Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Subcutaneous Isatuximab by On-Body-Injector plus Bortezomib, Lenalidomide, and dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma: ISASOCUT (IFM 2022-05) study

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Table S1. Causes of death in the ISASOCUT study

Date of death	Reason for death
Nov. 19th, 2025	Road traffic accident
Dec. 27th, 2023	Myocardial infarction
May 11th, 2025	Endocarditis
Dec. 28th, 2024	Cardio-respiratory arrest
Sep 24th, 2025	Cardiac arrest due to hypoxemic pneumonia caused by *Moraxella Catarrhalis*

Summary of deaths occurring during the study period, including date and cause of death.

Table S2. Second primary malignancies

Type of Cancer	Onset date	Grade
Adenocarcinoma of colon	Mar. 28 2024	Grade 3
Carcinoma in situ of skin	Oct. 08 2024	Grade 2
Squamous cell carcinoma of skin	Sep. 05 2024	Grade 1
Basal cell carcinoma	Dec. 19 2024	Grade 1
Squamous cell carcinoma of skin	Jan 28 2025	Grade 2

Second primary malignancies reported during the study, including cancer type, onset date, and maximum reported grade.

Table S3. On-body injector (OBI) device deficiencies

Patients	Device deficiency
004-01	The button did not work correctly
004-02	The red fill gauge was not in proximity to the empty marking
009-01	The button did not work correctly
022-03	The needle did not retract at the end of injection
041-01	The needle did not retract at the end of injection
041-04	Other
055-04	The button did not work correctly
056-01	Leak at the base of the administration device when the isatuximab syringe is connected
091-01	The device had come off
094-03	The red fill gauge was not in proximity to the empty marking
168-01	The injection time was > 20 minutes
184-01	The treatment did not flow during injection

Reported device deficiencies related to the on-body injector during subcutaneous isatuximab administration. No device deficiency resulted in an adverse event.

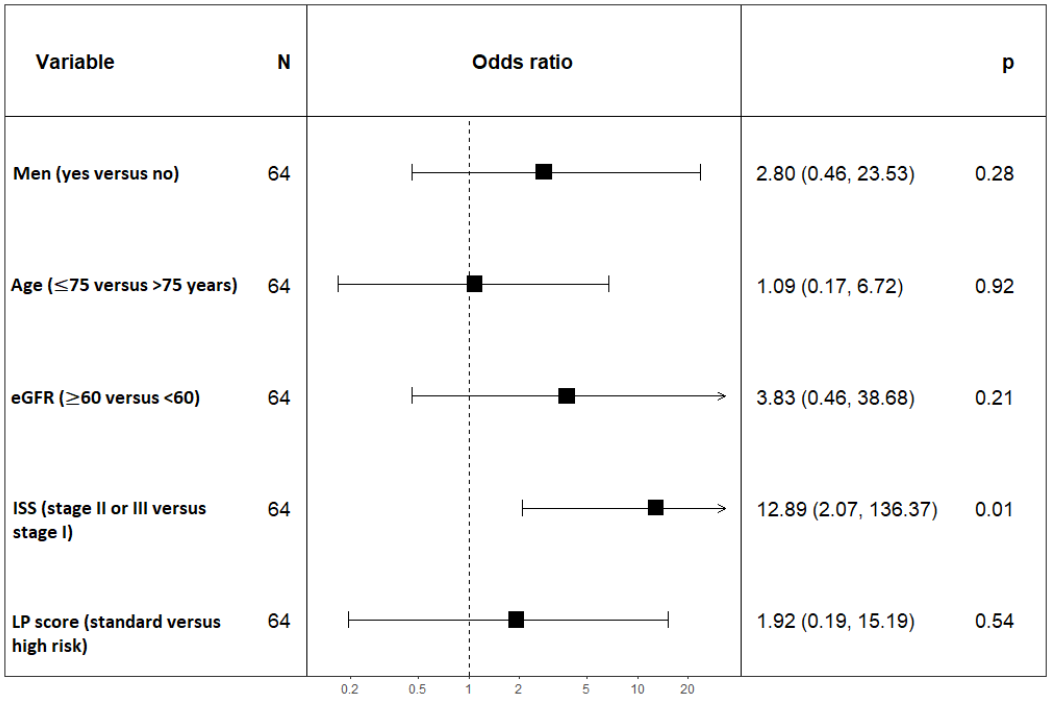
Supp Figures

CCI Weight	Comorbid Conditions
0	No comorbid conditions
1	Heart attack (myocardial infarction) Peripheral arterial disease Other diagnosed heart problems Stroke Asthma Ulcer disease Insulin-dependent diabetes Arthritis
2	Renal disease/kidney stones Diagnosed cancer
3	Cirrhosis

Figure S1. Charlon comorbidity index. Braithwaite D, Cancer Epidemiol Biomarkers Prev. 2012 Jul; 21(7): 1115–1125.

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Figure 2. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS CRITERIA. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655



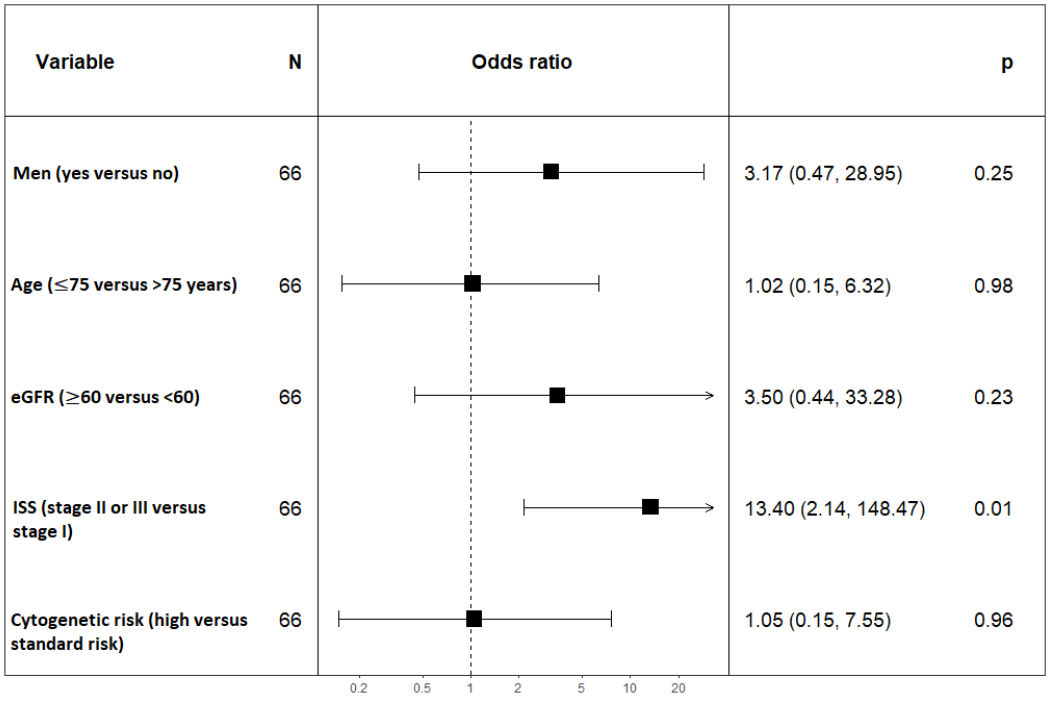


Figure S3. Subgroup analysis of ≥VGPR rate at 8 months. Forest plot showing ≥VGPR rates at 8 months across prespecified subgroups, including age, cytogenetic risk, and body weight. Error bars represent 95% confidence intervals.

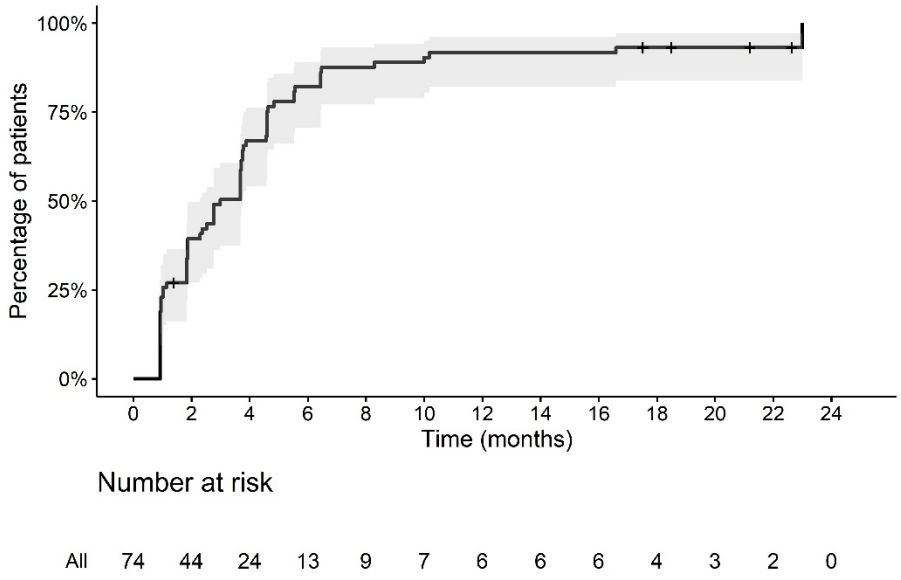


Figure S4. Time to VPGR. Kaplan–Meier curve depicting time to first achievement of ≥VGPR in the intention-to-treat population.

Patients

Eligibility Criteria

- Must be able to understand and voluntarily sign an informed consent form
- Must be able to adhere to the study visit schedule and other protocol requirements
- Patient able to swallow the various oral treatments
- Life expectancy > 6 months
- Subject, male or female, must be at least ≥ 65 years of age
- Must have a Newly diagnosed Multiple Myeloma requiring therapy (SLiM CRAB criteria) (see appendix 18.2) 6.1. Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma 6.2. Revised International Myeloma Working Group diagnostic criteria for multiple myeloma
- Myeloma defining events:
- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) • Renal insufficiency: creatinine clearance ≤40 mL per min† or serum creatinine ≥177 µmol/L (≥2 mg/dL)
- †Measured or estimated by validated equations
- Anemia: hemoglobin value of ≥ 20 g/L below the lower limit of normal, or hemoglobin value ≤100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT ‡
- If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
- Any one or more of the following biomarkers of malignancy:
- Clonal bone marrow plasma cell percentage* ≥60%
- Involved/uninvolved serum free light chain ratio ≥100
- >1 focal lesion on MRI studies (Each focal lesion must be 5 mm or more in size.)
- Must have measurable disease as defined by any of the following:
- Serum monoclonal paraprotein (M-protein) level ≥5 g/L or urine M- protein level ≥200 mg/24 hours; or Serum immunoglobulin free light chain ≥100 mg/L and abnormal serum immunoglobulin kappa lambda free light chain ratio (any method)*The same method must be used along the study for a given patient.
- Must be nontransplant eligible 8.1. Newly diagnosed and not considered candidate for high- dose chemotherapy with SCT. 8.2. Subject must have Charlson comorbidity index ≤1 8.3. ECOG ≤2
- Adequate bone marrow function, documented within 72 hours and without transfusion 72 hours prior to the first intake of investigational product (C1J1) with no growth factor support (one week), defined as:
- Absolute neutrophils ≥ 1 x109/L,
- Untransfused Platelet count ≥ 75 x109/L,
- Hemoglobin ≥8.5 g/dL.
- Adequate organ function documented within one week prior to the first intake of investigational product (C1J1) defined as:
- Serum total bilirubin < 2x upper limit of normal (ULN),
- Creatinine clearance ≥ 30ml/min calculated with MDRD formula,
- Serum SGOT/AST or SGPT/ALT < 3x upper limit of normal (ULN).
- Person affiliated to the French social security system or equivalent

- A man who is sexually active with a pregnant woman or a woman of childbearing potential must agree to use a barrier method of birth control e.g., condom with spermicidal foam/gel/film/cream/suppository during the study and for at least 5 months after the last dose of treatment, even he has had a vasectomy.
- A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
- Not a female of childbearing potential Or 13.2. A FCBP* who must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 - 14 days prior to and again within 24 hours prior to starting study medication and before each cycle of study treatment.
- A FCBP* must understand and agree to continue abstinence from heterosexual intercourse or to use 2 reliable effective methods of contraception (a very effective method and an effective additional method) simultaneously without interruption:
- For at least 28 days before starting experimental treatments, 13.2.2. Throughout the entire duration of experimental treatments, 13.2.3. During dose interruptions, 13.2.4. And for at least 5 months after the last dose of experimental treatments.
- All patients must understand and accept to comply with the conditions of the Lenalidomide pregnancy prevention plan

Exclusion Criteria

- Subject has a diagnosis of primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma.
- Subject has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.
- Subject has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.
- Subject has a history of ongoing malignancy (other than multiple myeloma) within 3 years (date of diagnosis of the malignancy) before inclusion in the study treatment (exceptions are malignancies considered cured with minimal risk of recurrence within 3 years, even though the patient receives treatment).
- Subject has had radiation therapy within 7 days study treatment*

unless done for antalgic reason or in case of functional risk for the patient.

- Subject has had plasmapheresis within 7 days study treatment *

unless patient disease is still measurable (inclusion criteria n°6) after the plasmapheresis.

- Subject is exhibiting clinical signs of meningeal involvement of multiple myeloma.
- Known to be seropositive for history of human immunodeficiency virus (HIV).
- Known to have hepatitis B active or uncontrolled infection (positive HBsAg and/or HBV DNA)
- Known to have hepatitis C active infection (positive HCV RNA and negative anti-HCV)
- Subject has any clinically significant medical or psychiatric condition or disease (e.g., uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) in the investigator's opinion, would expose the patient to excessive risk or may interfere with compliance or interpretation of the study results.
- Subject has active systemic infection and severe infections requiring treatment with a parenteral administration of antibiotics.
- Subject has clinically significant cardiac disease, including:

- myocardial infarction within 6 months before study treatment, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV)
- uncontrolled cardiac arrhythmia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5 Grade ≥2) or clinically significant ECG abnormalities or LVEF < 40 % 14. Subject has known allergies, hypersensitivity, or intolerance to steroids, mannitol, pregelatinized starch, sodium stearyl fumarate, histidine (as base and hydrochloride salt), arginine hydrochloride, poloxamer 188, sucrose or any of the other components of study intervention that are not amenable to premedication with steroids and H2 blockers or would prohibit further treatment with these agents, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure).
- Known hypersensitivity, allergy to one of the study product (isatuximab, lenalidomide, bortezomib), dexamethasone, boron or to one of the excipients. Allergy to bandages or adhesives (acrylic).
- Acute diffuse infiltrative pneumopathy, pericardial disease 17. Subject has plasma cell leukemia (according to World Health Organization [WHO] criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2 × 109/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
- Subject is known or suspected of not being able to comply with the study protocol (e.g., because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol- specified assessments. Subject is taking any prohibited medications.
- Subject has had major surgery within 2 weeks before study treatment or has not fully recovered from surgery, excluding surgery related to myeloma.
- Subject has received an investigational drug (including investigational vaccines) within 14 days or 5 half-lives of the investigational drug prior to initiation of study intervention, whichever is longer, or used an invasive investigational medical device within 4 weeks before study treatment or is currently enrolled in an interventional investigational study.
- Persons referred to in Articles L1121-5 to L1121-8 of the CSP 22. Subject has contraindications to required prophylaxis for deep vein thrombosis and pulmonary embolism.
- Incidence of gastrointestinal disease that may significantly alter the absorption of oral drugs.

MRD assessment

MRD was performed on bone marrow aspiration in patients who achieved at least a partial response (≥PR) for the primary endpoint timepoint of 18 months 18,19. MRD was analyzed in accordance with International Myeloma Working Group (IMWG) response criteria 20. The patients with primary refractory disease, stable disease and minor response, along with patients failing or not tested for MRD analysis, have been considered as patients with positive MRD at 10-5. The MRD test was centrally and primarily determined by next generation sequencing (NGS) with a 10-6 sensitivity (Professor Avet Loiseau / Professor Corre, Toulouse Oncopole, France). In the case of failure to perform MRD by NGS, MRD assessment was then performed centrally using multiparametric flow cytometry (MFC) with a 10-5 sensitivity (Dr Vergez, Toulouse Oncopole, France) (Supplementary Appendix) 21.

The sustained MRD rate 12 months at 10-5 (similar time points 12, 18 and 24 months) was defined as the proportion of patients with two consecutive MRD-negative 10–5 results (12, 18 and 24 months) at least 12 months apart, without any MRD-positive results in between. MRD 12-24 was defined as the proportion of patients with two consecutive MRD-negative 10–5 results at months 12 18 and 24. MRD

18-24 was defined as the proportion of patients with two consecutive MRD-negative 10–5 results at least 6 months apart at 18 and 24 months. The MRD 18-24 was given for descriptive purposes (shown in figures).

Cytogenetic risk assessment.

A recent international genomic staging consensus (GCS) has standardized the HR definition [IMS (International Myeloma society)/IMWG (International Myeloma working group)] 20.

Randomization was stratified by age (< 75 and ≥ 75) and cytogenetic risk at baseline. For this purpose and to limit bias in recruitment, cytogenetic risk assessment was performed by FISH (Modified Perrot score) using probes for chromosomes 17, 14, 4, and 1 6.

All patients had also cytogenetic risk assessed by NGS used for study analysis 18,19. Bone marrow samples were obtained at diagnosis and shipped overnight to a central laboratory. Upon receipt, plasma cells (PCs) were isolated using CD138+ MAC-Sorting (Miltenyi Biotec, Paris, France). Post-sorting purity was checked by cytologic analysis of a spin from positive fraction, and only samples with ≥ 70% PCs after sorting were kept for the analysis. The mean purity was 94%. PCs were analyzed by NGS using NextSeq 500 (Illumina). For each positive del(17p) by NGS, an additional FISH analysis was performed to assess the percentage of positive plasma cells. NGS sequencing was performed using a panel of specific probes targeting regions of interest, as previously described 6.

Statistical analysis.

The analysis was performed in the intention-to-treat (ITT) population, which included all randomized patients. The safety population included all patients who had received at least one dose of the assigned treatment.

All MRD and response endpoints was compared between treatment groups using a Wald test and treatment effect was assessed by OR and 95% CI using a mixed logistic regression with treatment as the explanatory variable and adjusting for randomization stratification factors in the global population. For analyses in subset of HRMM patients, treatment effect was assessed by OR and 95% CI using a logistic regression with treatment as the sole explanatory variable and no adjustment.

No correction for multiplicity was performed. All statistical analyses were performed using R software.

Inclusion and ethics

The study was sponsored by CHU (Centre Hospitalier Universitaire) Poitiers, France, in collaboration with the IFM (Intergroupe Francophone of Myeloma). The IFM and CHU Poitiers in collaboration with the investigators, designed the trial and compiled and maintained the data collected by the investigators. All authors had access to the data and were not restricted by confidentiality agreements. All authors reviewed, revised, and approved the manuscript. The sponsor and authors vouch for data accuracy and completeness and for adherence to the study protocol 1.

An independent ethics committee (CPP Est-II, Besancon, France, eudra CT 2020-004602-59) approved the study protocol along with ANSM (agence nationale de securite du medicament). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the principles originating from the Declaration of Helsinki. All patients provided written informed consent 1.

Data Availability Statement.

Data supporting this article are part of an ongoing clinical trial and are not publicly available. Data will be considered for sharing once the product and indication has been approved by major health authorities (for example, the US Food & Drug Administration, the European Medicines Agency), with restriction due to data privacy regulations, and the informed consent.

Requests for de-identified patient data by researchers with proposed use of the data can be made to the corresponding author with specific data needs, analysis plans and dissemination plans. Those requests will be reviewed by a study steering committee (IFM group) and the study sponsor for release upon publication. Response will typically be given in 3 months.

The trial protocol and statistical analysis plan can be found in the Supplementary Information.

Code Availability (If Relevant).

eCRF. V8.2.30 Ennov

All statistical analyses were performed using R software version 4.0.4.