HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Article
Open Access

Efficacy of Isatuximab With Pomalidomide and Dexamethasone in Relapsed Myeloma: Results of a UK-Wide Real-World Dataset

Faouzi Djebbari[1], Alexandros Rampotas[1,2], Grant Vallance[1], Fotios Panitsas[3], Nanda Basker[4], Gina Sangha[5], Beena Salhan[6,7,8,9], Farheen Karim[9,10], Firas Al-Kaisi[11], Amy Gudger[9,12], Loretta Ngu[13], Matt Poynton[14], Ho Pui Jeff Lam[15], Lowri Morgan[16], Laura Yang[17], Jennifer Young[18], Mairi Walker[19], Ismini Tsagkaraki[20], Laura Anderson[21], Saleena Rani Chauhan[9,22], Rebecca Maddams[23], Richard Soutar[24], Margarita Triantafillou[25], Steve Prideaux[26], Abubaker Obeidalla[27], Ceri Bygrave[16], Supratik Basu[9,10,28] Karthik Ramasamy[1]

Correspondence: Faouzi Djebbari (Faouzi.Djebbari@ouh.nhs.uk).

ABSTRACT

Real-world data on the efficacy and tolerability of isatuximab with pomalidomide and dexamethasone (IsaPomDex) in relapsed/refractory myeloma patients have not been reported. In this UK-wide retrospective study, IsaPomDex outcomes were evaluated across 24 routine care cancer centers. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), duration of response (DOR) for patients who achieved an objective response (≥partial response [PR]), and adverse events (AEs). In a total cohort 107 patients, median follow up (interquartile range [IQR]) was 12.1 months (10.1–18.6 mo), median age (IQR) was 69 years (61–77). Median (IQR) Charlson Comorbidity Index (CCI) score was 3 (2–4); 43% had eGFR <60 mL/min. Median (IQR) number of prior therapies was 3 (3–3). Median (IQR) number of IsaPomDex cycles administered was 7 (3–13). ORR was 66.4%, with responses categorized as ≥ very good partial response: 31.8%, PR: 34.6%, stable disease: 15.9%, progressive disease: 15%, and unknown 2.8%. Median PFS was 10.9 months. Median DOR was 10.3 months. There was no statistical difference in median PFS by age (<65: 10.2 versus 65–74 13.2 versus ≥75: 8.5 mo, log-rank $P = 0.4157$), by CCI score (<4: 10.2 mo versus ≥4: 13.2, log-rank $P = 0.6531$), but inferior PFS was observed with renal impairment (≥60: 13.2 versus <60: 7.9 mo, log-rank $P = 0.0408$). Median OS was 18.8 months. After a median of 4 cycles, any grade AEs were experienced by 87.9% of patients. The most common ≥G3 AEs were neutropenia (45.8%), infections (18.7%), and thrombocytopenia (14%). Our UK-wide IsaPomDex study demonstrated encouraging efficacy outcomes in the real world, comparable to ICARIA-MM trial.

INTRODUCTION

The multiple myeloma (MM) treatment landscape continues to evolve owing to the advent and approval of number of novel treatment combinations using distinct pharmacological classes such as immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (Mab), which

[1]Department of Clinical Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
[2]University Hospital Southampton, Southampton, United Kingdom
[3]Department of Haematology, Laiko General Hospital, Athens, Greece
[4]Oxford University Clinical Academic Graduate School, Oxford, United Kingdom
[5]Milton Keynes Hospital, Milton Keynes, United Kingdom
[6]Birmingham Heartlands Hospital, Birmingham, United Kingdom
[7]Good Hope Hospital, Birmingham, United Kingdom
[8]Solihull Hospital, Solihull, United Kingdom
[9]West Midlands Research Consortium (WMRC), West Midlands, United Kingdom
[10]The Royal Wolverhampton NHS Trust, Wolverhampton, United Kingdom
[11]Royal Derby Hospital, Derby, United Kingdom
[12]Queen Elizabeth Hospital, Birmingham, United Kingdom
[13]Royal Devon & Exeter NHS Foundation Trust, Exeter, United Kingdom
[14]Royal Berkshire Hospital, Reading, United Kingdom
[15]Guy's and St Thomas NHS Foundation Trust, London, United Kingdom
[16]University Hospital of Wales, Cardiff, United Kingdom
[17]University Hospitals Sussex NHS Foundation Trust, Sussex, United Kingdom
[18]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, United Kingdom
[19]University Hospital Crosshouse, Crosshouse, United Kingdom
[20]Stoke Mandeville Hospital, Aylesbury, United Kingdom
[21]Royal United Hospital Bath, United Kingdom
[22]Worcestershire Acute Hospitals NHS Trust, Worcester, United Kingdom
[23]Poole Hospital, Poole, United Kingdom
[24]Beatson Oncology Centre, Glasgow, United Kingdom
[25]Manchester Royal Infirmary, Manchester, United Kingdom
[26]Great Western Hospital, Swindon, United Kingdom
[27]Wexham Park Hospital, Slough, United Kingdom
[28]University of Wolverhampton, Wolverhampton, United Kingdom

Supplemental digital content is available for this article.
SB and KR are joint senior authors.
All relevant data are available and presented in this manuscript (tables, figures and descriptive results).

HemaSphere (2022) 6:6(e738).
http://dx.doi.org/10.1097/HS9.0000000000000738.
Received: March 26, 2022 / Accepted: May 2, 2022

enabled this incurable condition to become increasingly more manageable. Daratumumab was the first-licensed Mab in MM, targeting surface antigen CD38, which is widely and uniformly expressed on myeloma cells.[1] Daratumumab is now used both in the newly diagnosed and relapsed/refractory myeloma (RRMM) settings in combination with established standard of care agents.

However, patients who become relapsed or refractory to IMiDs and PIs, require a new treatment option. Isatuximab emerged as the second anti-CD38 Mab, which binds to a specific epitope on the CD38 antigen.[2] It was approved in the United Kingdom in combination with pomalidomide and dexamethasone (IsaPomDex), as fourth-line therapy for RRMM patients who previously received lenalidomide and a PI.[3]

Efficacy was demonstrated in the phase 3 ICARIA-MM trial, which randomized 154 patients to IsaPomDex and 153 patients to PomDex.[4] At a median follow up of 11.6 months, overall response rates (ORR) were (60% versus 35%, $P < 0.0001$). Median progression-free survival (PFS) showed superiority of the IsaPomDex arm (11.5 versus 6.5 mo, $P = 0.001$).[4] The most frequent any grade (G) adverse events (AEs) attributed to IsaPomDex were infusion reactions (38%), upper respiratory tract infections (28%), and diarrhea (26%); the most frequent G3 AE was pneumonia (15%).[4]

However, the decision to use continuous therapy (CT) in routine myeloma practice requires a careful account of a few patient-related factors, in addition to the disease. At least 30% of patients are frail, due to disease-related symptoms or age-related decline in physical capacity in addition to comorbidities, polypharmacy, nutritional status, and cognitive impairment.[5] The CONNECT-MM routine care registry reported that 40% of newly diagnosed patients were trial-ineligible.[6]

To optimize clinical outcomes in routine practice where there is an effectiveness gap compared to clinical trials, a better understanding of the tolerability and efficacy outcomes of this novel triplet therapy in unselected real-world patients is required. This is particularly important for patients with pre-existing comorbidities, frailty, and advanced age, which are common contributing factors to dose reductions as a result of increased toxicity burden, or to treatment discontinuations.

In this UK-wide real-world study, we set out to evaluate the efficacy and tolerability outcomes of IsaPomDex in unselected consecutively treated routine care patients from 24 treatment centers. To our knowledge, there are no published real-world data describing myeloma outcomes in this setting.

MATERIALS AND METHODS

Study design, inclusion criteria, and data collection

This study included unselected consecutive patients from 24 centers across the United Kingdom with a diagnosis of RRMM, who started therapy between January 2020 and May 2021 and received ≥1 cycle of IsaPomDex therapy. IsaPomDex is a 28-day regimen given until disease progression or unacceptable toxicity, as follows: isatuximab intravenous (IV) infusion at 10 mg/kg (weekly on cycle 1, and fortnightly thereafter), pomalidomide 4 mg orally once a day on days 1–21, and dexamethasone weekly at 40 mg (if <75 y old) or 20 mg (if ≥75 y old).

Patients' medical records were used to collect baseline patient and disease characteristics, at the start of IsaPomDex, such as age, World Health Organization performance status (PS) with a score range between 0 and 5, Charlson Comorbidity Index (CCI), renal function presented as the standard laboratory-provided value of the estimated glomerular filtration rate (eGFR), myeloma subtype, lactate dehydrogenase (LDH), myeloma International Staging System (ISS), and cytogenetics known since diagnosis. Depending on the laboratory at each respective hospital site, eGFR values were calculated using one of the two following methods: modification of diet in renal disease (MDRD) equation, or chronic kidney disease epidemiology collaboration (CKD-EPI) equation. High-risk cytogenetics was defined as one or more of the following abnormalities by fluorescence in situ hybridization (FISH): t (4, 14), t (14, 16), del(17p).

Treatment data included prior therapies, number of IsaPomDex cycles received, pomalidomide and dexamethasone dose reductions, reasons for treatment discontinuation, and the use prophylactic anti-infective medication (antiviral, antifungal, and PCP prophylaxis). AE data included the name and grading (1–5) using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, AE-related patient hospitalizations, isatuximab infusion reactions, and the use of supportive treatments such as granulocyte colony stimulating factor (GCSF), platelet transfusions, and red blood cell (RBC) transfusions. Service evaluation approval was obtained before starting the study in all participating sites.

Study endpoints

The primary endpoint was the ORR according to the International Myeloma Working Group (IMWG) response assessment criteria. Secondary endpoints were as follows: PFS, duration of response (DOR), in addition to AEs. Overall survival (OS) was an exploratory outcome in this study.

DOR was calculated for patients who achieved an objective response (ie, ≥partial response [PR]), from the date of best response until the date of documented relapse, or date of last follow up for patients alive with ongoing remission or date of death if this occurred prior to relapse. PFS was evaluated as the time in months between initiation of IsaPomDex and progressive disease (PD) or death, whichever occurred first. OS was defined as time in months from initiation of therapy to death from any cause. Patients were censored at the end of their follow-up period, if they did not experience a PFS or OS event

Statistical analyses

Descriptive statistics for quantitative variables are presented as median (interquartile range [IQR]) for baseline and treatment characteristics, and median (range) for AEs. Descriptive statistics for categorical variables are presented as frequency (percentage). Time-to-event outcomes were estimated using the Kaplan-Meier method and reported as median (IQR). Follow-up duration was estimated with the inverse Kaplan-Meier method, considering all types of events as censored. Time-to-event outcomes were compared between the different subgroups using log-rank tests and Cox regression analyses, with proportionality of hazards evaluated by visual assessment of "log-log" plots, and hazard ratios (HR) presented with 95% CI.

We used landmark analysis to compare groups of patients defined by time-dependent predictors (such as response), to address the issue of selection bias introduced by failure to survive long enough to achieve response status. The landmark time was set at 3 months, taking into account median time of attainment of response state. The probabilities of response and disease progression were estimated with the cumulative incidence method, taking into account the competing risk of early death before best response or relapse, respectively. Cumulative incidence curves were compared with Gray's test. Cumulative incidence covariate analysis was performed by competing risks regression, according to Fine and Gray's semiparametric model.

Univariate (UVA) logistic regression was conducted to assess factors associated with increased incidence rates of hospital admissions. Factors investigated were the following: age (<75 versus ≥75), eGFR (≥60 versus <60), CCI comorbidity score (<4 versus ≥4), anemia at baseline (No [N] versus Yes [Y]), lymphopenia at baseline (N versus Y), elevated LDH (Y versus N), number of chemo cycles (>4 versus ≤4), pomalidomide dose attenuation (Y versus N), dexamethasone dose attenuation (Y versus N), and infections (Y versus N).

For statistical analysis, we used STATA (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) and EZR 1.55.

RESULTS

Patient, disease, and treatment characteristics

A total of 107 patients from 24 UK centers were eligible for inclusion in the study. Median follow-up time (IQR) was 12.1 months (10.1–18.6 mo). The baseline patient, disease, and treatment characteristics of the total cohort are presented in Table 1. The median age (IQR) was 69 years (61–77). Median (IQR) CCI score was 3 (2–4), 61.7% had a CCI <4, and 80.4% had PS of <2. Renal presentation (eGFR<60 mL/min) was 43%; 32.9% had ISS III staging; and 14% had high-risk cytogenetics.

Median (IQR) number of prior therapies was 3 (3–3) in the total cohort. Prior therapies were transplant (60.7%), alkylator (99.1%), PI (99.1%), IMiD (100%), anti-CD38 (4.7%), and HDACi (3.7%). Median (IQR) number of IsaPomDex cycles administered was 7 (3–13). Pomalidomide and dexamethasone dose reductions were incurred in 45.8% and 51.4% of patients, respectively.

Treatment status and discontinuations

Treatment status as well as reasons for discontinuation is presented in Table 2. In the total cohort, 48.6% of patients continue to receive therapy, while 51.4% discontinued therapy due to death (15%), PD (30.8%), and toxicity (1.9%). Reasons for treatment discontinuation in individual subgroups by age and by comorbidities are also fully presented.

Response rates

Overall response rate and response categories in the total cohort and in subgroups by age and by comorbidity, are presented in Table 3. Among patients achieving PR or better, median time to objective response (≥PR) was 2.8 months (IQR 1.8–5 mo). The maximum cumulative incidence of response (PR or better), accounting for the competing risk of death, was 74.8% (95% CI, 64.1%-82.8%). A 50% cumulative incidence was reached at 4.6 months.

ORR was 66.4% in the total cohort, with responses categorized as ≥very good partial response: 31.8%, PR: 34.6%, stable disease: 15.9%, PD: 15%, and unknown 2.8%. Patients in the older subgroup and those with severe comorbidities achieved numerically but not statistically lower ORR, by age (<75: 67.6% versus ≥75: 63.6%, P = 0.622), and by comorbidities (CCI <4: 68.2% versus CCI ≥ 4:63.4%, P = 0.535).

Progression-free survival

Median PFS in the total cohort was 10.9 months (95% CI, 7.9-15.5; Figure 1). PFS survival probability at 3 months was 80.1% (95% CI, 70.8%-86.7%), at 6 months was 64.4% (95% CI, 53.8%-73.2%), at 9 months was 54.6% (95% CI, 43.7%-64.2%), and at 12 months was 49.2% (95% CI, 38.3%-59.3%). There was no statistical difference in median PFS by age (<65: 10.2 versus 65–74 13.2 versus ≥75: 8.5 mo, log-rank P = 0.4157), by comorbidity CCI score (<4: 10.2 mo versus ≥4: 13.2, log-rank P = 0.6531), but a trend for inferior PFS was observed with renal impairment (≥60: 13.2 versus <60: 7.9 mo, log-rank P = 0.0408). There was a statistically improved PFS in those who achieved ≥PR response (log-rank $P < 10^{-4}$) Figure 2.

Twenty-eight IsaPomDex, patients moved on to a subsequent line of therapy, due to: relapse in 26 patients, toxicity in one patient, and autologous transplant in one patient.

Duration of response

In 71 patients who achieved an objective response (≥PR), of whom 41 remain in ongoing remission and 3 who died before a relapse event and 27 experienced a relapse, median DOR was 10.3 months (95% CI, 7.7-not estimable), Figure 3. At 6 months and at 12 months following the date of best response, cumulative incidences of relapse were 31% (95% CI, 19.2%-43.4%) and 54.2% (95% CI, 37%-68.6%), respectively.

Table 1.

Baseline Patient, Disease, and Treatment Characteristics of the Total Cohort

Baseline Characteristics			Total Cohort, n = 107 (100%)
Patient	Age (y)	(median, IQR)	69, 61–77
	Months since Dx	(median, IQR)	54, 37–84
	Sex	Male	68 (63.5%)
		Female	39 (36.5%)
	Performance status	0–1	86 (80.4%)
		2–3	20 (18.7%)
		NK	1 (0.9%)
	Comorbidities	Median (IQR)	(3, 2–4)
	CCI score	CCI <4	66 (61.7%)
		CCI ≥4	41 (38.3%)
	Anemia	Yes	82 (76.6%)
	Hypercalcemia	Yes	12 (11.2%)
	(eGFR < 60 mL/min)	Yes	46 (43%)
Disease	MM subtype	Ig (G/A/M/D)	83 (77.6%)
		Light chain	24 (22.4%)
		Nonsecretory	0 (0%)
	Elevated LDH	Yes	37 (34.6%)
		NK	37 (34.6%)
	ISS staging	1	24 (22.4%)
		2	33 (30.8%)
		3	28 (32.9%)
		NK	22 (20.6%)
	Cytogenetics	High risk (HR)	15 (14%)
		Standard risk (SR)	47 (43.9%)
		NK	45 (42.1%)
	R-ISS staging	1	7 (6.5%)
		2	23 (21.5%)
		3	11 (10.3%)
		NK	66 (61.7%)
	Amyloidosis	Yes	1 (0.9%)
	PCL	Yes	1 (0.9%)
	EM disease	Yes	16 (14.9%)
Prior therapies	Number of therapies	Median (IQR)	3 (3–3)
	Prior transplant	Yes	65 (60.7%)
	Prior alkylator	Yes	106 (99.1%)
	Prior PI	Yes	106 (99.1%)
	Prior IMiD	Yes	107 (100%)
	Prior anti-CD38	Yes	5 (4.7%)
	Prior HDACi	Yes	4 (3.7%)
IsaPomDex	Number of	Median (IQR)	7 (3–13)
	IsaPomDex cycles	<7	52 (48.6%)
		≥7	55 (51.4%)
	IsaPom ongoing	Yes	52 (48.6%)
	Pomalidomide dose	Yes	49 (45.8%)
	reduction	No	58 (54.2%)
	Dex dose reduction	Yes	55 (51.4%)
	Antiviral PPx	Yes	99 (92.5%)
	Antifungal PPx[a]	Yes	87 (82.1%)
	PCP PPx[a]	Yes	56 (52.8%)

High-risk cytogenetics is defined as one or more of the following features: t(4;14), t (14;16), del(17p).
[a]Antifungal and PCP PPx status was not known in one patient.
CCI = Charlson Comorbidity Index; Dex = dexamethasone; Dx = diagnosis; EM = extramedullary; HDACi = histone deacetylase inhibitor; IQR = interquartile range; IMiD = immunomodulatory drug; IsaPomDex = isatuximab with pomalidomide and dexamethasone; ISS = international staging system for MM; MM = multiple myeloma; NK = not known; PCP = pneumocystis pneumonia; PI = proteasome inhibitor; PPx = prophylaxis; R-ISS = revised ISS staging; WHO PS = performance status.

Overall survival

Median OS for the total cohort was 18.8 months (95% CI, 14.4-NR), Figure 4. Overall survival probability at 3 months was 88.4% (95% CI, 80.4%-93.2%) at 6 months 77.6% (95% CI, 67.9%-84.7%), at 9 months 69.5% (95% CI, 59.1%-77.8%),

Table 2.

IsaPomDex Treatment Status and Reasons for Discontinuation in the Total Cohort, in Age Subgroups and in Comorbidity Subgroups: Data Presented as % or n (%)

IsaPomDex Treatment Status	Total Cohort (n = 107) 100%	Age Subgroups (y)*			Comorbidity Subgroups*	
		<65 (n = 37)	65–74 (n = 37)	≥75 (n = 33)	CCI < 4 (n = 66)	CCI ≥ 4 (n = 41)
Ongoing	52 (48.6%)	13 (35.1%)	19 (51.4%)	20 (60.6%)	30 (45.5%)	22 (53.7%)
Discontinued*	55 (51.4%)	24 (64.9%)	18 (48.6%)	13 (39.4%)	36 (54.5%)	19 (46.3%)
Discontinuation reason*						
Death	16 (15%)	9 (24.3%)	2 (5.41%)	5 (15.2%)	9 (13.6%)	7 (17.1%)
PD	33 (30.8%)	12 (32.4%)	15 (40.5%)	6 (18.2%)	23 (34.9%)	10 (24.4%)
Toxicity	2 (1.9%)	1 (2.7%)	0 (0%)	1 (3%)	1 (1.5%)	1 (2.4%)
NK	2 (1.9%)	0 (0%)	1 (2.7%)	1 (3%)	1 (1.5%)	1 (2.4%)

*One patient discontinued IsaPomDex due to ischaemic stroke and one patient discontinued IsaPomDex due to autologous stem cell transplant (ASCT).
CCI = Charlson Comorbidity Index; IsaPomDex = isatuximab with pomalidomide and dexamethasone; NK = not known; PD = progressive disease.

Table 3.

Response Rates to IsaPomDex Therapy in the Total Cohort, in Age Subgroups and in Comorbidity Subgroups: Data Presented as % or n (%).

Response to IsaPomDex	Total Cohort (n = 107)	Age Subgroups (y)			Comorbidity Subgroups	
		<65 (n = 37)	65–74 (n = 37)	≥75 (n = 33)	CCI < 4 (n = 66)	CCI ≥ 4 (n = 41)
ORR	71 (66.4%)	23 (62.2%)	27 (73%)	21 (63.6%)	45 (68.2%)	26 (63.4%)
Best response						
≥VGPR	34 (31.8%)	10 (27%)	15 (40.5%)	9 (27.3%)	21 (31.8%)	13 (31.7%)
PR	37 (34.6%)	13 (35.1%)	12 (32.4%)	12 (36.4%)	24 (36.4%)	13 (31.7%)
SD	17 (15.9%)	3 (8.1%)	8 (21.6%)	6 (18.2%)	10 (15.2%)	7 (17.1%)
PD	16 (15%)	10 (27%)	2 (5.4%)	4 (12.1%)	10 (15.2%)	6 (14.6%)
NK	3 (2.8%)	1 (2.7%)	0 (0%)	2 (6.1%)	1 (1.5%)	2 (4.9%)

CCI = Charlson Comorbidity Index; IsaPomDex = isatuximab with pomalidomide and dexamethasone; NK = unknown; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

and at 12 months 65% (95% CI, 53.9%-74%). Cause of the 38 death events experienced in this cohort were as follows: PD (21), infections (12), multiorgan failure (1), upper GI hemorrhage (1), subdural hemorrhage (1), cardiac arrest (1), and not known (1).

Median OS by age was (<65: 18.9 versus 65–74: 22.7 versus ≥75: 14.4, log-rank $P = 0.2163$) Suppl. Figure S1-A, and by comorbidities CCI subgroups (<4:18.6 versus ≥4: 15, log-rank $P = 0.6164$). Median OS was inferior in patients with eGFR

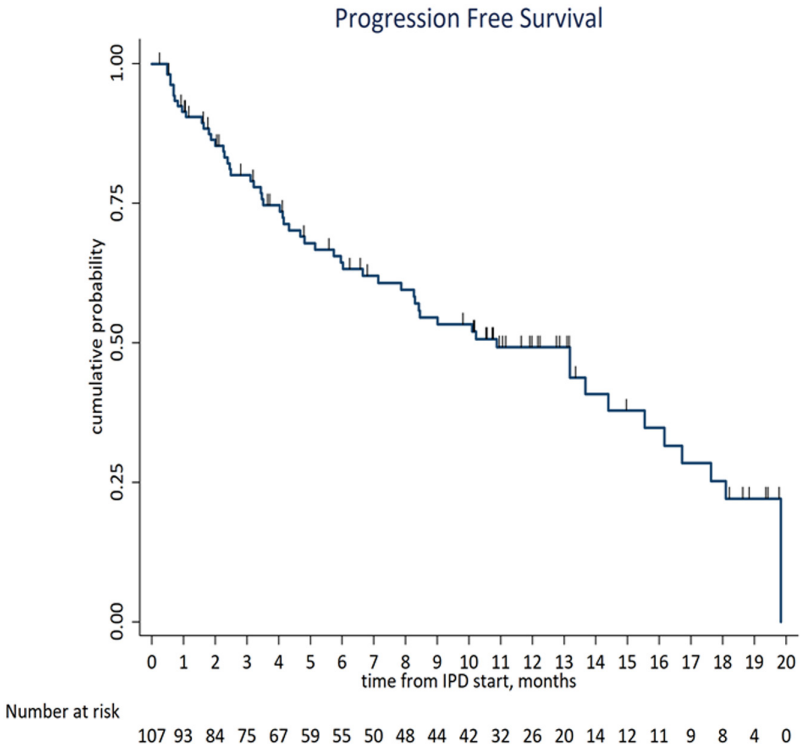

Figure 1. PFS in the total cohort. IPD = isatuximab with pomalidomide and dexamethasone; PFS = progression-free survival.

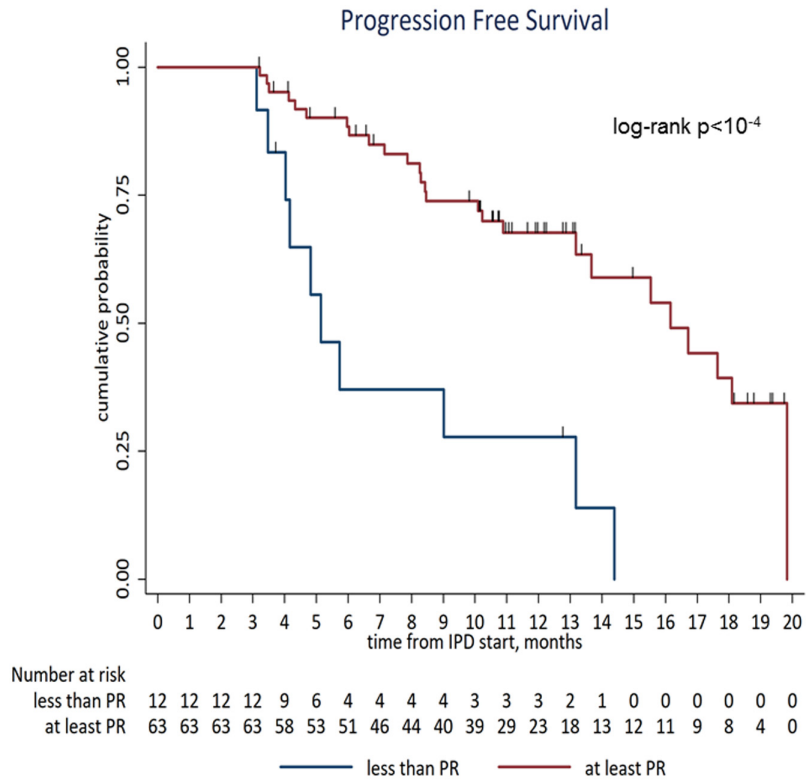

Figure 2. PFS 3-month landmark analysis by myeloma response (<PR vs ≥PR). IPD = isatuximab with pomalidomide and dexamethasone; PFS = progression-free survival; PR = partial response.

renal impairment (≥60: 22.7 versus <60: 14.4 mo, log-rank *P* = 0.048), Suppl. Figure S1-B.

Adverse events

Data on AEs were evaluable in all 107 patients and are presented here after a median number of cycles (IQR) of 4 (2–8), and a median follow up (IQR) of 3.7 months (0.5–12.4). The median (range) of all-grade (1–5) AEs per patient in the total cohort was 2 (1–9) for those who experienced them. The most common any grades AEs (experienced by ≥10% of patients) were neutropenia (65.4%), thrombocytopenia (23.4%), infections (23.4%), anemia (15.9%), and fatigue (10.3%), and are presented in Table 4.

The number of patients who experienced one or more hematological AE was 79 (73.8%). The number of patients who experienced one or more nonhematological AE was 60 (56.1%).

The total number of all ≥G3 AEs in the total cohort was 119; experienced by a total of 67 patients (ie, 62.6% of patients experienced at least one ≥G3 AE). The most common ≥G3 AEs (experienced by ≥10% of patients) were neutropenia (45.8%), infections (18.7%), and thrombocytopenia (14%) and are presented in Table 4.

After a median (IQR) of 4 cycles (2–8), 23.4% of patients experienced ≥1 any grade (G2–5) infection (total of 31 episodes) and 18.7% of patients experienced ≥1 high-grade (≥G3) infection (total of 22 episodes). Median time (IQR) from start of therapy to first episode was 29 days (16–75). The nature of the 22 high-grade (≥G3) infections were as follows: COVID-19 pneumonia (G4 = 2, G5 = 4), neutropenic sepsis (G3 = 1, G4 = 2, G5 = 2), *E. coli* infection (G4 = 2), urinary tract infection (G3 = 3), lung infection (G3 = 2), serratia liquefaciens infection (G5 = 1), pseudomonas sepsis (G4 = 1), bacteremia (G3 = 1), and skin infection (G3 = 1). Vaccination statuses during diagnosis with the 6 COVID-19 infections were as follows: not vaccinated (n = 5) and fully vaccinated (n = 1). The cumulative duration of infection-related hospitalizations was 159 days in the total cohort. Infection was the only statistically significant variable in the univariate analysis (UVA), associated with hospital admissions (odds ratio: 138.2).

The total number of all ≥G3 hematological AEs in the total cohort was 80; experienced by a total of 57 patients (ie, 53.2% of patients experienced at least one ≥G3 hem AE). For those patients, the median (range) number of ≥G3 hematological AEs was 1 (1–4).

Seven patients (6.5%) experienced an isatuximab infusion reaction, which was a low grade (G1) in all cases and did not lead to inpatient admission or treatment delays/discontinuations.

Sixty-three patients (58.9%) required neutrophil support with GCSF. Eleven patients (10.3%) required one or more platelet transfusions, with a median (range) of 1 (1–10) transfusion. Twenty-two patients (20.6%) required one or more RBC transfusions, with a median (range) of 1 (1–7) transfusion.

Twenty-four patients (22.4%) experienced one or more AEs leading to one or more inpatient admission, with a median (range) of 1 (1–4) AE per patient. The median (range) duration of hospitalization per patient was 8 (1–21) days. The cumulative number of hospitalization days related to AEs in the total cohort was 207 days.

DISCUSSION

Our study presents the first-reported real-world dataset on the clinical outcomes of IsaPomDex therapy in RRMM patients. We evaluated the UK-wide experience with this novel triplet therapy across 24 hematology treatment centers. Understanding the usage and outcomes of IsaPomDex in clinical practice is important for myeloma clinicians to optimize clinical outcomes, while improving tolerability, and to establish whether trial efficacy outcomes are observed in routine care.

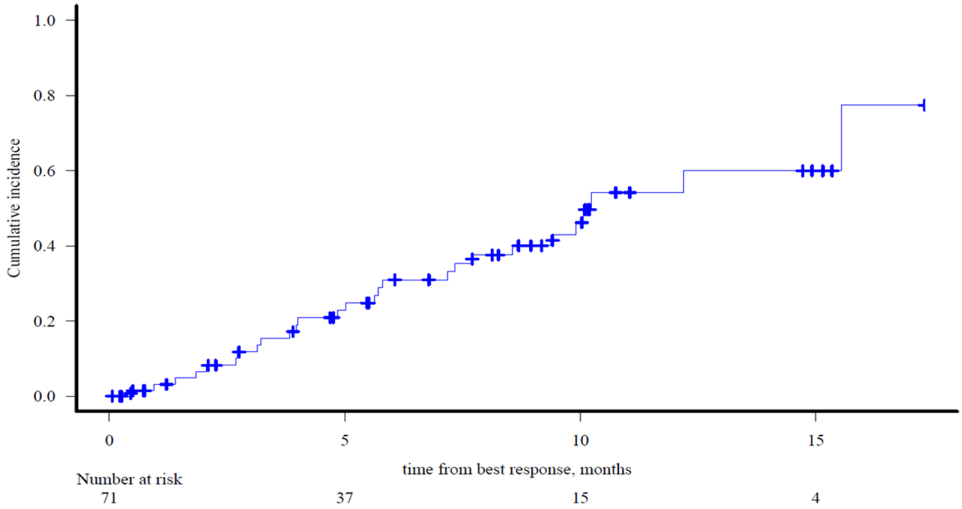

Figure 3. DOR to IsaPomDex, presented as cumulative incidence of relapse for responding patients (≥PR), from time of best response to time of myeloma relapse. DOR = duration of response; PR = partial response.

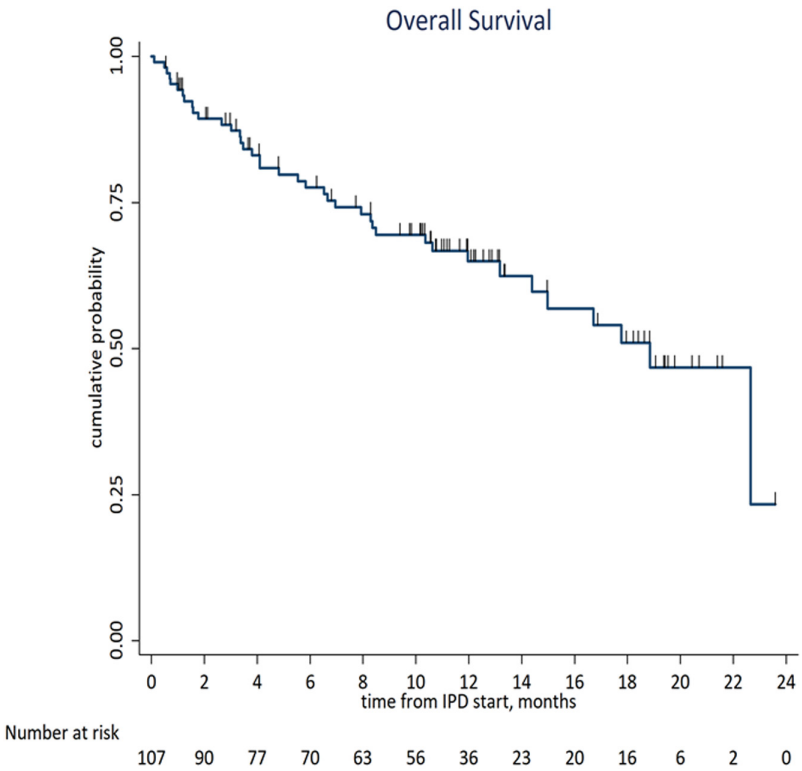

Figure 4. OS in the total cohort. IPD = isatuximab with pomalidomide and dexamethasone; OS = overall survival.

Median follow of 12.1 months in our cohort of 107 patients is comparable to a median follow up of 11.6 months from the first-interim analysis reporting ICARIA-MM trial results in 2019.[4]

Baseline characteristics in this cohort are comparable to trial data for median age (69 versus 68 y), renal impairment (eGFR<60 mL/min: 43% versus 39%), ISS III staging (32.9% versus 27%), high-risk cytogenetics (14% versus 16%), median number of prior therapies (3 versus 3), and the nature of prior therapies.[4]

Our study demonstrated numerically higher discontinuation rates in the youngest subgroup (<65 y) and those with a lower CCI score (CCI < 4), with two potential explanations. First, follow up was shorter in the older group (10.3 mo in ≥75 y, 12.7 mo in 65–74 y, 13.3 mo in <65 y group). As a result, more patients belonging to older age groups remained on treatment at data cutoff, considering that PFS did not differ significantly among the 3 groups. Likewise, CCI ≥ 4 subgroup had 11.2 months median follow up compared with 12.7 months in the CCI < 4 subgroup and PFS was also similar between the 2 CCI subgroups. Another consideration is that more patients in the younger groups had been exposed to more intensive therapy before IsaPomDex (such as previous high-dose therapy/ASCT) and, given that median time from diagnosis to IsaPomDex treatment was similar across age groups (Kruskal-Wallis,

Table 4.

AEs Experienced by ≥10% of Patients During IsaPomDex Therapy in the Total Cohort, After a Median of 4 Cycles of Treatment

		Total Cohort Evaluable for AEs, n = 107 (100%)			
		Incidence (Number of Events)		% of Patients	
AEs Experienced by ≥10% of Patients		Any grade (G1–5)	≥G3 (G3–5)	Any grade (G1–5)	≥G3 (G3–5)
Blood and lymphatic system AEs	Neutropenia	71	50	70 (65.4%)	49 (45.8%)
	Thrombocytopenia	25	15	25 (23.4%)	15 (14%)
	Anemia	22	14	17 (15.9%)	9 (8.4%)
Infections	Infections	31	22	24 (23.4%)	20 (18.7%)
General AEs	Fatigue	11	1	11 (10.3%)	1 (0.9%)

AEs = Adverse events.

P = 0.92 for the 3 age groups comparison and Mann-Whitney, *P* = 0.69 for comparison between <75 and ≥75 y), we can surmise that younger patients with more aggressive disease were more likely to be selected by clinicians for novel anti-CD38 combination therapy IsaPomDex.

We observed an ORR rate of 66.4% with 31.8% of patients experiencing ≥VGPR. These data are comparable to ICARIA-MM trial, which demonstrated an ORR of 60% with a ≥VGPR rate of 27%.[4] These results are encouraging because the trial ORR was observed in the real world. This can be partly explained by the restricted approval in the United Kingdom of IsaPomdex to third-relapse patients only.

The median PFS reported in our study is also consistent with trial data (10.9 versus 11.5 mo).[4] Our data showed no difference in PFS outcomes according to the different age subgroups (<65 y versus 65–74 versus ≥75, *P* = 0.4157). This is also consistent with age subgroup analyses of ICARIA-MM, which demonstrated that median PFS outcomes were statistically higher in all age groups who received IsaPomDex compared with those who received PomDex, but there was no difference in median PFS between the different IsaPomDex age subgroups (<65 y: 11.53 versus 65–74: 11.57 versus ≥75: 11.4 mo).[7]

Subgroup analysis of the ICARIA-MM trial showed consistent PFS benefit of the IsaPomDex regimen over PomDex, irrespective of renal impairment at baseline.[8] However, patients with renal impairment (eGFR < 60 and more so if eGFR < 45) had numerically inferior median PFS within the IsaPomDex arm of the trial (no renal impairment: 12.7 mo; eGFR < 60: 9.5 mo, eGFR < 45: 7.5 mo).[8] Within our cohort of IsaPomDex-treated patients, renal impairment was also associated with inferior PFS, with statistical significance. The adverse effect of renal impairment on PFS duration appears more accentuated in our study, likely as a result of the inclusion of more patients with more severe kidney disease (one-fifth of our cohort had stage 3b or worse, and stage ≥4 (eGFR <30) was documented in 8 of the 107 patients in our IsaPomDex cohort compared to only 2 of the 307 patients in the whole ICARIA-MM trial with 1 patient in each of the 2 arms IsaPomDex and PomDex).

Our study is the first to investigate the influence of comorbidities (by CCI score) on ORR and on PFS outcomes of IsaPomDex. Patients with severe comorbidities achieved numerically but not statistically lower ORR (CCI < 4: 68.2% versus CCI ≥ 4:63.4%, *P* = 0.535), and no statistically significant difference in median PFS (<4: 10.2 mo versus ≥4: 13.2, log-rank *P* = 0.6531).

ICARIA-MM trial team have recently published their longer follow-up data (median follow up of 35.3 mo), and this demonstrated a median OS of 24.6 months in the IsaPomDex group.[9] We report a median OS of 18.8 months, which is lower than ICARIA-MM trial, but this may be explained by a number of reasons. First, our data are less mature with shorter median follow up of 12.1 months, compared with a longer OS follow up in ICARIA-MM. More significantly, real-world analyses such as our study, include patients who would not meet trial eligibility criteria because of multiple comorbidities, which can contribute to death events during the treatment period, in addition to death events due to myeloma PD. Furthermore, real-world studies such us ours included some patients who have a more aggressive disease presentation, who may not be eligible for trial entry.

After a median of 4 cycles of treatment, the incidence rate of any grade neutropenia was lower in our cohort (65.4% versus 96%), while ≥G3 was 45.8%, compared with ICARIA-MM (G3: 23% and G4: 61%). Any grade thrombocytopenia was lower in our study (23.4% versus 84%), while ≥G3 was 14% which is comparable to trial data (G3: 15%, G4: 16%). The high incidence of neutropenia and thrombocytopenia in our cohort led to the usage of GCSF and platelet transfusions in 58.9% and 10.3% of patients, respectively. This is comparable to ICARIA-MM, which reported usage of GCSF in 69% of patients. However, this lower incidence of AEs compared with trial data needs to be interpreted with caution because of the relatively short-median follow up of our AE data. In addition, within the trial, blood counts were checked mid cycle, which is not reflected in routine care. Another possible explanation of the lower rate of AEs is the potential under-reporting of AEs during data collection for this real-world data.

Our study reported a lower incidence rate of isatuximab infusion reactions compared with ICARIA-MM (6.5% and all G1 versus 38%). This may be explained either by the effective institution of premedication before isatuximab in the real world, including the use of montelukast, or the under-reporting of low-grade infusion reactions.

Our data demonstrated significant infection-related morbidity from IsaPomDex (any grade: 23.4%, ≥G3: 18.7%). Therefore, a careful assessment and infection risk stratification are required before starting this therapy, to rationalize the use of anti-infective prophylaxis and limit infection episodes, particularly those leading to hospital admissions. Optimal vaccination strategies are also very important to reduce infections.[10]

Close monitoring and dose adjustments when required, are crucial for the long-term management of AEs related to this therapy, and for maintaining patients on treatment, particularly those who have already achieved an optimal myeloma response, or those presenting with frailty, advanced age, or significant comorbidity burden.

Our study is limited by its retrospective, nonrandomized nature with the inherent possibility of unmeasured confounding factors, patient selection bias, the potential for medical chart misinterpretation, reporting of toxicities, and lack of quality of life data. Despite these limitations, we demonstrated encouraging ORR and PFS results of this therapy in the real world at a median of 12.1-month follow up, and we described in detail AE outcomes and their impact on healthcare resources after a median of 4 cycles.

CONCLUSION

To our knowledge, this is the first nationwide study to describe IsaPomDex outcomes in the real world. It demonstrated

encouraging ORR and PFS outcomes in RRMM in the routine care setting after 12.1 months follow up, and these were comparable to ICARIA-MM trial data. However, close monitoring and dose adjustments when required, are crucial measures in order to manage toxicities and to maintain patients on therapy.

ACKNOWLEDGMENTS

We thank all participating sites in this study.

AUTHOR CONTRIBUTIONS

FD designed and led the study, contributed to the set up of the OpenClinica online data collection platform, co-ordinated the study across the United Kingdom, collected, analyzed, and curated data. GV executed the set up the OpenClinica platform. FP conducted statistical analysis. AR collected and analyzed data. IT collected and analyzed data. All other authors collected data for each of their respective hospital sites. FD wrote the article, which all authors critically reviewed and approved.

DISCLOSURES

FD received honoraria for education evening for hematologists from Sanofi. SB received honoraria and advisory board from Sanofi. KR received honoraria and advisory board from Sanofi and research support, honoraria, advisory board, and travel support from BMS. All other authors have no conflicts of interest to declare.

REFERENCES

1. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet*. 2016;387:1551–1560.
2. Richardson PG, Beksaç M, Špička I, et al. Isatuximab for the treatment of relapsed/refractory multiple myeloma. *Expert Opin Biol Ther*. 2020;20:1395–1404.
3. National Institute for Health and Care Excellence. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma. 2020. Available at: https://www.nice.org.uk/guidance/TA658. Accessed June 22, 2021.
4. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394:2096–2107.
5. Zweegman S, Engelhardt M, Larocca A. Elderly patients with multiple myeloma: towards a frailty approach? *Curr Opin Oncol*. 2017;29:315–321.
6. Shah JJ, Abonour R, Gasparetto C, et al. Analysis of common eligibility criteria of randomized controlled trials in newly diagnosed multiple myeloma patients and extrapolating outcomes. *Clin Lymphoma Myeloma Leuk*. 2017;17:575–583.e2.
7. Schjesvold FH, Richardson PG, Facon T, et al. Isatuximab plus pomalidomide and dexamethasone in elderly patients with relapsed/refractory multiple myeloma: ICARIA-MM subgroup analysis. *Haematologica*. 2021;106:1182–1187.
8. Dimopoulos MA, Leleu X, Moreau P, et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. *Leukemia*. 2021;35:562–572.
9. Richardson PG, Perrot A, San-Miguel J, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. *Lancet Oncol*. 2022;23:416–427.
10. Djebbari F, Panitsas F, Eyre TA, et al. Infection-related morbidity in a large study of transplant non-eligible newly diagnosed myeloma patients treated with UK standard of care. *Haematologica*. 2020;105:e474–e479.