Update of Safety and Efficacy of Isatuximab Short-Duration Fixed-Volume Infusion Plus Bortezomib, Lenalidomide, and Dexamethasone Combined Therapy for NDMM Ineligible/With No Immediate Intent for ASCT

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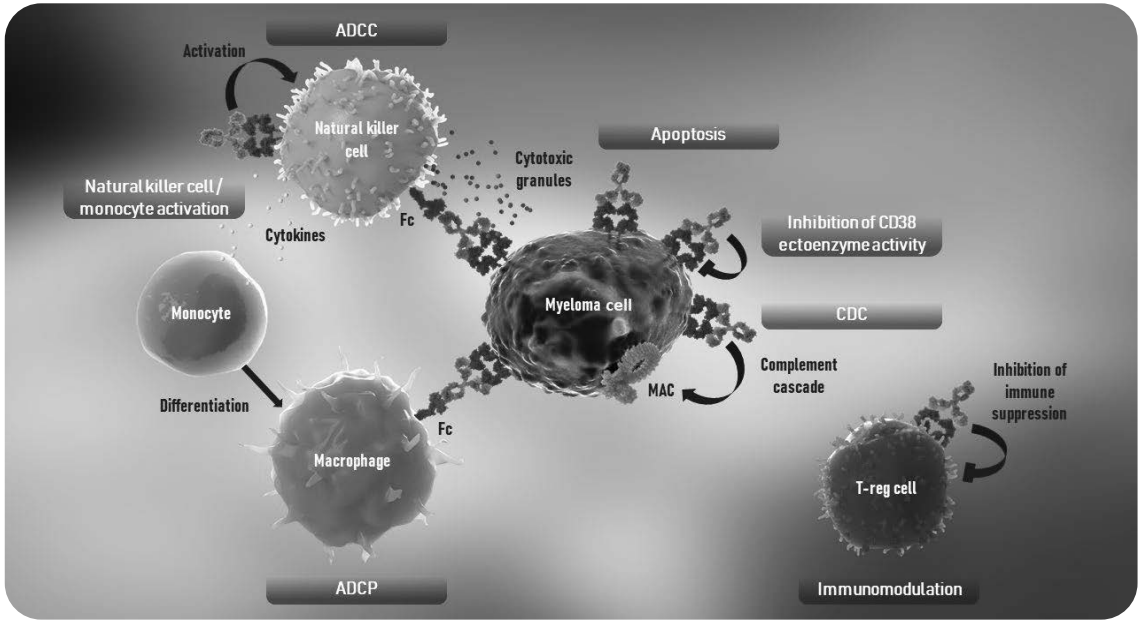
Isatuximab targets a specific epitope on CD38, a transmembrane glycoprotein widely and uniformly expressed on myeloma cells[1–3]



Isatuximab is approved in several countries in combination with dexamethasone plus either pomalidomide or carfilzomib in adult patients with relapsed/refractory MM who have received prior therapies[4,5]

Here, we report the updated efficacy and safety results for Part B of the Phase 1b study evaluating the fixed-volume infusion of isatuximab, combined with VRd in patients with NDMM ineligible for/with no immediate intent for ASCT

ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; ASCT, autologous stem cell transplantation; CD, cluster of differentiation; CDC, complement dependent cytotoxicity; d, dexamethasone; Fc, fragment, crystallizable; MAC, membrane attack complex; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; R, lenalidomide; T-reg cell, regulatory T cell; V, bortezomib

1. Deckert J, et al. Clin Cancer Res. 2014;20:4574–83. 2. Jiang H, et al. Leukemia. 2016;30:399–408. 3. Moreno L, et al. Clin Cancer Res. 2019;25:3176–87. 4. Sanofi. SARCLISA® [Package Insert]; 2021. 5. European Medicines Agency (EMA). Medicines. Sarclisa. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/sarclisa-0

Key patient demographics and baseline characteristics

Patient characteristic	All-treated population (N=46)
Age in years, median (range)	70.0 (49–87)
Age in years by category, n (%)	
<65	8 (17.4)
≥65 to 74	30 (65.2)
≥75	8 (17.4)
Gender, female, n (%)	24 (52.2)
ECOG performance status, n (%)	
0	23 (50.0)
1	22 (47.8)
2	1 (2.2)

Patient characteristic	All-treated population (N=46)
Eligible but no immediate intent for SCT, n (%)	13 (28.3)
ISS stage at study entry, n (%)	
Stage I	22 (47.8)
Stage II	20 (43.5)
Stage III	4 (8.7)
Cytogenetic risk[a] at study entry, n (%)	
High	8 (17.4)
Standard	23 (50.0)
Unknown/missing	15 (32.6)

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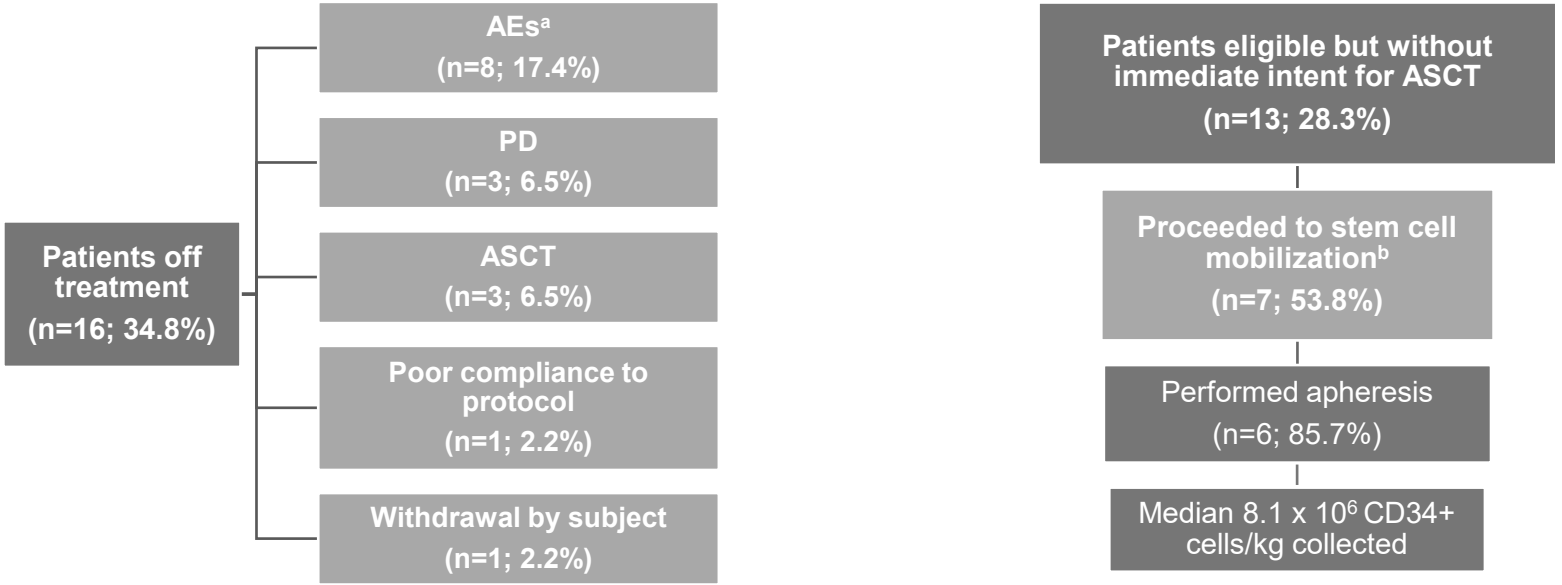
[a]Cytogenetic high risk was defined as presence of del(17p), t(4;14), or t(14;16)
ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; SCT, stem cell transplantation

Patient disposition



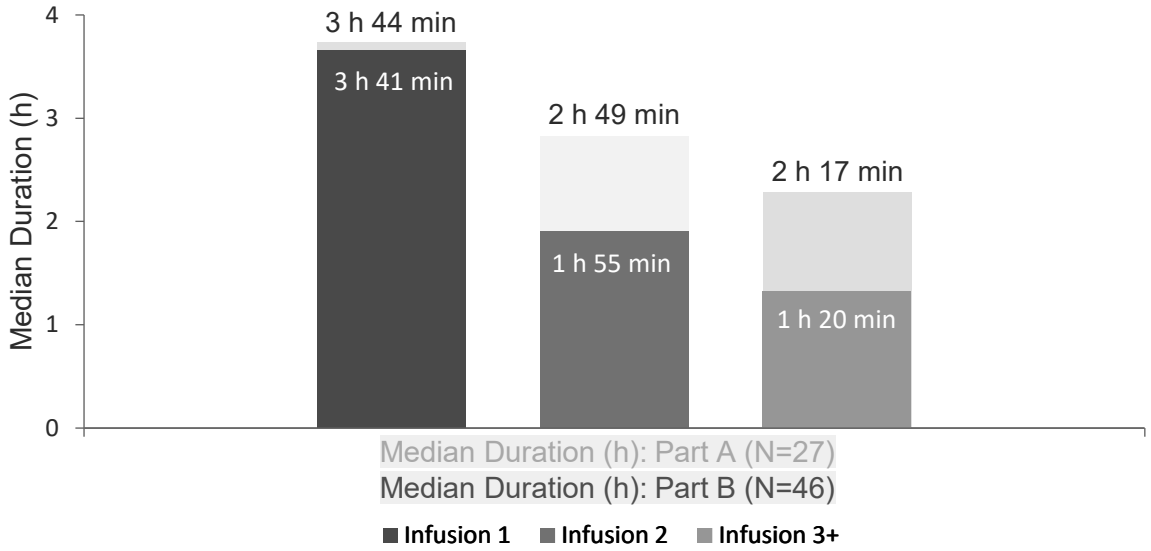
[a]TEAEs leading to discontinuation included COVID-19 (n=2), diverticulitis (n=1), metastatic malignant melanoma (n=1), peripheral sensory neuropathy (n=1), cerebral venous sinus thrombosis (n=1), acute respiratory distress syndrome (n=1), and hepatocellular injury (n=1)

[b]Mobilization regimens included G-CSF (n=2; 33.3%), Plerixafor (n=2; 33.3%), and G-CSF + Plerixafor (n=2; 33.3%)

At the March 17, 2021, data cutoff, 30/46 (65.2%) patients were still receiving study treatment

AE, adverse event; ASCT, autologous stem cell transplant; CD, cluster of differentiation; GCSF, granulocyte colony-stimulating factor; PD, progressive disease; TEAE, treatment-emergent adverse event

Duration of isatuximab infusion



The median duration of fixed-volume Isa infusion (Part B) decreased from 3 h 41 min during the first infusion to 1 h 20 min during the third infusion and onward

Isa, isatuximab; h, hours; min, minutes

Safety summary

	All-treated population (N=46)
Median treatment duration, months (range)	15.3 (1.4–21.4)
Median treatment cycles, n (range)	14 (1–21)
Any Grade TEAEs, n (%)	46 (100)
Grade ≥3 TEAEs, n (%)	32 (69.6)
Any serious TEAEs, n (%)	20 (43.5)
TEAEs leading to death, n (%)[a]	6 (13.0)
TEAEs leading to definitive Isa discontinuation, n (%)[b]	8 (17.4)
TEAEs leading to premature V, R, or d discontinuation, n (%)	10 (21.7)

[a]There were 4 deaths during the treatment period, defined as within 30 days of the last dose of the study drug: disease progression (n=1); metastatic breast cancer (n=1); COVID-19 (n=2).

There were 2 deaths occurring during the post-treatment period: metastatic malignant melanoma (n=1); diverticulitis (n=1)

[b]TEAEs leading to discontinuation included COVID-19 (n=2), diverticulitis (n=1), metastatic malignant melanoma (n=1), peripheral sensory neuropathy (n=1), cerebral venous sinus thrombosis (n=1), acute respiratory distress syndrome (n=1), and hepatocellular injury (n=1)

TEAEs occurring in ≥20% of patients

n (%)	All-treated population (N=46)	
	All grades	Grade ≥3
Constipation	32 (69.6)	1 (2.2)
Asthenia	31 (67.4)	3 (6.5)
Diarrhea	26 (56.5)	4 (8.7)
Peripheral sensory neuropathy	23 (50.0)	1 (2.2)
Peripheral edema	18 (39.1)	2 (4.3)
Insomnia	13 (28.3)	2 (4.3)
Back pain	12 (26.1)	1 (2.2)
Pain in extremity	12 (26.1)	0
Rash	11 (23.9)	1 (2.2)
Nausea	11 (23.9)	0
Dyspnea	10 (21.7)	1 (2.2)
Decreased appetite	10 (21.7)	0
Hematologic abnormalities		
Anemia	46 (100)	3 (6.5)
Lymphopenia	45 (97.8)	35 (76.1)
Neutropenia	41 (89.1)	19 (41.3)
Leukopenia	45 (97.8)	14 (30.5)
Thrombocytopenia	40 (87.0)	16 (34.7)

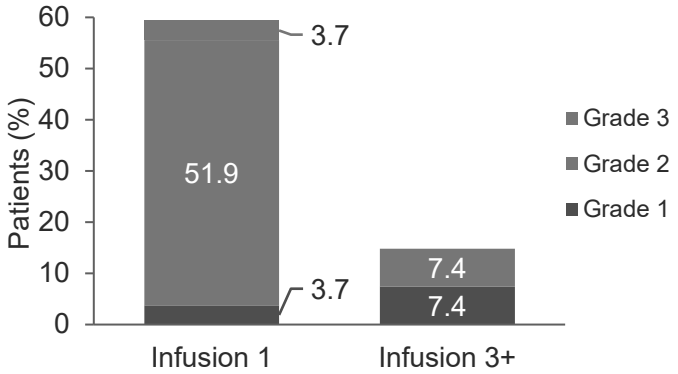
Isa-VRd had a manageable safety profile with no new safety signals

d, dexamethasone; Isa, isatuximab; R, lenalidomide; TEAE, treatment-emergent adverse event; V, bortezomib

Management of IRs

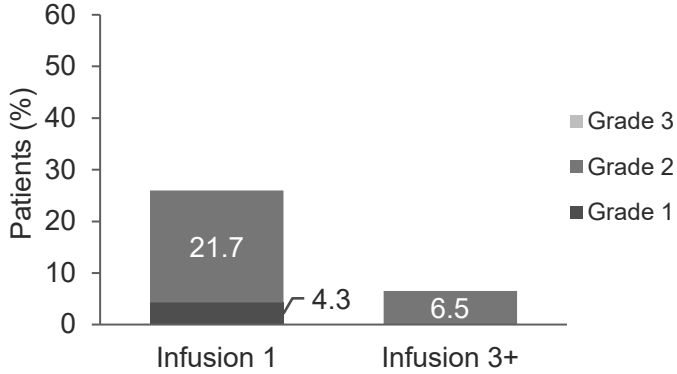
PART A: Weight-based dosing (N=27)[1,2]

- IRs occurred in 63% of patients; mostly Grade 2
- Grade 3 IR in 1 patient resulted in discontinuation
- Occurred predominantly during the first infusion (76.5%)



PART B: Fixed-volume infusion (N=46)

- IRs occurred in 28% of patients; mostly Grade 2
- No Grade ≥3 IRs
- Occurred predominantly during the first infusion (76.9%)



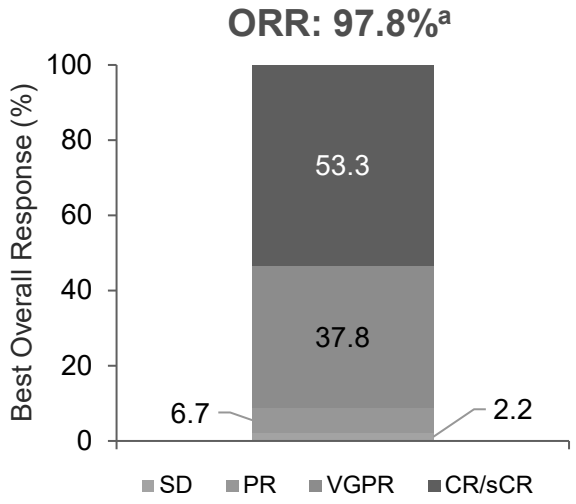
In Part A, 2 (7.4%) patients received montelukast as premedication; among them, 1 (50.0%) had an IR. **In Part B, 31 (67.4%) patients received montelukast** as premedication; among them, 7 (22.6%) had an IR.

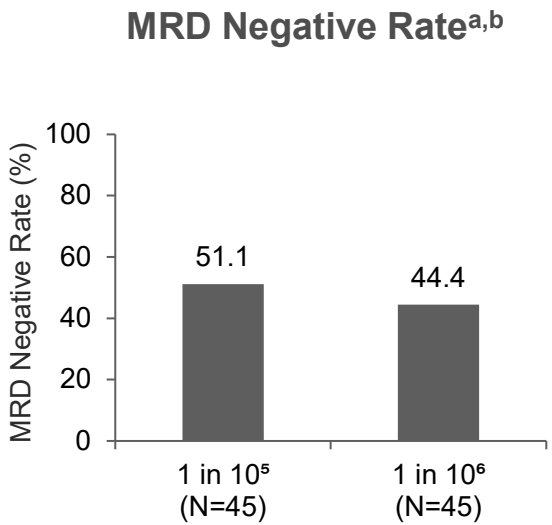
The fixed-volume infusion reduced the incidence and severity of IRs

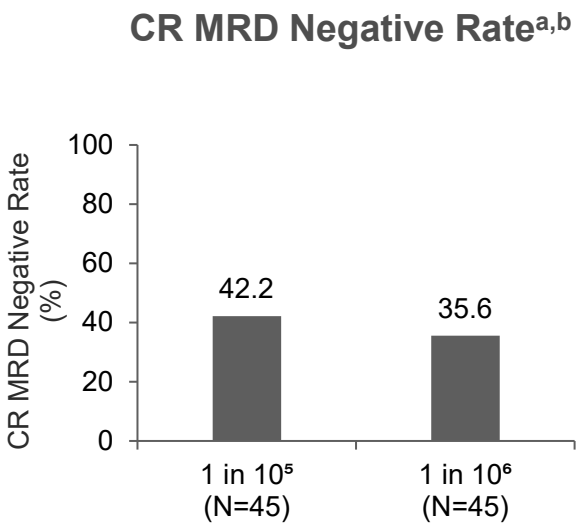
d, dexamethasone; IR, infusion reaction; Isa, isatuximab; R, lenalidomide; TEAE, treatment-emergent adverse event; V, bortezomib

1.Ocio EM, et al. Presented at: ASH; Dec 5–8, 2020; Virtual Meeting. Abstract 1413. 2. Sanofi data on file. TCD13983C Appendix 16.2.7

Depth of response with fixed-volume Isa-VRd







Median duration of follow-up: 15.24 months

[a]Data adjusted by incorporating results from 21 patients whose samples underwent testing with Hydrashift isatuximab IFE test, an immunofixation test assessing serum M-protein without isatuximab interference. The Hydrashift 2/4 isatuximab assay was launched by Sebia in February 2021

[b]MRD was determined by next-generation flow (NGF) and next-generation sequencing (NGS) methods, and MRD negativity was determined by combining both methods in the case of at least 1 method yielding negative results and the other method showing no positive result at the same time

97.8% patients responded: CR/sCR rate of 53.3% & 51% of MRD negativity

CR, complete response; d, dexamethasone; IFE, immunofixation electrophoresis; Isa, isatuximab; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; R, lenalidomide; sCR, stringent complete response; SD, stable disease; V, bortezomib; VGPR, very good partial response

Summary

- The median duration of the approved short-duration, fixed-volume Isa infusion decreased from 3 hours and 41 minutes for the first infusion to **80 minutes for the third infusion and onward**
- Isa-VRd had a **manageable safety profile** with no new safety signals
- **IRs decreased** from 63% of patients in Part A and in **28% of patients in Part B**
- The overall response rate was 97.8%, including **53.3% with CR/sCR**
- **51.1% of patients achieved MRD negativity**
- These results confirm the feasibility, safety, and good efficacy of the approved short-duration fixed-volume infusion method of Isa in combination with VRd in patients with NDMM ineligible/with no immediate intent for ASCT
- Isa-VRd is under investigation in **ongoing Phase 3 studies** (eg, NCT03319667 – IMROZ; NCT03617731 – GMMG HD7)

Isa-VRd represents an option for patients with NDMM ineligible for or with no immediate intent for ASCT

ASCT, autologous stem cell transplant; CR, complete response; d, dexamethasone; IR, infusion reaction; Isa, isatuximab; MM, multiple myeloma; NDMM, newly diagnosed MM; R, lenalidomide; sCR, stringent complete response; V, bortezomib

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