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Full Length Article
Analysis

Isatuximab Plus Carfilzomib and Dexamethasone Versus Carfilzomib and Dexamethasone in Patients with Relapsed Multiple Myeloma: IKEMA Subgroup Analysis by Prior Transplantation

Thomas G. Martin[1,*], Marcelo Capra[2], Mohamad Mohty[3], Kenshi Suzuki[4], Hang Quach[5], Michele Cavo[6], Philippe Moreau[7], Meletios Dimopoulos[8], Kwee Yong[9], Christina Tekle[10], Meredith C. Foster[11], Yvonne Barnes[12], Marie-Laure Risse[13], Joseph Mikhael[14]

[1] *University of California San Francisco, San Francisco, California*
[2] *Centro Integrado de Hematologia e Oncologia, Hospital Mãe de Deus, Porto Alegre, Brazil*
[3] *Hôpital Saint-Antoine, Sorbonne University, Paris, France*
[4] *Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan*
[5] *Department of Haematology, St Vincent's Hospital, University of Melbourne, Melbourne, Australia*
[6] *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy*
[7] *University of Nantes, Nantes, France*
[8] *Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens School of Medicine, Athens, Greece*
[9] *Department of Haematology, University College Hospital, London, United Kingdom*
[10] *Sanofi, Oncology, Cambridge, Massachusetts*
[11] *Sanofi, Global Medical Affairs, Cambridge, Massachusetts*
[12] *Sanofi, Cambridge, Massachusetts*
[13] *Sanofi, Vitry-Sur-Seine, France*
[14] *Applied Cancer Research and Drug Discovery, Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, Arizona*

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A B S T R A C T

In the era of highly active novel agents for multiple myeloma (MM), the role, ideal timing, and impact of transplantation on further therapy after relapse remains a matter of debate. The impact of prior transplantation on treatment benefit from monoclonal antibodies in patients with relapsed/refractory MM (RRMM) is largely unknown. Few Phase 3 studies of monoclonal antibody combinations with proteasome inhibitors or immunomodulatory agents have reported outcomes according to transplantation status. This subgroup analysis examined efficacy and safety in patients from the Phase 3 IKEMA study with and without previous transplantation. IKEMA (NCT03275285) was a randomized, open-label, multinational, parallel-group Phase 3 study that investigated isatuximab (Isa), an anti-CD38 monoclonal antibody, combined with carfilzomib and dexamethasone (Isa-Kd; experimental group) versus Kd (control group) in 302 patients with RRMM and 1 to 3 prior lines of therapy. Patients were randomized in a 3:2 ratio to either Isa-Kd or Kd, with stratification by number of prior lines (1 versus more than 1) and Revised International Staging System (R-ISS) stage (I or II versus III versus not classified). Treatment was given until progressive disease, unacceptable adverse events, or patient choice. Of the 302 randomized patients in IKEMA, 185 (61.3%) had received a prior transplant, comprising 116 of 179 (64.8%) patients in the Isa-Kd arm and 69 of 123 (56.1%) patients in the Kd arm. After a median follow-up of 20.6 months, median progression-free survival (PFS) in patients with prior transplant was not reached with Isa-Kd versus 19.15 months with Kd (hazard ratio [HR] = 0.60; 99% confidence interval [CI], 0.31-1.16). After a median follow-up of 20.8 months, median PFS in patients without prior transplant was not reached with Isa-Kd versus 18.99 months with Kd (HR = 0.44; 99% CI, 0.18-1.05). The overall response rate in patients with prior transplant was 87.9% (Isa-Kd) versus 85.5% (Kd). More patients in the Isa-Kd arm achieved a complete response or better compared with the Kd arm (43.1% versus 29.0%). The overall response rate in patients without prior transplant was 84.1% (Isa-Kd) versus 79.6% (Kd). More patients in the Isa-Kd arm achieved a complete response or better compared with the Kd arm (33.3% versus 25.9%). The minimal residual disease negativity rate was higher with Isa-Kd versus Kd in patients with (31.9% versus 13.0%) and without prior transplantation (25.4% versus 13.0%). In patients with prior

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*Corresponding author: Thomas G. Martin, MD, UCSF Medical Center, 400 Parnassus Ave, Box 0324, A502, San Francisco, CA 94143.
E-mail address: Tom.Martin@ucsf.edu (T.G. Martin).

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transplant, Grade 3 or higher treatment-emergent adverse events (TEAEs) were more common with Isa-Kd; however, no increases in serious TEAEs or definitive treatment discontinuations were seen versus Kd. Among patients without prior transplant, serious treatment-related TEAEs were similar, and there were fewer TEAEs leading to definitive discontinuation with Isa-Kd. The most common Grade 3 or higher TEAEs in patients with and without prior transplant were hypertension and pneumonia. For patients who underwent prior transplantation, Isa-Kd is an effective treatment option. Overall, these data demonstrate that Isa-Kd represents a standard of care for patients with RRMM, regardless of prior transplant status.

In the era of highly active novel agents for multiple myeloma (MM), the role, ideal timing, and impact of transplantation on further therapy after relapse remains a matter of debate [1–3]. Upfront transplantation has been associated with prolonged progression-free survival (PFS), even in the age of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) [1,2]. Subgroup analyses of ASPIRE and ENDEAVOR suggested that carfilzomib-based therapies yield improved PFS and response rates in patients with relapsed/refractory MM (RRMM) regardless of prior transplantation status [4]. In a subgroup analysis of TOURMALINE-MM1, PFS benefit with ixazomib plus lenalidomide and dexamethasone appeared greater in patients *without* prior transplant versus with prior transplant [5].

The impact of prior transplantation on treatment benefit from monoclonal antibodies in patients with RRMM is largely unknown. Patients with previous transplant may differ in terms of immune profile, demographics, and overall performance status, as well as molecular features of disease [6,7]. Few Phase 3 studies of monoclonal antibody combinations with PIs or IMiDs have reported outcomes according to transplantation status.

Isatuximab (Isa) is a monoclonal antibody that binds to a specific epitope of CD38 and exerts anti-MM effects through several modes of action [8]. Based on the Phase 3 ICARIA-MM study, Isa is approved in combination with pomalidomide (P) and dexamethasone (d) for the treatment of adult patients with RRMM who have received ≥2 prior therapies, including lenalidomide and a PI [9]. Based on the Phase 3 IKEMA study results, Isa in combination with carfilzomib (K) and d is approved in the United States for the treatment of adult patients with RRMM who have received 1 to 3 prior lines of therapy, in the European Union for the treatment of adult patients with relapsed MM who have received ≥1 prior therapy, and in Japan for the treatment of adult patients with RRMM who have received 1 prior treatment [9–11].

IKEMA was a prospective, multinational, randomized, open-label, parallel-group study that investigated treatment with Isa-Kd versus Kd alone [12]. Eligible patients had RRMM and had received 1 to 3 prior lines of therapy. A prespecified interim efficacy analysis of the Phase 3 IKEMA study showed that Isa-Kd significantly improved PFS compared with Kd in patients with RRMM (hazard ratio [HR] = 0.53; 99% confidence interval [CI], 0.32-0.89; one-sided P = .0007), with a clinically meaningful increase in very good partial response (VGPR) or better (≥VGPR; 72.6% versus 56.1%), minimal residual disease (MRD) negativity (29.6% versus 13.0%), complete response (CR; 39.7% versus 27.6%) rates, and a manageable safety profile [13]. This subgroup analysis examined efficacy and safety in patients from the Phase 3 IKEMA study with and without previous transplant.

METHODS

The IKEMA study has been described previously [12,13]. Briefly, IKEMA (NCT03275285) was a randomized, open-label, multinational, parallel-group Phase 3 study that investigated Isa-Kd (experimental group) versus Kd (control group) in 302 patients with RRMM who had received 1 to 3 prior lines of therapy. Patients were not eligible if they had prior carfilzomib exposure or if they were refractory to prior anti-CD38 therapy (prior anti-CD38 therapy was allowed if not refractory). Patients were randomized in a 3:2 ratio to either Isa-Kd or Kd, with stratification by number of prior lines (1 versus more than 1) and Revised International Staging System (R-ISS) stage (I or II versus III versus not classified). Treatment was given until progressive disease, unacceptable adverse events, or patient choice.

The primary endpoint was PFS [13]. Key secondary endpoints included overall response rate (ORR), rate of ≥VGPR, MRD negativity, CR rate (defined as stringent CR or CR), and overall survival (OS). A prespecified interim analysis was planned when 103 PFS events (65% of the 159 planned events) occurred as per the Independent Response Committee. The cutoff date for this analysis was February 7, 2020. This subgroup analysis examined efficacy and safety in patients by prior transplant status.

RESULTS

Patient Demographics and Baseline Characteristics

Of the 302 randomized patients in IKEMA, 185 (61.3%) had received a prior transplant, comprising 116 of 179 (64.8%) patients in the Isa-Kd arm and 69 of 123 (56.1%) patients in the Kd arm. Baseline patient characteristics were generally balanced, with the exception that a larger proportion of patients with prior transplant were aged <65 years compared with those without prior transplant (Table 1). Among patients without prior transplant, the Kd arm included a larger proportion of younger patients, more patients with R-ISS Stage I at study entry, more patients with 3 or more prior lines of therapy, and a larger proportion of patients refractory to lenalidomide or to both an IMiD agent and a PI.

Patient Disposition

Of the randomized patients, 2 with prior transplant (1 in each arm) and 1 patient without prior transplant (Isa-Kd arm) were not treated. At data cutoff, among patients with prior transplant, 59 (50.9%; Isa-Kd) and 20 (29.0%; Kd) remained on treatment, and among patients without prior transplant, 34 (54.0%; Isa-Kd) and 18 (33.3%; Kd) remained on treatment.

Efficacy

After a median follow-up of 20.6 months, median PFS in patients with prior transplant was not reached with Isa-Kd versus 19.15 months with Kd, with a HR of 0.60 (99% CI, 0.31-1.16), favoring Isa-Kd (Figure 1A). After a median follow-up of 20.8 months, median PFS in patients without prior transplant was not reached with Isa-Kd versus 18.99 months with Kd, with a HR of 0.44 (99% CI, 0.18–1.05), favoring Isa-Kd (Figure 1B). This PFS improvement was consistent with the HR in the overall population [13].

Consistent with the striking PFS improvement, deeper responses were seen with Isa-Kd in patients with and without prior transplant, similar to results for the overall population. The ORR in patients with prior transplant was 87.9% in the Isa-Kd arm versus 85.5% in the Kd arm (Figure 2). VGPR or better occurred in more patients in the Isa-Kd arm versus the Kd arm (72.4% versus 55.1%). More patients in the Isa-Kd arm also achieved a CR compared with the Kd arm (43.1%

Table 1
Patient Demographics and Baseline Characteristics

	Patients With Prior Transplant (n = 185)		Patients Without Prior Transplant (n = 117)	
	Isa-Kd (n = 116)	Kd (n = 69)	Isa-Kd (n = 63)	Kd (n = 54)
Patients with at least 1 prior transplant, n (%)	116 (100)	69 (100)	NA	NA
Age in years, median (range)	61.0 (37–76)	61.0 (39–75)	70.0 (38–86)	70.5 (33–90)
Age in years, by category, n (%)				
<65	76 (65.5)	52 (75.4)	12 (19.0)	14 (25.9)
65-74	39 (33.6)	16 (23.2)	35 (55.6)	31 (57.4)
≥75	1 (0.9)	1 (1.4)	16 (25.4)	9 (16.7)
R-ISS stage at study entry, n (%)				
Stage I	34 (29.3)	18 (26.1)	11 (17.5)	15 (27.8)
Stage II	69 (59.5)	40 (58.0)	41 (65.1)	30 (55.6)
Stage III	9 (7.8)	4 (5.8)	7 (11.1)	4 (7.4)
Unknown or not classified	4 (3.4)	7 (10.1)	4 (6.3)	5 (9.3)
Cytogenetic risk at study entry,* n (%)				
High	27 (23.3)	18 (26.1)	15 (23.8)	13 (24.1)
Standard	75 (64.7)	43 (62.3)	39 (61.9)	35 (64.8)
Missing	14 (12.1)	8 (11.6)	9 (14.3)	6 (11.1)
Prior lines of therapy at study entry, median (range)	2.0 (1–4)	2.0 (1–3)	1.0 (1–3)	2.0 (1–4)
Prior lines of therapy at study entry, n (%)				
1	47 (40.5)	33 (47.8)	32 (50.8)	22 (40.7)
2	41 (35.3)	18 (26.1)	23 (36.5)	18 (33.3)
≥3	28 (24.1)	18 (26.1)	8 (12.7)	14 (25.9)
Patients refractory to, n (%)				
Lenalidomide	38 (32.8)	18 (26.1)	19 (30.2)	24 (44.4)
IMiD and PI	25 (21.6)	10 (14.5)	10 (15.9)	17 (31.5)

Abbreviations: d, dexamethasone; IMiD, immunomodulatory agent; Isa, isatuximab; K, carfilzomib; PI, proteasome inhibitor; R-ISS, Revised International Staging System; Transplant, autologous stem cell transplant.

* High-risk cytogenetics was defined as presence of del(17p), t(4;14), and/or t(14;16) by FISH. Cytogenetics was performed by a central laboratory with cutoff 50% for del(17p), 30% for t(4;14) and t(14;16).

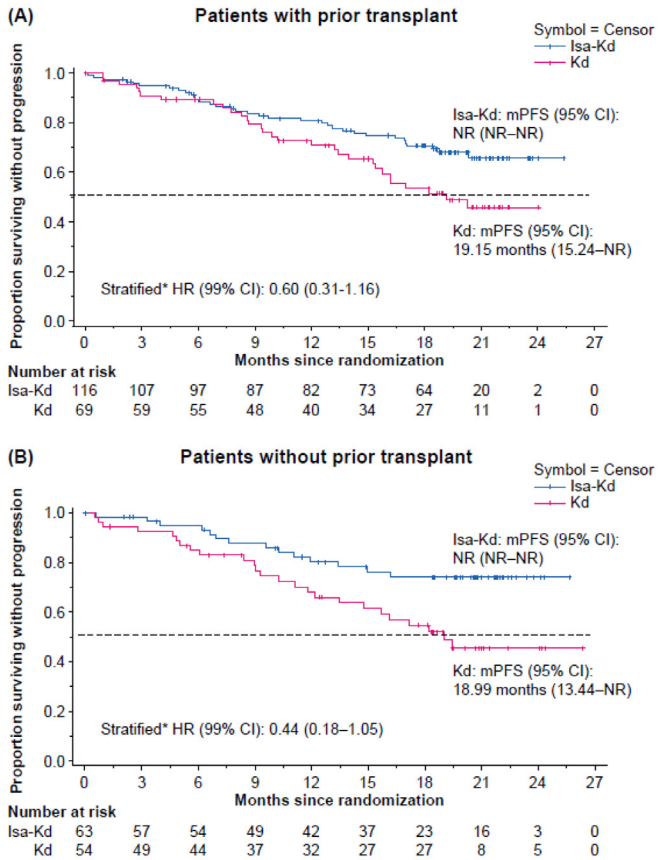

Figure 1. Progression-free survival in patients (A) with prior transplant and (B) without prior transplant.

*Stratified on number of prior lines of therapy (1 versus >1) and R-ISS stage (I or II versus III versus not classified) according to IRT. IRT indicates interactive response technology.

Abbreviations: CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; m, median; NR, not reached; PFS, progression-free survival; R-ISS, Revised International Staging System; Transplant, autologous stem cell transplant.

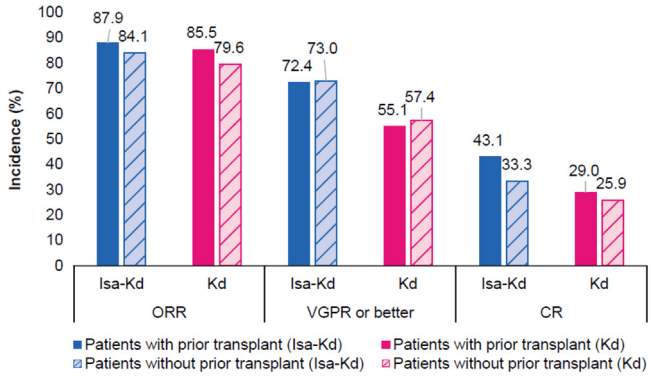

Figure 2. Best overall response in patients with and without prior transplant.

Abbreviations: CR, complete response; d, dexamethasone; Isa, isatuximab; K, carfilzomib; ORR, overall response rate; Transplant, autologous stem cell transplant; VGPR, very good partial response.

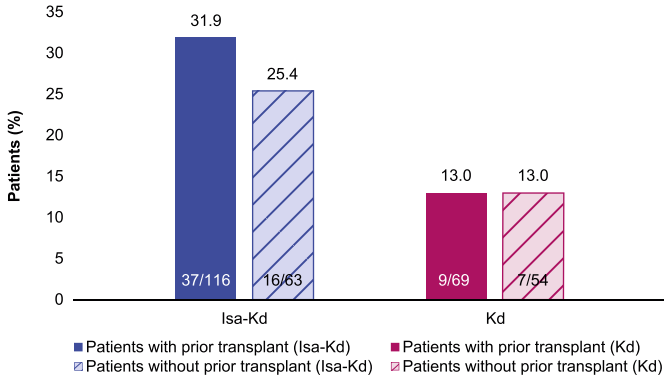

Figure 3. MRD negativity* in patients with and without prior transplant.

*Adaptive Biotechnologies NGS, MRD testing performed at time of VGPR or CR.

Abbreviations: CR, complete response; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; neg, negative; NGS, next generation sequencing; Transplant, autologous stem cell transplant.

versus 29.0%). The ORR in patients without prior transplant was 84.1% in the Isa-Kd arm versus 79.6% in the Kd arm (Figure 2). VGPR or better occurred in more patients in the Isa-Kd arm versus the Kd arm (73.0% versus 57.4%). More patients in the Isa-Kd arm also achieved a CR compared with the Kd arm (33.3% versus 25.9%).

MRD negativity was assessed in bone marrow aspirates from patients who achieved ≥VGPR by next-generation sequencing at a sensitivity level of 10^{-5}. The MRD negativity rate was higher with Isa-Kd versus Kd (31.9% versus 13.0%) in patients with prior transplant, which was similar to the MRD negativity rates observed in the overall population (Figure 3). The MRD

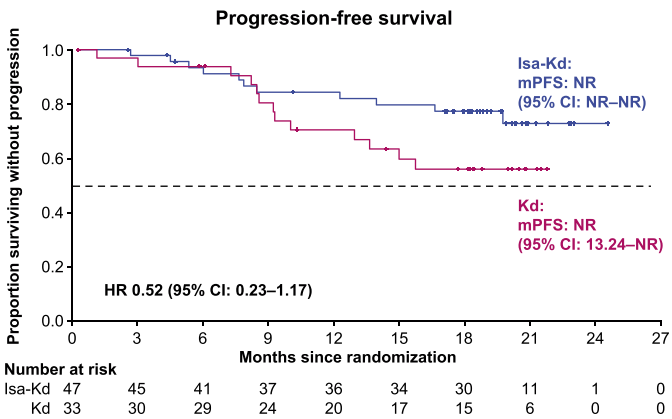

Figure 4. Progression-free survival among patients who received a transplant as their 1 prior line of therapy.

Abbreviations: CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; m, median; NR, not reached; PFS, progression-free survival; Transplant, autologous stem cell transplant.

Table 2
Exposure to Study Treatments

Safety population	Patients With Prior Transplant		Patients Without Prior Transplant	
	Isa-Kd (n = 115)	Kd (n = 68)	Isa-Kd (n = 62)	Kd (n = 54)
Median treatment duration (wk), (range)*	80.0 (2–104)	61.6 (2–103)	79.3 (1–111)	57.9 (1–114)
Relative dose intensity, median % (range)				
Isatuximab	94.55 (67.9-108.2)	–	93.53 (66.7-102.2)	–
Carfilzomib	91.80 (18.2-107.5)	91.07 (48.5-108.6)	90.59 (25.9-108.7)	91.55 (41.8-103.7)
Dexamethasone	85.81 (26.8-101.1)	90.31 (34.9-101.1)	82.81 (24.5-100.3)	85.64 (27.4-101.6)
Median cycles started (range)*	19.0 (1–25)	15.0 (1–25)	19.0 (1–27)	14.0 (1–28)

Abbreviations: d, dexamethasone; Isa, isatuximab; K, carfilzomib; Transplant, autologous stem cell transplant.
* Based on interim analysis with data cutoff on February 7, 2020.

negativity rate was also higher with Isa-Kd versus Kd (25.4% versus 13.0%) in patients without prior transplant (Figure 3).

Efficacy—Transplantation as the Only Prior Line of Therapy

A specific subgroup of interest are those patients who received a transplant as their 1 prior line of therapy, so these patients received Isa-Kd (n = 47) or Kd (n = 33) as their second line. The HR for PFS was 0.52 (95% CI, 0.23-1.17), favoring Isa-Kd, which is consistent with the results for the prior transplant and intent-to-treat populations (Figure 4). Isa-Kd also led to high response rates and improved MRD negativity in these patients, consistent with what was seen in the overall transplant population and the intent-to-treat population. The ORR was 87.2% for patients receiving Isa-Kd and 90.9% for patients receiving Kd. The rate of CR or better was 46.8% with Isa-Kd compared with 36.4% with Kd. The MRD negativity rate was higher among patients treated with Isa-Kd compared with Kd (40.4% versus 15.2%).

Treatment Exposure

A longer treatment duration was observed with Isa-Kd; patients with prior transplant received a median of 19 cycles (range 1-25) of Isa-Kd versus 15 cycles (range 1-25) of Kd (Table 2). Similar results were seen among patients without prior transplant, where patients with Isa-Kd received a median of 19 cycles (range 1-27) and patients with Kd received a median of 14 cycles (range 1-28). This was similar to the treatment duration in the overall safety population, where patients received a median of 19 cycles (range 1-27) of Isa-Kd versus 14.5 cycles (range 1-28) of Kd [13].

Safety

Reasons for definitive treatment discontinuation (discontinuation of all study treatments) included progressive disease (with prior transplant: 31.9% [Isa-Kd] and 47.8% [Kd]; without prior transplant: 23.8% [Isa-Kd] and 29.6% [Kd]), adverse events (with prior transplant: 8.6% [Isa-Kd] and 8.7% [Kd]; without prior transplant: 7.9% [Isa-Kd] and 20.4% [Kd]), patient request (with prior transplant: 5.2% [Isa-Kd] and 11.6% [Kd]; without prior transplant: 7.9% [Isa-Kd] and 11.1% [Kd]), and other (with prior transplant: 2.6% [Isa-Kd] and 1.4% [Kd]; without prior transplant: 4.8% [Isa-Kd] and 5.6% [Kd]). Among patients with prior transplant, 17/115 (14.8%; Isa-Kd) and 3/68 (4.4%; Kd) had premature discontinuation of at least 1 study drug (where at least 1 study drug is continued), all due to adverse events. Among patients without prior transplant, 17/62 (27.4%; Isa-Kd) and 2/54 (3.7%; Kd) had premature discontinuation of at least 1 study drug, all because of adverse events.

In patients with prior transplant, Grade 3 or higher TEAEs were more common in the Isa-Kd arm versus the Kd arm, which is similar to what was observed in the overall population (Table 3). However, no increases in serious TEAEs or definitive treatment discontinuations were seen in the Isa-Kd arm versus the Kd arm. Although there were more serious TEAEs in the Isa-Kd arm versus the Kd arm among patients without prior transplant, serious TEAEs deemed treatment-related were similar, and there were fewer TEAEs leading to definitive discontinuation.

The most common Grade 3 or higher TEAEs in patients with and without prior transplant were hypertension and pneumonia (Table 4). Overall, Isa-Kd had a similar safety profile in the prior transplant population compared with the overall population [13].

Table 3
Safety Summary (Safety Population)

TEAE Overview, n (%)	Patients With Prior Transplant		Patients Without Prior Transplant	
	Isa-Kd (n = 115)	Kd (n = 68)	Isa-Kd (n = 62)	Kd (n = 54)
Any TEAE	112 (97.4)	64 (94.1)	60 (96.8)	53 (98.1)
Grade ≥3 TEAEs	88 (76.5)	40 (58.8)	48 (77.4)	42 (77.8)
Treatment-related grade ≥3 TEAEs	54 (47.0)	30 (44.1)	33 (53.2)	28 (51.9)
Serious TEAEs	61 (53.0)	35 (51.5)	44 (71.0)	35 (64.8)
Serious treatment-related TEAEs	23 (20.0)	13 (19.1)	21 (33.9)	18 (33.3)
Any TEAE leading to definitive* discontinuation	10 (8.7)	6 (8.8)	5 (8.1)	11 (20.4)
Any TEAE leading to premature† discontinuation of Isa	1 (0.9)	NA	0	NA
Any TEAE leading to premature† discontinuation of K	13 (11.3)	1 (1.5)	13 (21.0)	0
Any TEAE leading to premature† discontinuation of d	6 (5.2)	2 (2.9)	5 (8.1)	2 (3.7)
Fatal TEAEs during study treatment	4 (3.5)	1 (1.5)	2 (3.2)	3 (5.6)

Abbreviations: d, dexamethasone; Isa, isatuximab; K, carfilzomib; NA, not applicable; TEAE, treatment-emergent adverse event; Transplant, autologous stem cell transplant.
* Discontinuation of all study treatments.
† At least 1 study treatment is continued.

Table 4
Safety Summary—Selected TEAEs (Safety Population)

Selected TEAEs Preferred Term, n (%)	Patients With Prior Transplant				Patients Without Prior Transplant			
	Isa-Kd (n = 115)		Kd (n = 68)		Isa-Kd (n = 62)		Kd (n = 54)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reaction	61 (53.0)	1 (0.9)	1 (1.5)	0	18 (29.0)	0	3 (5.6)	0
Hypertension	40 (34.8)	20 (17.4)	19 (27.9)	10 (14.7)	25 (40.3)	16 (25.8)	19 (35.2)	14 (25.9)
Diarrhea	40 (34.8)	4 (3.5)	17 (25.0)	2 (2.9)	24 (38.7)	1 (1.6)	18 (33.3)	1 (1.9)
Upper respiratory tract infection	35 (30.4)	4 (3.5)	14 (20.6)	1 (1.5)	29 (46.8)	2 (3.2)	15 (27.8)	1 (1.9)
Fatigue	28 (24.3)	2 (1.7)	15 (22.1)	0	22 (35.5)	4 (6.5)	8 (14.8)	1 (1.9)
Dyspnea	31 (27.0)	7 (6.1)	12 (17.6)	1 (1.5)	18 (29.0)	2 (3.2)	14 (25.9)	0
Pneumonia	24 (20.9)	16 (13.9)	12 (17.6)	6 (8.8)	18 (29.0)	13 (21.0)	12 (22.2)	9 (16.7)
Bronchitis	29 (25.2)	3 (2.6)	10 (14.7)	0	11 (17.7)	1 (1.6)	5 (9.3)	1 (1.9)

Abbreviations: d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event; Transplant, autologous stem cell transplant.

DISCUSSION

Of the 302 patients randomized in IKEMA, 61.3% had received a prior transplant. Of these patients, 43.2% entered the study with progression after prior transplantation as their 1 prior line of therapy. The addition of isatuximab to Kd improved PFS in patients with RRMM and prior transplant (HR = 0.60; 99% CI, 0.31–1.16) and in patients without prior transplant (HR = 0.44; 99% CI, 0.18–1.05), which was consistent with the HR in the overall study population. Isa-Kd also improved PFS in patients with prior transplantation as their 1 prior line of therapy (HR 0.52; 95% CI: 0.23–1.17). The high ORR with Isa-Kd was maintained among patients with (87.9%) and without prior transplant (84.1%). In patients with and without prior transplant, treatment with Isa-Kd led to improved CR (43.1% and 33.3%) and MRD negativity rates (31.9% and 25.4%).

Differences in patient population, study design, and methods provide limitations for cross-trial comparisons; however, we would like to contextualize the results of this subgroup analysis with other analyses involving the monoclonal antibodies daratumumab (targets CD38) and elotuzumab (targets the MM cell surface marker signaling lymphocytic activation molecule family member 7), which are also approved for the treatment of MM.

In the Phase 3 CASTOR study, 498 patients with relapsed MM or RRMM were randomized to receive daratumumab, bortezomib, and dexamethasone or bortezomib and dexamethasone [14]. Of these patients, 156/251 (62.2%) and 149/247 (60.3%) had received a prior autologous stem cell transplant (ASCT). In a prespecified subgroup analysis of PFS among patients who received a prior transplant, median PFS was not estimable (NE) for patients receiving the daratumumab combination versus 6.7 months for patients receiving bortezomib and dexamethasone (HR = 0.38; 95% CI, 0.26–0.57). These findings were similar to PFS results observed among patients without prior transplant (NE versus 7.2 months; HR = 0.34 [95% CI, 0.19–0.59]). No data on response rate, MRD negativity rate, or safety were presented for patients who had received a prior transplant. Results from the current analysis demonstrate a PFS benefit of Isa-Kd in patients both with and without prior transplant, as well as increased CR and MRD negativity rates in both subgroups, with no new safety signals reported.

In the Phase 3 POLLUX study, 569 patients with MM who had received at least 1 previous line of therapy were randomized to receive the combination of daratumumab, lenalidomide, and dexamethasone, or lenalidomide and dexamethasone [15]. In the overall population, 63.3% of patients received prior ASCT, including 180/286 (62.9%) patients receiving the daratumumab combination and 180/283 (63.6%) receiving lenalidomide and dexamethasone. PFS at 12 months was higher with the daratumumab combination compared with the control group (83.2% [95% CI, 78.3–87.2] versus 60.1% [95% CI, 54.0–65.7]). Higher ORRs (92.9% versus 76.4%; $P < .001$) and MRD negativity rates (22.4% versus 4.6%; $P < .001$) were also observed with the daratumumab combination compared with lenalidomide and dexamethasone. In the Phase 3 CANDOR study, 466 patients with RRMM were randomized to receive daratumumab plus Kd or Kd alone [16]. In this study, 195/312 (63%) of patients treated with daratumumab plus Kd and 75/154 (49%) of patients treated with Kd had received a prior transplant. In the overall population, a PFS benefit was observed with daratumumab plus Kd compared with Kd alone (HR = 0.63; 95% CI, 0.46–0.85). No information is available, however, on the relative benefits of daratumumab combinations with K versus bortezomib.

The Phase 3 ELOQUENT-2 study, which included 646 patients with RRMM and 1 to 3 prior lines of therapy who were randomized to receive the combination of elotuzumab, lenalidomide, and dexamethasone or lenalidomide and dexamethasone, demonstrated a PFS benefit with elotuzumab, lenalidomide, and dexamethasone compared with lenalidomide and dexamethasone [17]. In a preplanned final OS analysis, the elotuzumab combination led to a significant improvement in OS (HR = 0.82; 95.4% CI, 0.68-1.00), which was also observed among patients who received a prior stem cell transplant (HR = 0.79; 95% CI, 0.61-1.02) [18]. No other subgroup analyses focused on patients who had received a prior transplant. The Phase 2 ELOQUENT-3 study included 117 patients with MM refractory or relapsed/refractory to lenalidomide and a PI who were randomized to receive elotuzumab, pomalidomide, and dexamethasone, or pomalidomide and dexamethasone [19]. Although a PFS benefit was observed for the elotuzumab combination (HR = 0.54; 95% CI, 0.34–0.86), no subgroup analyses were conducted to investigate the potential benefit for patients who had received a prior transplant. Therefore a consistent benefit of an elotuzumab combination cannot be concluded in patients with versus without prior transplant.

Studies investigating additional therapies with alternative mechanisms of action have also revealed outcomes based on transplantation status. Melphalan flufenamide, or melflufen, increases aminopeptidase activity to selectively release alkylating agents within tumor cells [20,21]. The Phase 3 OCEAN study, which included adult patients with RRMM who had received 2 to 4 prior lines of therapy and were randomized to receive 28-day cycles of melflufen and dexamethasone (n = 246), or pomalidomide and dexamethasone (n = 249), demonstrated significantly prolonged PFS with melflufen

(n = 121) compared with pomalidomide (n = 129) in patients without a previous transplant (HR = 0.59; 95% CI, 0.44-0.79; P = .0004) [22]. A benefit for OS was observed among patients treated with pomalidomide (n = 120) compared with melflufen (n = 125) who had received a previous transplant (HR = 1.61; 95% CI, 1.09-2.40; P = .017), suggesting that previous exposure to high-dose melphalan may be driving the negative prognostic effect among patients who had received a previous transplant. Isa-Kd is effective irrespective of prior transplant, which may be due in part to its different mechanism of action compared with prior therapies, whereas melflufen is similar to high-dose melphalan conditioning for ASCT.

In conclusion, our presented results suggest that the degree of benefit with Isa-Kd versus Kd is similar regardless of prior transplant. Importantly, Isa-Kd exhibited a benefit in patients without prior transplant who may not have been eligible for transplantation. The use of frontline carfilzomib, or any of the agents in the triplet combination, is rare in transplantation-ineligible patients, but here it is used in early relapse, which may provide a preferred option for second-line or later treatment.

Isa-Kd led to improved PFS and a high CR rate and MRD negativity rate, with a manageable safety profile in patients with and without prior transplant, consistent with the overall population. For patients who underwent frontline transplantation, Isa-Kd is an effective treatment option. Overall, these data demonstrate that Isa-Kd represents a standard of care for patients with RRMM, regardless of prior transplant status.

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