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Isatuximab Plus Pomalidomide and Dexamethasone in Patients With Relapsed and/or Refractory Multiple Myeloma in Real-Life Context in France: IMAGE Subgroup Analysis Based on Subgroups of Interest

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INTRODUCTION

- Isatuximab (Isa) is an anti-CD38 monoclonal antibody that targets a specific CD38 epitope, inducing myeloma cell death via multiple mechanisms[1-4]
- Prior to Isa regulatory approval, Isa was available in France under 2 early access programs (EAPs) – compassionate early access and early-access authorization[5]
  - In compassionate early access, Isa in combination with pomalidomide and dexamethasone (Isa-Pd) was given to participants with relapsed/refractory multiple myeloma (RRMM) after ≥2 prior lines of treatment (LOT)
  - In early-access authorization, Isa-Pd was given to participants with RRMM after ≥2 prior therapies
- IMAGE was a non-interventional, retrospective cohort study of participants with RRMM enrolled in EAPs for Isa-Pd in France[6]
  - The median progression-free survival (PFS) in the overall effectiveness population has been previously reported at 12.4 months after a median follow-up of 14.2 months[6]
- There are several high-risk characteristics that are associated with poor treatment outcome and shorter survival in multiple myeloma (MM) participants, such as advanced age, renal impairment, and high-risk cytogenetics[7-10]
- Here, we report the results from the subgroup analyses of IMAGE based on subgroups of interest – elderly (aged ≥75 years), severe renal impairment (<30 mL/min/1.73 m^2) and high-risk cytogenetics (presence of del[17p], t[4;14], and t[14;16])

METHODS

- Data were collected from the medical records of adult participants with RRMM who received at least 1 dose of Isa under the EAPs between 29 July 2019 and 1 September 2020
- The effectiveness analysis was restricted to participants with 1 year or more follow-up after initiating Isa, while the safety analysis included all participants who received ≥1 dose of Isa under the EAPs
- Effectiveness endpoints included PFS and response rates
- The Kaplan-Meier method was used to analyze all time-to-event variables
- Very good partial response (VGPR) was assessed differently from the International Myeloma Working Group criteria. VGPR was defined as a reduction of at least 90% in serum M-protein (for each type of immunoglobulin), or in urine M-protein, or in the difference between involved and non-involved free light chain
- High cytogenetic risk was defined as at least 1 chromosomal abnormality detected amongst del(17p), t(4;14), and t(14;16)
- Verbatim terms for adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities, and AEs were not graded for severity

RESULTS

Baseline characteristics

- The total effectiveness population consisted of 294 participants, and the safety population of 299 participants
- 83 (28.2%) participants were aged ≥75 years, 25 (8.5%) participants had severe renal impairment (<30 mL/min/1.73 m^2), and 40 (13.6%) participants had high-risk cytogenetics. Of note, 120 (40.8%) participants had unknown cytogenetic risk
- Roughly one third of participants across all subgroups had International Staging System Stage III disease – 30.1%, 44.0%, and 37.5% in elderly participants, severe renal impairment, and high-risk cytogenetics, respectively
- All subgroups had a median of 2 prior LOT, apart from participants with severe renal impairment, who had a median of 3 prior lines of therapy
- Similar to the overall effectiveness population, around 70% of participants in all subgroups were refractory to lenalidomide and to their last line of therapy
- A higher percentage of daratumumab-refractory participants was observed in participants with severe renal impairment (36.0%) and high-risk cytogenetics (32.5%) compared with the overall effectiveness population (19.1%) and the elderly subgroup (13.2%)
- A summary of baseline characteristics can be found in **Table 1**

Table 1. Participant baseline characteristics in the overall effectiveness population and elderly, severe renal impairment, and high-risk cytogenetics subgroups

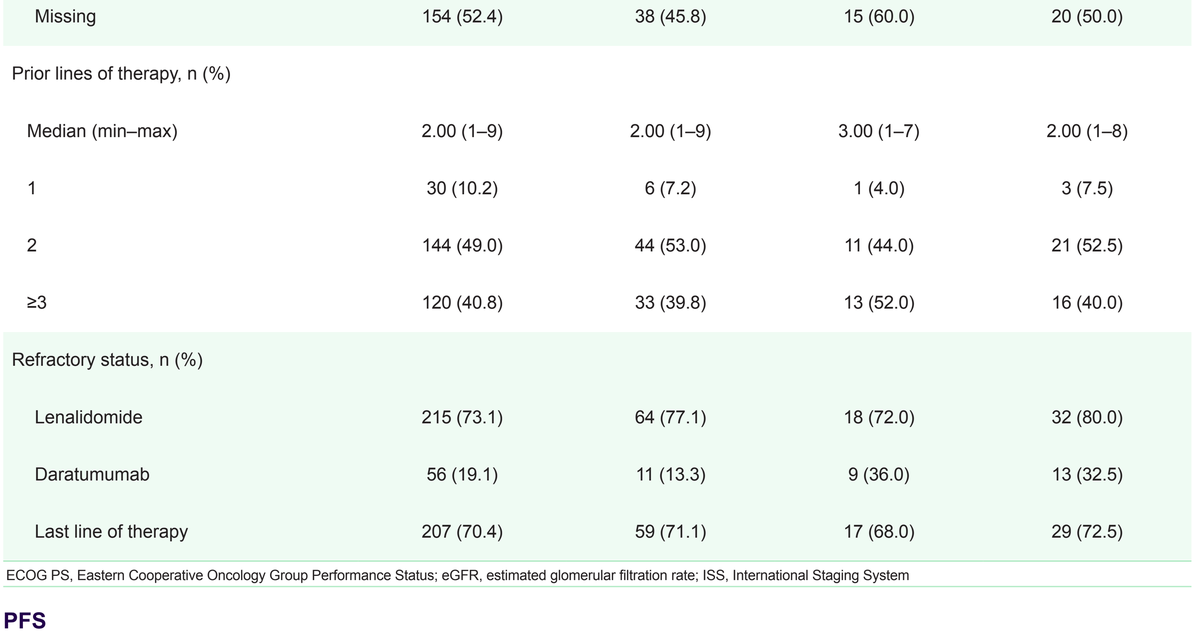
	Effectiveness population (N=294)	Elderly (aged ≥75 years; n=83)	Severe renal impairment (eGFR <30 mL/min/1.73 m^2; N=25)	High-risk cytogenetics (n=40)
Median age, years (min–max)	70.2 (39.9–89.8)	79.1 (75.1–89.8)	69.9 (39.9–85.5)	67.8 (49.2–84.9)
ISS Stage, n (%)				
Stage I	46 (15.6)	7 (8.4)	3 (12.0)	6 (15.0)
Stage II	41 (13.9)	11 (13.3)	2 (8.0)	4 (10.0)
Stage III	107 (36.4)	25 (30.1)	11 (44.0)	15 (37.5)
Unknown/missing	100 (34.0)	40 (48.2)	9 (36.0)	15 (37.5)
ECOG PS, n (%)				
0	45 (15.3)	13 (15.7)	4 (16.0)	10 (25.0)
1	51 (17.3)	18 (21.7)	5 (20.0)	5 (12.5)
2	28 (9.5)	9 (10.8)	0	4 (10.0)
≥3	16 (5.4)	5 (6.0)	1 (4.0)	1 (2.5)
Missing	154 (52.4)	38 (45.8)	15 (60.0)	20 (50.0)
Prior lines of therapy, n (%)				
Median (min–max)	2.00 (1–9)	2.00 (1–9)	3.00 (1–7)	2.00 (1–8)
1	30 (10.2)	6 (7.2)	1 (4.0)	3 (7.5)
2	144 (49.0)	44 (53.0)	11 (44.0)	21 (52.5)
≥3	120 (40.8)	33 (39.8)	13 (52.0)	16 (40.0)
Refractory status, n (%)				
Lenalidomide	215 (73.1)	64 (77.1)	18 (72.0)	32 (80.0)
Daratumumab	56 (19.1)	11 (13.3)	9 (36.0)	13 (32.5)
Last line of therapy	207 (70.4)	59 (71.1)	17 (68.0)	29 (72.5)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; eGFR, estimated glomerular filtration rate; ISS, International Staging System

PFS

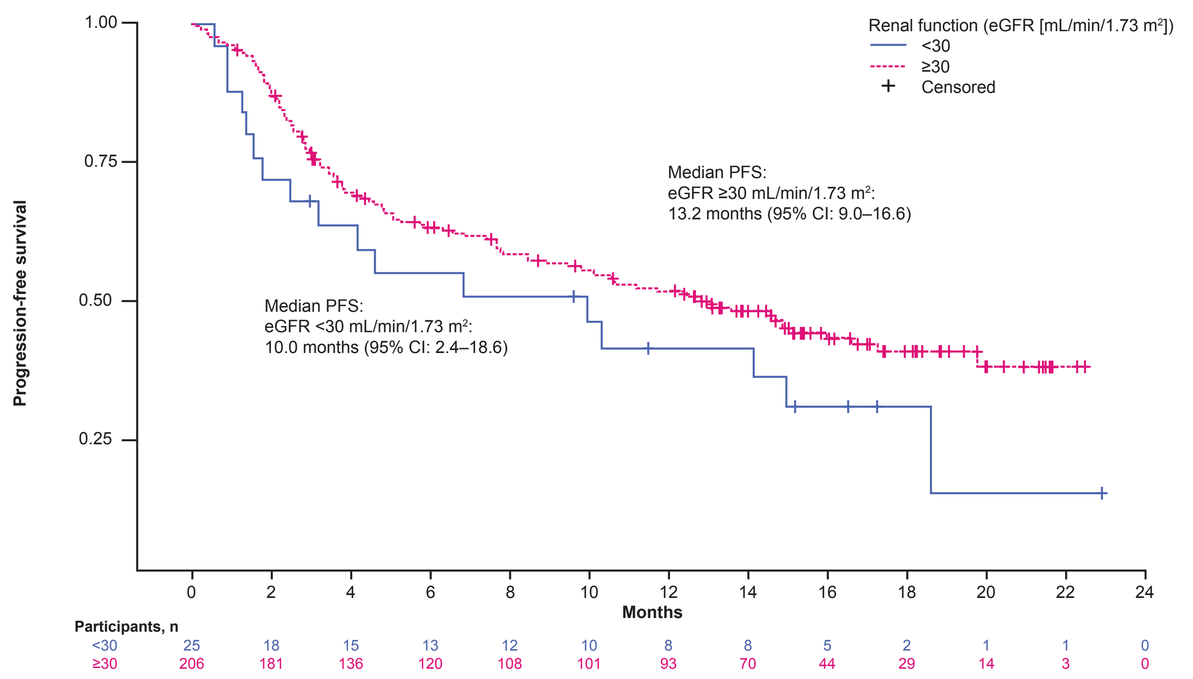
- Median PFS in the elderly subgroup (aged ≥75 years) was 13.2 months, similar to that observed in participants aged <75 years at 12.4 months (**Figure 1**)
- Participants with severe renal impairment (eGFR <30 mL/min/1.73 m^2) had a slightly shorter median PFS of 10.0 months compared with 13.2 months observed in those with renal function ≥30 mL/min/1.73 m^2 (**Figure 2**)
- Participants with high-risk cytogenetics had a median PFS of 7.6 months, as compared with 10.2 and 15.0 months in participants with standard- or unknown-risk cytogenetics, respectively (**Figure 3**)

Figure 1. Kaplan-Meier curve of median PFS stratified by age



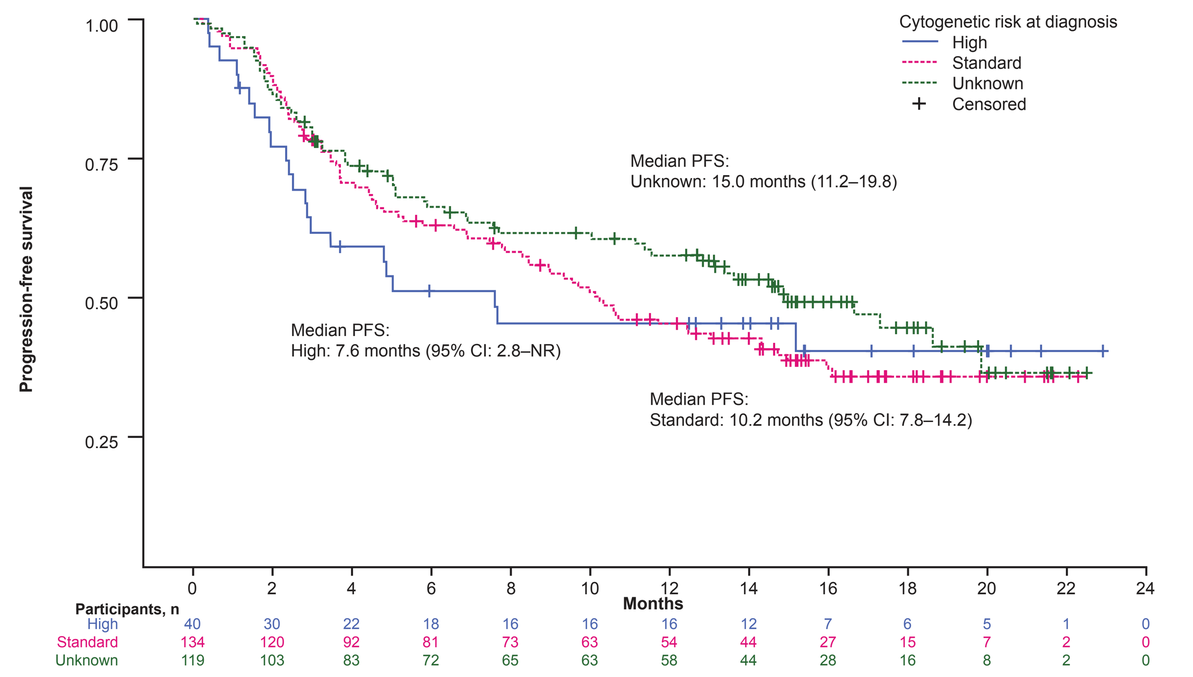
CI, confidence interval; PFS, progression-free survival

Figure 2. Kaplan-Meier curve of median PFS stratified by renal impairment



CI, confidence interval; eGFR, estimated glomerular filtration rate; PFS, progression-free survival

Figure 3. Kaplan-Meier curve of median PFS stratified by cytogenetic risk status

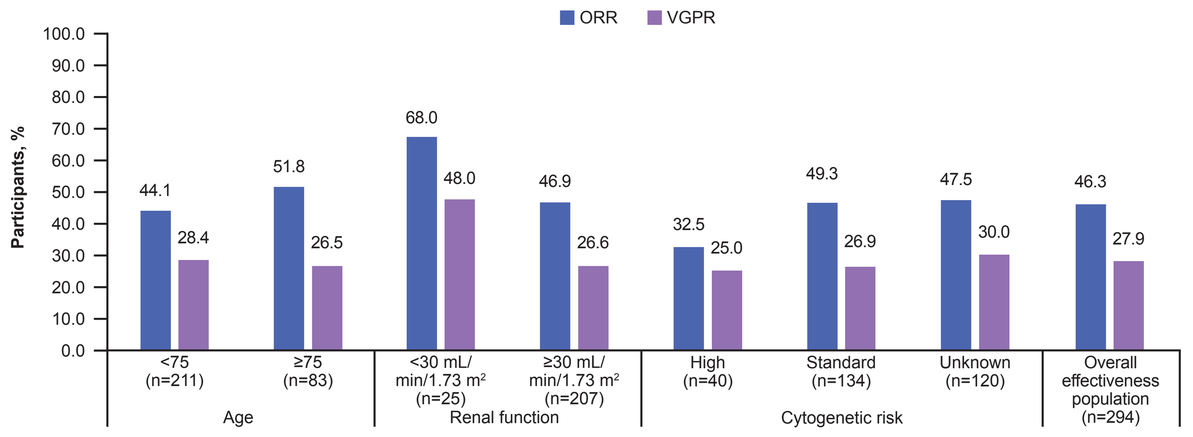


CI, confidence interval; NR, not reached; PFS, progression-free survival

Response rates

- Elderly participants had a similar overall response rate (ORR) and very good partial response (VGPR) rate (51.8% and 26.5%, respectively) to that of the overall effectiveness population (46.3% and 27.9%)
- Participants with severe renal impairment had an ORR and VGPR of 68.0% and 48.0%, although with a small population size
- Participants with high-risk cytogenetics had a lower ORR of 32.5% and VGPR rate of 25.0% (**Figure 4**)

Figure 4. ORR and VGPR rate by subgroup of interest



ORR, overall response rate; VGPR, very good partial response

Safety

- A safety summary of AEs across subgroups is shown in **Table 2**
- Few participants discontinued Isa permanently due to AEs, consistent with observations from clinical trials
- Neutropenia and thrombocytopenia were the 2 most commonly occurring AEs amongst the subgroups apart from participants with renal impairment who observed no incidence of neutropenia (**Table 3**)
- Infections and infestations occurred in 3 participants in the overall safety population, of which 2 were in the elderly subgroup. There was also 1 occurrence of pneumonia in a participant with renal impairment. No participants with high-risk cytogenetics experienced an infection or infestation

Table 2. Safety summary of AEs by subgroup of interest

n (%)	Safety population (N=299)	Elderly (aged ≥75 years; n=83)	Severe renal impairment (eGFR <30 mL/min/1.73 m^2; n=26)	High-risk cytogenetics (n=40)
At least 1 event	79 (26.4)	24 (28.9)	8 (30.8)	10 (25.0)
Leading to Isa temporary discontinuation	24 (8.0)	8 (9.6)	1 (3.8)	4 (10.0)
Leading to Isa permanent discontinuation	4 (1.3)	3 (3.6)	0	1 (2.5)
Leading to pomalidomide dose reduction	17 (5.7)	4 (4.8)	1 (3.8)	3 (7.5)
Leading to pomalidomide temporary discontinuation	32 (10.7)	14 (16.9)	3 (11.5)	2 (5.0)
Leading to Isa-Pd permanent discontinuation	9 (3.0)	1 (1.2)	1 (3.8)	0

AE, adverse event; d, dexamethasone; eGFR, estimated glomerular filtration rate; Isa, isatuximab; Isa-Pd, isatuximab pomalidomide and dexamethasone

Table 3. Any-grade AEs with ≥5% incidence by system organ class and preferred term

Primary system organ class preferred term, n (%)	Safety population (N=299)	Elderly (aged ≥75 years; n=83)	Severe renal impairment (eGFR <30 mL/min/1.73 m^2; n=26)	High-risk cytogenetics (n=40)
Blood and lymphatic system disorders	54 (18.1)	16 (19.3)	4 (15.4)	6 (15.0)
Neutropenia	28 (9.4)	10 (12.0)	0	3 (7.5)
Thrombocytopenia	15 (5.0)	4 (4.8)	1 (3.8)	2 (5.0)
Cytopenia	8 (2.7)	3 (3.6)	2 (7.7)	1 (2.5)
General disorders and administration site conditions	10 (3.3)	6 (7.2)	2 (7.7)	2 (5.0)
Asthenia	4 (1.3)	4 (4.8)	0	1 (2.5)

AE, adverse event; eGFR, estimated glomerular filtration rate

CONCLUSIONS

- The effectiveness and safety profiles across elderly and severe renal impairment subgroups were similar to those observed in the overall effectiveness and safety population, despite a higher percentage of daratumumab-refractory participants in the severe renal impairment subgroup
- Of note, participants with severe renal impairment had greater response rates than the effectiveness population, although with a small sample size
- Participants with high cytogenetic risk had slightly worse outcomes than those observed in the overall effectiveness population, although there was a higher proportion of daratumumab-refractory participants, small sample size, and large proporation of participants with unknown cytogenetic risk
- A real-world study of Isa-Pd use in the UK has reported a median PFS of 10.9 months after a median follow-up of 12.1 months, which is generally similar to that observed in IMAGE. In this dataset, 30.8% of participants were aged ≥75 years, 43% had eGFR <60 mL/min, and 14% had high cytogenetic risk[11]
- The results of these subgroup analyses continue to support Isa-Pd for the treatment of RRMM across subgroups

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QUESTIONS:
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