

Updates on Isatuximab in Relapsed/Refractory and Newly Diagnosed Multiple Myeloma



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Speakers:	Philippe Moreau, ¹ Katja Weisel ² 1. Department of Hematology, University Hospital Hôtel-Dieu, Nantes, France 2. Department of Oncology and Hematology, University Hospital Hamburg-Eppendorf, Germany
Disclosure:	Moreau has received honoraria from and has served in a consulting or advisory role for Amgen, Celgene, Janssen Pharmaceuticals, Novartis, and Takeda Pharmaceutical Company. Weisel has received honoraria from and has served in an advisory board role for Amgen, Adaptive Biotech, Bristol Myers Squibb, Celgene, Janssen Pharmaceuticals, Sanofi, Takeda Pharmaceutical Company, GlaxoSmithKline, Abbvie, and Karyopharm Therapeutics. Moreau and Weisel have received institutional research funding from Amgen, Celgene, Sanofi, and Janssen Pharmaceuticals.
Acknowledgements:	Medical writing assistance was provided by Allison Kirsop, Scientific Writers Ltd., Edinburgh, UK.
Support:	This article is sponsored by Sanofi Genzyme with no input on editorial content except for a check on factual accuracy.
Citation:	EMJ Hematol. 2022;10[Suppl 1]:2-10.

Meeting Summary

Key talks and poster sessions from the 25th and 26th Annual Congress of the European Hematology Association (EHA), held virtually in both 2020 and 2021, respectively, are featured in this summary article. New data regarding the efficacy and safety of isatuximab (Isa), an anti-CD38 monoclonal antibody (mAb) with demonstrated anti-tumour activity in CD38+ malignancies, are reported in patients with relapsed/refractory (RR) and newly diagnosed (ND) multiple myeloma (MM).

Philippe Moreau discussed the findings of IKEMA, the first planned interim analysis of the large multicentre Phase III study that investigated the therapeutic effect of Isa added to carfilzomib (K) and dexamethasone (d) in RRMM patients, along with IKEMA trial subgroup analyses by Facon et al., Spicka et al., and Dimopoulos et al. Additional updates to the current data available for Isa treatment in this patient population are also covered in this article, taken from poster sessions by Usmani et al., Davies et al., and Dimopoulos et al. An update on the ICARIA-MM trial presented at EHA 2021 is included from Perrot et al. Katja Weisel presented findings from the GMMG-CONCEPT study (induction with Isa, K, lenalidomide [R], and d in high-risk patients with NDMM who were transplant eligible [Te] and transplant ineligible [Ti]), including an exploratory interim analysis of the mobilisation of autologous stem cells in these patients from a poster by Asemissen et al. In addition, an update from a Phase IB study of Isa, bortezomib (V), and d plus cyclophosphamide, or R combination therapy in Ti patients with NDMM was presented in a poster by Ocio et al.

Introduction

In the past decade, therapies that are more effective and less toxic have transformed the treatment landscape for patients with MM.

Nevertheless, many patients will eventually become refractory to the current haematologic standard of care treatments of proteasome inhibitors (PI), immunomodulatory agents (IMiD), and mAb therapies, with relapse almost

a certainty.¹ Isa, a CD38 mAb, is approved in combination with pomalidomide (P) and low-dose d in adult patients with RRMM who have had at least two prior therapies, including R and a PI.² To date, Isa in combination with K and d is approved in the USA for the treatment of adult patients with RRMM who have received one to three prior lines of therapy,² and in the European Union (EU) for the treatment of adult patients with MM who have received at least one prior therapy.³

Generally, treatment patterns in MM reveal that for triple-class exposed (TCE) patients receiving PI, IMiD, and anti-CD38 therapies, outcomes have been somewhat better than in individuals who received previous regimens.⁴ However, for patients who relapse, the options are still limited. A systematic review evaluated the published evidence regarding the treatment of TCE patients with RRMM (≥ 3 prior therapies), and revealed that only three studies, one real-world (MAMMOTH) study and two clinical studies (STORM part 2; DREAMM-2), have reported data on treatment efficacy and safety in these patients. The authors also established that no head-to-head randomised clinical studies comparing novel RRMM treatments in TCE patients had been identified in the literature searched.⁵ More recently, results of the first prospective real-life study in heavily pre-treated, TCE patients with RRMM were also published.⁶

In this article, summaries of the first interim analyses of two clinical studies are presented: the pivotal Phase III IKEMA study investigating Isa added to Kd in RRMM⁷ and the Phase II GMMG-CONCEPT study investigating Isa-KRd quadruplet treatment in NDMM.⁸ In addition, an update of the ICARIA-MM study along with selected data from the aforementioned poster sessions are also included. Updated findings from the EHA 2021 congress highlight the most recent study results and subgroup analyses.

Relapsed/Refractory Multiple Myeloma

Interim Analysis of the IKEMA Study

In a late breaking abstract at the EHA 2020 congress, Moreau presented exciting new data from the first planned interim analysis of the large

multicentre Phase III IKEMA study,^{7,9} published in 2021,¹⁰ which sought to determine the risk-benefit ratio of adding Isa to Kd in RRMM. The primary endpoint of the interim analysis was progression-free survival (PFS), assessed by an independent review committee. Secondary endpoints included overall response rate (ORR), very good partial response (VGPR), minimal residual disease (MRD) negativity, complete response (CR), and overall survival (OS).

Patient demographics

A total of 302 patients with RRMM who had previously undergone one to three lines of treatment were randomised 3:2 to receive either Isa-Kd (n=179) or Kd (n=123). Eligible patients had no prior treatment with K and were not refractory to prior anti-CD38 therapy. The Isa-Kd arm received intravenous Isa (10 mg/kg) weekly for 4 weeks, then every 2 weeks. Both arms received K (20 mg/m² for Days 1 and 2, then 56 mg/m² thereafter) twice weekly for 3 or 4 weeks, and d (20 mg) twice weekly. Patients continued to receive treatment until disease progression or the occurrence of an unacceptable adverse event. The median number of prior lines of treatment was two (interquartile range [IQR]: 1-2), although a line calculation error resulted in three patients enrolled with four previous lines of therapy (Isa-Kd group: 1; control group: 2). The large majority of patients were previously exposed to PIs and IMiDs, with 33% of patients refractory to R at study entry.¹⁰

Efficacy data

An improvement in PFS was clearly demonstrated with Isa-Kd in this patient population; improved CR, \geq VGPR, and MRD-negativity rates were also more evident in patients with a gain of chromosome arm 1q21 than in those with high-risk cytogenetic abnormality alone.¹¹ Compared with the Kd arm in the Phase III IKEMA study, the Isa-Kd arm showed improvement in PFS after 27 months, with a 47% reduction of risk of disease progression or death (hazard ratio [HR]: 0.53; p=0.0007). The PFS benefit was observed across all patient subgroups: patients who were ≤ 65 or ≥ 65 years of age, with or without prior PI or IMiD treatment, and who were or were not refractory to R.

Baseline renal impairment (estimated glomerular filtration rate: < 60 mL/min per 1.73 m²) was 26%

compared with 16% in the Isa-Kd and control groups, respectively. In a subgroup analysis, an evaluation of the efficacy and safety of Isa-Kd by number of prior lines of therapy (1 versus >1) and refractory status to R or V was carried out to investigate better options for patients.¹² An improvement in PFS was observed with Isa-Kd compared with Kd alone in patients who received one and more than one prior lines of therapy, as well as those refractory to R and V. The depth of response for CR, \geq VGPR, and MRD-negativity rates were all improved with Isa-Kd, and Grade \geq 3 treatment emergent adverse events (TEAEs) were comparable between subgroups. TEAEs leading to discontinuation were 9% versus 11% for patients with one prior line of therapy, and 8% versus 16% for those with more than one.¹²

Patient disposition

Baseline characteristics for study participants were balanced in both arms. The median age for the patient population was 64 years, with 9% of the cohort over 75 years. High-risk cytogenetics were found in 23% of patients in the Isa-Kd group compared with 25% in the control group, as defined by a cut-off of 50% for 17p deletion and 30% for translocations 4;14 and 14;16. As of 7th February 2020, patient disposition data showed that discontinuation of treatment due to disease progression or adverse event was 37% and 54% in the Isa-Kd versus Kd arms, respectively. Median duration of follow-up was 20.7 months (IQR: 19.4–22.1) and a higher percentage of patients (52%) were still receiving treatment in the Isa-Kd arm at this time, compared with 31% in the Kd arm. The primary endpoint of PFS had not been reached in the Isa-Kd arm; the control arm performed well with a median PFS of 19.15 months, consistent with that reported in the ENDEAVOR study of Kd versus Vd for relapsed MM.¹³

Depth of response improvement was achieved in both arms of the study, but deeper responses were observed with Isa-Kd: the ORR for patients taking Isa-Kd versus Kd alone was 87% and 83%, respectively (one-sided $p=0.19$). The addition of Isa to Kd did, however, appear to improve the quality of response of patients reaching VGPR or better (Isa-Kd: 73%; Kd: 56%; $p=0.0011$), and CR rates of 40% and 28% were achieved, respectively. Consistent with the striking improvement in PFS, deeper responses were

seen with Isa-Kd in MRD-negativity, assessed by next-generation sequencing at threshold 10^{-5} , which was approximately 30% in the intention-to-treat population versus 13% in the Kd arm ($p=0.004$), demonstrating improved PFS across all patients.

Importantly, time-to-next-treatment (TTNT) was significantly delayed with Isa-Kd (HR: 0.57) and was consistent with PFS improvement. A total of 26% of patients in the Isa-Kd group received at least one additional anti-myeloma treatment, compared with 43% in the control group. Of those receiving a subsequent treatment, daratumumab (dara) was administered to 21% (47 out of 179) and 47% (53 out of 123) of patients, respectively. Health-related quality of life (HRQoL), which was measured by the QLQ-C30 Global Health Status score, was also maintained with Isa-Kd. Regarding OS, there was no significant difference between the two study arms at 20.7 months; therefore, data for this specific outcome will be reported in a future publication once the data are more mature. In the Isa-Kd arm, exposure to study treatments was longer, with a median duration treatment time of 80.0 weeks (IQR: 40.0–89.0) compared with 61.4 weeks (IQR: 28.9–84.0) in the Kd arm.

Safety data

Overall, Isa-Kd had a manageable safety profile with no new safety signals and adding Isa to Kd did not appear to increase toxicity; for example, cardiac failure events of Grade \geq 3 were 4% for both arms of the study. A higher rate of Grade \geq 3 TEAEs was observed in the Isa-Kd arm compared with Kd (77% and 67%, respectively), which may be related to the longer treatment exposure in the Isa-Kd group. However, despite this observation, there was no difference in the number of fatal TEAEs (6 versus 4 patients [3%]), nor did the addition of Isa to Kd produce any increase in serious TEAEs or events leading to definitive discontinuation (8% versus 14%, respectively).

The safety analysis showed that infusion-related reactions mainly occurred during the first infusion and were higher for the Isa-Kd group; however, these were mostly Grade 1 or 2, with a K-induced Grade 3 reaction occurring in one patient in the Isa-Kd group. There were more Grade \geq 3 respiratory infections reported in the Isa-Kd group than in the control group (32%

versus 24%), largely due to pneumonia, but these did not lead to increased fatal infections or treatment discontinuations. Laboratory Grade ≥ 3 neutropenia was higher in the Isa-Kd group (19% versus 7%), although Grade 4 neutropenia events were similar between the groups (2% versus 1%, respectively). Febrile neutropenia and neutropenic infection occurred in 3% of patients in the Isa-Kd group compared with none in the control group. A high relative dose intensity of both K and d in the Isa-Kd arm demonstrated the feasibility of the triplet combination, as in both arms (i.e., with or without Isa) there was a dose intensity of over 90% for K and more than 84% for d.

Moreau concluded that the IKEMA study had successfully met its primary endpoint, and the results from this had led to Isa-Kd approval in the USA and EU. The addition of Isa to Kd significantly improved PFS (HR: 0.53), corresponding to a 47% reduction in the risk of disease progression or death. The benefit of the Isa-Kd combination therapy was observed across multiple subgroups, including patients with high-risk cytogenetics, renal impairment, and the elderly, providing potential new treatment options for those patient populations.

A subgroup analysis of IKEMA by Facon et al.¹⁴ examined efficacy and safety in patients aged <70 and ≥ 70 years. With Isa-Kd, CR, \geq VGPR, and MRD-negativity rates were higher, along with improvement in PFS and quality of response in elderly patients. The most common Grade ≥ 3 TEAEs in patients <70 and ≥ 70 years treated with Isa-Kd versus Kd were similar for hypertension (18% versus 17% [<70 years] and 25% versus 26% [≥ 70 years]) and pneumonia (14% versus 9% [<70 years] and 22% versus 21% [≥ 70 years]), thus providing a potential new treatment option for elderly patients with relapsed MM.

An Update from the ICARIA-MM Study

During the EHA 2021 congress, the updated results of a pre-planned second interim analysis from the Phase III ICARIA-MM study were reported by Perrot et al.¹⁵ The study previously demonstrated a marked improvement in PFS with Isa-Pd compared with Pd ($p=0.001$) and a manageable safety profile for patients with RRMM (N=307; Isa-Pd: n=154; Pd: n=153) who had received ≥ 2 lines of prior therapy, including R and a PI.¹⁶ In this second interim analysis, the

median follow-up was 35.3 months. A significant improvement was observed in TTNT and time to randomisation to disease progression on first subsequent therapy or death (PFS2) in the Isa-Pd group compared with the Pd group, along with an increased OS benefit of approximately 7 months¹⁵ with no reported change to the overall safety profile from previous analyses.¹⁶

Follow-up at 35.3 months revealed that 18% of patients in the Isa-Pd group were still receiving treatment compared with 8% of patients taking Pd alone; median TTNT was 15 months versus 9 months (HR: 0.56; $p<0.0001$) and 24% versus 58% of patients received dara as a subsequent therapy. ORR with dara monotherapy was higher after Pd alone (38%) than with Isa-Pd (14%), but similar in both groups with dara combination therapy. Serious TEAEs occurred in 73% versus 60% of patients taking Isa-Pd and Pd, respectively, and Grade 3–4 neutropenia was more frequent in the Isa-Pd group (85% versus 71%).¹⁵ Isa-Pd demonstrated a significant improvement in TTNT and PFS2 compared with Pd; OS benefit in the Isa-Pd arm, which is not yet statistically significant; and a median OS improvement of approximately 7 months. The overall safety profile was unchanged from prior analyses.

ICARIA-MM: Quality of Life Outcomes in Renally-Impaired Patients

Addressing the key HRQoL outcomes in patients with RRMM who are renally-impaired, a post hoc analysis was conducted using data from the Phase III ICARIA-MM clinical study.^{16,17} Previously, Isa-Pd had been shown to improve PFS while maintaining HRQoL in patients with RRMM compared with Pd alone.^{16,18} Although sample sizes were small, observations aligned with those reported for the intention-to-treat population in the ICARIA-MM study. Researchers used data for two difficult-to-treat subgroups from the ICARIA-MM study: heavily pre-treated patients and patients with renal impairment. HRQoL was maintained in key domains, including physical functioning, role functioning, and global health status. There was no worsening of pain, fatigue, or disease symptoms in patients who received Isa-Pd compared with Pd, adding to the evidence that Isa may therefore provide an important new option in difficult-to-treat subgroups of patients with RRMM.

Isatuximab Short-Duration Fixed-Volume Infusion

In a multicentre, open-label, non-comparative Phase 1B safety and feasibility study, outlined in a poster by Usmani et al.,¹⁹ researchers sought to determine the benefit of a one-step infusion process to minimise the risk of infusion rate errors and reduce duration of infusion time for patients. In this evaluation (Part B) of a fixed volume infusion of Isa-Pd, the primary endpoint was the incidence of Grade ≥ 3 infusion reactions (IR) during the first six Isa infusions (across ≥ 2 cycles) in patients ≥ 18 years of age treated with ≥ 2 prior lines of therapy (including R and a PI), and who demonstrated disease progression during or after completion of the last therapy. Secondary endpoints included infusion duration, safety profile, immunogenicity, and efficacy. Efficacy and safety were consistent with earlier findings (Part A),²⁰ and with the pivotal ICARIA-MM study.^{16,21} IRs of Grade 1 or 2 severity were reported in 19 patients (40.4%) and occurred only with the first infusion. Reactions were managed with dose interruption in 18 patients (38.0%) and resolved on the same day. Compared with the weight-based Isa infusion in Part A of this study,²⁰ the second infusion time was reduced by >60 minutes and >90 minutes for subsequent infusions, which are the shortest infusion times of any approved anti-CD38 mAb, thereby improving convenience to the patient.²²⁻²⁵ These data supported the use of Isa 10 mg/kg administered with a 250 mL fixed infusion volume in combination with Pd in heavily pre-treated patients with RRMM.

Newly Diagnosed Multiple Myeloma

An Interim Analysis of the GMMG-CONCEPT Study

At the EHA 2020 congress, Weisel presented the interim analysis of the first 50 patients on response from the Phase II GMMG-CONCEPT clinical study,²⁶ the first study to investigate the Isa-KRd quadruplet treatment in NDMM. The study was conducted across 20 centres in Germany and recruited a total of 153 patients with high-risk NDMM between August 2017 and April 2020. High-risk was defined as either having 17p deletion, translocations 4;14 or 14;16, or having

>3 copies of 1q21, in addition to the presence of an International Staging System (ISS) Stage 2 or 3 disease, which applied to all patients. The study investigated MRD-negativity in this patient population, who were treated with Isa-KRd regardless of whether they had any subsequent autologous stem cell transplants.

Study design

Two separate study arms were based on the A'Hern single-stage design. Arm A (at the time of this interim analysis; $n=46$) was comprised of patients who were Te, and Arm B (at the time of this interim analysis; $n=4$) of patients who were Ti. Median age was 58 years and there was a near equal distribution between Eastern Cooperative Oncology Group (ECOG) performance status 0 and 1, with only 6 patients (12%) showing ECOG 2 status. Patients were eligible for inclusion if they had received no more than one prior cycle of anti-myeloma therapy and showed adequate organ function. All patients received Isa-KRd in induction, consolidation, and maintenance, and patients who were Te underwent a stem cell transplant after 6 cycles of Isa-KRd induction. The primary endpoint of the trial is MRD-negativity measured by next-generation flow (threshold 10^{-5}) after consolidation. The secondary endpoint was PFS, and key tertiary endpoints included ORR, duration of MRD-negativity, OS, and HRQoL.

Results from this interim analysis²⁷ regarding best response to therapy during the 6 induction cycles showed that the ORR was 100% (ORR: \geq PR) and that 90% of patients showed \geq VGPR (Arm A: 41 out of 46 patients \geq VGPR; Arm B: all 4 patients). A total of 46% of patients had CR or stringent CR (sCR). In Arm A, MRD-assessment was performed in 33 patients during induction, of whom 20 patients (61.00%) were MRD-negative, 11 patients (33.00%) were MRD-positive, and 2 patients were not assessable (0.06%). Most patients achieved a PR early (up to one treatment cycle) and responses rapidly deepened over time towards VGPR or CR/sCR. A total of 3 patients experienced progressive disease during induction, and 3 patients terminated their treatment with varying reasons.²⁷ In Arm B, all 4 patients (>70 years of age) completed six induction treatment cycles and showed a rapid remission, with VGPR achieved quickly in all patients. Overall, 44 out of 50 patients (88%)

completed induction, although a concern is that stem cell collection may be hampered by the use of the anti-CD38 mAb.

Stem cell collection

C-based stem cell collection was performed according to specific institutional guidelines for protocol, choice of growth factor, and target stem cell yield. Detailed data on stem cell mobilisation under induction therapy was presented in the poster session by Asemissen et al.,²⁸ who investigated whether mobilisation was impeded by quadruplet-therapy containing R and anti-CD38 mAb in a cohort of 62 patients (aged ≥ 70 years) with Te MM from the GMMG-CONCEPT study.

First results suggested that some patients were poor mobilisers, and the protocol was amended so that mobilisation could be performed earlier, after 3 induction cycles (n=38) rather than after 6 cycles (n=24). A total of three patients did not receive mobilisation treatment due to disease progression during induction, and these patients were not included in the analysis. Patient demographics showed no significant difference between the 3- and 6-cycle induction groups regarding age, gender, myeloma type, or bone marrow infiltration. There were slightly more poor mobilisers after 6 cycles compared with after 3 cycles, although the difference was not significant in this low number of patients and was in line with previous data reported on mobilisation following IMiD.²⁹ The median stem cell yield for the whole group was 6.6×10^6 CD34+ /kg body weight. Mobilisation was not successful in 2 out of 36 evaluable patients (6%) after 3 or 4 cycles, and in 2 out of 24 patients (8%) after 5 or 6 cycles of Isa-KRd. Plerixafor was used as a rescue treatment in 21 out of 62 patients (34%). The median time to stem cell collection was dependent upon mobilisation protocol and, when performed after 3 cycles of induction therapy, there was no time delay between the end of induction and high dose therapy. It was determined that mobilisation failure in patients receiving Isa-KRd was lower than reported in other standard of care induction therapies.³⁰

Safety data

Weisel presented the safety data from this interim study analysis. The most common Grade 3 or 4 haematologic TEAEs were neutropenia (34%),

lymphopenia (28%), and leukopenia (26%), with low rates of Grade 3 or 4 thrombocytopenia (14%). The most common non-haematologic TEAE was upper respiratory tract infection (any Grade: 18%; Grade 3 or 4: 0%). Peripheral sensory neuropathy was documented in 16% of patients for all Grades and in 2% for Grade 3 or 4. Hypertension and cardiac failure of Grades 3 or 4 were reported in 12% and 4% of patients, respectively, and a total of 32% of patients experienced an IR after or during the first Isa infusion. However, all IRs were Grade 1 or 2 and no deaths were reported in this interim study analysis. These results show that Isa-KRd can be safely administered in patients with MM who were Te and Ti. Further analyses are ongoing and these reported data support other studies investigating quadruplet therapy³¹⁻³⁵ as the new standard of care in NDMM, in particular for high-risk patients.

Isatuximab with Bortezomib, Cyclophosphamide, and Dexamethasone or Bortezomib, Lenalidomide, and Dexamethasone in Patients with Transplant Ineligible Newly Diagnosed Multiple Myeloma

A poster session by Ocio et al.³⁶ provided an update from a Phase Ib study of patients with NDMM who were Ti and were treated with two different Isa combination therapies of R, d, V, and cyclophosphamide.³⁷ Two cohorts were investigated. These cohorts formed part of a single study, although the investigations were performed sequentially, and not as a comparative study. In one cohort, patients were treated with Isa-VCd (n=17) with a median follow-up duration of 39.9 months in 15 efficacy-evaluable patients; in the second cohort, patients received Isa-VRd (n=27) with a median follow-up duration of 24.4 months in 26 efficacy-evaluable patients. The median age was 71 years in both cohorts and patients were enrolled up to the age of 80 years.

Efficacy data showed that in the Isa-VCd cohort, ORR was 93%, 8 patients achieved CR, and median PFS was not reached within 39.9 months of follow-up. In the Isa-VRd cohort, ORR was 100% with 3 patients experiencing sCR, 8 patients having CR, 14 patients achieving VGPR, and one patient having a PR. The median PFS was not reached within the follow-up duration of two years. At a sensitivity level of 10^{-5} , 53.3%

(8 patients) and 38.5% (10 patients) reached MRD-negativity in the Isa-VCd and Isa-VRd cohorts, respectively. Safety data showed that both Isa-VCd and Isa-VRd were well tolerated with a manageable safety profile and reported IR events were generally Grade 1 or 2 in severity, the majority occurring during the first infusion. Both regimens showed excellent clinical activity and depth of response in patients with NDMM, indicating that a quadruplet including anti-CD38, PI, IMiDs, and steroids is feasible and effective in patients with MM who are Ti, including those with advanced age. These data set the basis for a Phase III study of Isa-VRd compared with VRd in patients with NDMM who are ineligible for autologous stem cell transplants, which is currently ongoing.³⁸

Conclusion

Data from the IKEMA study of Isa-Kd showed that the study had met its primary endpoint of increasing PFS versus Kd in patients with RRMM, and represents a potential new standard of care for patients with relapsed MM. In this patient population, the addition of Isa demonstrated a favourable risk-benefit ratio along with a manageable safety profile. A profound depth of response was observed in patients treated with Isa-Kd compared with Kd alone, revealing a consistent benefit across multiple subgroups, including difficult-to-treat patients with high unmet medical needs. The number of R-refractory patients after first line therapy appears to be increasing rapidly and Isa-Kd may offer better results. Possible future options for the use of Isa

include Isa-Pd in second line therapy, rescuing dara-refractory patients, and Isa combination therapy in first-line treatment.

In the GMMG-CONCEPT study, data for Isa-KRd quadruplet therapy showed that Isa-KRd induction provoked a rapid and deep response in high-risk patients with NDMM. The first description of stem cell mobilisation under an Isa quadruplet combination therapy highlighted how stem cell collection performed after 3 cycles versus 6 cycles of treatment resulted in no time delay for patients initiating high dose therapy after induction. Based on evidence from the IKEMA (Isa-Kd) and ICARIA-MM (Isa-Pd) studies, these Isa-based regimens are now approved in multiple countries. The current European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) therapeutic indications for Isa-combined therapies are as follows.

EMA:³

- Isa-Pd for the treatment of adult patients with RRMM who have received at least two prior therapies, including R and a PI, and who have demonstrated disease progression on the last therapy.
- Isa-Kd for the treatment of adult patients with MM who have received at least one prior therapy.

FDA:²

- Isa-Pd for the treatment of adult patients with MM who have received at least two prior therapies, including R and a PI.
- Isa-Kd for the treatment of adult patients with RRMM who have received one to three prior lines of therapy.

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