Updates From ICARIA-MM, a Phase 3 Study of Isatuximab Plus Pomalidomide and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Relapsed and Refractory Multiple Myeloma

Paul G. Richardson[1], Aurore Perrot[2], Jesus San-Miguel[3], Meral Beksac[4], Ivan Spicka[5,6], Xavier Leleu[7], Fredrik Schjesvold[8], Philippe Moreau[9], Meletios A. Dimopoulos[10], Jeffrey Shang-Yi Huang[11], Jiri Minarik[12], Michele Cavo[13], H. Miles Prince[14], Cheng Zheng[15], Franck Dubin[16], Helgi van de Velde[15], Kenneth C. Anderson[1]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [3]Clinical and Translational Medicine, Clínica Universidad de Navarra, Navarra, CIMA, IDISNA, CIBER-ONC, Pamplona, Spain; [4]Ankara University, Department of Hematology, Ankara, Turkey; [5]General Faculty Hospital, Prague, Czech Republic; [6]First Faculty of Medicine, Charles University, Prague, Czech Republic; [7]Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France; [8]Oslo Myeloma Center, Department of Haematology, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, University of Oslo, Oslo, Norway; [9]University of Nantes, Nantes, France; [10]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [11]Department of Hematology, National Taiwan University Hospital, Taiwan; [12]Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University and University Hospital Olomouc, Olomouc, Czech Republic; [13]Department of Experimental, Diagnostic and Specialty Medicine, Seràgnoli Institute of Hematology, University of Bologna, Bologna, Italy; [14]Immunology and Molecular Oncology, Epworth Healthcare, University of Melbourne, Melbourne, VIC, Australia; [15]Sanofi Oncology, Cambridge, MA, USA; [16]Sanofi Oncology Development, Vitry-sur-Seine, France

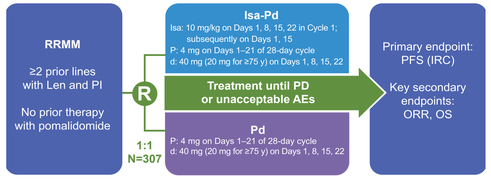
INTRODUCTION

- Isatuximab (Isa) is a monoclonal antibody targeting a specific epitope on CD38, a transmembrane glycoprotein widely expressed on myeloma cells[1-3]
- The ICARIA-MM study (NCT02990338) was a randomized, open-label, active-controlled, multicenter Phase 3 trial which demonstrated that the addition of Isa to pomalidomide (P) and dexamethasone ([d], Isa-Pd) resulted in a significant improvement in progression-free survival (PFS) vs Pd alone (11.5 vs 6.5 months), with a hazard ratio (HR) of 0.596 (95% confidence interval [CI] 0.436–0.814, p=0.001), and a manageable safety profile[4]
  - Based on this study, Isa-Pd is approved in a number of countries for the treatment of adult patients with relapsed/refractory multiple myeloma (RRMM) who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor (PI)[5]
- Based on the Phase 3 IKEMA study, Isa is also approved in the United States in combination with carfilzomib (K) and dexamethasone (d) (Isa-Kd), for the treatment of adult patients with RRMM who have received 1–3 prior lines of therapy, and in the European Union for the treatment of adult patients with relapsed multiple myeloma who have received at least 1 prior therapy[5]
- This poster reports an updated interim analysis of ICARIA-MM efficacy and safety results

METHODS

- The ICARIA-MM study design and dosing schedule are shown in **Figure 1**[6]
- This pre-planned second interim analysis assessed long-term outcomes, including time to next treatment (TTNT), overall survival (OS), time from randomization to disease progression on first subsequent therapy or death (PFS2), and safety
  - Data cut-off date for this analysis was October 1, 2020 (90% OS analysis at 198 OS events); and October 7, 2020 for all other analyses (ie, safety, disposition, exposure)

Figure 1. ICARIA study design: Isa-Pd vs Pd in patients with RRMM[6]



Patients in the Isa-Pd arm received premedication before infusion that consisted of ranitidine (50 mg or equivalent), diphenhydramine (25 to 50 mg or equivalent), and acetaminophen (650 to 1000 mg). Dexamethasone was used both as part of premedication and as part of the backbone combination in the Isa-Pd arm
AE, adverse event; d, dexamethasone; HR, hazard ratio; IRC, independent response committee; Isa, isatuximab; Len, lenalidomide; ORR, overall response rate; OS, overall survival; P, pomalidomide; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; R, randomization; RRMM, relapsed/refractory multiple myeloma; y, years

RESULTS

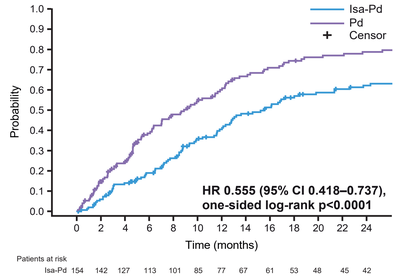
Patient characteristics

- Baseline characteristics were similar between the 2 treatment arms, as previously published[4]
- Patients had received a median of 3 prior lines of therapy, all had been previously treated with lenalidomide and PIs and 94% vs 92% of patients in the Isa-Pd vs Pd arms were refractory to lenalidomide, respectively
- At 35.3 months follow-up (October 1, 2020 data cut-off), more patients in the Isa-Pd arm (n=27/154 [17.5%]) remained on treatment vs the Pd arm (n=12/153 [7.8%])

PFS and TTNT

- 60% vs 72% of patients receiving Isa-Pd vs Pd proceeded to subsequent therapy.
- Isa-Pd resulted in a clinically meaningful delay of subsequent therapy. Median TTNT was 15.5 vs 8.9 months for Isa-Pd vs Pd; (HR 0.555; 95% CI 0.418–0.737; p<0.0001; **Figure 2**)
- With prolonged follow-up, Isa-Pd continues to improve PFS as reported by investigators: median 11.1 months vs 5.8 months (HR 0.599, p<0.0001)

Figure 2. Time to next treatment

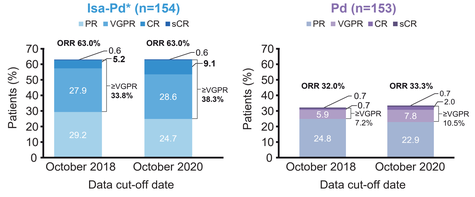


CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; P, pomalidomide

Depth of response per investigator assessment

- Overall response rate (ORR) per investigator assessment was 63.0% with Isa-Pd vs 33.3% with Pd, largely unchanged for Isa-Pd from the primary analysis (**Figure 3**)
- Depth of response with Isa-Pd improved in this secondary analysis, with ≥very good partial response rate of 38.3% vs 33.8% at the time of primary analysis

Figure 3. Overall response rate

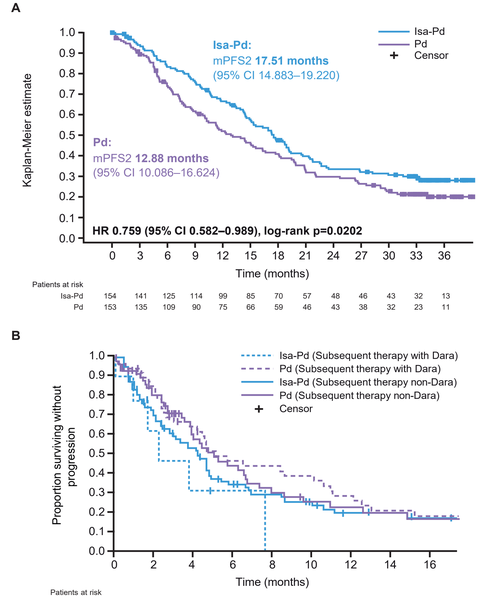


*Data not adjusted per M-protein interference
CR, complete response; d, dexamethasone; Isa, isatuximab; ORR, overall response rate; P, pomalidomide; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

PFS2 and PFS on subsequent therapy

- Isa-Pd significantly improved PFS2. Median PFS2 was 17.5 vs 12.9 months with Isa-Pd vs Pd (HR 0.759; 95% CI 0.582–0.989; one-sided p=0.0202; **Figure 4A**)
- PFS on first subsequent therapy was similar between treatment arms receiving first subsequent non-daratumumab therapy:
  - Isa-Pd patients (n=82) had 4.2 months mPFS (95% CI 2.79–4.76)
  - Pd patients (n=64) had 5.0 months mPFS (95% CI 3.78–6.64)
- In patients receiving daratumumab during first subsequent therapy, mPFS was lower in Isa-Pd treated patients (n=9), with 2.2 months (95% CI 0.03–7.62) vs 5.1 months (95% CI 3.75–10.51) in patients in the Pd arm (n=46; **Figure 4B**)

Figure 4. (A) PFS2: significant treatment benefit continues to be observed following subsequent therapy. (B) PFS on first subsequent therapy



d, dexamethasone; Dara, daratumumab; Isa, isatuximab; P, pomalidomide; PFS, progression-free survival; PFS2, time from randomization to disease progression on first subsequent therapy or death

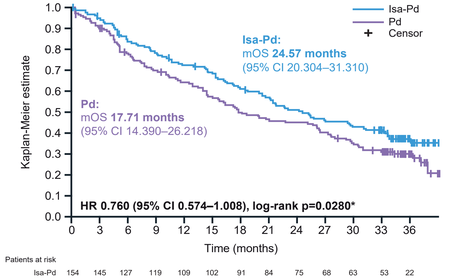
Type of and response to subsequent therapy

- Of patients receiving subsequent therapy, daratumumab was given to 22/92 (23.9%) vs 64/110 (58.2%) Isa-Pd vs Pd patients. Alkylating agents (69.6% vs 47.3%), PIs (66.3% vs 54.5%), corticosteroids (89.1% vs 77.3%), and "other" therapies (37.0% vs 19.1%) were given as subsequent therapy more frequently to patients in the Isa-Pd arm, while immunomodulatory agents were given subsequently at similar rates in both arms (33.7% vs 30.9%)
- ORR for daratumumab as monotherapy or combined with steroids was 14.3% following Isa-Pd vs 37.9% following Pd; however, ORR for daratumumab in combination therapy (PI, immunomodulatory or alkylating agent) was similar in both arms (30.8% vs 31.8% following Isa-Pd vs Pd)

OS Benefit

- Median OS was 24.6 vs 17.7 months for Isa-Pd vs Pd patients (HR 0.760; 95% CI 0.57–1.01; one-sided p=0.0280) (**Figure 5**)
- OS results are based on the 198 events observed. The observed p-value of 0.0280 did not cross this prespecified stopping boundary; further follow-up for survival will continue and final analysis of OS will be performed as planned after a total of approximately 220 events

Figure 5. OS Benefit with 6.9 months improvement in median OS. OS HR (0.760) is consistent with PFS2 HR (0.759)



*p value, significance level is set to 0.018
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; mOS, median overall survival; OS, overall survival; P, pomalidomide; PFS2, time from randomization to disease progression on first subsequent therapy or death

Safety

- Cumulative exposure to treatment was longer with Isa-Pd vs Pd (184.9 patient-years vs 124.5 patient-years)
- Median treatment duration was 47.6 weeks (range 1.3–171.6) with Isa-Pd vs 24.0 weeks (range 1.0–168.6) with Pd
- The safety profile in both treatment arms is consistent with the primary analysis (**Table 1**)
- Serious adverse events (SAEs) were also more common in the Isa-Pd arm (73.0%) vs Pd arm (60.4%), however, treatment-emergent SAEs were not substantially different after adjustment for the longer treatment duration in the Isa-Pd arm (1.14 vs 1.06 incidence rate per patient-year in the Isa-Pd vs Pd arms, respectively)
- Most common non-hematologic treatment-emergent adverse events (TEAEs; any grade) with Isa-Pd were infusion reaction (38%), upper respiratory tract infection (34%), and diarrhea (30%)
- Grade 3–4 neutropenia (85% vs 72%) and thrombocytopenia (34% vs 25%) were more frequent with Isa-Pd than with Pd

Table 1. Updated safety results

	Isa-Pd (n=152)	Pd (n=149)
Patients with, n (%)		
Any TEAE	151 (99.3)	146 (98.0)
Any Grade ≥3 TEAE	138 (90.8)	112 (75.2)
Treatment-related Grade ≥3 TEAE	115 (75.7)	75 (50.3)
Any Grade 5 TEAE*	14 (9.2)	15 (10.1)
Any SAE	111 (73.0)	90 (60.4)
Any TEAE leading to definitive discontinuation	18 (11.8)	21 (14.1)

Non-hematologic TEAEs occurring in ≥20% of patients in either arm

Preferred term, n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Infusion reaction	57 (37.5)	4 (2.6)	2 (1.3)	0
URTI	52 (34.2)	5 (3.3)	29 (19.5)	2 (1.3)
Diarrhea	46 (30.3)	3 (2.0)	33 (22.1)	2 (1.3)
Pneumonia	42 (27.6)	35 (23.0)	38 (25.5)	31 (20.8)
Bronchitis	41 (27.0)	7 (4.6)	17 (11.4)	1 (0.7)
Fatigue	30 (19.7)	6 (3.9)	32 (21.5)	0
Constipation	25 (16.4)	0	30 (20.1)	0

Hematologic abnormalities (from laboratory values), %

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	28.3	36.8	34.9	0	26.5	43.5	28.6	0
Thrombocytopenia	34.9	14.5	14.5	19.7	44.9	10.9	10.2	15.0
Neutropenia	0.7	10.5	22.4	62.5	7.5	14.3	38.8	32.7

*TEAE with fatal outcome during the treatment period
d, dexamethasone; Isa, isatuximab; P, pomalidomide; SAEs, serious adverse events; TEAEs, treatment-related adverse events; URTI, upper respiratory tract infection

CONCLUSIONS

- This study met its primary objective in demonstrating PFS benefit with Isa-Pd, with continued improvement in investigator PFS consistent with the primary analysis
- Isa-Pd resulted in a significant improvement in time to next treatment and PFS2 compared with Pd alone
- Daratumumab monotherapy following Isa-Pd appears less effective than following Pd, however, no such difference was observed when daratumumab was given as combination therapy
- Isa-Pd also demonstrated a strong trend in OS benefit with a 7-month median improvement
- The overall safety profile in this cohort remained unchanged from the first interim analysis

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DISCLOSURES:
PGR: Research funding – Bristol Myers Squibb, Celgene, Oncopeptides, Takeda; honoraria – Celgene, Janssen, Karyopharm, Oncopeptides, Sanofi, Takeda; **AP:** Honoraria – Amgen, Bristol Myers Squibb/Celgene, Janssen, Sanofi, Takeda; **JS-M:** Honoraria – Amgen, Bristol Myers Squibb, Celgene, Janssen, MSD, Novartis, Roche, Sanofi, Takeda; **MB:** Research funding – Amgen, Celgene, Janssen-Cilag, Takeda; honoraria – Bristol Myers Squibb; **IS:** Honoraria – Amgen, Celgene, Janssen-Cilag, Bristol Myers Squibb, Takeda, Novartis; **XL:** Honoraria – AbbVie, Amgen, Bristol Myers Squibb, Carsgen Therapeutics Ltd, Celgene, Gilead Sciences, Janssen-Cilag, Karyopharm Therapeutics, Merck, Mundipharma, Novartis, Oncopeptides, Pierre Fabre, Roche, Sanofi, Takeda; non-financial support – Takeda ; **FS:** Honoraria – Amgen, Celgene, Janssen, MSD, Novartis, Oncopeptides, Sanofi, SkylineDX, Takeda; participation on an entity's Board of Directors or advisory committees – Amgen, Celgene, Janssen, MSD, Novartis, Oncopeptides, Sanofi, Takeda; **PM:** Honoraria – Sanofi, Celgene, Amgen, Janssen; **MAD:** Participation on an entity's Board of Directors or advisory committees – Amgen, Bristol Myers Squibb, Celgene, Janssen, Takeda; **JS-YH:** Research funding – Sanofi; **JM:** Honoraria – Amgen, Bristol Myers Squibb, Celgene, Janssen, Karyopharm, Oncopeptides, Sanofi, Takeda; **MC:** Honoraria – AbbVie, Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen China J&D, Takeda; **HMP:** Honoraria – Amgen, Celgene, Janssen China J&D, Novartis, Sanofi, Takeda; **CZ, FD,** and **HvdV** are employed by Sanofi and may have stock and/or stock options in the company; **KCA:** participation on an entity's Board of Directors or advisory committees – Bristol Myers Squibb, Celgene, Gilead, Janssen, Millennium, Sanofi-Aventis

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