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LETTER

30-Minute infusion of isatuximab in patients with newly diagnosed multiple myeloma: Results of a Phase 1b study analysis

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The addition of an anti-CD38 antibody to standard treatment regimens, in combination with an immunomodulatory drug or a proteasome inhibitor and dexamethasone, provides benefit to multiple myeloma (MM) patients in the relapsed/refractory setting (RRMM), as well as at an earlier disease stage in quadruplet combinations for transplant-eligible or non-eligible patients with newly diagnosed MM (NDMM).[1–3] Isatuximab (Isa) is approved in various countries in combination with pomalidomide-dexamethasone or carfilzomib-dexamethasone for the treatment of RRMM patients.[4–6]

Study findings in transplant-eligible NDMM patients demonstrated significant efficacy of Isa in quadruplet combinations with bortezomib-lenalidomide-dexamethasone (VRd) for induction therapy in the Phase 3 GMMG-HD7 trial (minimal residual disease [MRD] negativity: 50% with Isa-VRd vs 36% with VRd; $p = 0.00017$), and with carfilzomib-lenalidomide-dexamethasone (KRd) for induction/consolidation treatment in the Phase 3 IsKia/EMN24 trial (MRD negativity after consolidation: 77% with Isa-KRd vs 67% with KRd; $p = 0.049$), without new safety signals.[7,8]

In transplant-ineligible NDMM patients, significant PFS benefit (hazard ratio [HR], 0.60; 98.5% confidence interval [CI], 0.41–0.88; $p < 0.001$) and deep, sustained responses were reported with Isa in combination with VRd followed by Isa-Rd versus VRd followed by Rd, in a prespecified interim analysis of the Phase 3 IMROZ trial, with a manageable safety profile.[9] In the Phase 3 BENEFIT trial, the addition of weekly bortezomib to Isa-Rd (reduced-dose VRd) induced a significant improvement in MRD negativity at 18 months versus Isa-Rd (53% vs. 26%, $p < 0.0001$).[10]

The evaluation of Isa with either bortezomib-cyclophosphamide-dexamethasone (VCd) or VRd has shown safety and efficacy of these quadruplet regimens in the Phase 1b trial TCD13983 (NCT02513186) in transplant-ineligible NDMM patients (all cohorts) or patients with no immediate intent for autologous stem cell transplantation included in Isa-VRd/Part-B, as previously reported.[11,12]

To enhance the convenience of long-term treatment with IV Isa for patients and healthcare providers, by improving the current duration of Isa infusion (75 min), we prospectively evaluated the feasibility, safety, and tolerability of a novel, fast, 30-min infusion method for Isa in patients who were on maintenance therapy in the TCD13983 study.

All patients on maintenance treatment, regardless of treatment cohort, were switched to 30-min infusion with Isa at 10 mg/kg (250-mL fixed-volume infusion). Details on study treatments before switching, premedications, and patient characteristics are provided in Supporting Information and Supporting Information S1: Figure S1. To accelerate the infusions to a target duration of 30-min, Isa 10 mg/kg diluted in a 250-mL infusion bag of 0.9% sodium chloride was administered for the first infusion at an initial 250 mL/h rate for 30 min, then at 500 mL/h for 15 min (Supporting Information S1: Table S1). In the absence of infusion reactions (IRs), subsequent infusions were to be administered at a 500 mL/h rate in ~30 min. There were no exclusion criteria for switching patients based on health status or previous IRs; however, the last Isa dose should have been administered 1 month before switching (±7 days). The study objective

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(secondary endpoint per protocol amendment) was to evaluate safety in terms of incidence and severity of IRs during the first 2 full 30-min Isa infusions.

Between January 2023 and January 5, 2024, 45 patients in maintenance treatment were switched to the new 30-min infusion method: 4 in Isa-VCd, 13 in Isa-VRd/Part-A, and 28 in Isa-VRd/Part-B. At the time of this analysis (last patient last visit, January 22, 2024), median follow-up was 71.1 months in the Isa-VCd cohorts ($n = 15$), 55.1 months in Isa-VRd/Part-A ($n = 26$), and 38.1 months in Isa-VRd/Part-B ($n = 45$), with a median duration of overall treatment exposure of 63.3 (range, 0.2–87.2), 53.9 (0.2–79.5), and 41.5 months (1.4–49.4), respectively.

During the evaluation period, 210 fast infusions were administered to the 45 patients switched across cohorts: 45 first infusions with the intermediate rate (starting at 250 mL/h for 30 min then 500 mL/h for 15 min) and 165 subsequent infusions at the fast rate (500 mL/h) (Supporting Information S1: Table S2). By data cut-off, the median number of 30-min infusion cycles was 4 (range, 2–11); 45 patients received the first intermediate-rate infusion and a first 30-min infusion; 44 patients received ≥2 30-min infusions, with a median duration of exposure after switch of 16 weeks (8.0–46.1). Switching occurred at a median of 45 cycles (38–88) for all 45 patients, with a median of 80, 64, and 41 cycles in the Isa-VCd, Isa-VRd/Part-A, and Isa-VRd/Part-B cohorts, respectively (Supporting Information S1: Table S3).

With the new fast procedure, the median duration of Isa infusion in all switched patients was 49 min at the first infusion (intermediate rate; 31–67), 32 min at the second infusion (30–75), 32 min at third infusion (30–80), and 30 min at subsequent infusions (23–75) across the Isa-VCd, Isa-VRd/Part-A, and Isa-VRd/Part-B cohorts (Table 1). The median relative dose intensity for Isa after the switch was 99.7% (52.6%–105.0%).

30-min infusion of Isa was well tolerated as only 1 of the 45 (2.2%) patients switched to the new method (0.5% of all fast-infusion cycles) had an IR (grade 2, in Isa-VRd/Part-A), who recovered within the same day with interruption of the infusion and steroid therapy (Table 2). Study treatment had been held for 5 months in this patient, after 3 full fast infusions, while awaiting cholelithiasis surgery and then recovering from the surgery. Treatment was restarted with Isa infusion directly at the 500 mL/h rate and the IR occurred near the end of the infusion (30 min after start). Afterward, this patient entered the long-term safety study and received one full fast Isa infusion without IRs. Although only one IR was observed in this analysis, it suggests that after a period of time without Isa infusion, it is preferable to restart treatment at the intermediate infusion rate (250 mL/h for 30 min followed by 500 mL/h for 15 min), rather than directly at 500 mL/h.

No dose delays or dose omissions occurred during treatment across all study cohorts. IR premedications received by the switched patients are listed in Supporting Information S1: Table S4. All patients received diphenhydramine or equivalent and 95.6% received acetaminophen/paracetamol at the first infusion; 48.9%, 44.4%, and 31.8% of switched patients received montelukast at the first, second, and third infusion, respectively.

Overall, since the study started, in Isa-VCd, Isa-VRd/Part-A, and Isa-VRd/Part-B, 41.2%, 14.8%, and 10.9%, of patients definitively discontinued treatment due to progressive disease, and 29.4%, 33.3%, and 17.4%, respectively, due to AEs (Supporting Information S1: Table S5). After switching to fast, 30-min infusion during maintenance, 0%, 0%, and 3.6% ($n = 1$) of patients definitively discontinued treatment due to progressive disease, and 0%, 15.4% ($n = 2$), and 0%, respectively, due to AEs (Supporting Information S1: Table S5).

Overall, the most common AEs reported in the maintenance phase were arthralgia, hypertension, and upper respiratory tract infection (41.2% each; 7/17) in the Isa-VCd cohort and diarrhea in the Isa-VRd/Part-A (59.3%; 16/27) and Isa-VRd/Part-B cohorts (56.5%;

TABLE 1 Duration[a] of Isa infusion after switching to the 30-min infusion method.

	Isa-VCd			Isa-VRd		
	Isa 10 mg/kg ($n = 3$)	Isa 20 mg/kg ($n = 1$)	All ($n = 4$)	Isa 10 mg/kg ($n = 13$) Part-A	Isa 10 mg/kg ($n = 28$) Part-B	All ($N = 45$)
1st infusion[b]						
n	3	1	4	13	28	45
Median (min)	52	48	50	46	49	49
Range (min)	46–67	48–48	46–67	31–55	45–64	31–67
2nd infusion						
n	3	1	4	13	28	45
Median (min)	37	34	36	30	34	32
Range (min)	30–75	34–34	30–75	30–37	30–45	30–75
3rd infusion						
n	3	1	4	12	28	44
Median (min)	40	38	39	30	32	32
Range (min)	30–80	38–38	30–80	30–41	30–42	30–80
Subsequent infusions						
n	10	1	11	27	38	76
Median (min)	30	35	30	30	33	30
Range (min)	30–75	35–35	30–75	30–40	23–60	23–75

Abbreviations: C, cyclophosphamide; d, dexamethasone; h, hour; Isa, isatuximab; min, minute; R, lenalidomide; V, bortezomib.

[a]Duration of infusion was defined as the time from start to end of infusion, including time of interruptions (if any).

[b]The first infusion was an "intermediate-rate" infusion starting at 250 mL/h for 30 min and then at 500 mL/h for 15 min.

TABLE 2 Isa dose modifications after switching to the 30-min infusion method.

	Isa-VCd			Isa-VRd		
	Isa 10 mg/kg (*n* = 3)	Isa 20 mg/kg (*n* = 1)	All (*n* = 4)	Isa 10 mg/kg (*n* = 13) Part-A	Isa 10 mg/kg (*n* = 28) Part-B	All (*N* = 45)
N of pts who could have an infusion delay	3	1	4	13	28	45
Pts with at least 1 infusion delay within a cycle, *n*	0	0	0	0	0	0
Number of treated pts	3	1	4	13	28	45
Pts with at least 1 dose omission, *n*	0	0	0	0	0	0
Pts with at least 1 dose reduction, *n*	0	0	0	0	0	0
Pts with at least 1 infusion interrupted, *n*	0	0	0	1 (7.7)[a]	0	1 (2.2)
Pts with at least 2 infusions interrupted, *n*	0	0	0	0	0	0
Number of Isa cycles	19	4	23	65	122	210
Cycles with at least 1 dose omission, *n*	0	0	0	0	0	0
Cycles with at least 1 infusion interrupted, *n*	0	0	0	1 (1.5)	0	1 (0.5)

Abbreviations: C, cyclophosphamide; d, dexamethasone; Isa, isatuximab; min, minute; pts, patients; R, lenalidomide; V, bortezomib.

[a]An infusion interruption was reported in 1 patient (due to a grade 2 infusion reaction). The patient was due to receive 680 mg of Isa and the IR occurred after infusion of 660 mg. The IR resolved within the same day, but the remaining 20 mg were not administered. This patient had previously experienced 2 IRs: one on day 1/cycle 1 (resolved within 1 h) and one on Day 1/cycle 19 (resolved within the same day) when study treatment was restarted after a 6-month hold due to chronic gastritis and bowel obstruction. AEs were graded by NCI-CTCAE v.4.03.

26/46). After the switch to 30-min infusion, the most common AEs were upper respiratory tract infection in Isa-VCd (50.0%; 2/4) and diarrhea in Isa-VRd/Part-A (38.5%; 5/13) and Isa-VRd/Part-B (10.7%; 3/28).

The results of this prospective clinical trial analysis show that 30-min infusion is a feasible and well-tolerated option for IV Isa administration in patients who have been on long-term treatment with Isa. Although the time at which patients were switched to the 30-min infusions was shorter in Isa-VRd/Part-B (41 cycles) compared with the Isa-VRd/Part-A (64 cycles) and Isa-VCd (80 cycles) cohorts, due to sequential cohort initiation, no differences were observed in tolerability and incidence of IRs between the Isa-VRd/Part-B and Isa-VCd cohorts. Reports from other, prior studies to improve IV administration of anti-CD38 therapy did not show safety challenges in RRMM patients.[13,14]

Although the open-label design represents a limitation, the results of this prespecified, prospective analysis on the feasibility of switching to the new 30-min, fixed-volume Isa infusion method and particularly its tolerability were consistent across the cohorts evaluated in this study throughout several administrations. These findings suggest that MM patients could switch to fast, 30-min Isa infusion after prior fixed-volume infusions, thus deriving benefit from the increased convenience and time savings (Supporting Information S1: Figure S2) in settings where subcutaneous treatment may not be available or IV infusion is the preferred delivery route.

While these results were obtained in NDMM patients on long-term treatment, 30-min Isa infusion is currently being evaluated in the Phase 2 UMBRELLA trial (NCT04643002) to assess the switch to fast infusion from an earlier timepoint in RRMM patients. Furthermore, in addition to the 30-min infusion, subcutaneous administration of Isa by an on-body delivery system is being evaluated in Phase 3 trials in RRMM (IRAKLIA, NCT05405166) and NDMM patients (GMMG-HD8/HD9, NCT05804032/NCT06216158) and other Phase 2 studies, as an alternative, convenient option for Isa treatment delivery.

Fast, 30-min Isa administration will benefit patients across the MM therapeutic spectrum, in both the newly diagnosed and relapsed/refractory settings, with substantial time savings (Supporting Information S1: Figure S2). As this new infusion method reduces the length of the clinical visits associated with Isa administration, it offers more convenience to patients on a routine basis with improved quality of life and efficiencies in hospital care delivery.

In conclusion, reducing the overall duration of Isa infusion from 75 to 30 min with the new method, which is 2.5 times faster, is feasible, safe, and well tolerated, thereby facilitating IV administration in clinical practice and resulting in time savings for MM patients and their healthcare providers.

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AUTHOR CONTRIBUTIONS

Enrique M. Ocio, Aurore Perrot, Philippe Moreau, Maria-Victoria Mateos, Corina Oprea, Ercem Kodas, and Jesus San-Miguel contributed to the study design, analyzed the data, wrote/critically revised the manuscript, and approved the final version. Sara Bringhen, Joaquín Martínez-López, Lionel Karlin, Song-Yau Wang, and Yi Li analyzed the data, critically reviewed/revised the manuscript, and approved the final version.

CONFLICT OF INTEREST STATEMENT

Enrique M. Ocio received honoraria from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Pfizer, Regeneron, Sanofi, and Takeda; disclosed consulting/advisory role for AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Menarini/Stemline Therapeutics, Oncopeptides, Pfizer, Sanofi, and Takeda, and participation in speakers' bureau for Janssen; received travel/accommodation expenses from Bristol Myers Squibb, GlaxoSmithKline, Janssen, and Lilly. Aurore Perrot: received honoraria from AbbVie, Amgen, BMS/Celgene, GSK, Janssen, Pfizer, Sanofi, and Takeda; research funding from Takeda; and support for attending meetings and/or travel from Amgen, Janssen. Philippe Moreau: disclosed honoraria and consulting/advisory role for AbbVie, Amgen, Celgene, Janssen, Oncopeptides, Roche, and Sanofi. Maria-Victoria Mateos: received honoraria from AbbVie, Adaptive, Amgen, Bluebird bio, Celgene, GSK, Janssen, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi, Sea-Gen, and Takeda, and is on the Editorial Board of *HemaSphere*. Sara Bringhen: received honoraria from Amgen, BMS/Celgene, and Janssen, and consulting fees from BMS/Celgene, Janssen, and Takeda; disclosed participation on a data safety monitoring board or advisory board for Amgen, Celgene, GSK, Janssen, Karyopharm, and Sanofi. Joaquín Martínez-López received honoraria and consulting fees from BMS/Celgene, Incyte, Janssen, Novartis, Roche, and Sanofi; travel and accommodation support from BMS, Janssen, Novartis, Roche, and Sanofi. Lionel Karlin: received honoraria from AbbVie, Amgen, Celgene, Janssen, Sanofi, and Takeda; disclosed advisory role for Amgen, Celgene, GSK, Janssen, and Takeda. Song-Yau Wang: disclosed no conflicts. Corina Oprea, Yi Li, and Ercem Kodas are employed by Sanofi and may hold stock and/or stock options in the company. Jesus San-Miguel: received honoraria and consulting fees from Amgen, BMS/Celgene, GSK, Janssen, Karyopharma, Sanofi, and Takeda.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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