Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Subcutaneous Isatuximab by On-Body-Injector plus Bortezomib, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma: ISASOCUT study

Arthur Bobin

arthur.bobin@chu-poitiers.fr

CHU de Poitiers

Cyrille Touzeau

University hospital Nantes

Nicolas Branche

CHU NImes

Aurore Perrot

Institut Universitaire du Cancer-Oncopole https://orcid.org/0000-0003-0131-8689

Mamoun Dib

University Hospital, Angers

Jean Sebastien blade

Service de Santé des Armées

Thomas Chalopin

University Hospital, Tours https://orcid.org/0000-0002-9833-3115

Lydia Montes

University Hospital, Amiens

Julie gay

Centre Hospitalier de la Côte Basque

mourad Tiab

CHD vendee

margaret Macro

CHU caen

Titouan Cazaubiel

University Hospital, Bordeaux

Frederique Orsini-Piocelle

Hopital Annecy

Alberto Santagostino

Hématologie clinique, CH de Troyes

adrienne de thomas de labarthe

Centre Hospitalier de Chartres
Marlene ochmann
Centre Hospitalier Universitaire d'Orléans
Christophe roul
CH La Rochelle
reza tabrizi
Centre Hospitalier de Mont-de-Marsan
muriel newinger
GHR Mulhouse Sud-
Olivier Fitoussi
Polyclinique Bordeaux Nord
Mony Morisse
Sanofi
Rick Zhang
Sanofi
douaa dhari
Sanofi
murielle Roussel
CHU Limoges
Lionel Karlin
Hospices Civils de Lyon, Lyon
Mohamad Mohty
Hopital Saint Antoine
Philippe Moreau
Hematology Department, University Hospital Hôtel-Dieu https://orcid.org/0000-0003-1780-8746
Thierry Facon
CHRU de Lille
Cyrille Hulin
CHU Bordeaux https://orcid.org/0000-0002-3749-5161
Anaïs Schavgoulidze
Institut Universitaire du Cancer-Oncopole and Centre de Recherche en Cancérologie de Toulouse INSERM U1037
Jill Corre
Institut Universitaire du Cancer-Oncopole and Centre de Recherche en Cancérologie de Toulouse INSERM U1037 https://orcid.org/0000-0003-1580-6106
Salomon Manier
University of Lille
lisa durocher
CHU Poitiers
stephanie ragot

chu poitiers
Xavier Leleu
Universite and Inserm U 1313, 1402, CHU https://orcid.org/0000-0002-9822-4170

Article

Keywords: Newly Diagnosed Multiple Myeloma, Transplant-ineligible, Isa-VRd, OBI

Posted Date: March 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8969933/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: Yes there is potential conflict of interest.

Abstract

Isatuximab–bortezomib–lenalidomide–dexamethasone (Isa-VRd) has emerged as a standard of care for newly diagnosed multiple myeloma transplant-ineligible patients. A subcutaneous (SC) formulation of isatuximab delivered via an on-body injector (OBI) has been developed to facilitate treatment administration. ISASOCUT is a prospective, multicenter, phase 2 study evaluating the efficacy and tolerability of Isa SC-VRd administered via OBI. SC isatuximab (1400 mg) was given weekly during cycle 1, then on days 1 and 15 through cycle 12 in combination with VRd, followed by monthly isatuximab–lenalidomide until progression. The primary endpoint was the rate of ≥very good partial response (VGPR) at 8 months.

Seventy-four patients were treated, with a median age of 73 years. At 8 months, the ≥VGPR rate was 88% (95% CI, 78–94). Minimal residual disease negativity was achieved in 36% at 10^{-5} and 28% at 10^{-6}. At a median follow-up of 21.2 months, 14-month progression-free and event-free survival rates were 93.1% and 91.7%, respectively. The median relative dose intensity of isatuximab was 91.8%, with 99.3% of injections successfully completed. Infusion-related reactions occurred in 5% of patients, mostly low grade. ISASOCUT met its primary endpoint and supports SC isatuximab via OBI as a feasible alternative to intravenous administration.

INTRODUCTION

Phase 3 randomized studies IMROZ and BENEFIT have demonstrated the superiority of isatuximab plus bortezomib, lenalidomide, and dexamethasone (Isa-VRd) over VRd and Isa-Rd, respectively, in newly diagnosed multiple myeloma transplant-ineligible (NDMM TI) patients. In the IMROZ study, minimal residual disease (MRD) negativity at a sensitivity threshold of 10^{-5} was achieved in 58% of patients at best response and in 36.6% at 6 months[1,2]. In BENEFIT, using weekly bortezomib up to month 12 and every 2 weeks up to month 18, similarly deep responses were observed: 12-month and 18-month MRD negativity at 10^{-5} of 51% and 53%, respectively[3]. Based on these results, Isa-VRd is now recommended as a new standard of care for the treatment of NDMM TI[4,5].

Isatuximab is currently administered by intravenous (IV) infusion, with historical infusion durations of approximately 75 minutes from the third infusion onward[6,7]. Although recent data support a safely manageable 30-minute IV infusion[8,9], IV administration remains a practical limitation in the context of long-term frontline therapy, particularly in TI patients requiring sustained treatment. SC administration offers several advantages over IV infusion for both patients and healthcare providers, including shorter administration time, fewer infusion-related reactions (IRRs), and improved patient comfort[10–12]. The currently available manual push-based SC formulation of daratumumab presents practical limitations, including high viscosity related to the use of hyaluronidase and the need for large-bore needles, which may contribute to patient discomfort and anxiety[13,14], particularly in the context of treatments given for years.

An SC fixed dose of isatuximab (1400 mg/10 mL) administered via an innovative on-body injector (OBI) was evaluated in the phase 3 IRAKLIA study in patients with relapsed or refractory multiple myeloma (RRMM)[15].

IRAKLIA demonstrated non-inferiority of isatuximab SC OBI compared with IV administration for the co-primary endpoints, in combination with pomalidomide and dexamethasone. Importantly, the rate of IRRs was markedly lower with SC OBI (1.5%) compared with IV isatuximab (25%), while injection-site reactions (ISRs) occurred in only 0.4% of injections. This trial was the first to establish the safety and efficacy of a fixed dose of isatuximab SC delivered via an OBI in MM.

The phase 2 IZALCO study demonstrated that SC isatuximab, administered either manually or via an OBI system, was effective and well tolerated in combination with carfilzomib and dexamethasone in RRMM, with comparable pharmacokinetics and a strong patient preference for the OBI (74.5%, expressed a preference for the OBI vs. 17% for manual injection, p = 0.0004)[16].

We evaluated the Isa-VRd regimen in NDMM TI patients using an SC fixed dose of isatuximab administered via OBI. Here, we report the efficacy and safety results of the phase 2 ISASOCUT study.

METHODS

Study design and patients

ISASOCUT was an open-label, prospective, multicenter phase 2 study conducted across 23 centers in France. Eligible patients were aged ≥65 years with NDMM requiring treatment and considered TI according to standard criteria[17]. Patients were required to have an Eastern Cooperative Oncology Group performance status ≤2 and a Charlson comorbidity index ≤1 (**Data Supplement Figure S1 and S2**).

Ethics and oversight

The study was sponsored by the Centre Hospitalier Universitaire (CHU) of Poitiers, France, in collaboration with the Intergroupe Francophone du Myélome (IFM). The study was designed by the sponsor and the investigators. Data were collected, compiled, and maintained by the investigators and analyzed independently. All authors had full access to the data and were not restricted by confidentiality agreements. All authors reviewed and approved the manuscript and vouch for the accuracy and completeness of the data and for adherence to the study protocol.

The study protocol was approved by an independent ethics committee (CPP Lille, France; EudraCT number 2020-004602-59) and by the French National Agency for the Safety of Medicines and Health Products (ANSM). The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT 05889221

Treatment

Patients received SC isatuximab at a fixed dose of 1400 mg/10 mL administered via an OBI weekly during cycle 1 and on days 1 and 15 from cycle 2 to cycle 12. Lenalidomide was administered orally at a dose of 25 mg once daily on days 1 to 21 of each 28-day cycle. Dexamethasone was administered at a dose of 20 mg once weekly.

Bortezomib was administered at a dose of 1.3 mg/m² twice weekly during cycle 1 (days 1, 4, 8, and 11), followed by weekly administration on days 1, 8, 15, and 22 from cycle 2 to cycle 12.

From cycle 13 onwards, isatuximab was administered monthly, lenalidomide was continued, and both bortezomib and dexamethasone were discontinued. All treatments were administered in 28-day cycles and continued until disease progression, unacceptable toxicity, or patient withdrawal.

Endpoints and assessments

The primary endpoint was the proportion of patients achieving a very good partial response or better (≥VGPR) at 8 months, assessed according to the 2016 International Myeloma Working Group (IMWG) response criteria[18].

Key secondary endpoints included response rates, MRD status, survival times, and safety (**Data supplement**). High-risk multiple myeloma (HRMM) was defined using next-generation sequencing according to the IFM linear predictor (LP) score, with HRMM defined as a linear predictor score >1[19] (**Data supplement**). Recently published Consensus Genomic (CGS) Staging from the International Myeloma Society/IMWG was also applied to classify cytogenetic risk[20,21].

Event-free survival (EFS) was defined as the time from study inclusion to the first occurrence of disease progression, relapse, death from any cause, or permanent treatment discontinuation for any reason.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).

Statistical analysis

The planned sample size of 74 patients was calculated to demonstrate a ≥VGPR rate of 70%, with a power of 90% and a one-sided alpha level of 0.05, using a Fleming single-stage design. The critical number of responses was determined according to the A'Hern method based on exact binomial probability.

Survival times were estimated using the Kaplan–Meier method and reported with two-sided 95% confidence intervals (95% CI). A multivariable logistic regression model was used to evaluate factors associated with achieving ≥VGPR, with adjusted odds ratios calculated for sex (male vs. female), age (<75 vs. ≥75 years), cytogenetic risk at baseline (high vs. standard risk), revised International Staging System stage (I–II vs. III), and estimated glomerular filtration rate (<60 vs. ≥60 mL/min/1.73 m²).

All statistical analyses were performed using R version 4.0.4.

RESULTS

Patients and treatment

A total of 80 patients were enrolled in the ISASOCUT study; 6 patients were screen failures, resulting in 74 patients who received treatment with Isa SC OBI-VRd **(Figure 1**). At the data cut-off (November 27th, 2025),

5% (n=4) had progressed and 7% (n=5) had died (**Data Supplement Table S1**).

Baseline characteristics are summarized in **Table 1**. The median age was 73 years (interquartile range (IQR), 70–76), with 31% (n=23) aged ≥75 years. HRMM according to the CGS was identified in 36% (n=27).

Response

The ≥VGPR rate (n=65) at 8 months (primary endpoint) was 88% (95% CI, 77 to 93) (**Figure 2A**). The ≥ complete response (CR) rate was 19% (n=14). MRD negativity was achieved in 36% at a sensitivity of 10^{-5} (n=27) and in 28% at 10^{-6} (n=21) **(Figure 2B**). The ≥VGPR rates at 8 months were consistent across subgroups, with no clinically meaningful difference, ranging from 83% to 92% according to cytogenetic risk, body weight, or age at inclusion (**Data Supplement Figure S3**). The median time to ≥VGPR was 3.0 months [95% CI, 2.3–3.7] (**Data Supplement Figure S4**).

At a median follow-up of 21.2 months [95% CI, 20.2 to 21.4], progression-free survival (PFS) and event- EFS estimates at 14 months were similar (93.1% and 91.7%, respectively) suggesting a favorable safety profile with minimal early treatment discontinuation related to toxicity (**Figure 2C and 2D**).

Safety

The median relative dose intensity of isatuximab SC OBI was 91.8% [range, 53.3–111]. Nearly all SC isatuximab administrations were successfully completed using the OBI (2553/2570 injections, 99.3%) without interruption. The median injection duration was 12 minutes. IRRs occurred in 5% of patients (n=4), predominantly grade 1 (**Table 3**). Injection-site reactions were reported in 30% of patients (n=22), with 89.5% grade 1.

All patients experienced at least one adverse event (**Table 2**). Hematologic adverse events were dominated by neutropenia (all grades: n=61, 82%; grade ≥3: n=44, 59%) (**Table 3**). Peripheral sensory neuropathy occurred in 49% of patients (n=36), with grade ≥3 events reported in 7% (n=5). Grade ≥3 adverse events occurred in 68 patients (92%) (**Table 3**).

Second primary malignancies were reported in 4 patients (5%) (**Data Supplement Table S2**).

Regarding the OBI, 12 patients had at least one device deficiency (**Data Supplement Table S3**).

DISCUSSION

The ISASOCUT study demonstrates that SC isatuximab fixed dose of 1400 mg administered via an OBI in combination with bortezomib, lenalidomide, and dexamethasone is effective, safe, and feasible in NDMM TI patients. The study met its primary endpoint, with a ≥VGPR rate of 88% at 8 months with 36% and 28% MRD negativity rates at sensitivities of 10^{-5} and 10^{-6}, respectively. The safety profile was consistent with that previously reported for Isa-VRd in the BENEFIT study, with high treatment adherence, preserved dose intensity, and low rates of administration-related toxicity.

The treatment landscape for NDMM TI has been reshaped in recent years by the incorporation of CD38 monoclonal antibodies into frontline regimens. The MAIA trial first established daratumumab–lenalidomide–dexamethasone (DRd) as a standard of care, reporting a median PFS exceeding five years in the overall population, which included frail patients, suggesting particularly durable disease control in non-frail patients[22–24]. More recently, phase 3 studies including IMROZ and BENEFIT demonstrated the superiority of Isa-VRd over VRd and Isa-Rd, respectively, and confirmed the benefit of CD38-based quadruplet regimens in this population[1,3,25] These data led to the inclusion of Isa-VRd as a recommended standard of care in recent international guidelines.

The efficacy outcomes observed in ISASOCUT are consistent with those reported in pivotal phase 3 trials. The ≥VGPR rate and MRD negativity rates at 8 months fall within the range of depth of response observed in IMROZ, MRD 10^{-5} negativity rate at 6 months was 36.6%, and in CEPHEUS, 12-month MRD 10^{-5} negativity rate was 43.1%. In addition, the phase 2 REST study evaluated a dexamethasone-sparing Isa-VRd strategy with early discontinuation of bortezomib in NDMM TI patients, including frail individuals (median age 77 years [range, 70–88], with 65% aged ≥ 75 years), and reported an MRD 10^{-5} negativity rate in 37% of patients[26]. Taken together, these data suggest that SC fixed dose isatuximab delivered via OBI preserves the depth of response achieved with IV administration and that the efficacy observed in ISASOCUT is comparable to other Isa-VRd regimens, despite differences in bortezomib scheduling and treatment adaptations.

Beyond efficacy, the main contribution of ISASOCUT lies in the optimization of treatment delivery. SC administration of isatuximab via OBI for NDMM TI was associated with excellent feasibility, with nearly all injections successfully completed, a median injection time of approximately 12 minutes, and minimal need for nursing intervention. IRRs were infrequent (5%) and predominantly low grade, and injection-site reactions were generally mild and manageable. These findings extend the results of the IRAKLIA study, which demonstrated non-inferiority of isatuximab SC OBI compared with IV administration in relapsed or refractory disease, with markedly fewer IRRs (1.5% vs. 25%)[15].

Patient-centred considerations related to treatment delivery are increasingly recognized as critical in MM, particularly in populations requiring prolonged therapy. In this regard, results from the phase 2 IZALCO study further support the relevance of OBI systems, showing comparable pharmacokinetic exposure between SC administration modalities and a strong patient preference for OBI over manual injection[27]. Together, these studies support a paradigm shift toward simplified, patient/nurse/pharmacist-friendly administration strategies for CD38 mAbs.

Beyond patient preference, the cumulative burden of treatment delivery represents a major and often underappreciated challenge in NDMM TI, where frontline therapy is administered over many years. In ISASOCUT, nearly 2,000 SC isatuximab injections were delivered to 74 patients within the first year of treatment alone. When extrapolated to the prolonged PFS expected with CD38-based frontline regimens—often extending to 8–10 years—this translates into a very large number of injections at both the individual patient and healthcare system levels. While manual push-based SC administration was initially considered a major advance over IV infusion, these findings illustrate that technological innovation can further optimize

long-term treatment delivery. The OBI enables standardized, hands-free administration, reduces nursing workload, and improves feasibility in the context of sustained therapy, thereby addressing key limitations of manual injection approaches.

Compared with manual SC injection, the OBI represents a meaningful technological advance in treatment delivery. It does not require any battery or electrical input and minimizes human handling throughout the administration process. This standardized, hands-free, and needle-shielded system enhances safety for both patients and nursing staff. In addition, the OBI allows patients autonomy during administration. Beyond improved comfort and workflow efficiency, this approach may ultimately facilitate at-home administration strategies, opening new perspectives for the long-term management of chronic disease.

Several limitations of the present study should be acknowledged. The follow-up remains relatively short, and survival outcomes are immature, precluding definitive conclusions regarding long-term PFS and EFS. In addition, although patients aged > 80 years were eligible for inclusion, the study population was relatively fit compared with the broader TI population, and extrapolation to frailer patients should therefore be undertaken with caution. Pharmacokinetic data were not collected, however, the preserved depth of response and MRD negativity provide indirect clinical evidence supporting adequate drug exposure with SC administration via OBI – these data were collected in the IRAKLIA study. Finally, while MRD negativity was assessed, longitudinal MRD kinetics (sustained MRD negativity rates) and correlations with survival outcomes will require longer follow-up.

In conclusion, ISASOCUT demonstrates that SC fixed dose isatuximab delivered via an OBI can be safely and effectively integrated into frontline Isa-VRd therapy for NDMM TI patients. By preserving efficacy while substantially improving treatment delivery both for patients and healthcare providers, this approach represents a meaningful advance in the practical management of this patient population and supports broader adoption of OBI-based SC isatuximab in routine clinical practice.

The study protocol was approved by an independent ethics committee (CPP Lille, France; EudraCT number 2020-004602-59) and by the French National Agency for the Safety of Medicines and Health Products (ANSM). The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT 05889221

Declarations

The study protocol was approved by an independent ethics committee (CPP Lille, France; EudraCT number 2020-004602-59) and by the French National Agency for the Safety of Medicines and Health Products (ANSM). The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT 05889221

ACKNOWLEDGMENTS

This study was sponsored by the CHU of Poitiers, France. It was funded by Sanofi who also provided the supplies of isatuximab and the OBI.

We gratefully acknowledge the patients and their families for their willingness to participate in this study.

We also give a special thanks to the ISASOCUT study project managers: Ahmed Amine Kasmi, Aurelie Gontier, Veronique Ferrand Rigallaud, at the sponsor, the CHU of Poitiers. We would like to thank the sponsor project team, Stéphanie Noel, Céline Abonneau, Marcia Stefanini.

We thank the IFM team Chanaz Louni, Gilles Belot, Marie-Odile Petillon, Sandrine Rollet, Laurent Gibel.

AUTHOR CONTRIBUTIONS STATEMENT

A.B., R.Z., A.S., S.R., C.R., T.C., L.M., M.D., M.T., H.M., T.B., J.G., L.V., A.D., R.T., M.N., J.B., A.S., D.D., M.M., P.M., M.M., M.R., L.K., C.T., A.P., T.F., C.H., and X.L. enrolled and treated patients.

L.D. and S.R. performed statistical analyses.

A.B., X.L., A.K., and A.G., designed the study.

J.C., and A.S. performed the MRD analysis

All authors analysed and interpreted the data. All authors contributed to the writing of the manuscript and approved its final version.

Competing interests

The authors report the following competing interests. A.B. reports consultancy and honoraria from Johnson and Johnson, Sanofi, Amgen, Pfizer, Stemline Menarini and Bristol Myers Squibb. C.T. has received consultancy, honoraria and travel fees from Sanofi, Johnson and Johnson, Kite/Gilead, Amgen, Novartis, Takeda, Pfizer, Oncopeptide, AbbVie, GSK and Bristol Myers Squibb. A.P. has received consultancy, honoraria and travel fees from Sanofi, Johnson and Johnson, Pfizer, Stemline Menarini and Bristol Myers Squibb. T.C. has received consultancy, honoraria and travel fees from Amgen, Sanofi, Johnson and Johnson, Pfizer, Stemline Menarini. M.Macro reports consultancy travel fees from Amgen, Celgene/BMS, GlaxoSmithKline, Janssen, Novartis, Pfizer, Sanofi, Takeda. M. Mothy has received consultancy, honoraria and travel fees from Sanofi, Janssen-Cilag, Kite/Gilead, Amgen, Novartis, Pfizer, GSK and Bristol Myers Squibb. P.M. has received consultancy, honoraria and travel fees from Sanofi, Janssen-Cilag, Kite/Gilead, Amgen, Pfizer, GSK and Bristol Myers Squibb. S.M. has received consultancy, honoraria and travel fees from Sanofi, Janssen-Cilag, Kite/Gilead, Amgen, Pfizer, GSK and Bristol Myers Squibb. X.L. has received consultancy, honoraria and travel fees from Sanofi, Janssen-Cilag, Kite/Gilead, Amgen, Novartis, Takeda, Pfizer, Oncopeptide, AbbVie, GSK and Bristol Myers Squibb. The other authors declare no competing interests.

References

1. Facon T, Dimopoulos MA, Leleu XP, et al. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2024;391(17):1597-1609. doi:10.1056/NEJMoa2400712
2. Manier S, Dimopoulos MA, Leleu XP, et al. Isatuximab plus bortezomib, lenalidomide, and dexamethasone for transplant-ineligible newly diagnosed multiple myeloma patients: a frailty subgroup analysis of the IMROZ trial. *Haematologica*. 2025;110(9):2139-2150. doi:10.3324/haematol.2024.287200
3. Leleu X, Hulin C, Lambert J, et al. Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. *Nat Med*. 2024;30(8):2235-2241. doi:10.1038/s41591-024-03050-2
4. Dimopoulos MA, Terpos E, Boccadoro M, et al. EHA-EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. *Nat Rev Clin Oncol*. 2025;22(9):680-700. doi:10.1038/s41571-025-01041-x
5. Kumar SK, Callander NS, Adekola K, et al. NCCN Guidelines® Insights: Multiple Myeloma, Version 1.2025. *J Natl Compr Canc Netw*. 2025;23(5):132-140. doi:10.6004/jnccn.2025.0023
6. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107. doi:10.1016/S0140-6736(19)32556-5
7. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet*. 2021;397(10292):2361-2371. doi:10.1016/S0140-6736(21)00592-4
8. Ocio EM, Perrot A, Moreau P, et al. 30-Minute infusion of isatuximab in patients with newly diagnosed multiple myeloma: Results of a Phase 1b study analysis. *Hemasphere*. 2024;8(11):e70041. doi:10.1002/hem3.70041
9. Kotb R, Geirnaert M, Rimmer E, et al. Real-World Safety and Tolerability of Rapid, 30-Minutes, Intravenous Isatuximab in Patients With Multiple Myeloma. *Clinical Lymphoma Myeloma and Leukemia*. 2025;25(7):e510-e512. doi:10.1016/j.clml.2025.01.022
10. Jackisch C, Manevy F, Frank S, Roberts N, Shafrin J. White Paper on the Value of Time Savings for Patients and Healthcare Providers of Breast Cancer Therapy: The Fixed-Dose Combination of Pertuzumab and Trastuzumab for Subcutaneous Injection as an Example. *Adv Ther*. 2022;39(2):833-844. doi:10.1007/s12325-021-01996-0
11. Rummel M, Kim TM, Aversa F, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). *Ann Oncol*. 2017;28(4):836-842. doi:10.1093/annonc/mdw685
12. Harvey MJ, Zhong Y, Morris E, Beverage JN, Epstein RS, Chawla AJ. Assessing the transition from intravenous to subcutaneous delivery of rituximab: Benefits for payers, health care professionals, and patients with lymphoma. *PLoS One*. 2022;17(1):e0261336. doi:10.1371/journal.pone.0261336

13. Avello NS, Pajares PC, Cordero P, Suzan F, Barlas C. Subcutaneous administration of isatuximab in patients with multiple myeloma by an on-body delivery system : results of a nurse survey. *Front Oncol*. 2025; Jun 18;15:1547108 https://doi.org/10.3389/fonc.2025.1547108
14. Desai M, Kundu A, Hageman M, Lou H, Boisvert D. Monoclonal antibody and protein therapeutic formulations for subcutaneous delivery: high-concentration, low-volume vs. low-concentration, high-volume. *MAbs*. 2023;15(1):2285277. doi:10.1080/19420862.2023.2285277
15. Ailawadhi S, Špička I, Spencer A, et al. Isatuximab Subcutaneous by On-Body Injector Versus Isatuximab Intravenous Plus Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Phase III IRAKLIA Study. *J Clin Oncol*. 2025;43(22):2527-2537. doi:10.1200/JCO-25-00744
16. Inc MG. EFFICACY AND SAFETY OF ISATUXIMAB SUBCUTANEOUS (SC) PLUS... by Gurdeep Parmar. Accessed December 16, 2025. https://library.ehaweb.org/eha/2025/eha2025-congress/4160801/gurdeep.parmar.efficacy.and.safety.of.isatuximab.subcutaneous.28sc29.plus.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Asearch%3Disatuximab
17. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2021;32(3):309-322. doi:10.1016/j.annonc.2020.11.014
18. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346. doi:10.1016/S1470-2045(16)30206-6
19. Perrot A, Lauwers-Cances V, Tournay E, et al. Development and Validation of a Cytogenetic Prognostic Index Predicting Survival in Multiple Myeloma. *J Clin Oncol*. 2019;37(19):1657-1665. doi:10.1200/JCO.18.00776
20. Avet-Loiseau H, Davies FE, Samur MK, et al. International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the Definition of High-Risk Multiple Myeloma. *J Clin Oncol*. 2025;43(24):2739-2751. doi:10.1200/JCO-24-01893
21. Schavgoulidze A, Perrot A, Leleu X, et al. High-risk genomic consensus validation for patients with newly diagnosed multiple myeloma using next-generation sequencing. *Blood*. Published online 24 September 2025:blood.2025029999. doi:10.1182/blood.2025029999
22. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N Engl J Med*. 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249
23. Perrot A, Facon T, Plesner T, et al. Sustained Improvement in Health-Related Quality of Life in Transplant-Ineligible Newly Diagnosed Multiple Myeloma Treated With Daratumumab, Lenalidomide, and Dexamethasone: MAIA Final Analysis of Patient-Reported Outcomes. *Eur J Haematol*. 2025;114(5):883-889. doi:10.1111/ejh.14392
24. Facon T, Moreau P, Weisel K, et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. *Leukemia*. 2025;39(4):942-950. doi:10.1038/s41375-024-02505-2
25. Usmani SZ, Facon T, Hungria V, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized

phase 3 CEPHEUS trial. *Nat Med*. 2025;31(4):1195-1202. doi:10.1038/s41591-024-03485-7

26. Askeland FB, Haukås E, Slørdahl TS, et al. Isatuximab, bortezomib, lenalidomide, and limited dexamethasone in patients with transplant-ineligible multiple myeloma (REST): a multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2025;12(2):e120-e127. doi:10.1016/S2352-3026(24)00347-8
27. Parmar G, Capra M, Seguro F, et al. Efficacy and safety of isatuximab subcutaneous plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma: results of the Phase 2 study IZALCO. *Blood Cancer J*. 2025;16(1):16. doi:10.1038/s41408-025-01436-0

Tables

Table 1. Baseline demographics and disease characteristics (n=74)

Characteristics	Isa SC OBI + VRd
Sex, n (%)	
Male	38 (51)
Female	36 (49)
Age, years (range)	73.0 (66-83)
Age subgroup years, n (%)	
≤70	22 (30)
70-75	29 (39)
≥75	23 (31)
BSA, m^2 (range)	1.8 (1.4-2.3)
ECOG performance status, n (%)	
0	26 (35)
1	36 (49)
2	12 (16)
eGFR (MDRD Formula) (mL/min/1.73m^2) n (%)	
<60	18 (24)
≥60	56 (76)
R-ISS, n (%)	
1	14 (21)
2	40 (61)
3	12 (18)
Cytogenetic profile (LP score), n (%)	
Standard-risk	56 (86)
High-risk	9 (14)
Cytogenetic risk (CGS), n (%)	
Standard-risk	40 (54)
High-risk	27 (36)
Cytogenetic anomalies, n (%)	
Del(17p)	9 (12)
t(4;14)	6 (8)

t(14 ;16)	2 (3)
t(14 ;20)	2 (3)
Gain/amp 1q	23 (32)
Del(1p32)	8 (10)
TP53 mutation	2 (3)

Abbreviations: Isa SC OBI, isatuximab subcutaneous on-body-injector; VRd, bortezomib–lenalidomide–dexamethasone; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; R-ISS, revised International Staging System; CGS, consensus genomic staging; LP, linear prognostic index.

Table 2. Overview of adverse events (safety population), n=74

Isa SC OBI + VRd	
Any AE	74 (100)
Grade ≥3 AE	68 (92)
Drug-related AE	47 (64)
Any TEAE leading to permanent full discontinuation	6 (8)
Any AE leading to temporary full discontinuation	42 (57)
Any AE leading to permanent partial discontinuation of:	
Isatuximab	0
Bortezomib	9 (12)
Dexamethasone	9 (12)
Lenalidomide	3 (4)
Grade 5 TEAE	4 (5)

Abbreviations: Isa SC OBI, isatuximab subcutaneous on-body injector; VRd, bortezomib–lenalidomide–dexamethasone; AE, adverse event; TEAE, treatment-emergent adverse event

All results are expressed as n (%).

Table 3. Summary of adverse events (safety population) (n=74)

	All grades (N=74)	Grade 2	Grade ≥3
Hematologic AEs, n (%)			
Anemia	17 (23)	/	8 (11)
Thrombocytopenia	25 (34)	/	21 (28)
Neutropenia	61 (82)	/	44 (59)
Lymphopenia	49 (66)	/	49 (66)
Non-hematologic AEs, n (%)			
Infections			
Pneumonia	8 (11)	7 (9)	2 (3)
COVID-19	13 (18)	10 (14)	1 (1)
Upper respiratory infection	1 (1)	0	0
Bronchitis	23 (31)	17 (23)	2 (3)
Dyspnea	8 (11)	3 (3)	0
Peripheral neuropathy	36 (49)	20 (27)	5 (7)
Diarrhea	48 (65)	30 (41)	2 (3)
Constipation	33 (45)	17 (23)	2 (3)
Nausea	12 (16)	0	3 (4)
Insomnia	20 (27)	11 (15)	0
Asthenia	33 (45)	17 (23)	2 (3)
Weight loss	10 (14)	7 (9)	0
Cutaneous rash	8 (11)	3 (4)	1 (1)
Peripheral oedema	15 (20)	4 (5)	2 (3)
Isatuximab-related AEs, n (%)			
Infusion-related reaction	4 (5)	/	0
Injection site reaction	22 (30)	/	0
Injection site pain	1 (1)	/	0

Abbreviations: AEs, adverse events. AEs reported by grade according to Common Terminology Criteria for Adverse Events v5.0.

Figures

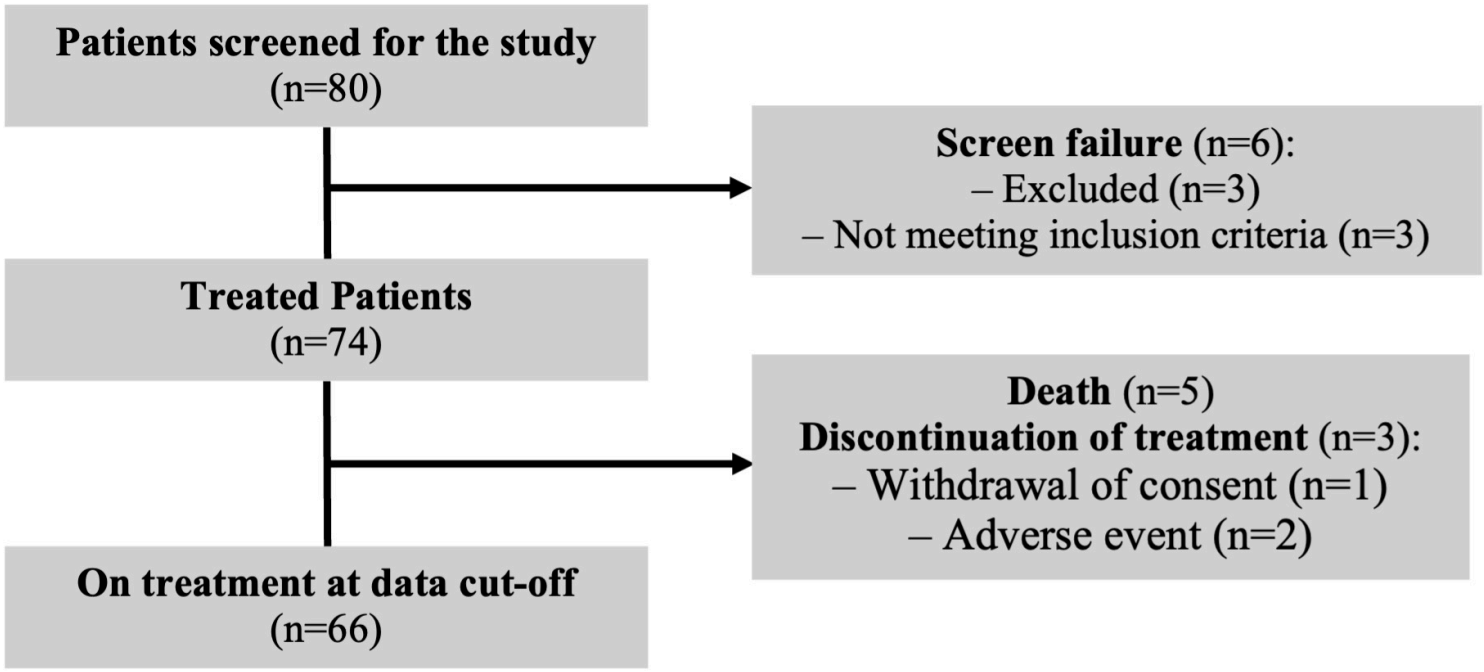


Figure 1

CONSORT diagram. Flow diagram showing patient enrollment, treatment, and disposition in the phase 2 ISASOCUT study. Of the 80 patients screened, 6 were screen failures: 3 were excluded (1 plasma cell leukemia, 1 clinically significant cardiac disease, and 1 significant medical or psychiatric condition), and 3 did not meet inclusion criteria (1 inadequate documented organ function and 2 absence of SLiM-CRAB criteria). Seventy-four patients received study treatment. At the data cutoff (November 27, 2025), 5 patients had died and 3 permanently discontinued treatment: 1 withdrew consent and 2 due to adverse events (recurrent cutaneous toxicity and pyelonephritis).

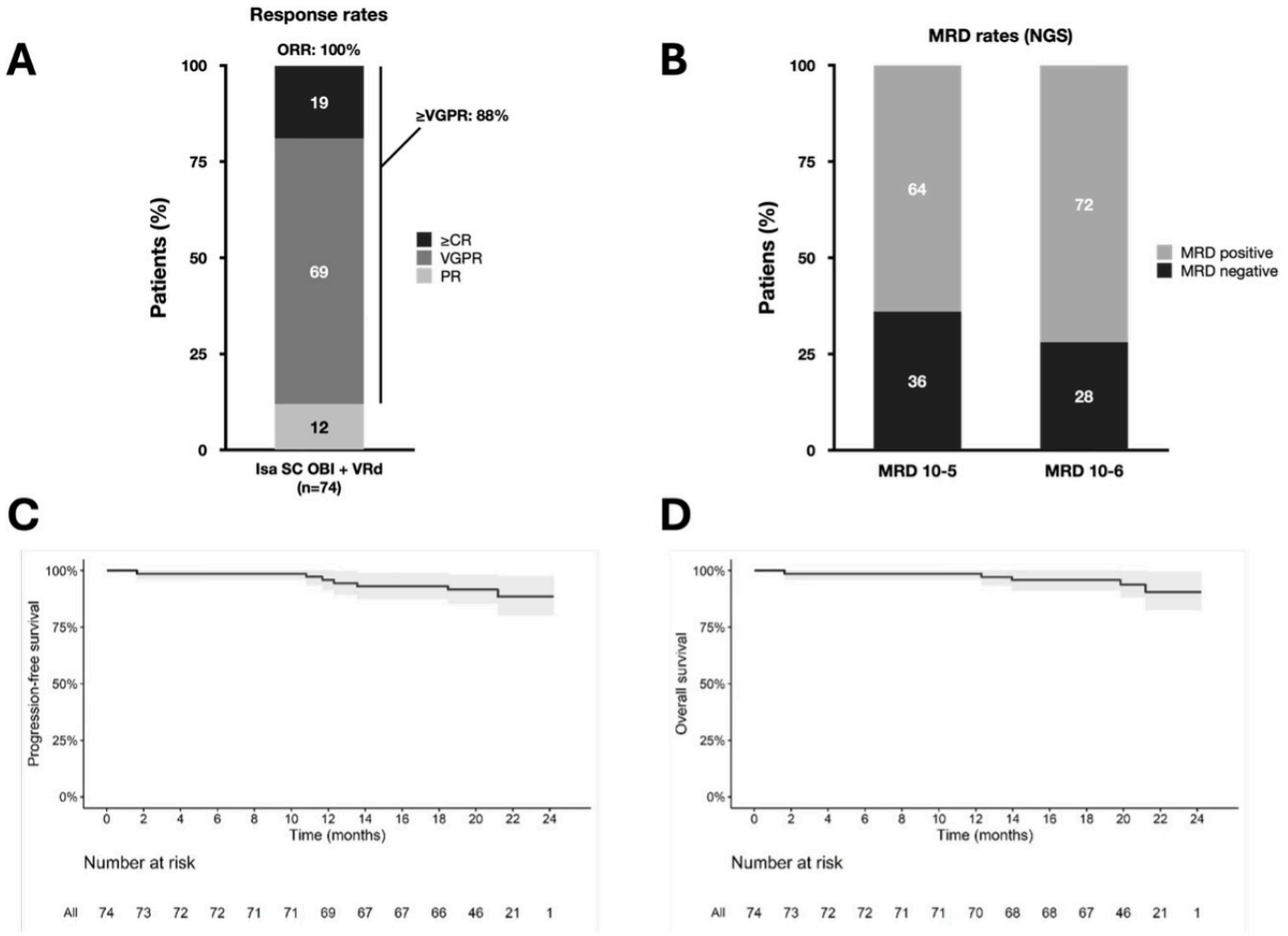


Figure 2

Response at 8 months, MRD status and survival. (**A**) response rates at 8 months in patients treated with Isa SC OBI–VRd, showing the distribution of sCR, CR, VGPR, PR and SD. The ORR is indicated above the bar. (**B**) MRD status assessed by next-generation sequencing at sensitivity thresholds of 10^{-5} and 10^{-6}. Percentages represent the proportion of patients achieving each response category or MRD status. (**C**) Kaplan–Meier estimates of progression-free survival (PFS) and event-free survival (EFS) (**D**) in the overall study population treated with Isa SC OBI-VRd. The number of patients at risk at each time point is shown below each panel. At the time of data cut-off, survival outcomes were immature, with identical PFS and EFS curves, reflecting the low incidence of treatment discontinuation due to toxicity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ISASOCUTBobinetalDataSupp.pdf