Comparative Analysis of Subcutaneous Isa VRd (ISASOCUT) and Intravenous Isa VRd (IMROZ) in Patients With Transplant-Ineligible Newly Diagnosed Multiple Myeloma Across Age Groups

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Introduction

- In patients with transplant-ineligible newly diagnosed multiple myeloma (Ti-NDMM), **isatuximab given intravenously in combination with bortezomib, lenalidomide, and dexamethasone (Isa IV VRd)** has been approved in the United States, European Union, Japan, China, and several other countries, based on the **phase 3 IMROZ study** (NCT03319667)[1–5]
- Utilizing the **innovative on-body injector (OBI)**, efficacy and safety of subcutaneous Isa in combination with VRd (Isa SC OBI VRd) have recently been demonstrated in patients with **Ti-NDMM (ISASOCUT study**, NCT05889221)[6]
- A key difference in treatment administration schedules between the IMROZ and ISASOCUT studies involved the **bortezomib regimen: twice-weekly during weeks 1–4 of each cycle in IMROZ compared with weekly in cycles 2-12 following twice-weekly in cycle 1 in ISASOCUT**[1,6]
  - Bortezomib, although effective for NDMM, can be associated with peripheral neuropathy (PN) as a key dose-limiting toxicity, often requiring dose reduction/discontinuation[7]
  - Weekly bortezomib has demonstrated significant clinical benefit and favorable tolerability in Ti-NDMM patients across multiple studies, with its efficacy within the Isa-VRd regimen compared with Isa-Rd notably evidenced by the phase 3 BENEFIT study[7–11]
  - Optimizing bortezomib dosing to decrease the incidence of PN while maintaining efficacy is crucial, especially in older patients[12]

Here, we evaluate the comparative safety and efficacy of the Isa SC OBI VRd regimen from ISASOCUT and the Isa IV VRd regimen from IMROZ at 8 months of follow-up after the first dose, including in patients <75 years old and ≥75 years old

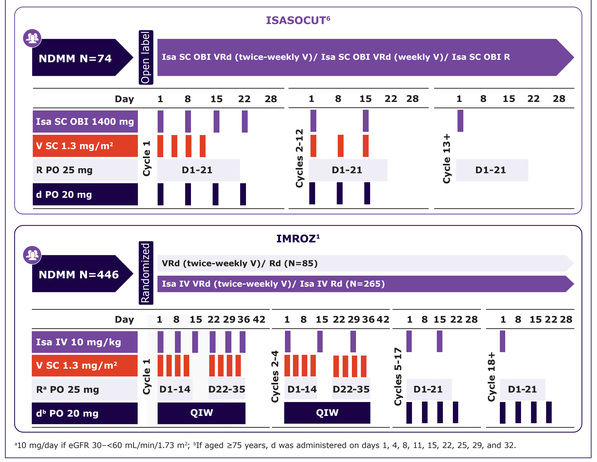
Methods

- This analysis included patients with Ti-NDMM treated with Isa-based quadruplet combinations from 2 distinct studies (**Figure**):
  - **Isa SC OBI VRd patients from ISASOCUT**, an externally-sponsored, prospective, multicenter, phase 2 study (N=74)
  - **Isa IV VRd patients from IMROZ**, a company-sponsored, global, randomized, phase 3 study (N=265)
- AE reporting criteria for hematological laboratory abnormalities differed between the studies:
  - ISASOCUT: all laboratory abnormalities (grade 1–4) were recorded as TEAEs, regardless of clinical significance
  - IMROZ: laboratory abnormalities were reported as TEAEs if they led to treatment changes, met a serious criterion, or were defined as an AESI

Planned bortezomib (V) dosing

- The full **V planned dose is slightly lower in IMROZ (41.6 mg/m²) than in ISASOCUT (48.1 mg/m²)**
- However, with a follow-up of 8 months post-C1D1:
  - The full planned V dose has been administered in IMROZ patients (41.6 mg/m²)
  - ISASOCUT patients would have received approximately 32.5 mg/m² (assuming full V dose and no cycle delay)

FIGURE. Study designs of ISASOCUT and IMROZ clinical trials



[a]10 mg/day if eGFR 30–<60 mL/min/1.73 m²; [b]If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

Results

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics were generally similar between Isa SC OBI VRd (ISASOCUT) and Isa IV VRd (IMROZ) populations (**Table 1**)
- At baseline, ISASOCUT had lower soft-tissue plasmacytoma rates, and slightly higher rates of patients aged ≥75 years, with stage III R-ISS, and with high-risk chromosomal abnormalities (**Table 1**)

TABLE 1. Baseline demographics and disease characteristics

	Isa SC OBI VRd (N=74)	Isa IV VRd (N=265)
Age in years by category, n (%)		
<75 years	49 (66.2)	196 (74.0)
≥75 years	25 (33.8)	69 (26.0)
Baseline weight (kg), mean (SD)	71.1 (15.5)	72.4 (15.5)
ECOG PS, n (%)		
0	26 (35.1)	123 (46.4)
1	41 (55.4)	112 (42.3)
2	7 (9.5)	29 (10.9)
3	0	1 (0.4)
Participants with soft-tissue plasmacytoma at study entry as per eCRF, n (%)	1 (1.4)	49 (18.5)
R-ISS stage at study entry, n (%)		
Stage I	17 (23.0)	66 (24.9)
Stage II	35 (47.3)	163 (61.5)
Stage III	13 (17.6)	27 (10.2)
Unknown/missing	9 (12.2)	9 (3.4)
Cytogenetic risk, n (%)		
High-risk CA	16 (21.6)	40 (15.1)
Standard-risk CA	48 (64.9)	207 (78.1)
Unknown or missing	10 (13.5)	18 (6.8)
eGFR <60 mL/min/1.73m²	17 (23.0)	66 (24.9)

Safety

- The incidences of TEAEs and serious TEAEs were generally similar between the Isa SC OBI VRd and Isa IV VRd populations, with a higher rate of nervous system disorder TEAEs leading to bortezomib dose reduction observed in the Isa IV VRd group (twice-weekly V) vs Isa SC OBI VRd (weekly V) (**Table 2**)
- The incidence of respiratory infections was higher in the Isa IV VRd group compared to the Isa SC OBI VRd group (**Table 2**)
- Systemic infusion reaction rates were lower with Isa SC OBI VRd (5%) vs Isa IV VRd (22.8%) (**Table 2**)
- Hematological laboratory abnormalities neutropenia and thrombocytopenia showed similar incidences in the 2 treatment populations (**Table 2**)

TABLE 2. Overall safety summary, selected TEAEs, and hematological laboratory abnormalities at 8-month follow-up (safety population)

	Isa SC OBI VRd (N=74)	Isa IV VRd (N=263)
TEAE overview, n (%)		
Any TEAE	74 (100)	259 (98.5)
Grade ≥3 non-hematological TEAE	32 (43.2)	161 (61.2)
Grade ≥3 treatment-related non-hematological TEAE	17 (23.0)	115 (43.7)
Serious TEAE	26 (35.1)	111 (42.2)
Serious treatment-related TEAE	13 (17.6)	61 (23.2)
Grade 5 TEAE with fatal outcome during the treatment period	1 (1.4)	11 (4.2)
Any TEAE leading to definitive discontinuation of all study treatment	2 (2.7)	23 (8.7)
Any TEAE leading to discontinuation of isatuximab	0	3 (1.1)
Any TEAE leading to discontinuation of bortezomib	8 (10.8)	32 (12.2)
Any nervous system disorder TEAE leading to bortezomib dose reduction	14 (18.9)	97 (36.9)
Selected toxicities, n (%)		
All-grade respiratory infections	29 (39.2)	157 (59.7)
Grade ≥3 respiratory infections	6 (8.1)	47 (17.9)
Grade ≥3 neutropenic complications*	2 (2.7)	10 (3.8)
All-grade polyneuropathy	0.00	16 (8.2)
All-grade peripheral neuropathy	33 (44.6)	150 (57.0)
Grade ≥2 peripheral neuropathy	16 (21.6)	103 (39.2)
Any systemic infusion reactions	4 (5.0)	60 (22.8)
Hematological laboratory abnormalities, n/N (%)		
All-grade neutropenia	49/67 (73.1)	206/263 (78.3)
All-grade anemia	73/74 (98.6)	258/263 (98.1)
All-grade thrombocytopenia	62/73 (84.9)	245/263 (93.2)

*Reporting criteria for neutropenia and hematological events differed between the studies. In ISASOCUT, all such events (grade 1–5) were recorded as TEAEs, regardless of clinical significance. In IMROZ, they were reported as TEAEs if they led to treatment changes, met a serious criterion, or were defined as an AESI.

- The difference between Isa SC OBI VRd (weekly V) and Isa IV VRd (twice-weekly V) groups in nervous system disorders leading to bortezomib dose reductions was more pronounced for those aged <75 years (**Table 3**)
- The incidence of all-grade respiratory infections was higher with Isa IV VRd vs Isa SC OBI VRd across both age subgroups. Grade ≥3 respiratory infections occurred at a higher rate with Isa IV VRd than with Isa SC OBI VRd, specifically in the subgroup aged <75 years (**Table 3**)
- Across both age subgroups, a lower incidence of grade ≥2 PN was observed with Isa SC OBI VRd (weekly V) vs Isa IV VRd (twice-weekly V) (**Table 3**)
- Only 1 patient in the Isa SC OBI VRd (weekly V) had grade 3 PN in the <75 age subgroup vs none in the ≥75 age subgroup, whereas 8.7% and 5.9% of Isa IV VRd patients experienced grade 3 PN, respectively (**Table 3**)

TABLE 3. Overall safety summary, selected TEAEs, and hematological laboratory abnormalities at 8-month follow-up by age subgroup (safety population)

	Isa SC OBI VRd (N=74)	Isa IV VRd (N=263)	Isa SC OBI VRd (N=74)	Isa IV VRd (N=263)
	Age <75 (N=49)	Age <75 (N=195)	Age ≥75 (N=25)	Age ≥75 (N=68)
TEAE overview, n (%)				
Any TEAE	49 (100)	193 (99.0)	25 (100)	66 (97.1)
Grade ≥3 non-hematological TEAE	19 (38.8)	121 (62.1)	13 (52.0)	40 (58.8)
Grade ≥3 treatment-related non-hematological TEAE	12 (24.5)	87 (44.6)	5 (20.0)	28 (41.2)
Serious TEAE	15 (30.6)	85 (43.6)	11 (44.0)	26 (38.2)
Serious treatment-related TEAE	9 (18.4)	49 (25.1)	4 (16.0)	12 (17.6)
Grade 5 TEAE with fatal outcome during the treatment period	0	7 (3.6)	1 (4.0)	4 (5.9)
Any TEAE leading to definitive study discontinuation	0	16 (8.2)	2 (8.0)	7 (10.3)
Any TEAE leading to partial/ permanent discontinuation of bortezomib	6 (12.2)	18 (9.2)	2 (8.0)	14 (20.6)
Any TEAE leading to discontinuation of isatuximab	0	3 (1.5)	0	0
Any nervous system disorder TEAEs leading to bortezomib dose reduction	7 (14.3)	73 (37.4)	7 (28.0)	24 (35.3)
Selected toxicities, n (%)				
All-grade respiratory infections	20 (40.8)	118 (60.5)	9 (36.0)	39 (57.4)
Grade ≥3 respiratory infections	3 (6.1)	38 (19.5)	3 (12.0)	9 (13.2)
Grade ≥3 neutropenic complications[a]	1 (2.0)	8 (4.1)	1 (4.0)	2 (3.0)
Any systemic infusion reactions	3 (6.1)	45 (23.1)	1 (4.0)	15 (22.1)
All-grade polyneuropathy	0.0	13 (6.7)	0.0	3 (1.5)
All-grade peripheral neuropathy	24 (49.0)	110 (56.4)	9 (36.0)	40 (58.8)
Grade ≥2 peripheral neuropathy	11 (22.4)	74 (37.9)	5 (20.0)	29 (42.6)
Grade 3 peripheral neuropathy	1 (2.0)	17 (8.7)	0.0	4 (5.9)
Grade 4 peripheral neuropathy	0.0	1 (0.5)	0.0	1 (1.5)
Grade 5 peripheral neuropathy	0.0	0.0	0.0	0.0
Hematological laboratory abnormalities, n/N (%)				
All-grade neutropenia	30/42 (71.4)	150/195 (76.9)	19/25 (76.0)	56/68 (82.4)
All-grade anemia	49/49 (100)	191/195 (97.9)	24/25 (96.0)	67/68 (98.5)
All-grade thrombocytopenia	40/48 (83.3)	178/195 (91.3)	22/25 (88.0)	67/68 (98.5)

[a]Reporting criteria for neutropenia and hematological events differed between the studies. In ISASOCUT, all such events (grade 1-5) were recorded as TEAEs, regardless of clinical significance. In IMROZ, they were reported as TEAEs if they led to treatment changes, met a serious criterion, or were defined as an AESI.

Efficacy

- Isa SC OBI VRd (weekly V) and Isa IV VRd (twice-weekly V) showed high and generally comparable ORRs and ≥VGPR rates regardless of age
  - ≥VGPR rates for Isa SC OBI VRd and Isa IV VRd were 87.8% and 83.2%, respectively (RR: 1.055; 95% CI: 0.934–1.192) in the <75 age subgroup and 80.0% and 82.6%, respectively (RR: 0.968; 95% CI: 0.774–1.211), in the ≥75 age subgroup
- CR rates are not directly comparable between the 2 studies because of differing bone marrow aspiration timing, with aspirations performed upon CR (or VGPR plateau) in IMROZ, whereas in ISASOCUT the timing was fixed at 8 months

Key Conclusions

- The analysis of Isa SC OBI VRd (weekly V) from the ISASOCUT study and Isa IV VRd (twice-weekly V) from the IMROZ study showed that safety and efficacy were consistent between the treatment groups with no new safety signals, further supporting the efficacy and safety of the OBI delivery method
  - Systemic infusion reaction rates were lower with Isa SC OBI VRd than with Isa IV VRd for both age subgroups
  - ORRs and ≥VGPR rates were comparable in the Isa SC OBI and Isa IV VRd populations, regardless of age subgroup
- There was a lower incidence of PN with Isa SC OBI VRd (weekly V) than with Isa IV VRd (twice-weekly V), regardless of age subgroup
  - Specifically, only 1 patient treated with Isa SC OBI VRd (weekly V) had grade ≥3 PN
  - No patient from the Isa SC OBI VRd group (weekly V) in either age subgroup experienced a grade ≥3 nervous system disorder TEAE leading to bortezomib dose reduction
- These findings suggest that the weekly bortezomib schedule in an Isa-based quadruplet regimen, as administered in the ISASOCUT study, may be more tolerable for patients than the twice-weekly schedule administered in IMROZ with regard to PN, while maintaining efficacy in patients aged <75 years and ≥75 years
- The efficacy and safety profile of Isa-based quadruplet therapy (Isa VRd) in ISASOCUT was consistent with what was observed in the IMROZ study as well as in the BENEFIT study in Ti-NDMM patients[1,6,11]

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Abbreviations
AE, adverse event; AESI, adverse event of special interest; C, cycle; CA, chromosomal abnormality; CR, complete response; D, day; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; Isa, isatuximab; IV, intravenous; NDMM, newly diagnosed multiple myeloma; OBI, on-body injector; ORR, overall response rate; P, pomalidomide; PN, peripheral neuropathy; PO, orally; QIW, 4 times per week; R, lenalidomide; R-ISS, Revised International Staging System; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; TEAE, treatment-emergent adverse event; V, bortezomib; VGPR, very good partial response.

Disclosures
Arthur Bobin: Sanofi, Janssen-Cilag; **Mohamad Mohty**: Pfizer, Astellas, Sanofi, Janssen, Therakos, Novartis, GSK, Takeda, MaaT Pharma, Oncopeptides, Medac Pharma, Jazz Pharmaceuticals, Adaptive Biotechnologies, Celgene-BMS, Gilead, Amgen; **Philippe Moreau**: Nothing to disclose; **Hartmut Goldschmidt**: Grants and/or provision of investigational medicinal product: BMS/Celgene, Dietmar Hopp Foundation, Janssen, Sanofi. Research support: Amgen, BMS, Celgene, GlycoMimetics Inc., GSK, Heidelberg Pharma, Hoffmann-La Roche, Janssen Research and Development, Millennium, Novartis, Pfizer, Oncopeptides, Sanofi. Advisory boards: BMS, Janssen, Sanofi, GSK. Honoraria: Amgen, BMS, GSK, Janssen, Sanofi, Pfizer, Oncopeptides. Support for attending meetings and/or travel: Amgen, BMS, GSK, Janssen, Sanofi, Pfizer, Oncopeptides; **Meletios Athanasios Dimopoulos**: Amgen, Sanofi, Regeneron, Menarini, Takeda, GSK, BMS, Janssen, Beigene, Swixx, AstraZeneca; **Robert Orlowski**: Janssen, Asylia Therapeutics, Inc., Lytica Therapeutics, CARsgen Therapeutics, Takeda Pharmaceuticals, BioTheryX, Meridian Therapeutics, Regeneron Pharmaceuticals, Inc., BMS, Heidelberg Pharma, Pfizer, Exelixis, Sanofi; **Cyrille Touzeau**: AbbVie, Amgen, Pfizer, Sanofi, GSK, Bristol Myers Squibb, Johnson & Johnson; **Aurore Perrot**: Pfizer, AbbVie, Amgen, Takeda, Menarini Stemline, Sanofi, Bristol Myers Squibb, Adaptive Biotechnologies, Johnson & Johnson, GSK; **Thomas Chalopin**: Amgen, Sanofi, Johnson & Johnson, Pfizer, GSK, Grifols, Stemline, BMS, Takeda; **Mamoun Dib**: Nothing to disclose; **Lydia Montes**: Nothing to disclose; **Thierry Facon**: Oncopeptides, Takeda, Amgen, Sanofi, Roche, Karyopharm, Johnson & Johnson, Celgene; **Xavier Leleu**: Regeneron, Novartis, Kite, Roche, Amgen, Sanofi, AbbVie, Bristol Myers Squibb, Janssen, Oncopeptides, Takeda, GlaxoSmithKline, Pfizer; **Umer Khan, Mony Morisse, Rick Zhang, Corina Oprea,** and **Florence Suzan** are employees of Sanofi and may hold stock and/or stock options in the company.

Acknowledgments
The data was originally presented as a poster at 2026 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–June 2, 2026; Chicago, US. The IMROZ study was sponsored by Sanofi and the ISASOCUT study was sponsored by Poitiers University Hospital. Medical writing support was provided by Yohana Ghebrechristos, PhD, of IMPRINT Science, funded by Sanofi. The editorial support was provided by Natalia de la Oliva, PhD, of Sanofi.