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Isatuximab, Carfilzomib, Lenalidomide, Dexamethasone Induction in Newly Diagnosed Myeloma: Analysis of the MIDAS Trial

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Abstract:
In patients with transplant-eligible newly diagnosed multiple myeloma, induction therapy with a quadruplet regimen prior to autologous transplant is the standard of care. The phase III IFM2020-02-MIDAS study (NCT04934475) assessed a minimal residual disease (MRD)-driven consolidation and maintenance strategy following induction with isatuximab, carfilzomib, lenalidomide, and dexamethasone (IsaKRD). Here, we report safety and efficacy outcomes of six 28-day cycles of IsaKRD. Between December 2021 and July 2023, 791 patients were enrolled across 72 centers. The median age was 59 years; 13% had ISS-stage III, 5% had R-ISS-stage III, and 8% had high-risk cytogenetics (IFM Linear Predictor cytogenetic score >1). Overall, 96% (N=757) of patients completed induction. The median CD34+ cell yield was 7 × 106/Kg, with 94% of patients able to proceed with a potential tandem transplant. The best overall response rate was 95%. In the intent-to-treat population, 91% achieved a very good partial response or better after induction, with MRD-negativity rates of 63% at 10-5 and 47% at 10-6. MRD-negativity rates differed across ISS stages and cytogenetic subgroups. During induction, 7 patients experienced disease progression, and 5 died due to disease progression (N=1), cardiac events (N=2), or other causes (N=2). The most common grade 3/4 adverse events were neutropenia (25%), thrombocytopenia (5%), and infections (7%); only 13% of patients reported any grade peripheral neuropathy. IsaKRD induction yielded deep responses and high MRD-negativity rates while ensuring successful stem cell collection, with no new safety signals. Continued follow-up of this ongoing study is required to confirm these findings.

Conflict of interest: COI declared - see note

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Abstract

In patients with transplant-eligible newly diagnosed multiple myeloma, induction therapy with a quadruplet regimen prior to autologous transplant is the standard of care. The phase III IFM2020-02-MIDAS study (NCT04934475) assessed a minimal residual disease (MRD)-driven consolidation and maintenance strategy following induction with isatuximab, carfilzomib, lenalidomide, and dexamethasone (IsaKRD). Here, we report safety and efficacy outcomes of six 28-day cycles of IsaKRD. Between December 2021 and July 2023, 791 patients were enrolled across 72 centers. The median age was 59 years; 13% had ISS-stage III, 5% had R-ISS-stage III, and 8% had high-risk cytogenetics (IFM Linear Predictor cytogenetic score >1). Overall, 96% (N=757) of patients completed induction. The median CD34+ cell yield was 7×10^6/Kg, with 94% of patients able to proceed with a potential tandem transplant. The best overall response rate was 95%. In the intent-to-treat population, 91% achieved a very good partial response or better after induction, with MRD-negativity rates of 63% at 10^{-5} and 47% at 10^{-6}. MRD-negativity rates differed across ISS stages and cytogenetic subgroups. During induction, 7 patients experienced disease progression, and 5 died due to disease progression (N=1), cardiac events (N=2), or other causes (N=2). The most common grade 3/4 adverse events were neutropenia (25%), thrombocytopenia (5%), and infections (7%); only 13% of patients reported any grade peripheral neuropathy. IsaKRD induction yielded deep responses and high MRD-negativity rates while ensuring successful stem cell collection, with no new safety signals. Continued follow-up of this ongoing study is required to confirm these findings.

Running title

Induction with IsaKRD in TE NDMM

Key points

- Induction therapy with IsaKRD in the MIDAS study yielded the highest pre-transplant MRD-negativity rates ever reported in TE NDMM patients
- The favorable efficacy-toxicity balance with IsaKRD induction portends promising outcomes with long-term follow-up of the MIDAS cohort

Introduction

In patients with transplant-eligible newly diagnosed multiple myeloma (NDMM), induction therapy with a quadruplet regimen before autologous stem cell transplant (ASCT) is the standard approach.[1] Quadruplet regimens combining an anti-CD38 monoclonal antibody, a proteasome inhibitor (primarily bortezomib), an immunomodulatory drug, and dexamethasone have revolutionized frontline therapy and significantly improved prognosis. The phase III CASSIOPEIA trial led to the approval of the daratumumab–bortezomib–thalidomide–dexamethasone (DaraVTD) combination for induction and consolidation, demonstrating benefits in terms of stringent complete response (CR) and progression-free survival (PFS),[2] as well as overall survival (OS) with a 6-year-OS rate of 86.7%.[3] The GRIFFIN and PERSEUS trials demonstrated the superiority of daratumumab–bortezomib–lenalidomide–dexamethasone (DaraVRD) over VRD in the same setting,[4,5] with a 4-year PFS rate of 84% in PERSEUS. Isatuximab has also been evaluated in combination with VRD; preliminary results from the GMMG HD7 study of IsaVRD are promising.[6] Carfilzomib, lenalidomide and dexamethasone (KRD), a highly effective triplet induction regimen evaluated in the phase 2 FORTE trial,[7,8] has also been combined with anti-CD38 antibodies in the ASCT setting. Phase 2 trials of this approach demonstrated impressive results in patients with high-risk disease.[9,10] In the phase 3 IsKia trial, combining KRD with isatuximab (IsaKRD) yielded deeper responses before ASCT, compared to KRD alone;[11] these results confirm that the addition of isatuximab to KRD achieves superior responses. Additionally, the evaluation of the DaraKRD quadruplet regimen without ASCT in the phase 2 MANHATTAN trial[12] led some authors to advocate for the use of quadruplet regimens without routine upfront ASCT[13]. To date, no prospective trials have compared upfront ASCT versus (vs.) no ASCT following quadruplet induction. The role of upfront ASCT remains a topic of debate, and risk-adapted strategies are needed to determine the utility of upfront ASCT after quadruplet induction. Two tools can be used for stratifying risk in this context: cytogenetic risk at diagnosis, and measurable residual disease (MRD) assessment, which reflects functional risk. Robust data for induction response-based adjustment of treatment intensity are still lacking. The MASTER trial findings support continued treatment of patients with cytogenetically defined high-risk myeloma, even if the patient achieves MRD-negativity post-induction and post-transplant.[14] The phase 3 IFM2020-02- MIDAS (MRD Adapted Strategy) study (NCT04934475) is an ongoing study assessing an MRD-driven consolidation and maintenance strategy following IsaKRD induction. The choice of IsaKRD was driven by its potential to achieve deep responses and high MRD-negativity rates after induction. Based on MRD-negativity at a sensitivity of 10^{-5}, patients were categorized into two risk groups: standard-risk (MRD-negative), and high-risk (MRD-positive). Here, we present the efficacy and safety data of this induction regimen in the large cohort of patients included in the MIDAS study.

Methods

Study design and participants

The IFM2020-02-MIDAS study is an ongoing randomized, open-label, active-controlled, parallel-group, multicenter, phase 3 trial designed for patients with previously untreated MM. The study is being conducted across 72 centers within the IFM (Intergroupe Francophone du Myélome) group in France and Belgium. Eligible participants were under 66 years of age and had previously untreated symptomatic MM that met the CRAB and/or SLiM criteria, with measurable disease defined as serum M-component ≥5 g/L, urine M-component ≥200 mg/24 h, and/or serum free light chains ≥100 mg/L. Key inclusion criteria included: eligibility for high-dose therapy and ASCT, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, adequate hematological and renal function (calculated creatinine clearance ≥40 mL/min/1.73 m^2). Exclusion criteria included: significant cardiac medical history (e.g., uncontrolled hypertension, myocardial infarction within the previous 4 months, NYHA Class III or IV heart failure, uncontrolled angina, severe ventricular arrhythmias, or signs of acute ischemia or conduction abnormalities on electrocardiogram), known HIV infection, active hepatitis A, B, or C, a history of malignancy other than adequately treated basal cell or squamous cell skin cancer, or *in situ* cervical, breast, or prostate cancer without active disease within the last 5 years. All participants provided written informed consent. The study protocol and any amendments were approved by the relevant regulatory authorities and national ethics committees in France and Belgium. The trial adheres to the International Conference on Harmonization of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Randomization

After uniform IsaKRD induction, response was assessed, based on MRD-negativity evaluation at a sensitivity of 10^{-5}, and patients were randomized according to their MRD status. MRD-negative patients were randomly assigned (1:1) to upfront high-dose therapy with transplant (Arm B) or six additional cycles of IsaKRD (Arm A). Randomization was stratified according to cytogenetic risk (standard vs. high-risk), MRD negativity after induction at a sensitivity of 10^{-6}, and site number. MRD-positive patients were randomly assigned (1:1) to tandem transplant (Arm D) or single transplant (Arm C). Randomization was stratified according to cytogenetic risk (standard vs. high-risk)[15] and site number. There was no blinding.

Procedures

Eligible patients received six 28-day cycles of IsaKRD: isatuximab (10 mg/kg; weekly for the first 4 weeks, then every other week), carfilzomib (20 mg/m^2 on Day 1 of Cycle 1, then 56 mg/m^2 on Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of subsequent cycles), lenalidomide (25 mg/day from Days 1 to 21), and dexamethasone (40 mg/week). Patients received anticoagulation with low-molecular-weight heparin or apixaban to prevent deep vein thrombosis, antiviral prophylaxis for herpes zoster, cotrimoxazole for pneumocystis and amoxicillin or an equivalent antibiotic for bacterial infections. Stem cell mobilization was performed using G-CSF (recommended dose of 10 µg/kg/day for 5 days until the final day of collection) and plerixafor (recommended dose of 0.24 mg/kg/day) after Cycle 3. Stem cells were harvested based on response to mobilization, ensuring that sufficient stem cells were collected to enable multiple transplants according to institutional standards. Cytogenetic risk was assessed at diagnosis using next-generation sequencing (NGS), with the IFM Linear Predictor (LP) score identifying high-risk if LP >1, based on the detection of del(17p), t(4;14), del(1p32), gain 1q, trisomy 21, trisomy 5.[15] Cytogenetic high-risk classification according to the Revised International Staging System (R-ISS),[16] R2-ISS,[17] and International Myeloma Society (IMS)/International Myeloma Working Group (IMWG) consensus high-risk MM (HRMM) definition,[18] was conducted retrospectively for post-hoc comparative analyses. Myeloma response was evaluated based on the modified IMWG uniform response criteria,[19] at Day 1 of each cycle and at Cycle 6, Day 28 (C6D28). Hydrashift tests were not compulsory in this academic study; therefore, we also assessed near CR (nCR) according to NCI[20] and GMMG[6] definitions. MRD was assessed at C6D28 for all patients, regardless of response, using NGS as previously described,[21] or with flow cytometry in rare cases of NGS calibration failure. Patients are being followed until death or the end of the study. Safety is being monitored until 30 days after the last dose of the study drug, with secondary malignancies monitored continuously during follow-up. Toxicities are graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 5.0; Bethesda, MD).

Outcomes

The primary endpoint is MRD-negativity before maintenance, at a sensitivity of 10^{-6} for high-dose therapy and the ASCT vs. IsaKRD comparison and a sensitivity of 10^{-5} for the tandem ASCT vs. single ASCT comparison. Secondary endpoints included post-induction MRD, response rates according to IMWG criteria, PFS, OS, safety, sustained MRD-negativity, and patient-reported-outcomes for Arms C and D. Additional comparisons and ancillary studies are also planned: for example, exploratory analyses will include a comparison of Arms B and C, which differ only in the maintenance regimen (lenalidomide vs. iberdomide + isatuximab).

Statistical analyses

We designed the trial assuming that 50% of patients would be MRD-negative at the end for induction and with the aim of testing separate hypotheses for the MRD-negative and -positive subpopulations. For the MRD-negative standard-risk subgroup, we hypothesized that the MRD-negativity rates (at 10^{-6} sensitivity) before maintenance would increase from 70% with additional cycles of IsaKRD to 85% with transplant. For patients with functional high-risk disease, we hypothesized that tandem transplant would increase the MRD-negativity rates before maintenance from 25% with single transplant to 45%. With an additional assumption of loss to follow-up of 10% of patients and to ensure 90% power for both comparisons with a type I error rate of 5%, 716 patients were planned for treatment. This planned number would include 322 patients for the comparison of Arms A and B and 234 subjects for the comparison of Arms C and D; per this scheme, only 72% of MRD-negative patients following induction would be randomized. A planned blinded sample-size re-estimation based on the proportion of MRD-negative patients was performed in January 2023. Due to an imbalance

favoring the Arm A vs. Arm B comparison, the total sample size was increased to 788 patients and all patients who achieved MRD-negativity were randomized.

The current planned analysis focuses on induction data, i.e., all data occurring before the latest induction visit (C6D28). All adverse events (AEs) until 30 days after the C6D28 visit or after the last administration of induction treatment were included in the safety analysis. Data pertaining to AEs possibly, probably, or very likely related to transplant are not presented here. The efficacy analysis was performed on the induction intent-to-treat (ITT) population -i.e., all included patients- and the per protocol (PP) population –i.e., all patients who completed the induction phase. The safety analysis was performed on the induction safety population, which included all patients who received at least one dose of induction treatment. Quantitative data are described using medians, ranges, and interquartile ranges. Qualitative data are presented as frequencies and percentages (based on non-missing sample sizes). MRD and response rates are provided along with the corresponding two-sided 95% confidence intervals (CIs). Factors associated with MRD-negativity were evaluated using either the Chi-squared or Fisher's exact test. All statistical tests were two-sided, with a significance level set at 5%. Statistical analyses were performed using R statistical software v.4.2.1 (https://www.R-project.org/).

Results

Patients

Between December 2021 and July 2023, 791 patients were enrolled across 72 centers. Patients' demographic and baseline disease characteristics are summarized in Table 1. The median age was 59 years (range, 25-66) and 57% were male. Osteolytic lesions were present in 75%, and 27% had fractures. Sixty-one patients (8%) met only the SLiM criteria. MM was classified as ISS-stage III in 99 patients (13%) and R-ISS-stage III in 43 patients (5%), with 186 patients (24%) having elevated lactate dehydrogenase (LDH) levels. Cytogenetic evaluation was performed in 757 patients; 8% were classified as high-risk with an LP score >1; 17% were high-risk according to the new IMS-IMWG consensus. Finally, 35% and 5% were intermediate-to-high and high-risk according to the R2-ISS score, respectively. Patients without evaluable cytogenetics (4.3%) were considered as standard-risk. The distribution of individual cytogenetic characteristics was as follows: t(11;14), t(4;14), and t(14;16) were present in 26%, 8%, and 3% of patients, respectively. Del(17p) was present in 6% (using a 50% cancer clonal fraction cut-off), *TP53* mutation in 4%, del(1p32) in 7%, and 1q gain in 26%. Positron emission tomography/computed tomography (PET/CT) was performed at baseline in 700 patients, among whom five had extramedullary disease (EMD) (excluding paramedullary lesions). Fifty-three patients (7%) had circulating plasma cells, 9 presented with primary plasma cell leukemia (PCL) (per the updated IMWG criteria with the 5% circulating plasma cell cut-off).[22]

The study flowchart is summarized in Figure 1. Screening failures were primarily due to unmet eligibility criteria (90%), investigator decision (3%), and consent withdrawal (3%). Nineteen patients could be re-screened and were included. Overall, 757 patients (96%) completed induction; among those who did not, 3 patients experienced progressive disease (PD), 5 died, and 13 discontinued due to AEs.

Stem-cell collection

Among the 791 patients who began IsaKRD induction, 767 completed Cycle 3, and 766 initiated peripheral stem cell (PSC) mobilization. Of these, 761 patients (99%) underwent at least one apheresis session, with a median collection of 7×10^6 CD34+ cells/kg over a median of two days. The five patients unable to undergo apheresis completed the study treatment by the end of the induction phase. For the others, the PSCs collected were sufficient to potentially support tandem transplants in 721 patients (94% of those who underwent mobilization), while 23 patients (3%) had enough cells for only one transplant. In 17 patients, the stem cell harvest was insufficient for any transplant. To achieve these results, 653 patients (85%) received plerixafor in addition to G-CSF; of these, 520 required only one dose, 117 needed two doses, and 16 required three doses.

Efficacy (response and MRD)

Response and MRD-negativity rates are summarized in Figure 2. The best overall response rate was 95%. In the ITT population, 92% of patients achieved a very good partial response (VGPR) or better at the C6D28 time point (Figure 2A). Response improves over time: 668 patients (84.4%) achieved a VGPR or better after 4 cycles of IsaKRD, compared to 92% after 6 cycles.

Per protocol, the VGPR rate or better after induction was 95%. The CR/nCR rate was 64%–66% according to the two definitions in the ITT population, and 69 to 71% per protocol.

MRD post-induction was evaluated at C6D28 in 751 patients, primarily using NGS; for 16 patients where initial sample calibration was not possible, flow cytometry was used. Patients with missing MRD data who were deemed to have PD or who ended treatment or study participation due to PD or death were considered MRD-positive. In the ITT population, the MRD-negativity rate was 63% at 10^{-5} and 47% at 10^{-6} (Figure 2B). Per protocol, the MRD-negativity rates were 66% at 10^{-5} and 50% at 10^{-6}. MRD-negativity rates varied according to (revised) ISS stages and cytogenetic subgroups, as shown in Figure 3. The percentage of patients achieving MRD-negativity after induction was 59%, 66%, and 69% in ISS stages I, II, and III, respectively; 58%, 65%, and 70% in R-ISS stages I, II, and III; and 61%, 62%, 64%, and 72% in R2-ISS stages I, II, III, and IV, respectively. Post-induction MRD-negativity rates did not differ according to initial cytogenetic risk, with rates of 63% in standard-risk patients and 62% in high-risk patients, using both the IFM LP score and the IMS-IMWG consensus definition. However, MRD-negativity rates differed according to the type of cytogenetic abnormality. Patients with t(4;14) achieved MRD-negativity at the end of induction in 81% of cases, whereas only 48% of patients with del(17p) and 40% of patients with t(11;14) reached MRD-negativity after six cycles of IsaKRD. The p-value for association with MRD negativity was significant for specific subgroups defined by cytogenetic abnormalities t(11;14), t(4;14), t(14;16) and del(17p).

Safety

Mortality during induction was low, with 5 deaths, representing <1% of the cohort. Two patients, aged 51 and 64 years, died at home from sudden cardiac arrest after Cycle 1, Day 8; both had a prior history of ischemic heart disease. Another patient with a history of pulmonary hypertension died from acute pulmonary edema just before starting Cycle 2. During Cycle 6, two additional patients died: one from septic shock in the context of progressive disease, and the other from an unknown cause.

A total of 260 serious AEs occurred during the induction phase (up to 31 days), affecting 177 (22%) patients. The most frequent cause was infection, affecting 44 (6%) patients; 9 patients experienced grade 2 infections, while 30 had grade 3 infections.

The most common AEs and those of particular interest (summarized in Table 2) include grade 3/4 neutropenia (25%), anemia (7%), thrombocytopenia (5%), hepatobiliary disorders (6%), and infections (7%). A total of 38 patients (5%) experienced any grade of arterial hypertension, with 10 patients (1%) reporting grade 3 or 4 hypertension. Peripheral neuropathy was reported in 103 (13%) patients, primarily grade 1 and 2 (10% and 3%, respectively). Only 3 patients experienced grade 3 neuropathy; no cases of grade 4 were observed. One patient developed thrombotic microangiopathy during induction, which resolved after specific treatment and the discontinuation of carfilzomib.

Discussion

Remarkable outcomes have been achieved with quadruplet combinations in the ASCT setting. One of the most critical challenges in improving outcomes for patients with transplant-eligible NDMM in 2024 is the development of risk-adapted strategies. Treatment can generally be adapted either to the initial risk (R2-ISS score) or to the quality of the response after induction, with MRD being the most sensitive tool for assessing depth of response. In this study, we chose the response-adapted approach. The MIDAS trial was designed, therefore, to tailor therapy based on MRD status after six cycles of IsaKRD. Our findings confirm that six cycles of IsaKRD induce exceptionally high MRD-negativity rates, not only at a sensitivity of 10^{-5} but also at 10^{-6}. These rates are among the highest reported to date. In the MIDAS study, MRD-negativity at 10^{-5} after induction was 63%, compared to 35%, 22%, and 50% in the CASSIOPEIA, GRIFFIN, and GMMG HD7 trials, respectively, which used quadruplet combinations with bortezomib (four 28-day cycles in CASSIOPEIA, four 21-day cycles in GRIFFIN, and three 42-day cycles in GMMG HD7) .[2-4,6] For carfilzomib-based quadruplets, MRD-negativity rates (at 10^{-5} sensitivity) were 34%, 37%, and 45% in the IFM2018-04, MASTER, and EMN24 IsKia trials, respectively, each of which included four 28-day induction cycles (Table 3).[10,14,11] Treatment schedules may have implications for overall treatment intensity and patient response. Notably, when focusing on the MRD sensitivity threshold at 10^{-6}, the MRD-negativity rate was 27% after four cycles of IsaKRD in IsKia, compared to

47% after 6 cycles in MIDAS. Overall, these data indirectly support the use of carfilzomib over bortezomib, and the use of six cycles upfront instead of four, provided they are well tolerated.

Even if the majority of patients achieve VGPR, the CR rate in monoclonal antibody studies can remain low due to a high proportion of positive serum immunofixation results, most likely because of the detection of isatuximab. In this academic study, the Hydrashift assay- which removes therapeutic monoclonal antibody interference in immunofixation assays- was not mandatory and was only performed on a case-by-case basis in certain centers. Therefore, we assessed 'nCR' rather than CR, according to the NCI criteria[20] and the methodology used in the GMMG HD7 trial.[6] With this approach, we found that 64%-66% of patients in the ITT population achieved CR/nCR after induction, with 69%-71% CR/nCR rates in the per-protocol analysis. These results compare favorably with those of the GMMG HD7 trial, which reported 41% CR/nCR rates after induction in the IsaVRD arm. Beyond these findings, we believe that, in the era of anti-CD38 monoclonal antibodies, the IMWG response criteria no longer fully reflect the reality of achieving CR. Residual circulating IgG CD38 antibodies which can be detected on electrophoresis may be misinterpreted as residual disease, potentially leading to an underestimation of true CR rates. The issue is critical for accurately assessing the efficacy of anti-CD38-based regimens, and international efforts to revise the response criteria are needed.

IsaKRD demonstrated efficacy across subgroups, including high-risk patients, consistent with findings from other quadruplet regimens containing anti-CD38 antibodies, such as DaraKRD.[10] Interestingly, MRD-negativity rates did not significantly differ between standard-risk and high-risk subgroups, regardless of the classification used (ISS, R-ISS, R2-ISS, IFM LP score, or IMS-IMWG HRMM definition). Therefore, MRD status after induction does not appear to align consistently with initial cytogenetic risk. However, MRD-negativity rates did differ significantly by the type of high-risk abnormality; the MRD-negativity rate was 81% in patients with t(4;14), but only 48% in patients with del(17p). A longer follow-up is needed to better interpret the significance of achieving MRD-negativity in patients with different cytogenetic abnormalities. Interestingly, patients with t(11;14), a subgroup not typically associated with poor prognosis, demonstrated a lower rate of post-induction MRD-negativity in our study. We hypothesize that this subgroup of patients may experience a slower and less profound response to treatment, although this does not seem to impact long-term outcomes[24]. Conversely, patients with t(4;14) exhibited the opposite trend. These observations suggest that it is crucial to reassess MRD before maintenance therapy to better understand the kinetics of MRD-negativity –specifically, the time to achieve MRD-negativity and the duration of sustained MRD-negativity-, across different cytogenetic subgroups. Tailoring MRD assessment timing based on cytogenetic subgroups may be an interesting avenue for further exploration.

No new safety signals were observed with IsaKRD, and the regimen was associated with a low (<1%) mortality rate. When compared to other regimens, such as KRD alone or KRD combined with an anti-CD38 antibody, and with standard-of-care regimens like CASSIOPEIA and PERSEUS, IsaKRD demonstrated a favorable safety profile, particularly with respect to the low rates of peripheral neuropathy. Additionally, we believe that the use of a weekly carfilzomib schedule may contribute to the reduced incidence of cardiac events. The low incidence of these AEs, alongside the overall favorable safety profile are important factors to consider in long-term treatment planning. Successful collection of substantial PSCs in patients who received IsaKRD induction further supports the use of this regimen in the setting of ASCT. Widespread use of plerixafor can foster collection of PSCs in patients intended for potential tandem transplants.

These results are encouraging, and further follow-up of the MIDAS cohort is required to confirm these benefits in the final analysis. Given the critical role of pre-transplant MRD-negativity in predicting long-term outcomes—an association clearly established in studies like CASSIOPEIA[3]—the early results with IsaKRD could have important implications for future MM treatment strategies.

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Authorship contributions

PhM, HAL, AP, CT, JL, JC designed the study; AP, CT, CH, DCa, LK, BA, PR, LG, MMa, MEB, JG, TC, RG, JMS, MT, MMo, FK, JF, SM, FOP, LV, SR, XL, BH, JVM, CJ, DCh, NM, WA, LM, RB, CS, HZ, AD, OA, MD, MR, SC, JD, NiB, HD, VR, BC, LF, MCV included the patients; HAL and JC generated cytogenetics and MRD data; JL and NoB analyzed the data; PhM, HAL, AP, CT, JL, JC interpreted the data; PhM and AP wrote the paper; all authors reviewed and approved the manuscript.

Conflict of interest statements

The authors disclose conflicts of interests with AbbVie, Amgen, BMS, GSK, Janssen, Pfizer, Sanofi, Takeda (AP), Janssen, BMS, Takeda, Amgen, Sanofi, Pfizer, Abbvie (CT), Amgen, BMS, GSK, Janssen, Sanofi, Takeda (CH), Amgen, BMS, Sanofi (LK), BMS, Janssen, Takeda, Sanofi, Amgen, GSK (BA), BMS, Janssen, Sanofi, Pfizer (LG), Amgen, BMS, GSK, Janssen, Sanofi, Takeda (MMa), Amgen, Janssen, Sanofi, Beigene (JG), Pfizer, Janssen, Amgen, Sanofi (TC),Sanofi, Pfizer (RG), Amgen, Janssen, Sanofi, GSK, AbbVie, Pfizer (JMS), Amgen, BMS, Janssen, Jazz Pharmaceuticals, Gilead, GSK, Novartis, Pfizer, Sanofi, Menarini Stemline, Takeda (MMo), AbbVie, Adaptive Biotechnology, Regeneron, Roche, Sanofi, Takeda (SM), Sanofi (FOP), Janssen, BMS, Sanofi, Pfizer, Takeda (LV), AbbVie, Amgen, BMS, Iteos, Gilead, GSK, Harpoon Therapeutics, Janssen, Merck, Novartis, Pfizer, Oncopeptide, Regeneron, Roche, Sanofi, Takeda (XL), Roche, Beigene (DCh), Janssen (NM), Sanofi (LM), BMS, Amgen, Janssen (AD), Janssen, Pfizer, Sanofi, Amgen, Takeda (OA), Pfizer, Sanofi, Janssen, BMS, GSK (JD), Pfizer (NB), Janssen, AbbVie, BMS, Pfizer, Sanofi (HD), Janssen, Sanofi, Pfizer, Amgen, AbbVie (LF), Janssen, BMS, Takeda, Amgen, Sanofi, Pfizer, Abbvie (PhM). DCa, PR, MEB, MT, FK, JF, SR, JVM, CJ, WA, RB, CS, HZ, MD, MR, SC, VR, BC, MCV, NB, JL, HAL, JC have nothing to disclose.

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Tables

Table 1. Patient Demographics and Baseline Disease Characteristics.

Characteristic	Whole cohort (N = 791) N (%)
Age (years), median [range]	58.7 [25.4-66]
>60 years	330 (42%)
Gender	
Male	454 (57%)
Female	337 (43%)
ECOG performance status	
0	338 (43%)
1	355 (45%)
2	98 (12%)
Criteria for symptomatic MM	
CRAB	726 (92%)
Osteolytic lesions	595 (75%)
Anemia	206 (26%)
SLiM only	61 (8%)
ISS stage	
I	346 (44%)
II	346 (44%)
III	99 (13%)
Elevated LDH	212 (27%)
R-ISS stage	
I	236 (30%)
II	511 (65%)
III	43 (5%)
R2-ISS stage	
I	193 (25%)
II	273 (36%)
III	265 (35%)
IV	36 (5%)
Cytogenetic score LP >1	63 (8%)
IMS/IMWG consensus HRMM	135 (17%)
Extramedullary disease	5 (1%)
Circulating plasma cells	
Any	53 (7%)
>5%	9 (1%)

Detailed cytogenetic abnormalities	
t(4;14)	63 (8%)
t(14;16)	19 (3%)
t(14;20)	11 (1%)
t(11;14)	199 (26%)
gain 1q	200 (26%)
monoallelic del(1p32)	55 (7%)
biallelic del(1p32)	8 (1%)
del(17p)	46 (6%)
TP53 mutation	31 (4%)
trisomy 5	307 (41%)
trisomy 21	202 (27%)

ECOG, Eastern Cooperative Oncology Group; MM, multiple myeloma; CRAB, Calcium elevation, Renal Dysfunction, Anemia, Bone disease; SLiM, Sixty percent or higher plasma cell infiltration, Light-chain ratio ≥100 of the involved serum light chain vs. the uninvolved serum light-chain, >1 focal lesion ≥5 mm in MRI; ISS, International Staging System; LDH, lactate dehydrogenase; R(2)-ISS, Revised(2)-ISS; LP, Linear Predictor; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; HRMM, High-Risk MM.

Table 2. Most Common Adverse Events and Those of Interest Reported Through The End of Induction.

	Any grade, N (%)	Grade >2, N (%)
Hematologic		
Anemia	134 (17%)	52 (7%)
Thrombocytopenia	100 (13%)	42 (5%)
Neutropenia	229 (29%)	204 (25%)
Non hematologic		
Gastrointestinal disorders	441 (56%)	22 (3%)
Infections	364 (46%)	54 (7%)
Hepatobiliary disorders	104 (13%)	46 (6%)
Cardiac disorders	49 (6%)	9 (1%)
Peripheral neuropathies	103 (13%)	3 (<1%)
Arterial hypertension	38 (5%)	10 (1%)
Thrombotic microangiopathy	1 (<1%)	1 (<1%)

Table 3. Indirect Comparisons of MRD-Negativity Rates After Induction in ITT Populations of Studies Focused on Transplant-Eligible NDMM Patients.

	Quadruplet regimen	Number of patients (specific population)	Induction details	Post-induction MRD-negativity rate (sensitivity level)
CASSIOPEIA[2,3]	DaraVTD	543	4 (4-week) cycles	35% (10^{-5})
GRIFFIN[4]	DaraVRD	104	4 (3-week) cycles	22% (10^{-5}) 1% (10^{-6})
PERSEUS[5,23]	DaraVRD	355	4 (4-week) cycles	NA

GMMG-HD7[6]	IsaVRD	331	3 (6-week) cycles	50% (10^{-5})
GMMG-CONCEPT[9]	IsaKRD	99 (HR*)	6 (4-week) cycles	NA
IFM2018-04[10]	DaraKRD	50 (HR*)	6 (4-week) cycles	42% (10^{-5}) 34% (10^{-6})
EMN24 IsKia[11]	IsaKRD	151	4 (4-week) cycles	45% (10^{-5}) 27% (10^{-6})
MASTER[14]	DaraKRD	123	4 (4-week) cycles	37% (10^{-5}) 23% (10^{-6})
IFM2020-02-MIDAS	IsaKRD	791	6 (4-week) cycles	63% (10^{-5}) 47% (10^{-6})

HR, high-risk by cytogenetics; ITT, intent-to-treat; NA, not available.

* The GMMG-CONCEPT and IFM2018-04 trials were specifically designed for patients with high-risk cytogenetics profiles in multiple myeloma.

Figure Legends

Figure 1. Study Flowchart.

PD, progressive disease; (S)AE, (serious) adverse event(s).

Figure 2. Response and MRD-negativity rates after induction.
A. Response rates according to IMWG, NCI, and GMMG criteria.
B. MRD-negativity rates at 10^{-5} and 10^{-6} sensitivity.
CR, complete response; GMMG, German-speaking Myeloma Multicenter Group; IMWG, International Myeloma Working Group; ITT, intent-to-treat; nCR, near-CR; PD, progressive disease; PP, per protocol, PR, partial response; VGPR, very good partial response.

Figure 3. Subgroup Analysis of MRD-Negativity Rates After Induction.

Isatuximab, Carfilzomib, Lenalidomide, Dexamethasone Induction in Newly Diagnosed Myeloma: Analysis of the MIDAS Trial

MInimal residual Disease Adapted Strategy

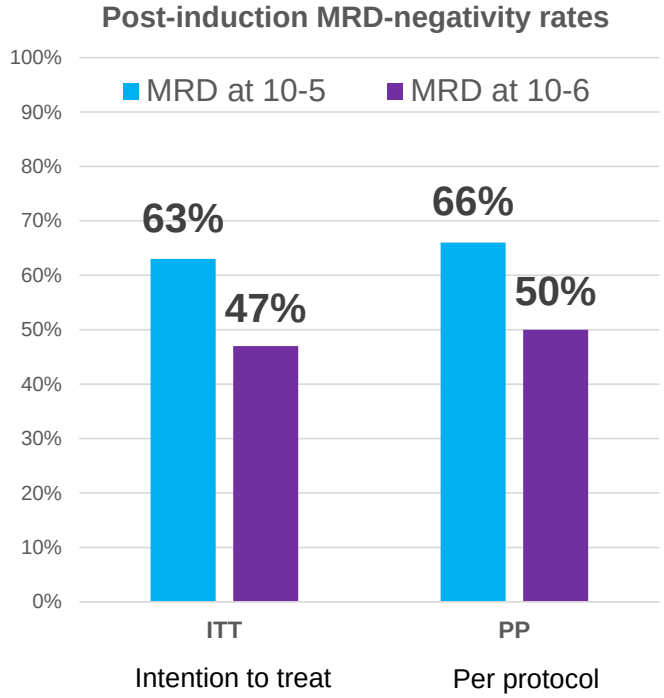
791 patients (pts) under 66 years
57% male
13% ISS III, 8% high-risk (LP score >1)

757 pts completed six 28-day cycles IsaKRD
5 pts dead
3 pts with progressive disease

761 pts did at least one stem cell harvest
Median of collected cells = **7×10^6 CD34+/kg**

Response rates after induction:

- **92% VGPR or better**
- **65% CR/nCR**



Six cycles of IsaKRD induce exceptionally high MRD-negativity rates

IsaKRD induction ensures successful stem cell collection, with no new safety signals

A. Perrot et al

Figure 1

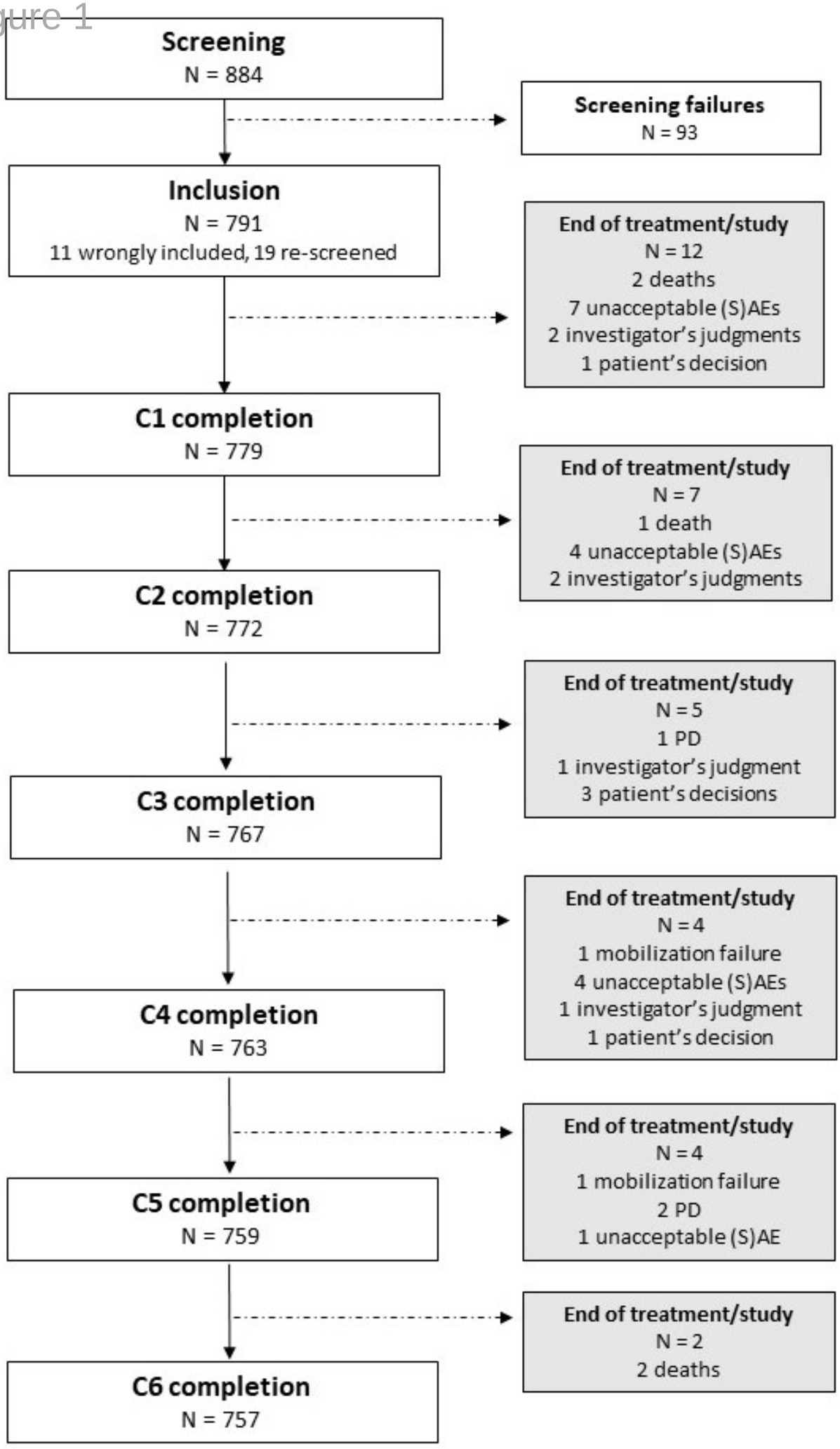
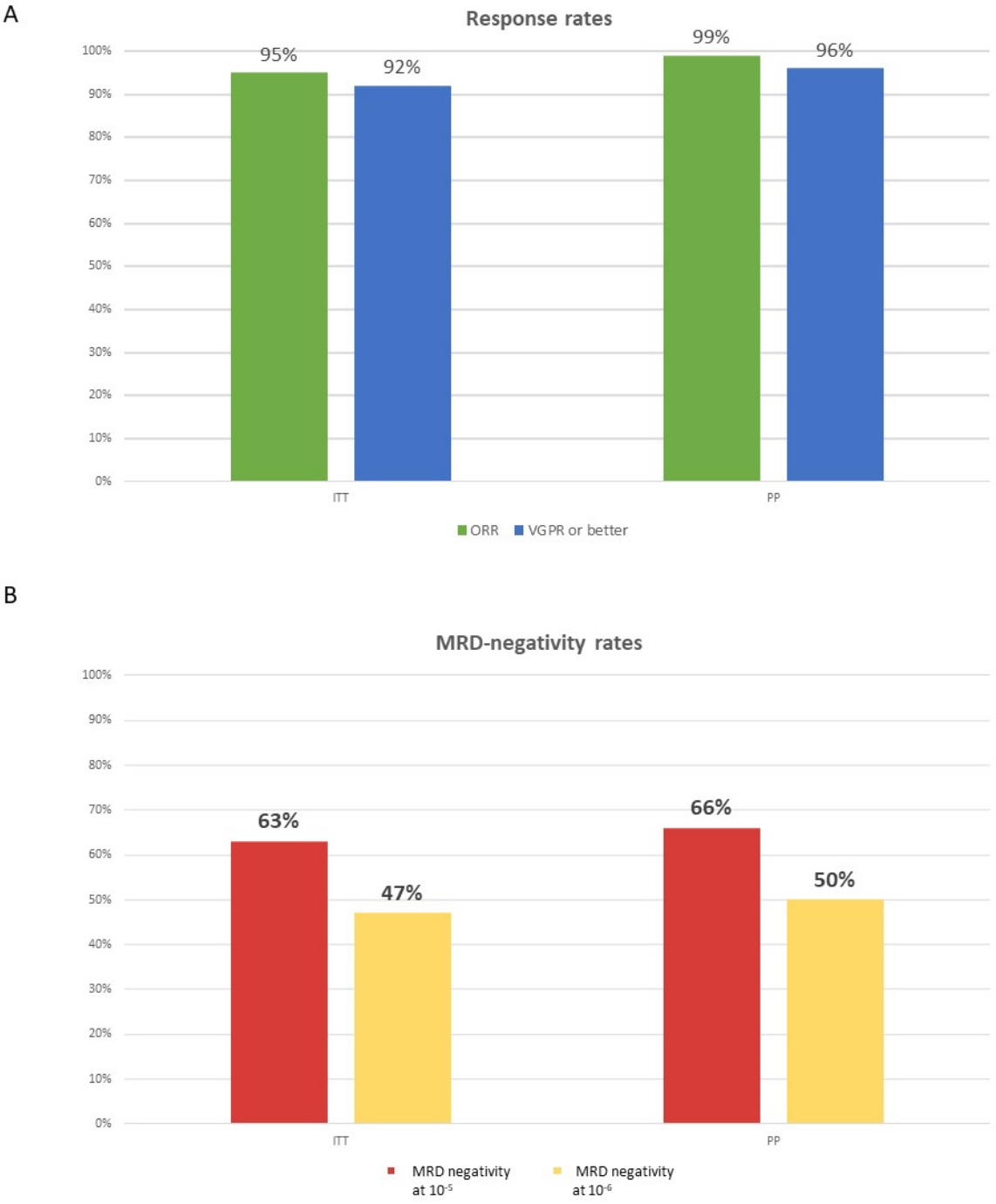

Screening
N = 884
Screening failures
N = 93
Inclusion
N = 791
11 wrongly included, 19 re-screened
End of treatment/study
N = 12
2 deaths
7 unacceptable (S)AEs
2 investigator's judgments
1 patient's decision
C1 completion
N = 779
End of treatment/study
N = 7
1 death
4 unacceptable (S)AEs
2 investigator's judgments
C2 completion
N = 772
End of treatment/study
N = 5
1 PD
1 investigator's judgment
3 patient's decisions
C3 completion
N = 767
End of treatment/study
N = 4
1 mobilization failure
4 unacceptable (S)AEs
1 investigator's judgment
1 patient's decision
C4 completion
N = 763
End of treatment/study
N = 4
1 mobilization failure
2 PD
1 unacceptable (S)AE
C5 completion
N = 759
End of treatment/study
N = 2
2 deaths
C6 completion
N = 757

Figure 2


A
Response rates
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
95%
92%
99%
96%
ITT
PP
ORR
VGPR or better
B
MRD-negativity rates
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
63%
47%
66%
50%
ITT
PP
MRD negativity at 10-5
MRD negativity at 10-6