd, respectively. In those who received Isa-Pd, the most common nonhematologic AE of any grade was IR, regardless of age group. There was a trend toward fewer IRs in patients aged ≥75 years (28.1%) compared with patients aged 65–74 years (36.4%) or less than 65 years (42.6%).

In the Isa-Pd arm, AEs with the greatest difference in incidence for patients aged ≥75 versus less than 65 years were IRs (28.1 vs 42.6%) and acute kidney injury (15.6 vs 1.9%). A similar difference in the incidence of acute kidney injury was seen among patients treated with Pd (10.7 vs 5.9%). In both treatment groups, grade ≥3 AEs were more frequent in patients aged ≥75 years than in those aged less than 65 years (Isa-Pd, 93.8 vs 85.2%; Pd, 75.0 vs 64.7%). The most common grade ≥3 nonhematologic AE was pneumonia, regardless of patient age or treatment group. Grade 3–4 neutropenia and thrombocytopenia, based on laboratory results, were more common with Isa-Pd than Pd, regardless of patient age group. Neutropenia and infections were reversible and manageable with appropriate supportive care (G-CSF/granulocyte-macrophage colony-stimulating factor and antibiotics, respectively). The incidence of grade 4 thrombocytopenia was higher following Isa-Pd treatment compared with Pd treatment for patients aged ≥75 and 65–74 years, whereas the contrary was true for patients aged less than 65 years. No patient discontinued isatuximab due to neutropenia or thrombocytopenia.

Overall, the addition of isatuximab to Pd improved PFS, ORR and rates of VGPR or better in elderly patients, consistent with the benefit observed in the overall study population [50]. There was a consistent trend toward higher rates of SAEs and discontinuation due to AEs in elderly patients in both the Isa-Pd and Pd arms, but no increase in fatal AEs was observed in the Isa-Pd arm. In the EQUULEUS study, the combination of daratumumab, pomalidomide and dexamethasone demonstrated an ORR of 60%, a PFS of 8.8 months and a median OS of 17.5 months at a median follow-up of 13.1 months [49]. The ORR was 57.7% among patients aged less than 65 and 62.7% among those aged 65 years or older. In a subgroup analysis of the Phase III POLLUX and CASTOR studies, daratumumab, lenaliidomide and dexamethasone led to significantly prolonged PFS in patients aged 65–74 years (HR: 0.25; 95% CI: 0.16–0.40) and in those aged 75 years or older (HR: 0.26; 95% CI: 0.10–0.65) [65]. The daratumumab combination also led to improved ORR and MRD-negative status in both age groups. Grade 3/4 AEs were more common in patients aged 75 or older compared with younger patients (86.2 vs 77.1%, respectively). The combination of daratumumab, bortezomib and dexamethasone also contributed to significantly prolonged PFS, VGPR or better, and MRD-negative status regardless of age, with more grade 3/4 AEs reported in patients aged 75 years or older with the daratumumab combination [65]. The patients in ICARIA-MM were older
than patients in EQUULEUS, CASTOR or POLLUX, and in particular, there was a higher percentage of patients aged 75 years or older included in ICARIA-MM. The ICARIA-MM study demonstrated a benefit with isatuximab treatment leading to improved PFS and ORR, with no increase in fatal AEs in this older patient population.

**ICARIA-MM subgroup: prior lines & refractory status**

The number of previous lines of treatment that a patient has received is an important consideration in treatment sequencing [66]. It is, therefore, important to evaluate novel therapies for RRMM based on patients’ prior therapies, and another prespecified subgroup analysis of ICARIA-MM was designed to evaluate the efficacy of isatuximab by prior lines of treatment and refractory status [40,67]. Furthermore, due to restrictive trial entry criteria in most clinical trials, refractory patients may be excluded, resulting in enrolled candidates that may not be representative of the typical patient with MM [58,59].

In the ICARIA-MM study, patients receiving Isa-Pd and Pd were heavily pretreated, with patients receiving a median of three prior lines of therapy (range: 2–11) [31]. Overall, 66.1% received 2–3 prior lines of therapy and 33.9% received greater than three prior lines of therapy. A total of 92.5% of patients were refractory to Len and 75.9% to a PI, 58.9% of patients were refractory to Len at last line of treatment before study entry and 71.0% of patients were double refractory (Len + PI). A subgroup analysis revealed that the median PFS among Len-refractory patients with Isa-Pd (n = 144) was 11.4 versus 5.6 months with Pd (n = 140; HR: 0.60; 95% CI: 0.43–0.82). Additionally, PFS was higher with Isa-Pd (n = 93) versus Pd (n = 88) for patients that were refractory to Len as their last line of treatment before study entry (11.6 vs 5.7 months; HR: 0.50; 95% CI: 0.34–0.76). Median PFS in PI-refractory patients with Isa-Pd (n = 118) was 11.4 versus 5.6 months in the control group (n = 115; HR: 0.58; 95% CI: 0.41–0.82). In double-refractory patients, median PFS was 11.2 months with Isa-Pd (n = 111) and 4.8 months with Pd (n = 107; HR: 0.58; 95% CI: 0.40–0.84). Finally, PFS was higher in the Isa-Pd arm compared with the Pd arm for patients who had received 2–3 prior lines of therapy (12.3 vs 7.8 months; HR: 0.59; 95% CI: 0.40–0.88) and greater than three prior lines of therapy (9.4 vs 4.3 months; HR: 0.59; 95% CI: 0.36–0.98).

Patients refractory to Len, PIs, Len-PI and Len at last line of treatment had a higher ORR with Isa-Pd than Pd. ORR in patients receiving Isa-Pd versus Pd, respectively, was 59.0 versus 31.4% in Len-refractory patients; 60.2 versus 32.2% in PI-refractory patients; and 58.6 and 29.9% in double-refractory patients. The proportion of Len-refractory patients achieving VGPR or better was also higher with Isa-Pd versus Pd. Among the patients who received Isa-Pd, 30.6% (95% CI: 0.23–0.39) achieved VGPR or better compared with 7.1% (95% CI: 0.03–0.13) of patients who received Pd. Comparable results were also seen in PI-refractory patients, with 30.5% (95% CI: 0.22–0.40) versus 7.8% (95% CI: 0.04–0.14); in double refractory patients, with 29.7% (95% CI: 0.21–0.39) versus 8.4% (95% CI: 0.04–0.15); and in patients who were refractory to Len at last line of treatment, with 32.3% (95% CI: 0.23–0.43) versus 4.5% (95% CI: 0.01–0.11) achieving VGPR or better rate in the Isa-Pd versus the Pd arm, respectively.

Because refractory status reflects the treatment resistance of the myeloma clone, it should not impact systemic safety; however, prior lines of therapy reflect the extent of treatment exposure, which may influence safety. Therefore, safety for patients treated with Isa-Pd and Pd based on prior therapy lines are described below.

Among patients who received two prior lines of therapy, TEAEs were reported by 45 (100%) patients treated with Isa-Pd and by 43 (97.7%) patients treated with Pd. Grade ≥3 TEAEs and treatment-emergent SAEs were more frequently reported in patients treated with Isa-Pd (86.7 and 60.0%) compared with Pd (63.6 and 47.7%). Fewer patients receiving Isa-Pd experienced TEAEs resulting in treatment discontinuation compared with patients receiving Pd (2.2 vs 6.8%).

Similar results were observed in patients receiving ≥3 prior lines of therapy. Grade ≥3 TEAEs and treatment-emergent SAEs were more frequently reported in patients treated with Isa-Pd (86.9 and 62.6%, respectively) compared with Pd (73.3 and 56.2%, respectively). Fewer patients receiving Isa-Pd experienced TEAEs, resulting in treatment discontinuation compared with patients receiving Pd (9.3 vs 15.2%, respectively).

The most common TEAE of any grade following isatuximab treatment was infection, affecting patients who had received 2 and ≥3 prior lines of therapy similarly (80.4 vs 82.2%, respectively), which was similar to the results reported for the overall ICARIA-MM population [31]. Patients receiving two prior lines of therapy experienced more IRs following Isa-Pd treatment compared with patients who had received ≥3 prior lines of therapy (48.9 vs 31.8%).

Overall, the addition of isatuximab to pomalidomide and dexamethasone improved PFS and ORR regardless of number of prior lines of therapy and in patients that were refractory to Len, refractory to Len at last line,
and double refractory, consistent with the benefit observed in the overall ICARIA-MM population. Although cross-trial comparisons must be approached with caution due to differences in patient populations, results from the EQUULEUS study demonstrated a 58% ORR among double-refractory patients treated with the combination of daratumumab, pomalidomide and dexamethasone [49]. Additionally, 52% of the 103 patients had received more than three prior lines of therapy and the ORR for this subgroup was not significantly different from that of the whole cohort. The primary analysis of APOLLO, an ongoing Phase III trial of daratumumab plus pomalidomide and dexamethasone, showed a median PFS of 12.4 months (HR: 0.63) and an ORR of 69% in patients receiving daratumumab, pomalidomide and dexamethasone after a median follow-up of 16.9 months [68]. Of note, the median number of prior therapy lines was lower in APOLLO than in ICARIA-MM (2 vs 3) and the percentage of patients refractory to Len (79 vs 94%), a PI (47 vs 77%) or Len-PI (42 vs 72%) was also lower in APOLLO (daratumumab/pomalidomide/dexamethasone) than in ICARIA-MM (Isa-Pd).

Conclusion
The addition of isatuximab to pomalidomide and dexamethasone led to more frequent durable complete renal responses and improved PFS and disease response rates across different subgroups of patients with RRMM, independent of the high-risk cytogenetic status, renal impairment, age of patients or number of prior lines of treatment or refractory status. Treatment with Isa-Pd was able to overcome the adverse risk factors of age, refractory status and number of prior lines, resulting in similar PFS compared with the overall ICARIA-MM population.

Future perspective
Triplet therapy has become the standard treatment option for patients with RRMM, with a focus on anti-CD38 monoclonal antibodies as part of these regimens. Although recent treatment combinations have contributed to substantial improvements in survival of patients with MM, these benefits are not always realized among patients with poor prognostic criteria, including those with high-risk cytogenetics, those who are refractory to prior lines of treatment, those who have renal impairment, and those who are elderly, highlighting a need for improved and novel therapeutic strategies. Results from the ICARIA-MM trial demonstrated improved PFS and disease response rates, regardless of prognostics, with the addition of isatuximab to pomalidomide and dexamethasone making Isa-Pd an important treatment option for patients with RRMM [69]. As additional combinations and therapies, including CAR T-cell therapy and bispecific antibodies, are investigated for the treatment of patients with RRMM, subgroups with poor prognostic factors must be considered and included to help mitigate the unmet need for this patient population.

Executive summary

Multiple myeloma
- Multiple myeloma (MM) is the second most frequent hematologic malignancy. Currently, the majority of patients with MM are not cured.
- Patients with MM continuously relapse over time, highlighting a need for new therapeutic approaches, particularly among subgroups of patients who have a poor prognosis, including those with high-risk cytogenetics, those who are refractory to prior lines of treatment, those who have renal impairment, and those who are elderly.

Isatuximab
- Isatuximab is a monoclonal antibody that binds to a specific epitope of CD38, resulting in antibody-dependent cell-mediated cytotoxicity and exerting synergistic effects in combination with pomalidomide.
- Based on the Phase III ICARIA-MM study, isatuximab (Sarclisa®) is approved in a number of countries in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory MM (RRMM) who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor. Based on the Phase III IKEMA study, isatuximab in combination with carfilzomib and dexamethasone is also approved in the USA for the treatment of adult patients with RRMM who have received one to three prior lines of therapy, and in the European Union for the treatment of adult patients with MM who have received at least one prior therapy.

ICARIA-MM
- ICARIA-MM was a prospective, randomized, open-label, Phase III trial, which was designed to compare treatment of isatuximab in combination with pomalidomide (P) and dexamethasone ([d], Isa-Pd) with Pd in patients with RRMM.
- Patients who received Isa-Pd exhibited prolonged progression-free survival (PFS), increased overall response rate (ORR) and longer median time to progression compared with patients who received Pd.
• There was consistent benefit in the overall ICARIA-MM population and the subgroup populations presented in this review article.

**High-risk cytogenetics**

• High-risk cytogenetic markers associated with reduced survival in MM include the presence of t(4;14), t(14;16), del (17p) and/or gain(1q21).

• The addition of isatuximab to pomalidomide and dexamethasone provides a consistent benefit over pomalidomide and dexamethasone therapy alone in the difficult-to-treat subgroup of patients with RRMM who have high-risk cytogenetics.

**Renal impairment**

• The addition of isatuximab to pomalidomide and dexamethasone led to improved PFS and ORR among patients with renal impairment.

• Renal function is improved with the addition of isatuximab to pomalidomide and dexamethasone in patients with RRMM.

**Elderly patients**

• Adding isatuximab to pomalidomide and dexamethasone led to improved PFS and ORR in elderly patients aged 65–74 years and ≥75 years.

• A trend toward higher rates of serious adverse events and discontinuation due to adverse events was observed with both Isa-Pd and Pd treatment; however, there was no increase in fatal adverse events with Isa-Pd treatment.

**Prior lines/refractory status**

• In ICARIA-MM, 76% of patients were refractory to lenalidomide or a proteasome inhibitor (PI), 59% were refractory to lenalidomide at last line of treatment and 71% of patients were refractory to both lenalidomide and a PI.

• The addition of isatuximab to pomalidomide and dexamethasone improved PFS and ORR regardless of the number of prior lines of therapy and in patients who are refractory to lenalidomide and/or a PI.

**Supplementary data**

An infographic accompanies this paper and is included at the end of the references section in the PDF version. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0568

**Author contributions**

F Campana, the funder's clinical study director, was responsible for oversight of the ICARIA-MM study. PG Richardson was a coprimary investigator of this study. PG Richardson, SJ Harrison, S Bringhen, F Schjesvold, K Yong and MA Dimopoulos were investigators of the study and contributed to data acquisition. PG Richardson, F Campana and S Le-Guennec designed the study. S Le-Guennec, S Macé, and F Campana contributed to the data analysis and interpretation. All the authors revised this work for important intellectual content and assume responsibility for integrity of the data and the decision to submit for publication; had full access to the study data; and edited and reviewed manuscript drafts, and approved the final draft for submission.

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Data sharing statement
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 anonymized, 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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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest


- **This initial study demonstrated the antitumor activity of isatuximab (SAR650984) in cell lines, primary multiple myeloma (MM) samples and MM xenograft models in immunodeficient mice. The findings warranted Phase I clinical trial investigation in patients with CD38+ B-cell malignancies.**


- **This pivotal Phase III study demonstrated the safety and efficacy of isatuximab in combination with pomalidomide and dexamethasone in patients with relapsed/refractory MM.**


- **This press release announced the approval of isatuximab by the European Commission for use in the 27 member states of the European Union, plus the UK, Iceland, Liechtenstein and Norway.**


- **This press release announced the approval of isatuximab in Japan.**


- **This press release announced the approval of isatuximab by the Russian Federation.**


- **This press release announced the approval of isatuximab by the Korean Ministry of Food & Drug Safety.**


- **This subgroup analysis of the Phase III ICARIA-MM study demonstrated that the addition of isatuximab to pomalidomide and dexamethasone provides a consistent benefit over pomalidomide and dexamethasone therapy alone in the difficult-to-treat subgroup of patients with relapsed/refractory MM who have high-risk cytogenetics.**


- **This subgroup analysis of the Phase III ICARIA-MM study demonstrated that the addition of isatuximab to pomalidomide and dexamethasone led to improved progression-free survival (PFS) and overall response rate (ORR) among patients with renal impairment.**
This subgroup analysis of the Phase III ICARIA-MM study demonstrated that the addition of isatuximab to pomalidomide and dexamethasone led to improved PFS and ORR among elderly patients aged 65–74 years and ≥75 years, with no increase in fatal adverse events.

This subgroup analysis of the Phase III ICARIA-MM study demonstrated that the addition of isatuximab to pomalidomide and dexamethasone led to improved PFS and ORR regardless of the number of prior lines of therapy and in patients who are refractory to lenalidomide and/or a proteasome inhibitor.


