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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

ISATUXIMAB (SARCLISA)

(Sanofi Genzyme)

Indication: In combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Final
Publication Date:	April 1, 2021
Report Length:	98 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
ASCT	autologous stem cell transplant
BOR	best overall response
CAR-T	chimeric antigen receptor T-cell therapy
CCO	Cancer Care Ontario
CI	confidence interval
CMRG	Canadian Myeloma Research Group
CR	complete response
CyBorD	cyclophosphamide plus bortezomib plus dexamethasone
DOR	duration of response
DVd	daratumumab plus bortezomib plus dexamethasone
ECOG PS	European Cooperative Oncology Group performance status
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
FISH	fluorescent in situ hybridization
G-CSF	granulocyte colony stimulating factor
GHS	global health status
HR	hazard ratio
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IQR	interquartile range
IRC	independent response committee
IsaPd	isatuximab plus pomalidomide plus dexamethasone
ISS	International Staging System
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous

Kd	carfilzomib plus dexamethasone
K-M	Kaplan-Meier
mAb	monoclonal antibody
LDH	lactate dehydrogenase
MC	Myeloma Canada
MCID	Minimal clinically important difference
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
ORR	overall response rate
OS	overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
Pd	pomalidomide plus dexamethasone
PD	progressive disease
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PI	proteasome inhibitor
PO	oral
PRO	patient-reported outcome
PVd	pomalidomide plus bortezomid plus dexamethasone
QoL	quality of life
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-MY20	Quality of Life Questionnaire Myeloma Module with 20 items
QoL	quality of life
Rd	lenalidomide plus dexamethasone
R-ISS	Revised International Staging System
RRMM	relapsed and refractory multiple myeloma
RVd	lenalidomide plus bortezomib plus dexamethasone
SOC	System Organ Class
SPM	secondary primary malignancy

TEAE	treatment-emergent adverse event
TTP	time to progression
VAS	visual analogue scale
Vd	bortezomib plus dexamethasone
VGPR	very good partial response
VMP	bortezomib plus melphalan plus prednisone
WDAE	withdrawal due to adverse event

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding isatuximab (Sarclisa) in combination with pomalidomide and dexamethasone for the treatment of patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the safety and efficacy of isatuximab (Sarclisa), in combination with pomalidomide (Pomalyst) and dexamethasone (generics), for the treatment of patients with RRMM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

On April 29, 2020 Health Canada issued marketing authorization without conditions for isatuximab in combination with pomalidomide and dexamethasone (IsaPd), for the treatment of patients with RRMM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI). The reimbursement request aligns with the Health Canada indication.

According to the product monograph,[1] isatuximab is an IgG1-derived monoclonal antibody (mAb) that binds to a specific extracellular epitope of CD38 and triggers several mechanisms leading to the death of CD38 expressing tumour cells. CD38 is a transmembrane glycoprotein with ectoenzymatic activity outside of the cell membrane and is expressed in hematological malignancies including multiple myeloma (MM). Isatuximab targets tumour cells through IgG Fc-dependent mechanisms including antibody dependent cell mediated cytotoxicity, antibody dependent cellular phagocytosis, and complement dependent cytotoxicity. Isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism. In vivo experiments have demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumour activity compared to the activity of isatuximab or pomalidomide alone.

The recommended dose of isatuximab is 10 mg/kg body weight administered as an IV infusion in combination with pomalidomide and dexamethasone. Each treatment cycle is a 28-day period, where the dosing schedule of IsaPd is weekly for cycle 1 (Days 1, 8, 15 and 22) and biweekly for cycle 2 and beyond (Days 1 and 15).[1] Treatment is repeated until disease progression or unacceptable toxicity. Premedication (i.e., dexamethasone, acetaminophen, an H2 antagonist, and diphenhydramine) should be administered prior to isatuximab infusion to reduce the risk and severity of infusion-related reactions.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial (RCT) was identified that met the selection criteria of the review. ICARIA-MM is an ongoing, open-label, randomized, phase III trial of IsaPd, compared to the combination of pomalidomide plus dexamethasone (Pd) in patients with refractory or RRMM who had received at least two prior lines of therapy that included lenalidomide and a proteasome inhibitor (PI). The study recruited adults ≥ 18 years of age who had documented measurable disease (via serum or urine monoclonal protein).[2] Enrolled patients must have failed treatment that included at least two consecutive cycles of lenalidomide and a PI (i.e., bortezomib,

carfilzomib, ixazomib), given alone or in combination. Treatment failure was defined as disease progression on or within 60 days after discontinuing treatment, disease progression within six months after achieving at minimum a partial response (PR), or drug intolerance. Additionally, patients were required to be refractory to the last received line of treatment. The trial aimed to include two categories of patients who progressed on or within 60 days after end of last treatment: a) refractory disease; and b) relapsed and refractory disease. Patients with primary refractory disease were excluded; all patients must have achieved a minimal response or better to at least one prior line of treatment. Enrolled patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. Prior treatment with an anti-CD38 monoclonal antibody was permitted, if the disease was not refractory to the treatment. Prior pomalidomide treatment was not permitted.[2]

Eligible patients were randomized in a 1:1 ratio to receive either IsaPd or Pd in 28-day cycles until occurrence of disease progression or unacceptable toxicity. Patients who entered the study were followed until death, consent withdrawal, or the data cut-off date for overall survival (OS), whichever occurred first. Dosing regimens for the IsaPd group consisted of: isatuximab 10mg/kg intravenously (IV) weekly (Day 1, 8, 15, 22) for the first cycle then every two weeks (Day 1 and 15) thereafter; pomalidomide 4 mg orally daily for the first three weeks (Day 1 to 21); and dexamethasone 40 mg (20 mg if ≥ 75 years) orally or IV weekly (Day 1, 8, 15, 22). The Pd regimen consisted of pomalidomide 4 mg orally daily for the first three weeks (Day 1 to 21) and dexamethasone 40 mg (20 mg if ≥ 75 years) orally or IV weekly (Day 1, 8, 15, 22).[2] Routine medications consisting of acetaminophen, ranitidine, diphenhydramine, and dexamethasone were given to patients in the IsaPd group for at least the first four administrations to reduce the risk and severity of infusion-related reactions associated with isatuximab. All patients received either aspirin or low molecular weight heparin for venous thromboembolism prophylaxis, unless there was an excess risk of bleeding.[2]

The study enrolled 307 patients, with 154 patients randomized to IsaPd and 153 patients randomized to Pd. Randomization was stratified by number of previous lines of treatment (2 to 3 vs. 3) and age (< 75 vs. ≥ 75 years). Efficacy analyses for the primary and secondary endpoints were conducted by a blinded independent response committee (IRC), and progressive disease (PD) was defined according to the International Myeloma Working Group (IMWG) criteria.[2]

The primary efficacy outcome was progression-free survival (PFS) by IRC assessment and according to IMWG criteria. Key secondary endpoints included overall response rate (ORR) by IRC assessment and OS. ORR was defined as patients who achieved a best overall response (BOR) of partial response (PR) or better according to the IMWG response criteria. Additional exploratory secondary endpoints, such as time to progression (TTP), duration of response (DOR), and PFS in the high risk cytogenetic population were also analyzed.[2] Several exploratory endpoints (e.g., time to first response, time to best response, ORR based on investigator assessment, very good partial response rate, minimal residual disease) were also investigated.[3] Subgroup analyses for numerous potential prognostic factors and/or treatment effector modifiers, as well as sensitivity analyses using different censoring and event rules for PFS were performed, most of which were prespecified.[2]

Patient enrolment occurred over approximately 13 months (January 10, 2017 to February 2, 2018). Two data cut-off dates were specified in this study: October 11, 2018 for efficacy analyses and November 22, 2018 for safety analyses.[4] At the October 11, 2018 data cut-off date for efficacy analyses (final PFS and interim OS analyses), the median duration of follow-up was 11.6 months. At that time, 47 patients (30.5%) in the IsaPd group and 63 patients (41.2%) in the Pd group had discontinued from the trial completely, mostly due to death.[2,3]

The median age of enrolled patients was 67 years; the majority were White (79.5%) and had an ECOG PS of 0 or 1 (89.6%). Most patients at study entry had International Staging System (ISS) Stage I (37.5%) or II (35.5%) disease; according to the revised International Staging System (R-ISS), most patients had Stage II disease (64.2%). All patients enrolled into the study had relapsed and refractory disease, and the median number of previous lines of treatment was three. One patient (0.3%) in the IsaPd group, received prior treatment with an anti-CD38 mAb (daratumumab).[4] There were some notable differences in baseline demographics and characteristics between treatment groups. Overall, more patients in the IsaPd group, compared to the Pd group, were older (65 to 74 years: 44.2% vs. 35.3%; <65 years: 35.1% vs. 45.8%), male (57.8% vs. 45.8%), with ECOG PS of 1 (53.9% vs. 44.4%). There was a slightly higher proportion of patients with renal impairment in the IsaPd group (38.7% vs. 33.8%). More patients in the IsaPd group also had ISS Stage I disease at study entry (41.6% vs. 33.3%) and fewer patients had high risk cytogenetic abnormalities (15.6% vs. 23.5%).[4,5] At the time of efficacy data cut-off, 42.2% of patients (n=65) in the IsaPd group were still receiving treatment and 26.0% (n=40) were in follow-up. In the Pd group, 22.9% of patients (n=35) were still receiving treatment, whereas 33.3% (n=51) were in follow-up.[3] Treatment was discontinued mostly due to progressive disease. Notably, the median duration of treatment was

different between IsaPd (41 weeks) and Pd (24 weeks). After assigned study treatment, a greater proportion of patients in the Pd group received subsequent systemic anti-cancer therapy than those in the IsaPd group (39.0%; n=60 IsaPd vs. 54.2%; n=83 Pd; November 22, 2018 data cut-off). In particular, daratumumab was administered to more patients in the Pd group (3.9%; n=6 vs. 29.4%; n=45 Pd).[5]

Analysis of all efficacy parameters were conducted in the intention-to-treat (ITT) population. Only the primary efficacy endpoint of PFS and key secondary endpoints of ORR and OS were part of the statistical testing hierarchy. The safety analysis included patients who received at least one partial or full dose of study medication, and patients were analyzed according to the actual treatment received. Patient-reported outcomes (PROs) were measured as part of secondary endpoints. The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and the accompanying Myeloma Module with 20 questions (EORTC QLQ-MY20) were used to measure health-related quality of life (HRQoL). Health status utility scores were obtained through the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L). Analysis of PRO endpoints were performed in the safety population, in patients who had completed the baseline assessment plus at least one assessment post-baseline.[2]

Efficacy

The key outcomes of the ICARIA-MM trial is provided in Table 1. As of the data cut-off date (October 11, 2018), the trial met its primary endpoint of PFS, which showed improvement in the IsaPd group compared to the Pd group. In total, 73 patients (47.4%) in the IsaPd group and 89 patients (58.2%) in the Pd group had experienced disease progression or died, and the corresponding stratified hazard ratio (HR) for disease progression or death was 0.596 (95% confidence interval [CI], 0.44 to 0.81; p=0.001). The median IRC-assessed PFS was longer in the IsaPd group at 11.53 months compared to 6.47 months in the Pd group.[4] Multiple sensitivity analyses were performed for PFS and they showed consistent results with the primary analysis. Subgroup analyses for PFS were also generally consistent with the results for the ITT population, with almost all HR estimates favouring treatment with IsaPd.[5]

The key secondary endpoint of IRC-assessed ORR, according to the IMWG response criteria, was higher in patients who were randomized to IsaPd (60.4%, n=93) compared to patients in the Pd group (35.3%, n=54), with a stratified Cochrane-Mantel-Haenszel (CMH) p-value of < 0.0001.[5] At the efficacy data cut-off date, 99 patients had died, including 43 patients (27.9%) in the IsaPd group and 56 patients (36.6%) in the Pd group. Median OS was not reached in either treatment group. The interim analysis data did not demonstrate a statistically significant difference between the two treatment groups, with a stratified HR of 0.687 (95% CI, 0.46 to 1.02; p=0.0631, one-sided significance level of 0.0008). The estimated probability of survival at 12 months was 72% and 63% in the IsaPd and Pd groups, respectively.[5] The final analysis of OS data was planned for after 220 deaths have occurred. Results for other secondary endpoints such as time to progression (TTP) and duration of response (DOR) also supported the primary endpoint, showing favourable results for IsaPd. Specifically, the median IRC-assessed TTP was 12.71 months in the IsaPd group and 7.75 months in the Pd group. The median IRC-evaluated DOR, assessed in patients who achieved a response of PR or better (i.e., 93 and 54 patients randomized to IsaPd and Pd, respectively), was 13.27 months in the IsaPd group and 11.07 months in the IsaPd group.[5]

Overall, multiple measures of HRQoL did not meet the pre-specified minimal clinically important difference (MCID) from baseline in either treatment group. Scores were maintained in both groups during treatment for all functional and symptom scales of the EORTC-QLQC30, subscales of EORTC QLQ-MY20, and EQ-5D-5L health state utility values and visual analogue scale (VAS) scores.[4,6] The lack of clinically meaningful differences from baseline in each treatment group suggest no improvement or detriment in HRQoL and related symptoms with either IsaPd or Pd.

Safety

Compared to the Pd group, patients randomized to IsaPd experienced more dose reductions of pomalidomide (42.8% vs. 24.2%) and dexamethasone (32.9% vs. 25.5%). The addition of isatuximab to pomalidomide and dexamethasone also resulted in more treatment cycle delays (57.9% vs. 43.0%) as well as longer cycle delays (> 7 days; 34.9% vs. 17.4%) which may be indicative of a less tolerable side effect profile of the three-drug combination. The triplet therapy also resulted in greater incidence of adverse events (AEs); treatment-emergent adverse event (TEAEs) of any grade were reported in a similar proportion of patients, but serious and

severe TEAEs were reported in more patients treated with IsaPd (Table 1).[3,5] A greater proportion of patients treated with IsaPd also experienced a TEAE (all grades, serious, and severe) deemed to be caused by at least one of the study drugs. The higher incidence of TEAEs in the IsaPd group did not contribute to increased discontinuation of study treatment, although individual agents in the treatment combination were prematurely discontinued due to a TEAE in more patients compared to the Pd group (9.2% vs. 2.0%).[4] Most TEAEs were manageable and reversible.[5]

The following TEAEs of any grade were reported at an incidence of 10% or greater, and more frequently (i.e., ≥ 5%) in patients treated with IsaPd compared to Pd: neutropenia (46.7% vs. 33.6%), infusion-related reaction (36.8% vs. 1.3%), upper respiratory tract infection (28.3% vs. 17.4%), diarrhea (25.7% vs. 19.5%), bronchitis (23.7% vs. 8.7%), dyspnea (15.1% vs. 10.1%), nausea (15.1% vs. 9.4%), vomiting (11.8% vs. 3.4%) and febrile neutropenia (11.8% vs. 2.0%). Grade ≥ 3 TEAEs reported in at least 10% of patients, and more frequently (i.e., ≥ 5%) in the IsaPd group were neutropenia (46.1% vs. 32.2%) and febrile neutropenia (11.8% vs. 2.0%).[4] The most common serious TEAEs (of all grades), reported in at least 3% of patients and with a higher incidence in the IsaPd group were: urinary tract infections (3.9% vs. 1.3%), neutropenia (3.3% vs. 1.3%), febrile neutropenia (6.6% vs. 2.0%), pathological fracture (3.3% vs. 2.0%), and infusion-related reactions (3.9% vs. 0.7%).[4]

Of TEAEs deemed related to treatment, the most commonly reported (i.e., ≥ 10%) and with an incidence of 5% or higher in the IsaPd group were: neutropenia (42.8% vs. 32.2%), infusion related reaction (36.2% vs 0.0%), upper respiratory tract infection (9.9% vs 4.4%), and febrile neutropenia (10.5% vs 2.0%).[5] The most commonly reported (i.e., ≥ 5%) treatment-related Grade ≥ 3 TEAEs, with an incidence of 5% or higher in the IsaPd group were: neutropenia (42.1% vs. 30.9%) and febrile neutropenia (10.5% vs. 2.0%).[5] Treatment-related serious TEAEs reported most frequently (i.e., ≥ 2%) in the IsaPd group were pneumonia (9.9%), febrile neutropenia (6.6%), infusion related reaction (3.9%), neutropenia (2.0%), pulmonary embolism (2.0%), and thrombocytopenia (2.0%).[6]

At the safety data cut-off date of November 22, 2018, nine patients had died due to a TEAE; three patients (2.0%) in the IsaPd group and six patients (4.0%) in the Pd group.[4] Fatal TEAEs were thought to be related to study treatment one patient (0.7%) in the IsaPd group, due to sepsis, and two patients (1.3%) in the Pd group, due to pneumonia and urinary tract infection.[4]

Limitations

Overall, the ICARIA-MM trial was well-designed, though there were some concerns with the conduct of the trial that could limit the interpretation and generalizability of the results. In terms of strengths, the randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. Eligibility criteria were well defined and appropriate. The study population characteristics overall reflect a heavily pre-treated patient population who would be eligible for treatment with IsaPd or Pd in Canada. The populations used for analyses were appropriate, with the key efficacy analyses conducted according to the ITT principle. However, there are a few key limitations and potential sources of bias that were noted by the CADTH Methods Team, as summarized below:

- Due to the open-label study design, the investigators and patients were aware of the treatment allocation. It is possible that due to this knowledge of the assigned treatment, the trial results may be at risk for biases related to the lack of blinding which can affect the measurement and reporting of outcomes. Accordingly, the results may be biased in favour of the IsaPd group compared to the Pd group. This could be particularly important in the reporting of subjective outcomes (e.g., adverse effects, patient-reported symptoms and outcomes) by the patients and care providers. However, efficacy endpoints were measured by a central, blinded independent review committee to reduce investigator bias.[2]
- The final analysis of OS, a key secondary outcome, was scheduled for after 220 deaths which have yet to occur (99 deaths had occurred by the data cut-off date, corresponding with 45% information fraction). Median survival was also not reached in either treatment group.[5] Although there was a non-statistically significant trend towards longer OS in patients randomized to IsaPd, current OS data are immature and reflect the interim analysis; therefore, longer follow-up of survival data is required to appropriately characterize the long-term effects of adding isatuximab to pomalidomide and dexamethasone.
- During the study follow-up period, patients were permitted to receive subsequent treatment for RRMM, which included daratumumab, lenalidomide, and PIs. The decision to administer subsequent treatment after disease progression and the choice of treatment was up to the investigator's discretion.[2] In an unblinded trial setting, the choice of subsequent therapy may be

influenced by the treatment recieved in the study. The impact of this bias is unknown. Overall, a higher proportion of patients randomized to the control arm received subsequent therapy (39.0% Isa Pd vs. 54.2% Pd).[5] This may confound the assessment of OS by prolonging survival beyond what would have occurred strictly with study treatment and overestimating survival benefit. The higher proportion of patients receiving subsequent treatment would also be expected to favour the Pd group.[5]

- To account for interim analyses as well as key secondary endpoints, the overall type 1 error rate was appropriately controlled using a closed test procedure. There were several subgroup analyses and secondary efficacy outcomes assessed in the trial that were not adjusted to account for multiple comparison testing to control the risk of type 1 error.[2] The trial was not powered to test specific hypotheses in these subgroups and outcomes; therefore, results of the subgroup analyses should be interpreted as exploratory in nature. Similarly, analyses of secondary endpoints (other than ORR and OS), and exploratory endpoints were not adjusted for multiplicity; these results may be considered as supplemental to the primary and key secondary endpoints but should also be interpreted with caution. Although pre-specified and a secondary endpoint in the trial, PRO measures were not adjusted for multiplicity and no statistical testing was done to compare within or between group differences; thus, results should only be considered descriptive and exploratory.
- Hematologic abnormalities, such as neutropenia and thrombocytopenia, were captured as both laboratory results as well as reports from investigators; however, only serious hematologic AEs or those which led to study treatment modification or discontinuation were documented as an AE (i.e., only those deemed clinically significant by the investigators). Similarly, abnormal serum chemistry values were only recorded as an AE if they were serious or led to modification or discontinuation of study treatment. Investigator bias may result in underreporting of these adverse events.[4]

Table 1: Highlights of Key Outcomes

Key Outcomes	ICARIA-MM	
	IsaPd	Pd
Efficacy Outcomes – ITT Population	**N=154**	**N=153**
Primary – PFS		
Median, months (95% CI)	11.53 (8.94 to 13.90)	6.47 (4.47 to 8.28)
Events, n (%)	73 (47.4)	89 (58.2)
Stratified HR (95% CI)*	0.596 (0.44 to 0.81)	
p-value	0.001	
Key Secondary – ORR‡		
Responders – PR or better, n	93	54
Responders – PR or better, % (95% CI)	60.4 (52.20 to 68.17)	35.3 (27.75 to 43.42)
p-value	< 0.0001	
Key Secondary – OS†		
Median, months (95% CI)	NR	NR
Events, n (%)	43 (27.9)	56 (36.6)
Stratified HR (95% CI)*	0.687 (0.46 to 1.02)	
p-value†	0.0631	
Secondary – TTP		
Median, months (95% CI)	12.71 (11.20 to 15.21)	7.75 (5.03 to 9.76)
Events, n (%)	62 (40.3)	78 (51.0)
Secondary – DOR		
Median, months (95% CI)	13.27 (10.61 to NR)	11.07 (8.54 to NR)
Events, n (%)§	32 of 93 (34.4)	19 of 54 (35.2)
HRQoL	**N=152**	**N=149**

Key Outcomes	ICARIA-MM	
	IsaPd	Pd
EORTC QLQ-C30 (GHS/QoL, functional scales, symptom scales)		
MCID: 10 points	No difference from baseline	No difference from baseline
EORTC QLQ-MY20 (functional scales, symptom scales)		
MCID: 10 points	No difference from baseline	No difference from baseline
Harms Outcomes, n (%)	**N=152**	**N=149**
TEAE¶ (any grade)	151 (99.3)	146 (98.0)
Treatment-related TEAE (any grade)	138 (90.8)	119 (79.9)
Grade ≥ 3 TEAE	132 (86.8)	105 (70.5)
Treatment-related grade ≥3 TEAE	109 (71.7)	71 (47.7)
Serious TEAE	94 (61.8)	80 (53.7)
Treatment-related serious TEAE	54 (35.5)	24 (16.1)
WDAE (one component)	14 (9.2)	3 (2.0)
WDAE (all components)	11 (7.2)	19 (12.8)
Grade 5 AE#	11 (7.2)	13 (8.7)
Deaths due to drug-related adverse event	1 (0.7)	2 (1.3)

AE = adverse event; CI = confidence interval; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-MY20 = Myeloma Module with 20 questions; GHS = global health status; HR = hazard ratio, HRQoL= health-related quality of life; ITT = intention-to-treat; NR = not reached; MCID = minimal clinically important difference; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; TEAE = treatment-emergent adverse events; TTP = time to progression; WDAE = withdrawal due to adverse event.

* HR < 1 favours IsaPd; stratification factors include number of prior lines of treatment (2 to 3 vs. 3) and age (< 75 vs. ≥ 75 years).
‡ ORR defined as partial response or better (i.e., stringent complete response, complete response, very good partial response, partial response) as best overall response, according to the IMWG response criteria.
† OS results represent data from first interim analysis. Based on 45% information (99 of 220 anticipated deaths), the multiplicity-adjusted one-sided significance level was 0.0008.
§ DOR was determined only for patients who achieved a response of PR or better.
¶ TEAEs were defined as AEs that developed, worsened, or became serious during the treatment period (i.e., time from administration of first dose to the last dose of study treatment, plus 30 days).
# Includes patients with any Grade 5 TEAE with fatal outcome during the treatment period as well as patients with any TEAE that worsened to Grade 5 during the post-treatment period (i.e., with fatal outcome during the post-treatment period). According to the sponsors, a Grade 5 TEAE is an adverse event that occurred or worsened during treatment period and led to death during the treatment period, regardless of cause. The number of patients with Grade 5 TEAE include all who died during the treatment period, whatever the cause, and had a TEAE is reported in the electronic case report form.
Data cut-off date: October 11, 2018 for efficacy outcomes, November 22. 2018 for harms outcomes.
Source: FDA Multi-disciplinary Review;[4] Checkpoint Meeting Materials, October 28, 2020 (Sanofi-Genzyme),[3] EPAR report;[5] CADTH Submission, Clinical Summary[7]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient group, Myeloma Canada (MC), provided input on isatuximab for the treatment RRMM in patients who had received at least two prior lines of therapies that included lenalidomide and a PI. MC obtained the input from Canadian patients through several patient surveys conducted in June and July 2020.

From the patient perspective, infections, kidney problems, and pain were the most common symptoms of MM; additionally, mobility, neuropathy, shortness of breath, and fatigue were reported to largely impact the daily lives of patients and their overall quality of life (QoL). In addition to physical symptoms, patients indicated that MM also affects QoL by significantly impacting work life, travel, and the ability to exercise and volunteer. MC indicated that living with MM has many financial implications for patients that include drug costs, loss of income due to absence of work, and parking costs for medical appointments. The majority of patients surveyed (60%) had received at least two prior lines of therapies including lenalidomide and bortezomib, carfilzomib, or ixazomib; and some patients

(14%) had used or were using Pd. Patient respondents indicated that they wanted to avoid all side effects of treatment; however, they cited confusion, infection, and pain as the symptoms they wanted most to avoid. Patients indicated that they wanted treatment options for MM that improve their overall QoL, with minimal side effects; and emphasized that various treatment options need to be available to improve patient prognosis and QoL. Most patients (88%) responded that when taking a drug or considering taking a MM drug it is “very important” that it improved their overall QoL.

Six patient respondents had direct experience with IsaPd. Patients reported QoL was improved on the regimen and that it was effective in controlling their disease. According to patients, the most common intolerable side effects of IsaPd included respiratory infections, anemia, and cold-like symptoms.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of isatuximab in combination with pomalidomide and dexamethasone:

Clinical factors:

- Place in therapy and sequencing with currently available treatments
- Addition to or switch from ongoing therapies
- Prior use of daratumumab

Economic factors:

- Mixed administration of IV and oral drugs
- High cost barrier

Registered Clinician Input

Two registered clinician inputs were provided on behalf of two clinicians from Ontario Health-Cancer Care Ontario Hematology Cancer Drug Advisory Committee (CCO) and 15 clinicians from the Canadian Myeloma Research Group (CMRG) for the review of IsaPd for the treatment of RRMM in patients who have received at least two prior therapies including lenalidomide and a PI.

Both clinician groups cited Pd and carfilzomib plus dexamethasone (Kd) as currently available treatments for RRMM in Canada, and that cyclophosphamide can be added to Pd treatment. In most provinces, patients whose disease is refractory to both lenalidomide and bortezomib are not eligible for publicly funded daratumumab.

CCO and CMRG clinicians considered the eligibility criteria of the ICARIA-MM pivotal trial to be reasonable and applicable to Canadian clinical practice; however, both groups indicated that there should not be restrictions based on renal function or blood counts. Unlike the pivotal trial, in clinical practice there is no requirement for patients to have measurable myeloma markers or less than grade one prior toxicity. Clinicians noted that IsaPd offers favourable efficacy results with a low rate of treatment-related AEs leading to treatment discontinuation, and is a regimen that has good tolerability, offers an oral component for ease of administration, and can be used in patients with renal insufficiency. The clinicians cited that the potential harms of the combination include the contraindication of a prior severe rash with lenalidomide, as there may exist some cross-reactivity with pomalidomide. Patients with a prior history of frequent sino-pulmonary infections requiring antibiotics may be at higher risk of developing upper respiratory tract infections and may warrant additional precautions at the time of initiation of IsaPd.

Both clinician groups indicated that IsaPd is an ideal therapy for patients with significant unmet need, which includes patients whose disease has progressed after both bortezomib and lenalidomide treatment and are ineligible for daratumumab. The clinicians from CMRG noted that IsaPd yields a PFS benefit in lenalidomide-refractory patients; and in Ontario, these patients do not currently have any funded access to an anti-CD38 mAb therapy, and they are currently ineligible for new immunotherapy treatments available through clinical trials. The clinicians also stated that currently there are a relatively small proportion of Canadian patients on lenalidomide plus bortezomib and dexamethasone (RvD) for RRMM; and patients who receive daratumumab with bortezomib plus dexamethasone (Dvd) until progression would not be eligible for IsaPd as a third line therapy. Access to IsaPd at next progression would be important for patients not previously treated with daratumumab. The clinicians stated that for patients currently on Pd (+/-

cyclophosphamide) who have not experienced disease progression, the addition of isatuximab, if not otherwise previously treated with daratumumab, would be optimal. Accordingly, the clinicians predicted that should IsaPd be reimbursed it would most likely replace Pd, Pd in combination with cyclophosphamide, and Kd due to the inability of using both pomalidomide and carfilzomib in the same patient.

Summary of Supplemental Questions

Summary and critical appraisal of a sponsor-submitted indirect treatment comparison (ITC) / network meta-analysis (NMA)

In the absence of direct evidence comparing IsaPd and Kd for the treatment of RRMM who have been exposed to two prior therapies (including lenalidomide and a PI), the sponsor submitted an unadjusted and unanchored ITC comparing the two treatments in this patient population. Two trials were included in the ITC: the ICARIA-MM trial provided individual patient-level data for IsaPd and the ENDEAVOR trial provided aggregate data for treatment with Kd in the analysis of OS. Published median values were used in the analysis of PFS.[7] Although statistical comparisons between the treatments were provided for these key outcomes, inherent limitations to the unanchored and unadjusted approach used in the ITC leads to a high level of uncertainty in the results. The heterogeneity in the patient populations of the two trials, particularly surrounding important treatment effect modifiers relating to prior treatment history (i.e., number and types of prior lines of therapy received) and prognostic factors have the potential to severely bias and limit the generalizability of the results. As such, no conclusions can be made regarding the comparative efficacy of IsaPd and Kd based on the submitted ITC, and its results should be interpreted with caution.

See Section 7 for more information.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of Generalizability of Evidence for IsaPd for RRMM

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(ICARIA-MM Trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Organ dysfunction</td><td>The entry criteria for the ICARIA-MM trial required patients to have adequate liver and renal function, as well as adequate hematological lab values as follows:
AST and/or ALT ≤ 3x ULN
Total bilirubin ≤ 2 ULN
CrCl ≥ 30 mL/min
ANC ≥ 1 x 10^9/L
PLT ≥ 75 x 10^9/L if < 50% of BM nucleated cells are plasma cells and ≥ 30 x 10^9/L if ≥ 50% of BM nucleated cells are plasma cells</td><td>Does the exclusion of patients with organ dysfunction or suboptimal hematological lab values limit the interpretation of the trial results with respect to the target population?</td><td>The exclusion of this presumed “higher risk” patient population may in principal inflate the outcomes of the ICARIA-MM trial. It is unknown to what degree this might occur; however, there is a precedence from previous registration studies. In clinical practice, one might expect to use IsaPd if the organ dysfunction and/or suboptimal lab values are deemed related to the underlying myeloma.</td></tr>
<tr><td>Age</td><td>Patients were enrolled in the trial if they were ≥18 years old.

Age groups of patients enrolled in the trial:<table><tr><th></th><th>IsaPd
n=154</th><th>Pd
n=153</th><th>Total
n=307</th></tr><tr><td>Median (range)</td><td>68 (36 to 83)</td><td>66 (41 to 86)</td><td>67 (36 to 86)</td></tr><tr><td><65</td><td>54 (35.1%)</td><td>70 (45.8%)</td><td>124 (40.4%)</td></tr><tr><td>65-74</td><td>68 (44.2%)</td><td>54 (35.3%)</td><td>122 (39.7%)</td></tr><tr><td>≥75</td><td>32 (20.8%)</td><td>29 (19.0%)</td><td>61 (19.9%)</td></tr></table>Subgroup analyses for age groups:
The trial results are reported by each age group (prespecified subgroup analysis, but exploratory in nature). For patients ≥75 years of age, there were 15/32 PFS events in the IsaPd group and 19/29 in the Pd group; HR 0.479 (95% CI, 0.24 to 0.95).</td><td>Are the overall findings from the ICARIA-MM trial generalizable to patients who are age ≥75 years old?</td><td>Yes, the findings of the trial can be generalized to patients who are age ≥75 years.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(ICARIA-MM Trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Response to prior treatment (intolerance)</td><td>To enrol in the ICARIA-MM trial, patients must have failed treatment with lenalidomide and a PI. Definition of failure included intolerance. Specifically, patients were considered to have failed therapy if intolerable toxicity developed after a minimum of two consecutive cycles of a treatment regimen containing lenalidomide and a PI, alone or in combination. Intolerable toxicity was considered as:
PI-containing regimens: any toxicity leading to discontinuation of PI. For symptoms of peripheral neuropathy, severity must be ≤ grade 1 prior to study entry.
Lenalidomide-containing regimens: any toxicity leading to discontinuation of lenalidomide. For rash or non-hematologic toxicity, severity must not have been grade 4. All non-hematologic toxicities must be ≤ grade 1 prior to study entry.
Details for patients who experienced intolerance are as follows:<table><tr><th></th><th>IsaPd
n=154</th><th>Pd
n=153</th><th>Total
n=307</th></tr><tr><td>Intolerance to lenalidomide</td><td>10 (6.5%)</td><td>12 (7.8%)</td><td>22 (7.2%)</td></tr><tr><td>Intolerance to PI</td><td>19 (12.3%)</td><td>21 (13.7%)</td><td>40 (13.0%)</td></tr><tr><td>Intolerance to lenalidomide and PI</td><td>4 (2.6%)</td><td>4 (2.6%)</td><td>8 (2.6%)</td></tr></table></td><td>Are the trial results generalizable to patients who were intolerant to lenalidomide and/or PI?</td><td>Yes, the results can be generalized to patients who were intolerant to lenalidomide and/or PI. One might expect the overall intolerant cohort to have an even better response to IsaPd than those who have progressed on lenalidomide and a PI.</td></tr>
<tr><td></td><td>Prior therapy</td><td>Patients were enrolled in the trial if they had received at least two prior lines of treatment, including at least two consecutive cycles of lenalidomide and a PI, given alone or in combination. Patients must also have failed on treatment with lenalidomide and a PI.

All patients received prior lenalidomide, PI, and a steroid. Most patients received alkylating agents (93.5%).

Select prior antimyeloma drugs:<table><tr><th></th><th>IsaPd
n=154</th><th>Pd
n=153</th></tr><tr><td>PIs, n (%)</td><td></td><td></td></tr><tr><td>Bortezomib</td><td>150 (97.4)</td><td>150 (98.0)</td></tr><tr><td>Carfilzomib</td><td>34 (22.1)</td><td>44 (28.8)</td></tr><tr><td>Ixazomib/ixazomib citrate</td><td>19 (12.3)</td><td>13 (8.5)</td></tr></table></td><td>Do the proportions of prior anti-myeloma therapies received by patients (and refractory status to different treatment) in the trial limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice patients)?</td><td>No. Data from the trial show that the IsaPd combination is effective in a diverse set of clinical scenarios.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(ICARIA-MM Trial)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>IMiDs, n (%)</td><td></td><td></td></tr>
<tr><td>Lenalidomide</td><td>154 (100)</td><td>153 (100)</td></tr>
<tr><td>Pomalidomide</td><td>1 (0.6)</td><td>0</td></tr>
<tr><td>Thalidomide</td><td>70 (45.5)</td><td>71 (46.4)</td></tr>
<tr><td>mAbs, n (%)</td><td></td><td></td></tr>
<tr><td>Daratumumab</td><td>1 (0.6)</td><td>0</td></tr>
<tr><td>Elotuzumab</td><td>1 (0.6)</td><td>2 (1.3)</td></tr>
</table>
Refractory status:
<table>
<tr><th></th><th>IsaPd
n=154</th><th>Pd
n=153</th></tr>
<tr><td>Refractory to IMiD, n (%)</td><td></td><td></td></tr>
<tr><td>Lenalidomide</td><td>144 (93.5)</td><td>140 (91.5)</td></tr>
<tr><td>Refractory to PI, n (%)</td><td></td><td></td></tr>
<tr><td>Bortezomib</td><td>95 (61.7)</td><td>89 (58.2)</td></tr>
<tr><td>Carfilzomib</td><td>28 (18.2)</td><td>40 (26.1)</td></tr>
<tr><td>Ixazomib</td><td>17 (11.0)</td><td>13 (8.5)</td></tr>
<tr><td>Refractory to IMiD and PI, n (%)</td><td></td><td></td></tr>
<tr><td>Lenalidomide and bortezomib</td><td>89 (57.8)</td><td>82 (53.6)</td></tr>
<tr><td>Lenalidomide and carfilzomib</td><td>26 (16.9)</td><td>39 (25.5)</td></tr>
<tr><td>Lenalidomide and ixazomib</td><td>17 (11.0)</td><td>11 (7.2)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Setting</td><td>Regional and racial/ethnic differences in countries participating in the trial</td><td>
The ICARIA-MM trial is being conducted at 102 sites in 24 countries, enrolling patients from Europe, North America, and Asia-Pacific regions. There were five patients treated at three Canadian sites, all of which are located in the province of Quebec.[8]
Patient enrolment from different geographical regions are as follows:
<table>
<tr><th></th><th>IsaPd
n=154</th><th>Pd
n=153</th><th>All
n=307</th></tr>
<tr><td>Western Europe</td><td>55 (35.7%)</td><td>76 (49.7%)</td><td>131 (42.7%)</td></tr>
<tr><td>Eastern Europe</td><td>28 (18.2%)</td><td>20 (13.1%)</td><td>48 (15.6%)</td></tr>
<tr><td>North America</td><td>7 (4.5%)</td><td>5 (3.3%)</td><td>12 (3.9%)</td></tr>
<tr><td>Asia</td><td>21 (13.6%)</td><td>15 (9.8%)</td><td>36 (11.7%)</td></tr>
<tr><td>Other Countries</td><td>43 (27.9%)</td><td>37 (24.2%)</td><td>80 (26.1%)</td></tr>
</table>
The race of patients enrolled in the study are as follows:
</td><td>Most patients were enrolled from Europe; is there a known difference in practice patterns that might yield a different result in a Canadian setting?

Is there a known difference in effect based on race or ethnicity that might yield a different result in a Canadian setting?</td><td>The Canadian RRMM patient population is more racially and ethnically diverse than the population studied in the ICARIA-MM trial. Therefore, the racial/ethnic profile of the study population is not fully representative of the Canadian RRMM patient population and underrepresents many minority groups. However, trial results are still generalizable to all Canadian RRMM</td></tr>
</table>

Domain	Factor	Evidence (ICARIA-MM Trial)	Generalizability Question	CGP Assessment of Generalizability
		See nested table below		patients. Please see Section *6.3.2.1 Detailed Trial Characteristics - e) Limitations/Sources of Bias* for further details on generalizability of the ICARIA-MM trial population to the Canadian MM patient population.

	IsaPd n=154	Pd n=153	All n=307
White	118 (76.6%)	126 (82.4%)	244 (79.5%)
Asian	21 (13.6%)	15 (9.8%)	36 (11.7%)
Black or African American	1 (0.6%)	3 (2.0%)	4 (1.3%)
Native Hawaiian or Other Pacific Island	2 (1.3%)	1 (0.7%)	3 (1.0%)
Missing/NR	12 (7.8%)	8 (5.2%)	20 (6.5%)

ASCT = autologous stem cell transplant; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; BM = bone marrow; CGP = clinical guidance panel; CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; IMiD = immunomodulatory drug; IsaPd = isatuximab plus pomalidomide plus dexamethasone; mAb = monoclonal antibody; NR = not reported; PAG = Provincial Advisory Group; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; PI = proteasome inhibitor; PLT = platelet; ULN = upper limit of normal.

Source: Attal et al., 2019;[2] EPAR;[5] Clinical Study Report;[6] CADTH Submission, Clinical Summary;[7] CADTH Submission, Pre-submission Form[8]

1.2.4 Interpretation

Effectiveness

The ICARIA-MM trial was the only study identified by the CADTH systematic review that evaluated the effectiveness of isatuximab compared to current standard of care in RRMM.[2] ICARIA-MM was a high-quality, randomized, multicentre, open-label, phase III RCT conducted at 102 hospitals in 24 countries in Europe, North America, and Asia-Pacific regions. The study sought to evaluate the efficacy of the triple therapy of isatuximab with pomalidomide and dexamethasone – IsaPd (experimental group) as compared with double therapy of pomalidomide and dexamethasone – Pd (control group), in patients with RRMM who had received at least two prior lines of therapy that included lenalidomide and a PI. Prior treatment with an anti-CD38 mAb was permitted in the trial, as long as patients were not refractory to the treatment. In Canada, Pd is commonly used and currently considered an effective standard of care therapy for RRMM.

The primary endpoint of the ICARIA-MM study was PFS, which is considered an accepted and valid endpoint in this patient population, as determined by an IRC and assessed in the ITT population. The secondary endpoints assessed included the number of patients who achieved an overall response, OS, TTP, DOR, PFS in the high-risk cytogenetic population, HRQoL, and safety.

There were 307 patients enrolled between January 10, 2017 and February 2, 2018 where 154 and 153 were assigned to the experimental and control groups, respectively. Key patient characteristics were balanced in both study groups and reflect the characteristics of patients with RRMM seen in Canadian clinical practice. Notably, 20% of the study population were ≥75 years of age and 19.5% had high-risk cytogenetics (del(17p), t(4;14), and t(14;16)) by fluorescent in situ hybridization (FISH)[4]. There was only one patient in the trial, in the IsaPd group, who had previous exposure to a mAb (i.e., daratumumab).

At a median follow-up of 11.6 months (interquartile range [IQR], 10.1 to 13.9), the median PFS was 11.53 months (95% CI, 8.94 to 13.90) in the IsaPd group versus 6.47 months (95% CI, 4.47 to 8.28) in the Pd group (HR= 0.596; 95% CI, 0.44 to 0.81; p=0.001), which represents a clinically meaningful five month difference in PFS in favour of IsaPd. Additionally, the results of all prespecified subgroup analyses of PFS in relevant clinical populations (i.e., age, disease stage, renal dysfunction, high-risk cytogenetics, prior therapies, and refractoriness to prior therapies) were in favour of the IsaPd group.

The trial data on OS remain immature but the results of the interim analysis showed an OS of 72% versus 63% at 12 months in favour of the IsaPd group (not statistically significant). All other secondary efficacy endpoints (i.e., IRC-assessed ORR, DOR, and TTP) examined also favoured IsaPd over Pd, demonstrating consistency of the treatment effect of IsaPd. HRQoL was measured in the trial using appropriate, validated myeloma scales, and the results did not meet the prespecified MCID thresholds for these measures over time from baseline in either treatment group.

Safety

Infusion reactions (36.8% vs. 1.3% all grades) and upper respiratory infections (28.3% vs. 17.4% all grades) were the most frequent AEs reported in the IsaPd group. The infusion reactions were reversible with the majority occurring with the first dose. Other notable AEs (all grades) that occurred more frequently in the IsaPd group included investigator-reported neutropenia (46.7% vs. 33.6%), bronchitis (23.7% vs. 8.7%), vomiting (11.8% vs. 3.4%), and febrile neutropenia (11.8% vs. 2.0%). All other AEs such as laboratory assessed hematologic toxicity, GI toxicity, and fatigue were otherwise balanced between the groups. A greater proportion of patients treated with IsaPd experienced serious or severe treatment-related AEs; however, the higher incidence of these AEs in the IsaPd group did not contribute to increased discontinuation of study treatment. Taken together, while the three-drug regimen of IsaPd is expected to be associated with more toxicity compared to Pd, the CGP considers the toxicities of IsaPd to be clinically manageable and not deemed of enough concern to refrain from using IsaPd.

Need

Given that patients with myeloma will eventually relapse, further therapy will be required. The treatment choice(s) available are complex and dependent on 1) prior therapies and responses, 2) side effects, 3) patient comorbidities/frailty, 4) funding, and 5) individual preferences. Moreover, it remains unclear how the relative contributions of such factors influence eventual treatment choice(s).

While the optimal sequencing of myeloma therapies remains elusive, the opportunity for more options and choice for therapy in an incurable disease is critical, from both a survival and psychosocial perspective. Indeed, historical population studies demonstrate improvements in survival[9,10] with the introduction and availability of newer agents in myeloma.

Additionally, in the absence of curative therapy, the presence and access of a "new" agent in myeloma is not considered a replacement for another approved and/or available agent. Rather, new agents are additional therapeutic options that can be utilized in combination with relatively older myeloma agents to optimize the chemotherapeutic care. In principle, the treating clinician should be afforded as many effective chemotherapeutic options as possible.

1.3 Conclusions

The CGP concluded that there is a net overall clinical benefit to IsaPd in the treatment of patients with RRMM who have received at least two prior therapies including lenalidomide and a PI. This conclusion was based on one high-quality RCT that demonstrated a statistically significant and clinically meaningful benefit in PFS for IsaPd compared with Pd, no clinically meaningful changes in HRQoL, and similar AE profiles between IsaPd and Pd.

In making this conclusion, the CGP considered the following factors:

- Similarity of the ICARIA-MM trial population with the Canadian population, and the current treatment landscape.
- Pertinent disease subgroups (i.e., older patients and those with high-risk cytogenetics) deriving clinical benefit with IsaPd.
- Maintenance of HRQoL with IsaPd
- Manageable safety profile of IsaPd

Data from the ICARIA-MM trial need to be considered in the context of current standard of care in Canada that includes daratumumab in combination with dexamethasone and either lenalidomide (DRd) or bortezomib (DVd), which are currently the predominant second-line treatment options for RRMM. Although the eligibility criteria of the ICARIA-MM trial allowed for the inclusion of patients with prior exposure (but who were not refractory) to daratumumab, which has a similar mechanism of action as isatuximab, only one patient with prior anti-CD38 mAb exposure was enrolled in the trial. As a result, the sequencing of isatuximab after at least two prior lines of therapy that includes daratumumab is unclear. Provincial funding of daratumumab is dependent on sensitivity to either bortezomib or lenalidomide where it must be used in a triple combination. The CGP considers IsaPd an appealing treatment option for patients with MM that is refractory to both bortezomib and lenalidomide without prior exposure to daratumumab; this subgroup of patients currently has no provincially funded opportunity to receive a mAb. Although difficult to quantify with certainty, the CGP estimates approximately 10% to 15% of the RRMM patient population are lenalidomide and bortezomib refractory without prior exposure to daratumumab; however, the CGP suspects that this subgroup of patients will diminish over time and this would suggest that the use of IsaPd may also decline over time.

Several questions were raised by the PAG, if IsaPd were to be recommended for reimbursement, specifically with respect to the eligible patient population, implementation factors, and sequencing of available treatments. The CGP's responses to these questions are summarized in Table 3. For the CGP's assessment of generalizability (external validity of the ICARIA-MM trial evidence related to specific factors), refer to Table 2 in Section 1 of this report.

Following the posting of the pERC Initial Recommendation, the CGP reviewed and discussed the feedback that was received by eligible stakeholder groups. The patient advocacy group (MC), one clinician group (CCO DAC), and the PAG all agreed with the pERC Initial Recommendation to conditionally reimburse IsaPd (upon cost-effectiveness being improved and budget impact being addressed) and supported early conversion to a Final Recommendation; while the sponsor agreed in part with the Initial Recommendation but did not support early conversion. As the sponsor's feedback was focused on the economic evaluation of IsaPd, their feedback is addressed in the pharmacoeconomic report. The CGP has provided a response to PAG's feedback related to the sequencing of IsaPd in patients who have progressed on PVd. Refer to the relevant section of Table 3 (below) for the CGP's response to PAG's feedback.

Table 3: CADTH CGP Response to PAG Implementation Questions

PAG Implementation Questions	CGP Response
Eligible Patient Population	
In view of the characteristics of the patient population and exclusion criteria in the ICARIA-MM trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with IsaPd:	
• Patients with ECOG performance status greater than 2.	• Patients with an ECOG performance status greater than 2 may be eligible for IsaPd depending on clinical response and this should be determined for patients on an individual basis.
• Patients with primary amyloidosis.	• There are no data from the ICARIA-MM trial that support the use of IsaPd in this population since the trial excluded patients with primary amyloidosis.
• Patients with primary refractory MM.	• The inclusion criteria used in the ICARIA-MM trial enrolled patients with RRMM who had been treated with at least two previous lines of treatment and had not responded to therapy with lenalidomide and a PI (i.e., bortezomib, carfilzomib, or ixazomib) given alone or in combination. The trial defined non-response as progression on or within 60 days, intolerance to lenalidomide or the PI, or disease progression within six months of achieving at least a PR. Accordingly, primary refractory patients would potentially be eligible for treatment with IsaPd as long as they had not responded to therapy with lenalidomide and a PI given alone or in combination.
• Patients with free-light chain measurable disease only	• Light chain myeloma can be measured with serum free light chain assays. It is managed in the same fashion as other subtypes of myeloma. As a result, IsaPd should be considered for this subtype of myeloma.
PAG also seeks information on:	
• Whether patients with high-risk cytogenetics exhibit a distinct response to IsaPd and should be treated differently	• Patients with known high-risk cytogenetics [del(17p), t(4;14), or t(14;16) by FISH] comprised 19.5% of the trial population.[4] Based on subgroup analysis, these patients appear to respond equally well to IsaPd when compared to patients without high-risk cytogenetics. As such, IsaPd can be offered to patients with high-risk cytogenetics that otherwise fit the ICARIA-MM trial eligibility criteria.
• PAG identified a potential time-limited need for patients currently on Pd or Kd who have not progressed, and seeks guidance on whether they could be switched to IsaPd, adding isatuximab in the case of patients on Pd. In the latter scenario, PAG would like to know if a switch from Pd plus bortezomib (PVd) could also be allowed.	• If patients are eligible for IsaPd, then this could be a consideration upon progression or intolerance to Kd or PVd. Patients on Pd that meet the ICARIA-MM trial eligibility criteria could have isatuximab added to this regimen. This approach has been used with other myeloma regimens and would also be considered for future combinations as well. ○ PAG disagreed with sequencing IsaPd after progression on PVd as patients with prior treatment with pomalidomide were excluded from the ICARIA-MM trial: The ICARIA-MM trial excluded patients who received prior pomalidomide; therefore, there are no data from the trial to address sequencing IsaPd after progression on PVd. However, the CGP believe that while the value of IsaPd in patients who have demonstrated intolerance to or progressed on pomalidomide would be expected to be less, it would not be absent. There is biologic rationale for

PAG Implementation Questions	CGP Response
	repeating treatment that has failed previously or adding a new agent to a failing regimen at the time of progression. As noted by the CMRG registered clinician group, patients with myeloma have subclones at diagnosis that ebb and flow for predominance with different relapses, and these subclones may have different drug sensitivities. This observation underpins the clinical findings that a drug which stopped working previously may be effective again later in the disease course. As well, there is evidence that the addition of a new drug to a failing regimen at the time of disease progression (i.e., on demand) can restore responsiveness.[11,12] It is important to acknowledge that there is an unmet need for the small minority of patients who have never received an anti-CD38 therapy despite having received pomalidomide. The CGP believe it would be wrong if there is no opportunity for public access to an anti-CD38 therapy for this small population, which is likely to decrease over time, that is equally deserving of access to the same suite of therapeutic options. Additionally, many clinical trials in RRMM require potential participants to have failed an anti-CD38 therapy. Therefore, to not support access to isatuximab would subject the patient to a double penalty and this is inconsistent with patient-centred care.
Implementation Factors	
PAG is seeking guidance on treatment duration and discontinuation criteria.	• Treatment should be continued until there is clear evidence of progression (as per IMWG) and/or unacceptable toxicity. Whether treatment should be continued beyond biochemical progression in the absence of clinical progression is unclear. Consistent with current clinical practice, it is reasonable to allow the clinician/patient to continue in the absence of clinical progression, which should be determined for patients on an individual basis. In general, the time to next treatment from time of progression is less than six months.
PAG noted that the IMWG consensus criteria mention that response or progressive disease require confirmation with two consecutive readings of the applicable disease parameter using two discrete samples; PAG seeks guidance on whether this should be required in clinical practice.	• Two consecutive readings should be performed as per IMWG consensus criteria; however, determination of disease progression that requires a change in current therapy in individual patients should not be solely based on biochemical progression alone and must also consider other factors such as clinical progression.
PAG also seeks advice on the addition of cyclophosphamide upon biochemical progression.	• There are no data from the ICARIA-MM trial to support the addition of cyclophosphamide to IsaPd upon biochemical progression. However, it is reasonable for the clinician/patient to consider the addition of cyclophosphamide as “bridging” therapy to the subsequent line of therapy. The CGP believe that this a low cost and low risk treatment option that should be available on an individual basis.
PAG seeks guidance on dose reduction for isatuximab to mitigate infusion reactions, given dose modifications were not permitted in the trial.	• The CGP do not support dose reductions as a primary strategy to mitigate infusion reactions. Instead, other strategies such as the use of antihistamines, steroids and slowing the infusion time

PAG Implementation Questions	CGP Response
	should be promoted; this is because dose reductions will lead to decreased efficacy of isatuximab.
Sequencing and Priority of Treatments	
PAG is seeking to confirm the place in therapy of IsaPd and sequencing with other regimens for MM, including the scenarios below:	
• Overall optimal sequence of therapies that should be given prior to IsaPd.	• The optimal sequence of therapies remains unknown and is a moving target given treatment is individualized based on: ○ Patient factors ○ Disease factors ○ Evolving therapy options ○ Participation in clinical trials ○ Provincial funding of MM medications
• Patient factors justifying preferential use of IsaPd over Pd or Kd in the third line setting.	• There is no specific set of clinician-determined or patient factors that justify the preferential use of Pd or Kd in the third-line setting. However, it is reasonable to consider not using Kd in patients with significant history of cardiopulmonary dysfunction and neuropathy.
• Use of IsaPd after first line RVd and no other prior line of therapy. Would this be considered off-label?	• Although this population would not be eligible for the ICARIA-MM trial (i.e., due to less than two prior lines of therapy), IsaPd should be considered for patients resistant and refractory to lenalidomide and bortezomib, with no prior exposure to an anti-CD38 mAb therapy, regardless of the line of therapy.
• If RVd was used in first line, what second line therapies can be given before patients are considered eligible to IsaPd?	• Patients who previously received lenalidomide and/or bortezomib and discontinued these treatments prior to becoming resistant or refractory could be rechallenged with regimens containing these agents prior to receiving IsaPd. Whether it is preferable to use Kd before or after IsaPd is unknown and the timing of its use would be at the discretion of the treating physician based on individual patient need.
• Evidence on the use of isatuximab after failure of any daratumumab-containing therapy.	• The ICARIA-MM trial excluded patients who were refractory to previous therapy with an anti-CD38 mAb. As such, based on the ICARIA-MM trial, there is no evidence on the efficacy of isatuximab after failure of any daratumumab-containing therapy.
• Using IsaPd in patients who discontinued daratumumab in a prior line of therapy without evidence of progression, if all other eligibility criteria are met.	• The CGP would consider it clinically reasonable to use IsaPd in patients who discontinued daratumumab prior to progression or due to intolerance. This would be a minority of cases. In the ICARIA-MM trial there was only one enrolled patient in the IsaPd treatment group who had prior daratumumab.
• Evidence on the use of isatuximab after carfilzomib-containing regimens in the RRMM setting.	• In the ICARIA-MM trial, 25% of patients previously received carfilzomib.[6] The available subgroup data from the trial suggest that there is value in using IsaPd after carfilzomib.
• Addition of isatuximab to Pd upon biochemical progression on the latter.	• The ICARIA-MM trial did not enroll patients who had biochemical progression on Pd. As such, the value of this approach is unknown. Nonetheless, the CGP believes it would be reasonable to consider the addition of isatuximab in patients who are mAb naive in an effort to better control the patient's myeloma. This approach should be considered in patients on an individual basis.
• Options after failure of IsaPd.	After failure on IsaPd, the CGP would consider the following treatment options: 1. Treatment with a carfilzomib-containing regimen if not already received.

PAG Implementation Questions	CGP Response
	2. Compassionate access to: a. Selinexor b. Belantamab 3. Clinical trial 4. Palliation with steroids/cyclophosphamide
• Continued use of isatuximab plus dexamethasone in cases of pomalidomide intolerance/discontinuation.	• The CGP would consider the continued use of isatuximab in cases of pomalidomide intolerance as this is consistent with clinical practice, especially in individual patients where there is evidence of a biochemical and/or clinical response.

ASCT = autologous stem cell transplant; CGP = Clinical Guidance Panel; IsaPd = isatuximab plus pomalidomide plus dexamethasone; ECOG = Eastern Cooperative Oncology Group; IMWG – International Myeloma Working Group; Kd = carfilzomib plus dexamethasone; mAb = monoclonal antibody; MM = multiple myeloma; PAG = Provincial Advisory Group; Pd = pomalidomide plus dexamethasone; PR = partial response; PVd = pomalidomide plus bortezomib plus dexamethasone; RVd = lenalidomide plus bortezomib plus dexamethasone

2 Background Clinical Information

2.1 Description of the Condition

Epidemiology

Symptomatic myeloma is an incurable plasma cell neoplasm that represents 1.5% of all new cancers in Canada with an estimated 3,400 new cases annually.[13] The second largest increase in male cancer incidence in 2019 was in symptomatic myeloma with an annual percentage change of 2.6%.[14] Symptomatic myeloma affects older adults with the average age at diagnosis being 62 years for men and 61 years for women, and only 4% of cases are diagnosed in individuals under the age of 45.[15] Symptomatic myeloma accounts for approximately 10% of all hematologic malignancies. In Canada, the five-year net survival rate for MM is 44%, with a higher incidence in males.[16]

Diagnosis

The diagnosis of symptomatic MM (myeloma that necessitates treatment) is made based on the IMWG recommendations.[17] Specifically, one must document clonal bone marrow plasma cells > 10% and any one of the following: 1) hypercalcemia, 2) renal insufficiency, 3) anemia, 4) bone lesions, or 5) clonal bone marrow plasma cells ≥ 60%, involved:uninvolved serum free light chain ratio ≥100 or > 1 focal lesions on MRI studies.

Prognosis

Patients can be stratified into groups with differing prognoses based on clinical and laboratory parameters. The IMWG defines high risk cytogenetic features of myeloma to include one or more of the following: FISH–detected t(4;14), t(14;16), t(14;20), del(17p), or gain(1q); non-hyperdiploid karyotype; high risk gene expression profile signature; and del(13) detected by conventional cytogenetics.

In addition to cytogenetic risk factors, two other clinical features that are also associated with aggressive disease biology are elevated serum lactate dehydrogenase (LDH), and evidence of circulating plasma cells on routine peripheral smear examination (plasma cell leukemia). The R-ISS combines elements of tumour burden (ISS) and disease biology (presence of high-risk cytogenetic abnormalities or elevated LDH) to create a unified prognostic index. The highest risk stage 3 patients includes those with serum beta-2-microglobulin > 5.5 mg/L and high-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated serum LDH.[18]

Goals of therapy

The morbidity and mortality from myeloma stem from direct and indirect effects of the malignant plasma cells and its monoclonal protein. Without effective therapy, the illness results in a significant decrease in HRQoL and is universally fatal. The management of symptomatic myeloma is to mitigate this risk and is reliant on effective systemic chemotherapy and supportive measures (pain control, antibiotics, kyphoplasty, radiation therapy, dialysis, and psychosocial supports).

The median survival of symptomatic myeloma has significantly improved over the last 20 years with concurrent improvements in HRQoL. Improvements in outcomes, including OS, have been predominantly attributed to improvements in chemotherapeutics.

Overall chemotherapeutic strategy

Based on an understanding of myeloma biology and clinical observations, there has been a paradigm shift in the “philosophy” in chemotherapeutic management. Previously, there has been a reluctance to use more effective medications or medication combinations sooner and/or upfront. Rather, clinicians were saving therapeutic options for the relapsed and/or refractory setting. This approach was rational when the chemotherapeutics “tool-box” was limited, less efficacious, and was associated with a significant side effect profile. However, with better understanding of biology such as clonal tiding, emergence of more targeted therapies, indirect data from multiple randomized trials, it is now widely accepted that effective combination novel therapies should be embraced early and continuously while paying attention to side effect profile.

Taken together, a strategy of early continuous therapy results in better outcomes (i.e., OS, PFS, and HRQoL) than a strategy of intermittent therapies based on symptoms.

Chemotherapeutic considerations

To date there has not been definitive evidence from randomized trials that has identified a superior treatment strategy which differs based on patient risk stratification.

Existing evidence suggests that triplet combinations consisting of a PI or a mAb and newer immunomodulatory (IMiD) drugs partly overcome the adverse prognostic significance of high-risk features; however, the same therapies are often recommended for non-high-risk patients. Specifically targeting genetic abnormalities with specific inhibitors, such as KRAS and NRAS genes, is another way to improve the outcome for myeloma patients. However, unfortunately, to date, no adequate RAS-inhibitors are clinically available to prevent targeted therapy.[19] Nevertheless, some expert clinicians have interpreted the existing evidence to recommend treating patients differently based on cytogenetic profile; for example, offering bortezomib rather than lenalidomide as maintenance therapy for patients with t(4;14) myeloma. This practice is applied by some Canadian clinicians.[20]

2.2 Accepted Clinical Practice

Goal of therapy for RRMM

The goal of therapy for patients with RRMM is to achieve disease control with acceptable toxicity and patient-defined decent HRQoL.[21] Older frailer patients have limited options and should most likely receive attenuated-dose therapies, where clinicians must be careful to prevent additional morbidity and preserve a patient-oriented HRQoL. It seems generally that continuous therapy prolongs remission duration as compared to a more defined duration of therapy. Many patients will therefore continue with frontline therapy until the disease demonstrates itself to be relapsed and/or refractory to the current treatment. Other patients will discontinue frontline therapy while still in remission, without the disease being demonstrably refractory to any drugs, in order to have a reprieve from the adverse effects of treatment.[21]

Chemotherapeutic options

Systemic therapy is the primary modality of treatment for MM. The four main, currently available, and approved classes of chemotherapeutics in Canada include: 1) alkylators such as melphalan and cyclophosphamide; 2) IMiDs such as thalidomide, lenalidomide, and pomalidomide; 3) PIs such as bortezomib and carfilzomib; and 4) mAbs such as daratumumab.

mAbs represent a group of agents with a unique mechanism of action that in recent years has substantially changed the management of RRMM, as evidenced by the CASTOR[22] and POLLOX[23] studies, which has been adopted provincially. Antibodies have an immune-based mechanism, induce durable responses with limited toxicity, and combine well with existing therapies. Furthermore, advances in bioengineering have enabled the development of a new generation of mAb-derived therapeutics, including antibody-drug conjugates and bispecific antibodies , with the potential to further improve clinical outcomes for patients.[24]

Outside of clinical trials where provincial funding is available, the current treatment options for patients with RRMM include 1) daratumumab and dexamethasone with either bortezomib (DVd) or lenalidomide (DRd), 2) Pd with or without cyclophosphamide, as well as 3) Kd. There is no strong evidence to prefer one over another where ultimately the adopted sequence is largely driven by provincial funding. Finally, heavily refractory patients can be enrolled in trials evaluating new bispecific or conjugated mAbs among other novel drugs, as well as the use of chimeric antigen receptor (CAR) T-cell therapy when applicable.[21]

Choice

There is no single clear choice of therapy in RRMM. The choice of agents used in this setting will depend on the outcomes with the regimens used in prior lines of therapy, the condition and age of the patient, the expected tolerance of adverse effects, and the availability of treatment options. Intuitively, an overall therapeutic strategy that optimizes and maximizes options is prudent.

Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority of patients and further therapy will be required. As MM advances, patients become increasingly refractory to treatment as the ability to respond declines and the durability of response and length of treatment-free intervals shorten as patients rapidly move through multiple lines of therapy.

Although patients are often not offered therapy with drugs that have been part of a regimen to which the disease has become refractory, there is evidence that combining such agents sometimes induces responses, particularly in the case of combining PIs and IMiDs.[17]

Additional chemotherapeutic considerations

The predominant second-line therapy in patients with RRMM is daratumumab and dexamethasone in combination with either bortezomib (DVd) or lenalidomide (DRd). However, provincial funding of daratumumab is dependent on sensitivity to either bortezomib or lenalidomide where it must be used in the triple combination.

For patients who are already refractory to both bortezomib and lenalidomide where there is no provincially funded opportunity to receive a mAb (daratumumab), the option of access to IsaPd is an attractive consideration. If IsaPd were provincially funded, it is currently unknown whether it would be preferable to receive IsaPd as second line therapy over DRd or DVd even in the absence of refractoriness to lenalidomide or bortezomib as there are no clinical data to support either strategy. However, the choice may be dependent on continued provincial funding for Kd or Pd as either third- or fourth-line therapy in patients who have received IsaPd, DRd or DVd.

3 Summary of Patient Advocacy Group Input

One input was provided by Myeloma Canada (MC) for the review of isatuximab (Sarclisa) for MM. MC conducted several patient and caregiver surveys to collect data on the impact of MM and its treatment options. The survey conducted was shared via email and through social media with patients across Canada. The survey was available for a 6-week period in June and July 2020. The survey was intended for patients who have previously received pomalidomide (Pomalyst) and dexamethasone and/or at least two prior lines of therapies including lenalidomide (Revlimid) with bortezomib (Velcade), carfilzomib (Kyprolis), or ixazomib (Ninlaro), and/or are receiving isatuximab (Sarclisa) for injection. Survey questions consisted of asking respondents to rate their experience with MM and suggested therapies or to rank criteria from least to most important. In total, 375 patients responded to the survey. The majority of patients resided in Ontario (n=143, 39%) and Quebec (n=83, 22%). There were no caregiver respondents. Three respondents resided outside of Canada, and 46 respondents were not eligible to respond to the survey and were thus excluded. Respondent characteristics are provided in Table 4.

Patients indicated that they wanted treatment options for myeloma that improve their overall QoL, with minimal side effects. Various treatment options need to be available to improve patient prognosis and QoL. From the patient perspective, infections, kidney problems, and pain were the most common symptoms of myeloma; additionally, mobility, neuropathy, shortness of breath, and fatigue were reported to largely impact day-to-day lives of patients and their overall QoL. It was highlighted that in addition to physical symptoms, living with myeloma affects patients QoL by significantly impacting work life, travel, and the ability to exercise and volunteer. MC indicated that living with myeloma has many financial implications for patients; namely, drug costs, loss of income due to absence of work, and parking costs for medical appointments. Patients surveyed indicated that they wanted to avoid all side effects of treatment; however, confusion, infection, and pain were the most reported by respondents to avoid. 268 of 306 patients (88%) responded that when taking a drug or considering taking a myeloma drug it is “very important” that it improved their overall QoL.

Among the 375 respondents, 226 (60%) had received at least two prior lines of therapies including lenalidomide (Revlimid) and bortezomib (Velcade), carfilzomib (Kyprolis), or ixazomib (Ninlaro) and 54 (14%) respondents had used or were using pomalidomide (Pomalyst) and dexamethasone alone. Six respondents had direct experience with the drug under review (isatuximab) in combination with pomalidomide and dexamethasone. Patients reported an improved QoL on this regimen and that it was effective in controlling their myeloma. The most commonly reported intolerable side effects on the treatment under review were respiratory infections, anemia, and cold-like symptoms.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

Table 4: Survey Respondent Characteristics

Respondents by Province (N=375)	Alberta	British Columbia	Manitoba	New Brunswick	Newfoundland & Labrador	Nova Scotia	Northwest Territories
Patients diagnosed with Myeloma who participated in the survey (n)	53	43	10	10	7	8	1
	Nunavut	**Ontario**	**Prince Edward Island**	**Quebec**	**Saskatchewan**	**Yukon**	**Outside of Canada**
	1	145	1	83	9	1	3

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Every day, nine Canadians are newly diagnosed with myeloma. However, despite the growing prevalence of this disease, it remains relatively unknown. To date there is no cure for myeloma. Respondents eligible to answer the survey (n=329) were asked to rate on a scale of 1 – 5 (1 is *"Not important"*, 5 is *"Very important*"), how important it is to control symptoms of MM. Respondents identified infections, kidney problems, pain, mobility, neuropathy, shortness of breath, and fatigue as the most important symptoms to control. Table 5 summarizes how respondents rated important symptoms to control.

Table 5: Symptoms of Myeloma Most Important to Control

Symptoms Most Important to Control	Respondents (n = 329)
Infections	84.3%
Kidney problems	76.7%
Pain	71.0%
Mobility	75.0%
Neuropathy	67.3%
Shortness of breath	61.3%
Fatigue	66.9%

When respondents were asked to *"rate on a scale of 1 - 5 (1 is "Not at all", and 5 is "Significant impact") how symptoms associated with myeloma impact or limit their day-to-day activities and QoL",* they indicated that it significantly impacted their ability to work (37%), to travel (35%), to exercise (29%), and to volunteer (25%). At a lower but still significant rate, respondents indicated that the disease impacted their ability to perform household chores (47%), to fulfill family obligations (44%), to spend time with family and friends (38%), and to concentrate (40%).

Table 6 summarizes the financial implications of treatment for MM. Almost 40% of the respondents indicated that they had no financial implications related to myeloma treatment. Respondents identified drug costs and lost income due to absence from work as the most important financial implications related to their treatment.

Figure 1: How important it is that a drug improve patient QoL

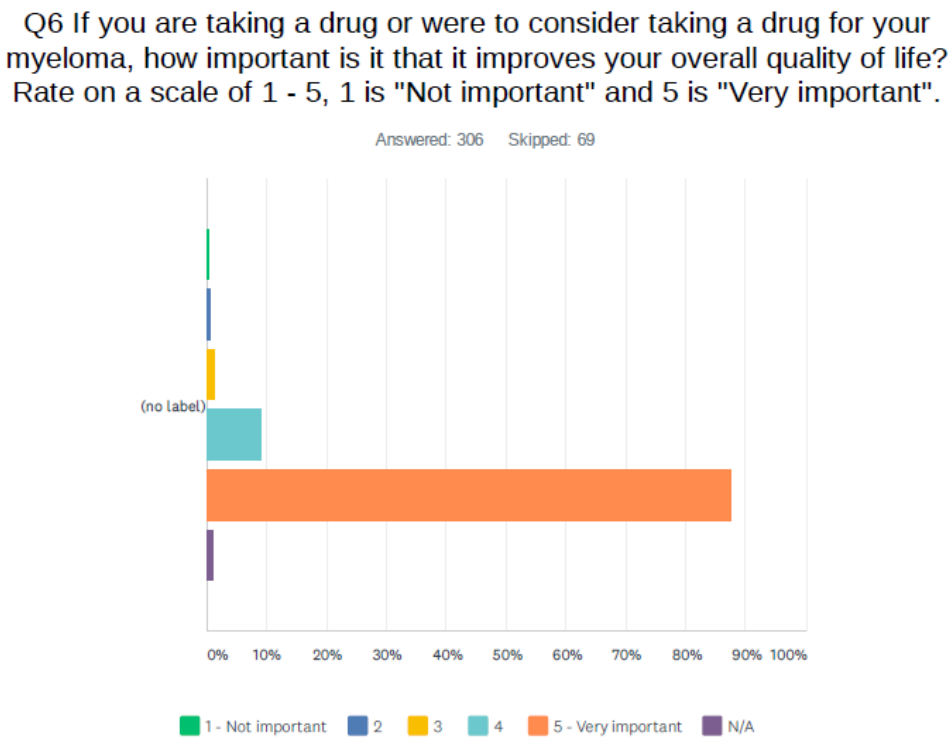


Table 6: Financial Implications of Living with Myeloma

Significant Financial Implications of Treatment for Myeloma	Respondents (n = 305)
Drug costs	48 (15.7%)
Lost income due to absence from work	42 (13.8%)
Parking costs	26 (8.5%)
Travel costs	19 (6.2%)
Medical supply costs	4 (1.3%)
Drug administration fees	4 (1.3%)
Accommodation costs	4 (1.3%)
I have had no financial implications related to my myeloma treatment	114 (37.4%)
Other	44 (14.4%)

3.1.2 Patients' Experiences with Current Therapy

Patients who responded to the survey identified how important it was that a drug improve their overall QoL. Respondents were asked to rate on a scale of 1-5, from 1 is *"not important*" to 5 is *"very important*", how important it is that a drug they were taking or considering taking improve their overall QoL. Out of the 271 eligible respondents, the majority of patients 268 (99%) answered that it was *"very important"*. When respondents were asked to identify what is most important aspect of treating their myeloma, they

answered remission, effective treatments, fewer side effects, and better QoL. The following respondent quotes indicate what is important to patients in a drug treatment when treating their myeloma:

- *"I have a good quality of life now and I am so grateful. The only thing I want is to be sure another treatment will be available for me when this one stop[s] working."*
- *"Extending remission, reducing pain, improving mobility to be able to enjoy regular activities."*
- *"That the treatment gives good results. Having a treatment that doesn't disrupt my life too much (going for infusions daily for a long period of time if once a week provided the same success)."*
- *"I want to live and look forward to being a grandfather!"*
- *"I am interested in the myeloma being held down to a low level so that I don't experience problems such as end [of life] organ damage."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

MC summarized that patients seek treatments with less side effects and those that will improve their overall QoL. When respondents were asked how important it is that they have access to effective treatments for myeloma, 305 (98%) answered it was very important. Avoiding side effects was identified as an important aspect of living with myeloma by respondents. Patients surveyed indicated that they wanted to avoid all side effects; however, confusion (n=54, 21%), infection (n=71, 25%), and pain (n=51, 20%) were the most reported by respondents to avoid (Table 7).

Table 7: Ranking Treatment Side Effects as Most to Least Important

Treatment side effects	1	2	3	4	5	6	7	8	9	N/A	Total, n
Confusion	54 (21%)	29 (11%)	22 (9%)	20 (8%)	23 (9%)	22 (9%)	20 (8%)	19 (8%)	27 (11%)	17 (7%)	253
Fatigue	27 (11%)	46 (18%)	41 (16%)	30 (12%)	33 (13%)	20 (8%)	17 (7%)	20 (8%)	17 (7%)	4 (2%)	255
Insomnia	11 (4%)	25 (10%)	38 (15%)	28 (11%)	20 (8%)	31 (12%)	27 (11%)	28 (11%)	38 (15%)	9 (4%)	255
Nausea	16 (6%)	22 (9%)	30 (12%)	41 (16%)	33 (13%)	30 (12%)	19 (8%)	27 (11%)	20 (8%)	19 (8%)	257
Neuropathy	29 (11%)	30 (11%)	36 (14%)	32 (12%)	37 (14%)	28 (11%)	21 (8%)	23 (9%)	20 (8%)	8 (3%)	264
Pain	51 (20%)	39 (15%)	27 (11%)	29 (11%)	30 (12%)	32 (13%)	19 (7%)	14 (6%)	7 (3%)	7 (3%)	256
Shortness of breath	9 (3%)	16 (6%)	19 (7%)	23 (9%)	36 (14%)	26 (10%)	59 (22%)	35 (13%)	16 (6%)	16 (6%)	264
Stomach issues	16 (6%)	24 (9%)	21 (8%)	24 (9%)	21 (8%)	32 (12%)	39 (14%)	53 (19%)	10 (4%)	10 (4%)	272
Infection	71 (25%)	32 (11%)	31 (11%)	24 (9%)	14 (5%)	17 (6%)	16 (6%)	16 (6%)	4% (12)	12 (4%)	280

*Respondents were asked to rate on a scale of 1-9, with 1 being the most important to avoid to 9 being the least important to avoid.

3.2.2 Patient Experiences to Date

MC reported on patients experience to date with myeloma treatments. Among the 375 respondents, 226 (60%) had received at least two prior lines of therapies including lenalidomide (Revlimid) and bortezomib (Velcade), carfilzomib (Kyprolis), or ixazomib (Ninlaro). 54 (14%) respondents had used or were treated with pomalidomide (Pomalyst) and dexamethasone alone. Patients were asked to

rate on a scale of 1-5 (1 is *"Not at all"*, and 5 is *"Significant impact"*), how symptoms associated with myeloma impact or limit their day-to-day activities and QoL since taking the treatment combination of pomalidomide (Pomalyst) and dexamethasone. Respondents (n=48) indicated that their ability to travel (35%), to exercise (38%), to volunteer (30%), and to concentrate (20%) were most significantly impacted. Patients treated with the combination of pomalidomide with dexamethasone were asked to rank from 1-6 (1 being the most important, 6 being least important), what their expectations were for this treatment combination of pomalidomide and dexamethasone. Out of the 46 respondents, remission (30%), disease control (28%), and enjoying a normal life (22%) were considered most important. When patients were asked "Which of your expectations has your treatment combination of pomalidomide with dexamethasone fulfilled", the majority of respondents (n=44) identified disease control (n=30, 68%), improved QoL (n=26, 59%), and prolonged life (n= 25, 57%) as the main fulfillments. Other responses included enjoying a normal life (n=20, 45%), fewer side effects than other treatments (n=18, 41%) and remission (n=16, 36%).

Of the 44 respondents, 19 respondents described their treatment experience with the combination of pomalidomide with dexamethasone. The following respondent quotes indicate their experiences:

- *"After 10 years of treatment I can no longer tolerate any dex [dexamethasone]. Switched to solumedrol. Much better tolerated."*
- *"It has decreased my ability to participate in sports e.g., tennis & long walks due to neuropathy in my feet & legs"*
- *"The least side effects but extreme fatigue and short of breath from blood clots caused by Deralex [Darzalex] infusions for six months."*
- *"Pomalyst has been much easier with regard to side effects than revlemid [Revlimid]."*

Six respondents had experience with isatuximab in combination with pomalidomide and dexamethasone. When patients were asked about the combined effectiveness of this treatment regimen in controlling their myeloma, two respondents answered, "*extremely effective*", one respondent answered "*effective*", one respondent answered, "*fairly effective*", and five patients did not respond to the question. When asked if the method of administration through injection had a negative impact on patients, two respondents answered "yes", one answered "no", and three preferred not to answer.

Respondents (n=7) were asked to rate the common side effects they experienced with isatuximab in combination with pomalidomide and dexamethasone. The most intolerable symptoms reported were respiratory infections (n=2, 29%), anemia (n=2, 29%), and cold-like symptoms (n=2, 29%).

When respondents (n=6) were asked how they would rate their QoL on a scale of 1-5 (1 being "*poor quality of life"* and 5 being "*excellent quality of life*") with isatuximab in combination with pomalidomide and dexamethasone, one respondent said "good", two said "fair", and three said it was not applicable to them. Furthermore, when respondents (n=6) were asked *if the combination of isatuximab with pomalidomide and dexamethasone met their expectations in treating myeloma,* three respondents said *"yes"* and three preferred not to answer. When patients (n=6) were asked *if isatuximab in combination with pomalidomide and dexamethasone improved their health and well-being*, one respondent said *"yes"*, one said it was too soon to tell, and four preferred not to answer. When asked *if isatuximab with pomalidomide and dexamethasone improved their long-term health outlook*, two respondents said *"yes"* and four preferred not to answer. The following quotes depict the respondents' experience with the drug under review in their own words:

- *"Like every treatment, there are positive and negative impacts, collateral damages, and consequences, but the follow-up is good. And we are still alive."*
- *"The feeling like fire under your feet was the worst plus the swelling an[d] over-eating is not a good thing for the bone, with all the extra weight on plus fluid retention."*
- *"I've been on this treatment since 2017, and it's working fine for me. It keeps my myeloma in a 'sleeping mode' which is what we all hope for. I got some allergic symptoms at the beginning, but it resolved itself quickly. Yeah, sometimes the schedule of treatment is hard to manage, and sometimes I am too tired to do anything. But I am alive, and I can say that some other treatments I got gave me much more problems than that."*

3.3 Companion Diagnostic Testing

None to report.

3.4 Additional Information

MC wanted to highlight to the CADTH review team and pERC that the patient group feels that since there is no single treatment effective for all myeloma patients. Various treatment options need to be available to improve patient prognosis and QoL. Patients are anxious to understand how this drug under review (isatuximab) will be placed in sequencing evaluation of myeloma treatments by pCODR. Those who are currently on daratumumab have indicated that they do not want to be excluded to having access to this new treatment should they start to relapse.

MC has described in their input that sequencing is important as patients need to strategize with their healthcare provider, the best plan of action for them to prolong their life. As described by the patient input, the treatment landscape is becoming complex as more new treatments are being approved and there is little comparison between them and previous treatments. There is a need for collating real-world evidence to refine decisions. As stated by the patient group, the myeloma community supports evidence generation post-approval and would be happy to support initiatives in this regard.

4 Summary of Provincial Advisory Group (PAG) Input

The PAG includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of isatuximab in combination with pomalidomide and dexamethasone:

Clinical factors:

- Place in therapy and sequencing with currently available treatments
- Addition to or switch from ongoing therapies
- Prior use of daratumumab

Economic factors:

- Mixed administration of IV and oral drugs
- High cost barrier

Please see below for more details.

4.1 Currently Funded Treatments

Treatment of RRMM patients who have experienced prior lenalidomide and a PI (typically bortezomib) includes Pd and Kd. Cyclophosphamide can be added to the regimens in some cases. In most provinces, patients whose disease is refractory to both lenalidomide and bortezomib are not eligible for publicly funded daratumumab.

PAG noted that the ICARIA-MM trial compared IsaPd to Pd. PAG seeks additional comparison of IsaPd with Kd.

4.5 Companion Diagnostic Testing

PAG noted that while no companion diagnostic is required to identify eligible patients, RBC genotyping will be needed prior to initiation of isatuximab.

4.2 Eligible Patient Population

The reimbursement request of IsaPd is for the treatment of patients with RRMM who have received at least two prior therapies including lenalidomide and a PI. In view of the characteristics of the patient population and exclusion criteria in the ICARA-MM trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with IsaPd:

- Patients with ECOG performance status greater than 2.
- Patients with primary amyloidosis.
- Patients with primary refractory MM.
- Patients with free-light chain measurable disease only.

PAG also seeks information on whether patients with high-risk cytogenetics exhibit a distinct response to IsaPd and should be treated differently.

PAG identified a potential time-limited need for patients currently on Pd or Kd who have not progressed, and seeks guidance on whether they could be switched to IsaPd, adding isatuximab in the case of patients on Pd. In the latter scenario, PAG would like to know if a switch from Pd plus bortezomib (PVd) could also be allowed. PAG noted potential indication creep of IsaPd to first- or second line use and to patients who have previously received pomalidomide. Additionally, there may be indication creep to use isatuximab as a single agent for salvage treatment of RRMM after failure of available therapies (e.g., after Pd or Kd) if a patient has not previously received daratumumab.

4.3 Implementation Factors

Isatuximab (10 mg/kg) is given by IV infusion on days 1, 8, 15 and 22 at Cycle 1, then on days 1 and 15 for subsequent cycles, in combination with oral pomalidomide 4 mg on days 1 to 21 of each 28-day cycle, and oral or IV dexamethasone 40 mg (or 20 mg for patients ≥75 years) on days 1, 8, 15 and 22. Treatment continues until disease progression or unacceptable toxicity. Vials would contain solution for infusion (20mg/mL); two strengths are anticipated: 100 mg and 500 mg. PAG is seeking guidance on treatment duration and discontinuation criteria. PAG noted that the International Myeloma Working Group consensus criteria mention that response or progressive disease require confirmation with two consecutive readings of the applicable disease parameter using two discrete samples; PAG seeks guidance on whether this should be required in clinical practice. Furthermore, PAG seeks advice on the addition of cyclophosphamide upon biochemical progression.

PAG voiced concerns regarding incremental costs due to drug wastage of isatuximab, specifically in centers where vial sharing would be challenging. The availability of two strengths would be an enabler.

PAG noted that isatuximab would be an add-on IV component to Pd, which is already in use in cancer care. Isatuximab would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Compared to current oral treatments, significant additional resources for IV infusion are anticipated. Resources will be required to monitor and treat toxicities (e.g., neutropenia, thrombocytopenia, neuropathies). Due to these effects, some patients may require a granulocyte colony-stimulating factor (G-CSF) while on therapy. PAG also noted high rates of infusion reactions to isatuximab. Additional resources (pre-medications, nurse time) may be required to manage these reactions. PAG seeks guidance on dose reduction for isatuximab to mitigate infusion reactions, given dose modifications were not permitted in the trial.

PAG remarked that like daratumumab, isatuximab can affect immunofixation on the serum protein electrophoresis (SPEP) and thus quantification of M-protein (a marker of response). Additionally, isatuximab binds to CD38 on red blood cells and may result in a false positive indirect antiglobulin test (indirect Coombs test). Laboratories will need to be aware if patients are on isatuximab to correctly interpret their results.

PAG noted that the combination of isatuximab with pomalidomide, which is also an expensive drug, would present a high cost barrier.

Intravenous oncology drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to for these patients. Conversely, PAG noted that pomalidomide is an oral option; chemotherapy chair time and nursing time would not be required. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy of IsaPd and sequencing with other regimens for RRMM, including the scenarios below:

- Overall optimal sequence of therapies that should be given prior to IsaPd.
- Patient factors justifying preferential use of IsaPd over Pd or Kd in the third line setting.

- Use of IsaPd after first line lenalidomide plus bortezomib plus dexamethasone and no other prior line of therapy. Would this be considered off-label? If len/bor/dex was used in first line, what second line therapies can be given before patients are considered eligible to IsaPd?
- Evidence on the use of isatuximab after failure of any daratumumab-containing therapy.
- Using IsaPd in patients who discontinued daratumumab in a prior line of therapy without evidence of progression if all other eligibility criteria are met.
- Evidence on the use of isatuximab after carfilzomib-containing regimens in the R/R setting.
- Addition of isatuximab to Pd upon biochemical progression on the latter.
- Options after failure of IsaPd.
- Continued use of isatuximab plus dexamethasone in cases of pomalidomide intolerance/discontinuation.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided on behalf of two clinicians from Ontario Health-Cancer Care Ontario Hematology Cancer Drug Advisory Committee (CCO) and 15 clinicians from the Canadian Myeloma Research Group (CMRG) for the review of IsaPd for the treatment of patients with RRMM who have received at least two prior therapies including lenalidomide and a PI. Pd and Kd were reported to be currently available for the treatment of RRMM in Canada. Cyclophosphamide can be added to Pd treatment. In most provinces, patients whose disease is refractory to both lenalidomide and bortezomib are not eligible for publicly funded daratumumab. Clinicians from CMRG specified that as lenalidomide treatment is often continuous, daratumumab in combination with lenalidomide and dexamethasone would not be a possible treatment option, unless the patient had prior lenalidomide exposure and was not refractory to this treatment or did not experience significant toxicities.

Both inputs indicated that IsaPd is an ideal therapy for patients with significant unmet need such as those individuals who have had disease progression after both bortezomib and lenalidomide treatment and are ineligible for daratumumab. Both CCO and CMRG clinicians specified that the inclusion and exclusion criteria of the ICARIA-MM pivotal trial appear to be reasonable and can be applied in clinical practice. However, both clinician groups indicated that there should not be restrictions based on renal function or blood counts. Unlike the pivotal trial, in clinical practice there is no requirement to have measurable myeloma markers or less than grade one prior toxicity in patients. Clinicians from CMRG noted that IsaPd would be ideal because it yields a greater PFS in lenalidomide-refractory patients; in Ontario these patients currently do not have any funded access to anti-CD38 mAb and they are currently ineligible for new immune treatments available through clinical trials. Clinicians noted that IsaPd has good tolerability, favourable results, and has an oral component for ease of administering and the ability to use in renal insufficiency with a low rate of treatment related adverse events leading to regimen discontinuation. Potential harms reported are the mentioned contraindication of a prior severe rash with lenalidomide, as there may exist some cross-reactivity with pomalidomide. Patients with a prior history of frequent sino-pulmonary infections requiring antibiotics may be at higher risk of developing upper respiratory tract infections and may warrant additional precautions at the time of initiation of IsaPd.

Patients who receive DVd until progression would not be eligible for another CD38 antibody like isatuximab, as a third line therapy. There are a relatively small proportion of Canadian patients currently on lenalidomide plus bortezomib and dexamethasone for relapsed or refractory myeloma. Being prescribed IsaPd at next progression would be important for patients not previously treated with daratumumab. For patients currently on Pd (+/- cyclophosphamide) and not progressing, the addition of isatuximab if not otherwise previously treated with daratumumab would be optimal. This regimen is predicted by clinician groups to replace Pd in patients who are eligible. Patients on Kd for relapse who have not had the opportunity to use daratumumab would be candidates for IsaPd. IsaPd would most likely replace Pd, Pd in combination with cyclophosphamide and Kd due to the inability of using both pomalidomide and carfilzomib in the same patient.

Please see below for details from the clinician inputs.

5.1 Current Treatments

Pd and Kd were reported to be the currently available drugs for the treatment of RRMM. Cyclophosphamide can be added to the Pd regimen. In most provinces, patients whose disease is refractory to both lenalidomide and bortezomib are not eligible for publicly funded daratumumab. PVd was conditionally recommended by pERC in September 2019, with the condition that the cost effectiveness be improved. In Ontario, it is currently under negotiation, however when it is funded this would be another treatment option in this therapeutic space. If the myeloma is relapsed (but not refractory) to prior use of bortezomib, then DVd could be used as a treatment regimen in Ontario. As lenalidomide treatment is often continuous, DRd would not be a possible treatment option, unless the patient had prior lenalidomide exposure and was not refractory to this treatment or did not experience significant toxicities.

Clinician groups indicated that the most appropriate comparators to the drug under review would be Pd (+/- cyclophosphamide) or Kd.

5.2 Eligible Patient Population

IsaPd is an ideal therapy for patients with a significant unmet need such as those individuals who have had disease progression after both bortezomib and lenalidomide treatment and are ineligible for daratumumab. As stated by clinicians at CMRG, this treatment would be ideal for many reasons because 1) the other funded options yield a PFS of no more than eight months in lenalidomide-refractory patients, 2) in Ontario these patients currently do not have any funded access to anti-CD38 monoclonal antibody therapy and 3) these patients are currently ineligible for new immune treatments available through clinical trials such as bispecific monoclonal antibodies, CAR-T cell therapy and CelMods due to the lack of exposure to an anti-CD38 monoclonal antibody.

The inclusion and exclusion criteria of the ICARIA-MM trial appear to be reasonable and can be applied in clinical practice. The majority of the eligibility criteria in the trial can be applied in clinical practice, except clinician groups have indicated that there should not be restrictions based on renal function because neither pomalidomide nor isatuximab are eliminated from the kidney. In addition, there should not be restrictions on blood counts since low blood counts may be due to myeloma marrow infiltration and may improve with therapy. In clinical practice there is no requirement to have measurable myeloma markers or less than grade 1 prior toxicity, as these were only requirements for the phase 3 trial.

Clinician groups indicated that the treatment under review would be expected to also be effective in patients with plasma cell leukemia and light chain amyloidosis. Subgroup analyses demonstrated a benefit of IsaPd; however, it will be critical that patients who are eligible for this regimen, not be required to be refractory to bortezomib and lenalidomide but be exposed to them. In many settings, bortezomib is funded for a fixed duration such as bortezomib with melphalan and prednisone (VMP) and cyclophosphamide in combination with bortezomib and dexamethasone (CyBorD) for 9 cycles as initial therapy in transplant-ineligible patients, and in several provinces for relapsed patients. CMRG clinicians stated that if retreatment with bortezomib is required to demonstrate that a patient is refractory, patients will be required to receive the losing control arm (bortezomib and dexamethasone [Vd]) of all phase three trials of Vd versus Vd plus a third agent or Vd versus Kd in patients with one to three prior regimens before they will be eligible for IsaPd. Clinician groups indicate that patient attrition due to more advanced disease and more complications from receiving suboptimal therapy would be expected to undermine the ability to offer this regimen to the relevant population of myeloma patients.

5.2.1 Implementation Question: Under what patient or clinical circumstances would clinicians choose IsaPd over Pd or carfilzomib-based regimens?

Both clinician groups identified that they would prefer to treat with an antibody triplet such as IsaPd, as they would want the opportunity to treat with a mAb. In general, clinicians felt that triplet therapy is superior to doublets for RRMM patients. CMRG clinicians felt that IsaPd would be preferred over Pd or carfilzomib-based therapy. IsaPd has demonstrated a low (7.2%) rate of treatment related AEs leading to regimen discontinuation, which reflects the excellent tolerance of IsaPd in myeloma patients. Carfilzomib-based therapy should be used with caution in patients with pre-existing cardiovascular disease. These regimens have a considerably higher rate of discontinuation due to TEAEs.

5.2.2 Implementation Question: Typically, there is a higher risk of upper respiratory tract infections and pneumonia with anti-CD38 antibody-based therapy for myeloma. Is there evidence that any specific patient subgroups are at higher risk of infection or should be given additional precautions or monitoring?

Clinicians from CMRG stated that patients with a prior history of frequent sino-pulmonary infections requiring antibiotics may be at a higher risk of developing upper respiratory tract infections and may warrant additional precautions at the time of initiation of IsaPd. These patients may already be on a monthly intravenous immunoglobulin or weekly subcutaneous gamma globulin supplementation. Otherwise, upper respiratory tract infections are a known and manageable side effect for patients with anti-CD38 antibody-based treatment for myeloma and the regular administered infection precautions for many other myeloma treatments are typically sufficient.

5.3 Relevance to Clinical Practice

One of the clinician groups (CMRG) had experience with using the treatment under review. The clinician group indicated that this treatment would be particularly beneficial for the subset of patients who could not benefit from taking daratumumab in combination

with lenalidomide or bortezomib, because they have experienced disease progression on these agents or may be taking these drugs without the addition of daratumumab. Another important subgroup identified by the clinician groups are those who cannot be re-treated with bortezomib when used with daratumumab, most commonly due to prior severe peripheral neuropathy. These patients typically start treatment with low, potentially suboptimal, doses of bortezomib when administered as DVd, and may still often quickly develop recurrent neuropathy which precludes the continuation of the PI.

The advantages reported by CMRG clinicians for the treatment under review is that the regimen has good tolerability, favourable results, an oral component for ease of administering and the ability to use in renal insufficiency. The one contraindication noted by CMRG clinicians is a prior severe rash with lenalidomide, as there may exist some cross-reactivity with pomalidomide. However, this can be potentially managed by a rapid oral desensitization procedure, the results of which have been published by the Princess Margaret group. CCO clinicians stated that the anti-CD38 treatment under review does not differ substantially from daratumumab in terms of its use, logistics and adverse events.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

Clinicians at CMRG indicated that after first line therapy the majority of autologous stem cell transplant (ASCT) patients are on lenalidomide maintenance and would be eligible for either a second ASCT or more likely DVd at first relapse. Since patients who receive daratumumab in this regimen do so until progression, they would not be eligible for another CD38 antibody like isatuximab, as a third line therapy. For the small proportion of ASCT patients not on lenalidomide maintenance, they would be eligible for DRd at first relapse, however, would again not be likely candidates for isatuximab at the next progression. There exist some patients with high-risk myeloma who are receiving both lenalidomide and either bortezomib or ixazomib for maintenance after ASCT, these patients would be good candidates for treatment with IsaPd at first relapse. The same considerations apply to transplant-ineligible patients who receive lenalidomide plus dexamethasone (Rd) or CyBorD as first-line therapy. Clinicians noted that patients treated with RVd via the compassionate program as a first-line therapy who progress before fixed-duration bortezomib is stopped would be high priority candidates even though they have only had one prior line of therapy. These patients would only have Pd or Kd available which is expected to be inferior to IsaPd. These patients would miss the opportunity to be eligible for a CD38 antibody.

There are a relatively small proportion of Canadian patients currently on RVd for RRMM. Being prescribed IsaPd at next progression would be important for patients not previously treated with daratumumab. For patients currently on Pd (+/- cyclophosphamide) and not progressing, the addition of isatuximab if not otherwise previously treated with daratumumab would be optimal. IsaPd is predicted by clinician groups to replace Pd, Pd (+/- cyclophosphamide), and (due to the inability to use both pomalidomide and carfilzomib in the same patient) Kd in patients who are eligible and relatively fit. Patients on Kd for relapse who have not had the opportunity to use daratumumab would be candidates for IsaPd.

Both clinician groups identified that sequencing with IsaPd should not be limited to patients who received only twoprior lines of treatment. The clinicians noted that the median number of prior lines of treatment in the ICARIA-MM trail was 3 (range 2-4), and there did not exist a cap on the number of prior lines of treatment.

5.4.1 Implementation Question: What evidence is there to support sequencing of IsaPd after daratumumab-based regimen? Or after a carfilzomib-based regimen? Please consider treatment failure and discontinuation without failure separately in your answer.

There is very little evidence to support sequencing of IsaPd after daratumumab-based regimen. Clinician groups have indicated that there only exists limited data for the use of isatuximab or daratumumab in combination with Pd in patients progressing on single agent daratumumab and/or pomalidomide. Combining the two regimens has produced responses and useful PFS in only a very small case series so far. ICARIA-MM excluded patients refractory to previous treatment with anti-CD38 mAb. Patients being treated with daratumumab based treatment tend to be treated until disease progression. Clinicians felt that given that both daratumumab and isatuximab have the same target, there is no biological rationale that isatuximab would be beneficial and effective in patients who have since progressed after daratumumab administration. However, there is a biologic rationale for repeating treatment that has been unsuccessful previously or adding a new agent to an unsuccessful regimen at the time of progression. Evidence from the lymphoma experience, as the inclusion of rituximab to chemotherapy for both induction and then again at relapse have become the

standard approach in CD20-positive patients. Myeloma patients have five to seven subclones at diagnosis that ebb and flow for predominance with different relapses, these subclones may have different drug sensitivities. This observation explains how a drug that has stopped working previously may be effective in the later disease course.

The addition of a new drug to an unsuccessful regimen at the time of disease progression has restored responsiveness and is a strategy evaluated both prospectively (adding pomalidomide to cyclophosphamide, daratumumab and dexamethasone;[25] adding low dose cyclophosphamide to lenalidomide or Rd[12]) and retrospectively (addition of cyclophosphamide to Rd at relapse)[26] at Princess Margaret Hospital. Studies of re-treatment with daratumumab and isatuximab are ongoing.

Clinician groups indicated that there is no difference between treatment failure or discontinuation without failure (such as intolerance). In both situations, patients would be eligible for IsaPd in the study. The requirements are to have at least two prior lines of therapy, if they are not refractory to prior anti CD38 antibody treatment.

Clinicians at the CMRG have submitted a database analysis assessing the efficacy of pomalidomide based regimens after use of carfilzomib-based regimens, and vice versa. The purpose of this analysis was to assess what patients might be deprived of with the new limitation that Canadian patients will only have funding for one of these agents of progression and not both. Both sequences had a very limited number of patients with whom the partner drug was daratumumab. The approximate outcomes in both scenarios were very similar.

5.4.2 Implementation Question: Is there evidence to support use of IsaPd after first line RVd and no other prior line of therapy? If not and RVd was used in first line, what second line therapies would you consider before patients may become eligible to IsaPd?

Clinicians from CCO noted that in Ontario, if a patient was treated with RVd upfront, they would be administered Kd as a second line therapy before becoming eligible to IsaPd. Clinicians from CMRG indicated that they are not aware of specific data for IsaPd after first line RVd therapy. However, the Celgene MM-014 trial allowed those patients progressing on lenalidomide-based treatment after one to two prior lines of therapy to receive daratumumab plus Pd.[27] In addition, 80% of these patients received bortezomib-based induction but had not necessarily progressed on it. The response rate on this treatment regimen was 78%, and the median PFS at one year was 75%.

5.4.3 Implementation Question: In patients experiencing toxicity to pomalidomide-dexamethasone, is there evidence that isatuximab can be continued as monotherapy?

CMRG clinicians indicated that continuous therapy is now standard and is funded for the majority of treatment settings in myeloma. The only exception to this has been fixed duration CyBorD or VMP as first-line therapy. This treatment stops after 9 cycles. Older studies that have presented data on continued bortezomib in combination with thalidomide for two to three years showed a significant PFS and OS benefit. The TOURMALINE MM4 trial showed that continuing ixazomib after induction therapy significantly prolonged PFS in this setting.[28]

CCO clinicians indicated that the ICARIA-MM study allowed dose adjustments and reductions for pomalidomide and dexamethasone but not for isatuximab. Clinicians commented that based on the study design, monotherapy would not be allowed. Extrapolating previous data from the daratumumab monotherapy study found that there was not much benefit to continue its use as monotherapy.

In contrast, CMRG clinicians indicated that the ALCYONE study continued daratumumab alone as maintenance after fixed duration VMP in newly diagnosed transplant ineligible myeloma.[29] Thus, there is a precedent for use of a single-agent antibody therapy. Some other daratumumab studies are underway with good preliminary results to understand this therapeutic space.

From their responses and presented data, CMRG clinicians felt that patients who respond to combination therapies may continue one or two agents after the disease is controlled and may experience prolonged PFS.

5.4.4 Implementation Question: Is there evidence or rationale to support the addition of isatuximab to Pd upon biochemical progression on the latter?

Clinicians from CCO noted that the ICARIA-MM study did not allow for crossover, post study treatment was left up to the investigator discretion. CMRG clinicians noted that the evidence for adding isatuximab to Pd is only anecdotal. However, as previously discussed, this strategy may re-establish disease control. Pomalidomide has a strong immunomodulatory effect that can enhance isatuximab's anti-tumour effect, which is the rationale for having it added as a combination therapy to isatuximab.

5.4.5 Implementation Question: What are the evidence-informed options after failure of IsaPd?

CMRG clinicians indicated that there is no standard therapy identified after progression on IsaPd. Previously, patients would have likely tried Kd if no more than three prior lines of therapy had been given. This is another area of unmet need. Clinicians at CMRG recommended using a PI combination such as CyBorD again or to try entering the patient in a clinical trial. A challenge with clinical trials is their common pharmaceutical approach, such as opening many sites to accelerate accrual. Consequently, each site may only have a few slots. The real-world Canadian data in patients progressing on lenalidomide regimens confirms that relatively few patients nationally can get on trials. CCO clinicians stated that both carfilzomib and selinexor would be potential options after the failure of IsaPd.

5.5 Companion Diagnostic Testing

The CCO and CMRG clinicians indicated that the testing for CD38 antibodies is a standard of care and is widely available. Funding for this has not been an issue. Due to potential interference, compatibility testing for red blood cell phenotyping before commencing with anti-CD38 agents are required. There is no additional companion diagnostic testing required.

5.6 Implementation Questions

Refer to implementation questions in respective sections above.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

The objective of this systematic review is to evaluate the safety and efficacy of IsaPd compared to the standard of care in Canada for the treatment of patients with RRMM who have received at least two prior therapies including lenalidomide and a PI.

A supplemental question relevant to the pCODR review and to the PAG was identified while developing the review protocol and is outlined below:

- Summary and critical appraisal of a sponsor-submitted ITC comparing efficacy data (OS and PFS) for IsaPd to Kd. The ITC is based on a subgroup of patients receiving Kd in the ENDEAVOR trial who were refractory to lenalidomide.[7] Refer to Section 7 for more information.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 8. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 8: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs.
 	
In the absence of RCT data, fully published clinical trials investigating the efficacy and safety of isatuximab in combination with pomalidomide and dexamethasone should be included.
	Adults (≥ 18 years of age) with RRMM who have received ≥ 2 prior therapies that include lenalidomide and a proteasome inhibitor.
	
	Subgroups of interest:
	• Number of prior lines of therapy
	• History of prior transplant
	• High risk cytogenetics
	  ○ E.g., t(4;14), t(14;16), del(17p)
	• Age
	  ○ < 75 years, ≥ 75 years
	• Disease Stage
	  ○ ISS or R-ISS stage I, II, III
	• Prior treatment with:
	  ○ Monoclonal antibody (e.g., daratumumab)
	  ○ Proteasome inhibitor (e.g., bortezomib, carfilzomib)
	• Treatment history with lenalidomide
	  ○ Intolerance
		Isatuximab + pomalidomide + dexamethasone (IsaPd)	• Pomalidomide + dexamethasone (Pd)
			
			• Pomalidomide + cyclophosphamide + dexamethasone (PCd)
			
			• Carfilzomib + dexamethasone (Kd)
				Efficacy
				• OS
				• **PFS**
				• TTP
				• TTNT
				• **ORR**
				• DOR
				• Depth of response (assessed by IMWG criteria)
				• **HRQoL**
				
				Safety
				• **AEs**
				• **SAEs**
				• WDAEs

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	○ Resistance			

AE = adverse event; DOR = duration of response; HRQoL = health-related quality of life; IMWG = International Myeloma Working Group; IsaPd = isatuximab, pomalidomide, dexamethasone; ISS = international staging system; Kd = carfilzomib, dexamethasone; ORR = overall response rate; OS = overall survival; PCd = pomalidomide, cyclophosphamide, dexamethasone; Pd = pomalidomide plus dexamethasone; PFS = progression-free survival; RCT = randomized controlled trial; R-ISS = revised international staging system; RRMM = relapsed and refractory multiple myeloma; SAE = serious adverse event; TTNT = time to next treatment; TTP = time to progression; WDAE = withdrawal due to adverse event.

* Standard and/or relevant therapies available in Canada. The selection of comparators was based on most commonly used, currently available and publicly funded regimens in patients with double refractory MM (to lenalidomide and bortezomib).

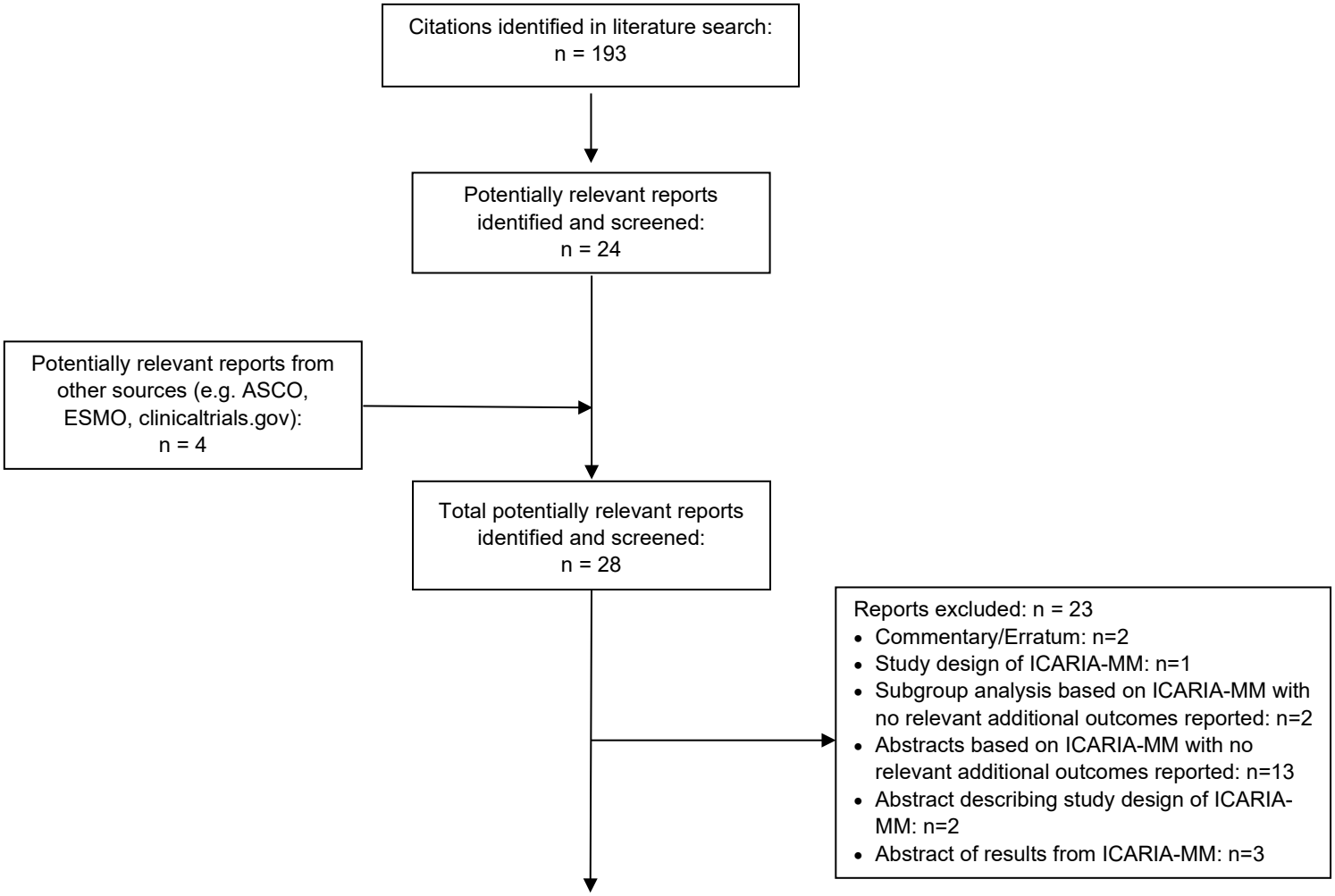
6.3 Results

6.3.1 Literature Search Results

The literature search identified 193 potentially relevant reports. An additional three potentially relevant reports were identified from searches of other sources that included other regulatory agency reviews, literature search updates and conference websites. After preliminary screening, a total of 27 reports that were initially deemed potentially relevant, of which 22 were excluded based on abstract or full text review for the reasons outlined in Figure 2. Reports were excluded because they were either an erratum[30] or commentary,[31] reported outcomes that were not relevant (i.e., subgroup analyses),[32,33] or described the trial design.[34]

After completion of screening, one unique study (ICARIA-MM)[2] was identified and included in the review. Several duplicate citations of this study (including conference presentations of study design) were found, all of which were conference abstracts and contained information reported in full publications.[35-38] Numerous conference abstracts presenting data from subgroup or post hoc analyses of data from the ICARIA-MM trial were identified;[39-51] however, most of these abstracts did not provide additional information or data on outcomes of interest, and were therefore excluded. One abstract, a post-hoc analysis further investigating HRQoL was included.[52] No studies that directly compared IsaPd to Kd or Pd in combination with cyclophosphamide were found.

Figure 2: Flow Diagram for Study Selection



5 citations and reports presenting data from 1 unique study included in this report
ICARIA-MM
Attal et al., 2019[2]
Clinicaltrials.gov (ICARIA-MM, NCT02990338 record)[53]
Subgroup analysis, conference abstract
Houghton et al., 2019 (HRQoL)[52]
Reports identified from other sources
European Medicines Agency – European Public Assessment Report (EPAR): Sarclisa[5]
US FDA Multi-disciplinary Review and Evaluation: Sarclisa (isatuximab)[4]

ASCO = American Society of Clinical Oncology; EPAR = European Public Assessment Report; ESMO = European Society for Medical Oncology; HRQoL = health-related quality of life.
Note: Additional data related to the ICARIA-MM study were also obtained through requests to the Sponsor by CADTH.[3,6-8,54]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One RCT[2] was identified that met the selection criteria of this review. ICARIA-MM is an ongoing, open-label, randomized, phase III trial that compares IsaPd to Pd in patients with refractory or RRMM.[2] Key characteristics of the ICARIA-MM trial are summarized in Table 9. Of note, since a phase III trial was identified, studies of other clinical trial phases (e.g., phase I or II) will not be summarized in this review.

Table 9: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes

Study[2,4]
ICARIA-MM (EFC14335)
NCT02990338
 	
Characteristics
Phase III, open-label, randomized (1:1), active-controlled trial
 	
N = 307 randomized (154 = IsaPd; 153 = Pd)
 	
Setting
102 sites in 24 countries (Canada, Australia, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Korea, New Zealand, Norway, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Taiwan, Turkey, United Kingdom, United States)
 	
Patient Enrolment Dates
January 10, 2017 to February 2, 2018
 	
Data cut-off
October 11, 2018 (for efficacy analysis)
	Key Inclusion Criteria
	• ≥ 18 years of age with documented diagnosis of MM with measurable disease*
	• Received ≥ 2 prior lines of anti-myeloma therapy‡, including ≥ 2 consecutive cycles of lenalidomide and PI†, given alone or in combination
	• Failed treatment with lenalidomide and PI, alone or in combination, occurring at any line of therapy§
	• Refractory to last received line of treatment¶
	
	Key Exclusion Criteria
	• Primary refractory MM#
	• Concurrent plasma cell leukemia
	• Measurable disease by Free Light Chain only
	• Active AL amyloidosis
	• ECOG PS > 2
	• Refractory to prior anti-CD38 mAb treatment (i.e., disease progression on or < 60 days after end of treatment or failure to achieve at least MR)
	• Prior pomalidomide treatment
	• Anti-myeloma drug < 14 days prior to randomization (including dexamethasone)
	• Prior allogenic SCT with active GvHD
	• Major procedure (surgery, radiotherapy, plasmapheresis) < 14 days prior to study treatment start
	• Prior investigational or prohibited therapy (for this study) < 28 days or 5 half-lives from randomization, whichever is longer
	• Inadequate hematologic and hepatic function**
	• Inadequate renal function defined as creatinine clearance < 30 mL/min (MDRD formula)
		Intervention
		(IsaPd)
		Isatuximab plus pomalidomide plus dexamethasone in 28-day cycles:
		
		Isatuximab 10 mg/kg IV
		Cycle 1: Days 1, 8, 15, 22
		Cycle 2+: Days 1, 15
		
		Pomalidomide 4 mg PO once daily on Days 1 to 21
		
		Dexamethasone PO or IV
		40 mg for < 75 years
		20mg for ≥ 75 years
		Days 1, 8, 15, 22
		
		Comparator
		(Pd)
		Pomalidomide plus dexamethasone in 28-day cycles:
		
		Pomalidomide 4 mg PO once daily on Days 1 to 21
		
		Dexamethasone PO or IV
		40 mg for < 75 years
		20mg for ≥ 75 years
		Days 1, 8, 15, 22
		
		Treatment continued until disease progression or unacceptable toxicity occurred.
			Primary
			• PFS
			
			Secondary
			Key efficacy endpoints
			• OS
			• ORR
			
			Other endpoints
			• TTP
			• DOR
			• PFS in high risk cytogenetic population
			• ADA to isatuximab
			• PK parameters
			• HRQoL
			  ○ EORTC QLQ-C30
			  ○ EORTC QLQ-MY20
			  ○ EQ-5D-5L
			
			Exploratory‡‡
			• Pharmacogenetic assessment
			• PK and Pdy relationship
			• MRD in CR patients

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
November 22, 2018 (for safety analysis) **Final Analysis Date** To be conducted after approximately 220 deaths have occurred (51 months after first enrolment) **Funding** Sanofi	• Ongoing > grade 1 toxicity from prior anti-myeloma treatment (except alopecia and those permitted under eligibility criteria) • Significant cardiac dysfunction (MI < 12 months, unstable poorly controlled angina)†† • Diagnosed and treated for another malignancy < 3 years prior to randomization • Malabsorption syndrome • Daily treatment for > 7 days with corticosteroid (equivalent to prednisone ≥ 10 mg/day), except inhaled formulations		

ADA = anti-drug antibodies; AL = amyloid light-chain; CR = complete response; DOR = duration of response; ECOG PS = European Cooperative Oncology Group performance status; EORTC = European for Research and Treatment of Cancer; EQ-5D-5L = EuroQol Group 5-dimension, 5-level per dimension; GvHD = graft vs. host disease; HRQoL = health-related quality of life; IMWG = International Myeloma Working Group; IsaPd = isatuximab plus pomalidomide plus dexamethasone; IV = intravenous; mAb = monoclonal antibody; MI = myocardial infarction; MM = multiple myeloma; MR = minimal response; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; Pd = pomalidomide plus dexamethasone; Pdy = pharmacodynamic; PFS = progression-free survival; PI = proteasome inhibitor; PO = oral; PK = pharmacokinetic; QLQ-C30 = Quality of Life questionnaire with 30 questions; QLQ-MY20 = Myeloma Module with 20 items; SCT = stem cell transplant; TTP = time to progression.

* Measurable disease defined as serum M protein ≥ 0.5 g/dL (via serum protein immunoelectrophoresis) and/or urine M protein ≥ 200 mg/24 hours (via urine protein immunoelectrophoresis)

‡ A complete transplant procedure (involving induction treatment, mobilization, conditioning, transplant, followed by consolidation/maintenance) is considered one line of treatment. Each of the other regimens were considered one line of therapy, regardless of reason for discontinuation (e.g., progression, adverse event, or patient request).

† Protease inhibitors include bortezomib, carfilzomib, ixazomib.

§ Treatment failure defined as:

- Occurrence of progression while on treatment or within 60 days from end of treatment
- If there was previous response ≥ PR to lenalidomide and/or PI, progression must have occurred within 6 months after discontinuing treatment
- Development of intolerable toxicity after minimum two consecutive cycles of a treatment regimen containing lenalidomide and a PI, alone or in combination. Intolerance defined as:
  - For PI-containing regimens: any toxicity leading to discontinuation of PI. If peripheral neuropathy, severity must be ≤ grade 1 prior to study entry.
  - For lenalidomide-containing regimens: any toxicity leading to discontinuation of lenalidomide. If rash or non-hematologic toxicity, severity must not have been grade 4. All non-hematologic toxicities must be ≤ grade 1 prior to study entry.

¶ Refractory disease defined as progression on or within 60 days after end of the previously received therapy (prior to study entry) and includes two categories:

- Refractory disease: patients who should have achieved at least a MR in one previous line, and who were refractory to all previous lines of treatment.
- Relapsed and Refractory disease: patients who had relapsed from ≥ 1 previous line of therapy and were refractory to the last line of treatment. Patients can also be refractory to other prior line(s) of treatment.

Primary refractory MM defined as patients who have never achieved at least a MR with any treatment

** Inadequate hematological, hepatic, or renal function includes the following:

- Platelet count < 75,000 cells/μL if < 50% of bone marrow nucleated cells are plasma cells, or < 30,000 cells/μL if ≥ 50% of bone marrow nucleated cells are plasma cells
- Absolute neutrophil count < $1x10^9$/L
- Total bilirubin > 2x upper limit of normal (ULN)
- Corrected serum calcium > 3.5 mmol/L
- Aspartate aminotransferase and/or Alanine aminotransferase > 3 x ULN

†† Exceptions include complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, in-situ malignancy, or low risk prostate cancer after curative treatment.

‡‡ Only pre-specified exploratory endpoints are listed. The study also evaluated the following exploratory endpoints which were not pre-specified in the protocol: time to first response, time to best response, ORR based on investigator assessment, very good partial response (VGPR) rate, and time to next treatment. Best overall response and clinical benefit rate were also explored.

Source: Attal et al., 2019[2]

a) Trial

ICARIA-MM is an ongoing, open-label, randomized, phase III trial that compares IsaPd to Pd alone in patients with RRMM who had received at least two lines of therapy, including lenalidomide and a PI. Enrolled patients must have failed treatment that included at least two consecutive cycles of lenalidomide and a PI, given alone or in combination. Additionally, patients were required to be refractory to the last received line of treatment. The primary objective of the study is to determine the benefit of adding isatuximab to

the combination of pomalidomide and low-dose dexamethasone on PFS when compared to Pd alone in patients with RRMM.[2] The study is being conducted at 102 sites in 24 countries, which are listed in Table 9, and includes five patients treated at three sites in Canada, all of which are located in the province of Quebec.[8] The manufacturer and distributor of isatuximab, Sanofi (Cambridge, MA, USA), provided funding for the trial as well as study oversight. The funder, along with the investigator steering committee, designed the study. The funder also had a role in the collection, analysis, and interpretation of data, as well as writing of the report. All authors interpreted the data, and also reviewed, edited, and approved the manuscript which was written by the lead authors.

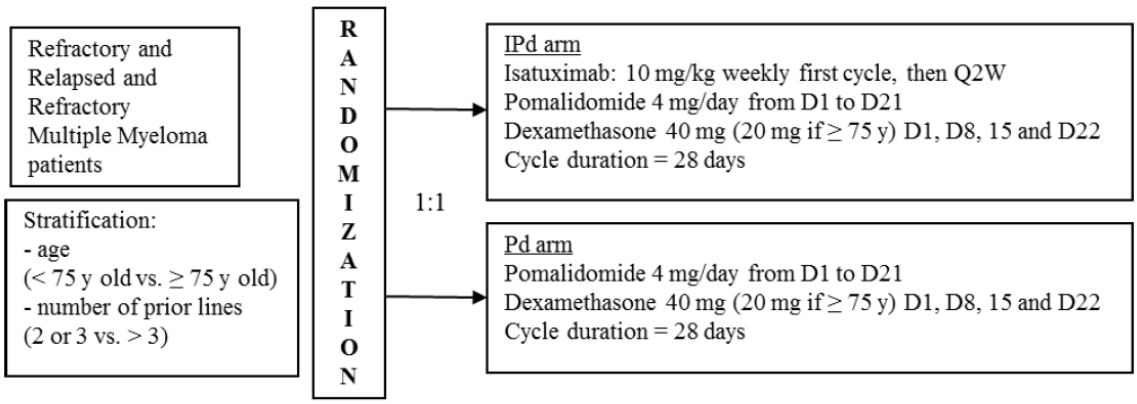
Trial design

Screening and Randomization

Patients were screened up to 21 days prior to randomization (or 28 days for female patients of child-bearing potential).[2] Key inclusion and exclusion criteria are outlined in Table 9 above. Briefly, the study recruited adults who had RRMM, with documented measurable disease (via serum or urine monoclonal protein). Patients must have received at least two previous lines of treatment that included at least two consecutive cycles of lenalidomide and a PI (i.e., bortezomib, carfilzomib, ixazomib), given alone or in combination. Enrolled patients must have also failed to respond to lenalidomide and a PI and be refractory to the last received line of treatment. Treatment failure was defined as disease progression on or within 60 days after discontinuing treatment, disease progression within six months after achieving at minimum a PR, or drug intolerance. The trial aimed to include two categories of patients who progressed on or within 60 days after end of last treatment: a) refractory disease; and b) relapsed and refractory disease. Patients with primary refractory disease were excluded; all patients must have achieved a minimal response or better to at least one prior line of treatment. Enrolled patients had an ECOG PS of 0 to 2. Prior treatment with anti-CD38 monoclonal antibody was permitted, as long as the disease was not refractory to the treatment. Prior treatment with pomalidomide was not permitted.[2]

Eligible patients were assigned in a 1:1 ratio, using a permuted-block randomization strategy with a block size of four, to receive open-label treatment with IsaPd or Pd. Treatment was administered in 28-day cycles until occurrence of disease progression or unacceptable toxicity. Randomization, performed through an interactive response technology system three to five working days prior to first dose, was stratified by the number of previous lines of treatment (2 to 3 vs. 3) and age (< 75 vs. ≥ 75 years).[2] The study design is summarized in Figure 3 below.

Figure 3: Overview of ICARIA-MM Study Design



D=study day, y=years; IPd=isatuximab, pomalidomide, and dexamethasone; Pd=pomalidomide and dexamethasone
Source: FDA Multi-disciplinary Review[4]

Disease and Response Assessment

Disease assessments for efficacy outcomes (i.e., response and disease progression) were determined by a blinded IRC.[2]

Disease assessments were performed at screening and at Cycle 1 Day 1 prior to starting study drug. During treatment, assessments were performed on Day 1 of each cycle until disease progression, and then performed again at the end of treatment (EOT). If treatment was stopped due to any reason other than PD, assessments continued every four weeks until disease progression.

Laboratory disease assessments, measured at a local and central laboratory, included serum and urine monoclonal proteins (M proteins) by immunoelectrophoresis and immunofixation, serum free light chains (quantification and ratio), as well as quantitative immunoglobulins.[2]

Bone marrow aspirates or biopsy were taken at baseline and then as clinically indicated for assessment of plasma cell infiltration (measured at a local laboratory), as well as minimal residual disease (MRD) and cytogenetic risk status via FISH, with the latter two measured by the central laboratory. During study treatment, bone marrow aspirates were used to confirm complete response (CR; via local laboratory) and to assess for MRD (via central laboratory) in patients who achieve CR; if the first MRD result was positive, the test was repeated in three months to check for late negativity. If MRD remained positive, collection of one additional sample in another three months was permitted.[2]

Skeletal surveys (of skull, spine, long bones, pelvis, and chest) or low-dose whole-body CT scans were performed to assess for bone disease at baseline then once a year or anytime if clinically indicated. In patients with documented extramedullary disease, including bone plasmacytoma, CT or MRI scans were performed at baseline, then every 12 weeks (± 1 week) to confirm CR. All radiology imaging was reviewed centrally. If patients discontinued treatment for reasons other than PD, assessment was continued until disease progression.[2]

Monitoring and Follow-up

Safety assessments were undertaken throughout treatment. Various laboratory tests were performed at baseline and at regular intervals until EOT (30 days after last dose), or as clinically indicated. Physical exams were performed prior to each treatment during Cycle 1 (i.e., Day 1, 8, 15, 22) then on Day 1 of each cycle thereafter and at EOT. Vital signs were collected similarly, but also on Day 15 of each cycle. Blood chemistry and hematology panels were performed at the local laboratory at baseline, prior to each dose during the first cycle, on Day 1 of each subsequent cycle, and at EOT. Hematology assessments were also done on Day 15 of Cycle 2 and 3. Urinalysis and coagulation tests were conducted at baseline and then as clinically indicated during treatment. Patient-reported outcomes were collected on Day 1 of each cycle, at EOT, and 60 days (± 5 days) after administration of last study treatment.[2]

In the isatuximab treatment group, serum samples for pharmacokinetic evaluation were collected at regular intervals during the first four cycles. Vital signs were also taken just prior to and one hour after the start of isatuximab infusion, as well as at the end of infusion during the first four cycles. Testing for anti-drug antibodies was performed on Day 1 and 15 of Cycle 1, then Day 1 of each cycle prior to isatuximab administration, at EOT, and also at 60 days (± 5 days) after administration of the last dose. If test results at 60 days was positive or inconclusive, additional testing was required every 30 days until the sample was negative.[2]

The treatment discontinuation visit occurred the earlier of 30 days after last treatment administration or prior to initiation of subsequent anti-myeloma therapy. During post-treatment follow-up, information on survival, initiation of new anti-cancer treatment, and development of second primary malignancies was collected at 60 and 90 days after the administration of last dose, then approximately every three months until death.[2]

Duration of Study Participation

Patients who entered the study were followed from the signing of informed consent until the first of either death, consent withdrawal, or the OS data cut-off date.

After initiating treatment, patients continued until disease progression, unacceptable AEs, patient wish, or other reasons. Patients who discontinued study treatment due to PD were followed until death or OS data cut-off date, whichever occurred first. Follow-up occurred every three months for further anti-myeloma treatment, second primary malignancies, as well as survival status. Patients who discontinued study treatment prior to PD were followed monthly until confirmed PD (even in patients who started subsequent anti-myeloma treatment without PD); thereafter, patients were followed every three months (also for subsequent anti-myeloma treatment, second primary malignancies, and survival status) until death or OS data cut-off date, whichever occurred earlier.

Study Endpoints

Efficacy Analyses

Primary Endpoint

The primary efficacy endpoint of the ICARIA-MM trial was PFS, defined as the time from date of randomization to the date that the first of the following occurred: a) disease progression as determined by the IRC or b) death from any cause.[2]

Progressive disease was defined according to the IMWG criteria as any of the following:

- Increase in serum M-component by ≥ 25% from nadir (with absolute increase of ≥ 0.5 g/dL) in two consecutive assessments
    - If starting M-component is ≥ 5 g/dL, then increase by ≥ 1 g/dL in two consecutive assessments could be used to define relapse
- Increase in urine M-component by ≥ 25% from nadir (with absolute increase of ≥ 200 mg/24 h) in two consecutive assessments
- Definite development of new bone lesions or soft tissue extramedullary disease, or the following:
    - For > 1 existing soft tissue extramedullary lesions, increase by ≥ 50% from nadir in the sum of perpendicular diameters, or
    - If there is a previous soft tissue extramedullary disease lesion > 1 cm in short axis, then ≥ 50% increase in the longest diameter[2]

For the primary analysis of PFS, clinical and/or symptomatic deterioration was not considered as progression. Also, PD was not diagnosed solely by Free Light Chain (FLC) progression.[2]

On Day 1 of each cycle, the IRC used central laboratory data, bone marrow aspirate/biopsy and central review of radiologic imaging to assess for disease progression and treatment response. If response or progression were based on serum and/or urine M protein, two consecutive assessments were required to confirm results. Decision to continue study treatment was based on investigator assessed local laboratory results.[2]

All efficacy analyses were conducted in the ITT population and patients were analyzed according to the group they were randomized to, regardless of the actual treatment received. A log-rank test was performed as primary analysis for comparison of outcomes between the treatment groups using a one-sided 0.025 alpha level, with stratification based on age and previous lines of therapy. A stratified Cox proportional-hazards model was used to estimate the HR and corresponding 95% CIs for each treatment effect, employing the same stratification factors as those used for the primary log-rank test. To estimate 25th, 50th, and 75th percentiles of PFS data, the Kaplan Meier (K-M) approach was used with Brookmeyer and Crowley method applied to estimate the corresponding 95% CIs.[2]

Patients who had not experienced disease progression or death before the data analysis cut-off date, or those who had initiated subsequent anti-myeloma treatment were censored in the analysis of PFS. Time of censoring was either the date of data analysis cut-off, or date of last valid disease assessment not showing disease progression (and taken prior to starting any subsequent anti-myeloma treatment), whichever came first. If no valid post-baseline disease assessments were available, patients were censored at the day of randomization.[2]

Sensitivity and Subgroup Analyses

Several sensitivity analyses were performed at a one-sided alpha level of 0.025, using the same statistical methods used in the primary analysis but with different censoring and event rules. Most, though not all sensitivity analyses were prespecified. Sensitivity analyses for PFS according to investigator assessment of response (including symptomatic deterioration as an event), PFS without censoring for subsequent anti-myeloma treatment, as well as PFS where initiation of further anti-myeloma treatment was considered an event were prespecified.[2] One sensitivity analysis was not prespecified and was added at the time of amendment (version 2) to the statistical analysis plan, which occurred after the data cut-off date (but prior to database lock).[3] This additional analysis explored PFS according to investigator assessment of response, ignoring symptomatic deterioration.[2]

Subgroup analyses of PFS were performed for numerous potential prognostic factors and/or treatment effect modifiers, in addition to the two stratification factors (age, lines of therapy), as seen in Table 10. Most were prespecified, though regulatory region of the world and refractory status to lenalidomide were added in an amendment to the statistical analysis after the data cut-off date.[2,3] In patients with available results, subgroup analysis was performed using a Cox proportional hazards approach and included terms for the factor, treatment, and their interaction. A 10% alpha level was used for performing the test of interaction.[2]

Table 10: Covariates Investigated in PFS Subgroup Analysis

Subgroup	Description
Age (eCRF)	<65 versus [65 - 75[versus ≥75 years
Number of previous lines of therapy (IRT)	(2 or 3) versus >3
Gender	Male versus female
Race	Caucasian versus Asian versus other
Region of the world (geographical)	Western Europe versus Eastern Europe versus North America versus Asia versus Other countries
Region of the world (regulatory)	Western countries versus Other countries
ECOG PS at baseline	0 or 1 versus 2
ISS staging at diagnosis	I vs II versus III
R-ISS staging at study entry	I vs II versus III
Cytogenetic abnormality (del(17p), t(4;14), t(14;16))	At least one versus none
Cytogenetic abnormality del(17p)	Yes versus No
MM type at diagnosis	IgG versus non-IgG
Baseline creatinine clearance (MDRD formula)	≥60 mL/min/1.73 m^2 versus <60 mL/min/1.73 m^2
Refractory to PI	Yes versus No
Refractory to lenalidomide	Yes versus No

ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; IRT=interactive response technology; MDRD=Modification of Diet in Renal Disease; MM=multiple myeloma; R-ISS=International Staging System

Note: White and Caucasian are used interchangeably in this document.

Source: FDA Multi-disciplinary Review[4]

Prognostic factors were identified among the variables (demographics and baseline characteristics) included in the subgroup analyses using a multivariate Cox proportional hazard model, with a stepwise selection procedure and 15% significant level for removal of effects. If major confounding was identified due to imbalance in an identified prognostic factor at baseline, an exploratory analysis of PFS was performed using the multivariate Cox proportional hazards model that was adjusted for the prognostic factors.[2]

Secondary Endpoints

Several secondary efficacy endpoints were prespecified in ICARIA-MM, as defined below. Two were considered key secondary endpoints and included ORR and OS. Only these key secondary endpoints of were part of the statistical testing hierarchy. All efficacy endpoints were analyzed in the ITT population. Time-to-event endpoints were analyzed using the K-M method; analyses were descriptive only and any testing performed on these secondary endpoints was considered exploratory.[2]

- ORR – defined as the proportion of patients who achieved the following responses as the BOR, according to IRC assessment and using the IMWG response criteria: stringent complete response (sCR), CR, very good partial response (VGPR), or PR. The IRC-assessed ORR was compared between treatment groups using a stratified CMH test, and the Clopper-Pearson method was used to calculate CIs.
- OS – defined as the time from date of randomization to date of death due to any cause. Patients who had not experienced death before the data analysis cut-off date were censored at the last date know to be alive or the data cut-off date, whichever occurred earlier. The OS analysis was based on similar statistical methods used in the primary PFS endpoint analysis. A sensitivity analysis adjusting OS for the use of subsequent anti-cancer treatment was added at the time of amendment to the statistical analysis plan, after the data cut-off date. This analysis was performed using the inverse probability of censoring weighting (IPCW) method.
- TTP – defined as the time from date of randomization to date of first documented PD, as determined by IRC. Disease progression was defined in the same manner as the primary PFS endpoint. Censoring rules were similar to those used in the primary PFS analysis.

- DOR – defined as the date of first IRC-determined response to the date that the first of the following occurred: first PD as per IRC or death. This endpoint was determined only for patients who achieved a response of PR or better. Censoring rules were similar to those used in the primary PFS analysis.
- PFS in high risk cytogenetic population – defined as PFS in the subgroup of patients with high risk cytogenetic changes as assessed by FISH, including del(17p), t(4;14), or t(14;16). A cytogenetic abnormality was defined as 50% of abnormal plasma cells for del(17p) and 30% of abnormal plasma cells for t(4;14) and t(14;16). High risk was defined as presence of one of these three cytogenetic abnormalities as detected by central FISH assessment. Analysis of PFS in this population was based on the K-M method employing the same censoring rules as primary PFS analysis.[2]

Exploratory Endpoints

Prespecified efficacy endpoints that were exploratory in nature included MRD. In patients who achieved CR on treatment, MRD in bone marrow samples was assessed by next-generation sequencing to determine depth of response. MRD status was summarized using descriptive statistics in the ITT population. Patients without MRD assessments were considered as being positive for MRD in the analysis.[2]

Several exploratory endpoints which were not pre-specified were included in an amendment to the statistical analysis plan. For example, ORR based on investigator assessment, and VGPR rate (VGPR or better) were added after the data cutoff date, but prior to data-base lock.[3] Additional analyses at the time of the PFS analysis included investigator-assessed BOR and clinical benefit rate (minimal response or better). BOR was defined as the best sequential response from start of treatment to the first of disease progression, death, initiation of subsequent anti-myeloma treatment, or data cut-off date. Response, according to the IMWG criteria were categorized as follows, from best to worse: sCR, CR, VGPR, PR, minimal response (MR), stable disease (SD), PD, and not evaluable (NE). A confirmation of any disease response (PR or better) or disease progression, using two consecutive assessments within four weeks was required. As these treatment response endpoints were not included in the formal testing hierarchy, such analyses are for descriptive purposes only.

Subsequent anti-myeloma therapy, given after discontinuation of study treatment was reported in this trial. Time to next treatment (TTNT) data was assessed as an exploratory endpoint, although this was not pre-specifed.[3] TTNT was defined as time from randomization to the start of subsequent anti-myeloma treatment, and was analyzed using the K-M methods. Patients who did not receive further treatment prior to the data cut-off date were censored at either the date of data cut-off or their last follow-up visit, whichever was earlier. For patients with no follow-up visit, censoring occurred on the earlier date of either data cut-off or last study treatment administration.[2]

<u>Patient-Reported Outcomes</u>

Patient-reported outcomes relating to disease and treatment-related symptoms experienced by study participants were measured electronically and as part of secondary endpoints. Health-related quality of life was measured using EORTC QLQ-C30 and the accompanying EORTC QLQ-MY20. Health status utility scores used in health economic analyses were obtained through administering the EQ-5D-5L questionnaire. The questionnaires were completed by patients on Day 1 of each treatment cycle prior to any other assessments, discussions of patient's health, or administration of study treatment. Questionnaires were also administered at treatment discontinuation (EOT visit). During post-treatment follow-up, questionnaires were completed at 60 (± 5) days after last administration of study treatment.[2]

Analysis of PRO endpoints were performed in the safety population, in patients who had completed the baseline assessment plus at least one assessment post-baseline. Compliance was evaluated based on the number and percentage of forms received compared to what was expected, as well as the number and percentage of evaluable forms compared to expected. Mean change in scores from baseline to each cycle, from baseline to EOT, and from baseline to 60 days after last administration of study treatment were analyzed using descriptive statistics for each of the three instruments.[2]

The MCID from baseline was defined as an increase or decrease of 10 points for EORTC QLQ-C30 and QLQ-MY20 summary scores, subscales, and symptom items. For EQ-5D-5L health state utility values, the MCID was defined as 0.074 points, and 7 points for EQ-5D-5L VAS. The differences within or between groups were not assessed for statistical significance.[4]

EORTC QLQ-C30 is a validated, multi-dimensional, cancer-specific instrument consisting of 30 questions, with a recall period of one week. The questionnaire assesses five aspects of patient functioning (i.e., cognitive, emotional, physical, role, social), three symptoms scales (i.e., fatigue, pain, nausea and vomiting), global health status (GHS)/QoL, and six single items (i.e., appetite loss, constipation, diarrhea, dyspnea, insomnia, financial difficulties) over the past week. Each score is converted onto a scale of 0 to 100 points; higher scores in the functional and global health scales imply better functioning or GHS, whereas higher scores in the symptom and single item scales indicate worse symptoms or problems. The EORTC QLQ-MY20 is a multiple myeloma-specific assessment used along with the EORTC QLQ-C30 and consists of 20 questions. The questionnaire includes measures for four independent subscales for two functional domains (i.e., future perspective, body image) and two symptoms scales (i.e., disease symptoms, side effects of treatment). A higher score in the functional domain indicates better outcomes, whereas a higher score in the symptom scales indicates more symptoms or side effects.[2]

The EQ-5D-5L is a standardized instrument that provides a measure of general health and wellbeing. The updated 2011 version was used, which includes a descriptive section comprised of five dimensions and a VAS. Each of the five dimensions (i.e., anxiety/depression, pain/discomfort, mobility, self-care, usual activities) has five response levels (i.e., no problems, slight problems, moderate problems, severe problems, and extreme problems). The EQ VAS provides a quantitative measure by recording a respondent's self-rated health on a 20cm vertical scale, between the best health to the worst health the patient can imagine. Global scores can be measured, with higher scores indicating better HRQoL. The health utility index was calculated according to the EuroQol country-specific algorithms. In the event a specific country algorithm was unavailable, health utility scores were generated based on value sets from the UK population.[2]

Safety

All patients who received at least one partial or full dose of study drug were included in the safety analysis population and were analyzed according to the actual treatment received. Adverse events were categorized by System Organ Class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA), and severity was measured using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. For patients with multiple occurrences of the same AE, the worst grade was used.[2]

Patients were monitored throughout the study for safety and tolerability. In addition to TEAEs and serious TEAEs, evaluation of other safety indicators such as laboratory parameters, vital signs, weight, ECOG PS and physical exams were also performed. All AEs were reported up to 30 days after the last dose of study treatment and followed until deemed resolved or stable. AEs related to the study treatment that occurred during the follow-up period were also followed until deemed resolved or stable.[2]

Several AEs of special interest were specified in the study protocol, including grade 3 or 4 acute infusion-related reactions, second primary malignancies, symptomatic overdose, as well as pregnancy of female patient or female partner of a male patient.[2]

Statistical Analysis

Sample Size

Sample size was determined based on the primary endpoint of PFS and supported by a key secondary endpoint of OS. Approximately 300 patients were planned for enrolment to achieve the targeted number of events for each endpoint (i.e., 162 PFS events, 220 deaths for final OS).[2]

The primary PFS analysis was planned for when 162 PFS events had occurred, with the study designed to have approximately 90% power in detecting a HR of 0.60 in PFS with a 1-sided significance level of 0.025 using a log-rank test. This corresponds to an improvement in the true median PFS time from 4 months to 6.67 months. The assumption was made that the control group (Pd) had a median PFS of 4.0 months, and that the addition of isatuximab would result in 40% risk reduction in the hazard rate compared to Pd alone.[2]

The OS analysis required 220 deaths to achieve approximately 80% power to detect a target HR of 0.685 in OS with a 1-sided significance level of 0.025 using a log-rank test. This corresponds to an improvement in OS of 6 months. The assumption was made

that the control group (Pd) had a median OS of 13.0 months, and that the addition of isatuximab would result in a 31.5% risk reduction in the hazard rate.[2]

Interim Analyses and Multiplicity

No interim analyses were planned for PFS. The final PFS analysis was estimated to occur approximately 18 months after randomization of the first patient. This estimation was based on the assumptions that 15 patients per month would be accrued, and PFS followed an exponential distribution in both treatment groups. For OS, one interim analysis was prespecified. The interim OS analysis was performed at the time of PFS analysis, which was estimated to occur when approximately 36% of required OS events (80 out of 220 deaths) were observed.[2]

Formal comparisons of the primary and key secondary endpoints were made at the time of final PFS analysis, using a closed test procedure at a one-sided significance level of 0.025 to control for type I error. Specifically, analysis of ORR and the interim analysis of OS were performed in a hierarchical manner if an improvement in median PFS was demonstrated (i.e., significance level reached). If an improvement in PFS was observed and deemed statistically significant, ORR was tested at the one-sided significance level of 0.025. If improvement in ORR was also deemed significant, OS was sequentially tested as a formal comparison which permitted early stopping due to superior efficacy. Exact stopping boundaries for superior efficacy depended on the actual number of deaths that occurred at the time of interim analysis. O'Brien and Fleming alpha spending functions were used to determine stopping boundaries.[2]

For OS, the final analysis is estimated to occur approximately 51 months after randomization of the first patient. The O'Brien and Fleming alpha spending function was used to identify the nominal significance level for the final OS analysis. For the final survival comparison, the nominal significance level is 0.0249 for 220 events, which corresponds to a HR of 0.767.[2]

Other secondary and exploratory endpoints were not adjusted for multiplicity.[4]

Protocol Amendments

The original protocol was issued on August 4, 2016. Six amendments were subsequently made: four global (Amendments 1,3a, 4, 5) and two country-specific (Amendment 2 for UK and Amendment 3 for Japan). Of the four global amendments, one (Amendment 1) was introduced before the inclusion of any patients, two (Amendment 4 and 5) occurred after patient enrolment was complete. When Amendment 3a was approved, seven patients had been randomized and 10 patients had signed consent. For Amendment 4, although it was submitted prior to the data cut-off date, it had not been implemented at all sites. Amendment 5 occurred after the data cut-off date. Three of the global protocol amendments were considered substantial, with key changes summarized in Table 11 below.[2,4]

Table 11: Summary of Key Changes in the Substantial Global Protocol Amendments

Protocol Number (Date)	Summary of Key Changes
Amended Clinical Trial Protocol 1 (Nov 1, 2016)	• Added ECG assessment to Cycle 2, Day 1 and at EOT as a precautionary measure; current data des not show evidence of repolarization issues, and isatuximab has low likelihood of inhibiting hERG. • Clarified the two options for radiographic assessment of bone disease (i.e., skeletal survey and low-dose whole-body CT scan). Also included an update for patients with known extramedullary disease at baseline assessment, that a CT scan or MRI was required at baseline and every 12 weeks. For patients with suspicion of extramedullary disease, a CT scan or MRI was required at baseline to rule out its presence. • Changes were made so that cytogenetic abnormalities other than del(17p), t(4:14), t(14:16) were explored. • Updated assessment of PROs to occur at EOT and 60 days after last administration of study treatment. Only patients who discontinued treatment without disease progression would not have PRO assessments after the EOT visit. • Added secondary primary malignancy to list of AEs of special interest. • Clarified that dexamethasone administration was not permitted within 14 days of entering study. • Clarified that for prior treatment with lenalidomide and a PI, agents could be given alone or in combination.

Protocol Number (Date)	Summary of Key Changes
	• Indicated that patients who discontinued treatment without PD were to continue in the follow-up period even if another anti-myeloma treatment was initiated. • Updated definition of renal dysfunction to CrCl <30 mL/min, from previous <45 mL/min
Amended Clinical Trial Protocol 3a (May 18, 2017)	• Updated number of OS events required prior to interim analysis; this adjustment was made due to reduction in the enrolment window, which occurred after Amendment 01. According to the sponsors, enrolment was occurring faster than anticipated to achieve the 162 PFS events for primary analysis, thus the estimated number of OS events (for interim analysis) was reduced to 36% of the required 220 final OS events. This update did not alter the study protocol, analysis plan, or results of the study. • Deleted IRC review of extramedullary disease (confirmation of presence of absence); IRC would only review and assess treatment response. • Added details to allow reassessment of pre-medications in patients who do not experience an infusion-related reaction after four administrations of isatuximab. • Clarified decision to continue study treatment according to investigator was based on results from the local laboratory. • Modified exclusion criteria to specify that patients treated with prior anti-CD38 monoclonal antibody must have achieved MR or better, in addition to not having PD within 60 days of the last dose. • Added secondary primary malignancy as item to monitor during follow-up. • Specified that although all infusion reactions would be collected, only reactions grade ≥3 were considered AESIs.
Amended Clinical Trial Protocol 5 (June 11, 2019)	• Required contraceptive measures and pregnancy testing timeline were revised from the original 3 months to 3 or 5 months after the last dose of isatuximab. Changes reflect updated pharmacokinetic data on isatuximab, showing a re-estimation of the plasma half-life as 28 days, which prompted changes to the duration of contraceptive measures (required for 5 half-lives).

AE = adverse event; AESI = adverse event of special interest; CrCl = creatine clearance; CT = computerized tomography; ECG = electrocardiogram; EOT = end of treatment; hERG = human Ether-à-go-go-Related Gene; IRC = Independent Response Committee; MR = minimal response; MRI = magnetic resonance imaging; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PI = proteasome inhibitor; PRO = patient-reported outcomes.
Source: Attal et al., 2019 (Study Protocol – Amended Protocol 5, June 2019);[2] FDA Multi-disciplinary Review;[4] Checkpoint Meeting Materials, October 28, 2020 (Sanofi-Genzyme)[3]

Statistical Analysis Plan Modifications

The Statistical Analysis Plan (version 2, issued on November 7, 2018) contains several major amendments from the initial version. According to the sponsor, these changes were approved after the data analysis cut-off date, but prior to database lock. Key changes were as follows:

- Endpoints and disease assessments
  - Exploratory endpoints – the following analyses were added to further characterize efficacy of treatments: time to first response, time to best response, overall response based on investigator assessment, proportion of patients with response rates VGPR or better
  - Disease assessment – death (due to PD) that occurred within 45 days of first documented PD (based on M protein) was considered as confirmation of death. This included deaths that occurred after starting subsequent treatment.
- Safety analyses
  - The following analyses were added to better characterize the safety profile of treatment: cumulative exposure to treatment (in patient-years), isatuximab dose reductions, infusion without medication for reactions, exposure-adjusted treatment-emergent adverse event analysis, indirect antiglobulin test, neutropenic complications, thrombocytopenia and hemorrhages, hemolytic disorders, and autoimmune disorders.
- Sensitivity analyses
  - The following were added:
    - Analysis of PFS according to assessment by investigator, ignoring symptomatic deterioration
    - OS analysis adjusting for switch to subsequent anti-cancer therapy

- Subgroup analyses
    - The following were added: age as per electronic case report form (eCRF), regulatory region, and refractory to lenalidomide
    - The following were removed: age as per interactive response technology, previous allogenic transplantation, previous treatment with anti-CD38 monoclonal antibody. Removal was based on not meeting the required number of patients and/or clinical evaluation for relevance.[2]

b) Populations

Patient Demographics and Baseline Characteristics

A total of 307 patients at 102 hospitals spanning 24 countries were randomly assigned to receive IsaPd (154 patients) or Pd (153) between January 10, 2017 and February 2, 2018.[2] A summary of patient demographics and disease characteristics at baseline are presented in Table 12. Overall, of the total number of patients enrolled, the median age was 67 years (range 36-86; IQR 60-73), 51.8% (n=159) were male and 42.7% (n=131) were enrolled from Western Europe and only 3.9% (n=12) of all enrolled patients were from North America.[2,5] The majority of enrolled patients was identified as White (79.5%; n=244); 11.7% (n=36) were Asian, and 1.3% (n=4) were Black or African American. Most patients had an ECOG PS of 0 (40.4%, n=124) or 1 (49.2%, n=151); a minority of enrolled patients had an ECOG PS of 2 (10.4%, n=32).[5]

The median time from initial diagnosis of MM to randomization was 4.23 years (range 0.5 to 20.5), with the IgG subtype seen most often at diagnosis (65.8%, n=202) and also at study entry (66.8%, n=205). Most patients at study entry had ISS Stage I (37.5%, n=115) or II (35.5%, n=109) disease; however, according to R-ISS, most patients had Stage II disease (64.2%, n=197). A median of 27.0% (range 0 to 100%) bone marrow plasma cell infiltration was reported. Soft tissue plasmacytoma according to IRC assessment was present in 7.8% (n=24) of enrolled patients, and bone lesions (as per IRC) were seen in 67.5% of patients (n=204); and more than ten lesions were reported in 33.1% (n=100) of patients.[5]

Results of cytogenetic testing were available for 78.5% of enrolled patients (n=241). The remainder of patients had missing samples or results or submitted poor quality samples of bone marrow aspirate. Of all randomized patients, 19.5% (n=60) had high-risk chromosomal abnormalities, mostly del(17p) and t(4;14). Eight patients (2.6%) had two high-risk chromosomal abnormalities.[4]

Prior Anti-Myeloma Treatment History

Greater than half of enrolled patients (56.4%, n=173) had received at least one previous autologous stem cell transplant, and 16.0% (n=49) had received two transplants. As per the protocol, all patients had received at least two prior lines of treatment, including lenalidomide and a PI. The median number of previous lines of treatment was three (range 2 to 11; IQR 2 to 4); overall, 34.9% (n=107) patients had received four or more prior lines of therapy.[2,4] All patients enrolled in the study were previously treated with an IMiD (100% received lenalidomide), PI, and a steroid. Most patients (93.5%, n=299) had also previously received an alkylating agent. Of the proteasome inhibitors used as part of prior therapy, the most commonly prescribed was bortezomib (97.7%, n=300). Carfilzomib was received as previous treatment in 25.4% (n=78) of patients, and ixazomib / ixazomib citrate was received by 10.4% (n=32). One patient (0.3%), in the IsaPd group was previously treated with pomalidomide, though this was considered a protocol deviation. One patient (0.3%), also in the IsaPd group, received prior treatment with an anti-CD38 monoclonal antibody (daratumumab).[4]

Response to Prior Anti-Myeloma Medication

All patients enrolled into the study had relapsed and refractory disease.[2,4] Aside from seven patients who had a major protocol deviation, all patients had failed prior treatment with lenalidomide and PI as per the definition outlined in the study entry criteria, which is broader than being refractory to these treatments (and includes intolerance to therapy as well as PD within six months of discontinuing lenalidomide and/or PI after achieving a PR or better).[3] Most patients (92.5%, n=284) were refractory to lenalidomide; 75.9% (n=233) were refractory to at least one PI; 72.6% (n=223) were refractory to both.[4] Specific to Pis, most patients (59.9%, n=184) were refractory to bortezomib, 22.1% (n=68) were refractory to carfilzomib, and 9.8% (n=30) were refractory to ixazomib. Of patients refractory to both an IMiD and a PI, most were refractory to the combination of lenalidomide and bortezomib (55.7%, n=171) followed by lenalidomide and carfilzomib (21.2%, n=65).[6] Refractory status to prior anti-myeloma treatment can be found in Table 13.

Of patients enrolled into the trial, 7.2% (n=22) had experienced intolerance to prior lenalidomide therapy, 13.0% (n=40) were intolerant to a proteasome inhibitor, and 2.6% (n=8) were intolerant to both.[4]

Table 12: Baseline patient demographics and characteristics, ITT population

Baseline Demographics and Characteristics	IsaPd (n=154)	Pd (n=153)
Stratification factors as per IRT		
Age, years, n (%) < 75 ≥ 75	 123 (79.9) 31 (20.1)	 122 (79.7) 31 (20.3)
Prior lines of therapy, n (%) 2 or 3 > 3	 102 (66.2) 52 (33.8)	 101 (66.0) 52 (34.0)
Baseline characteristics		
Age, years* Mean (StdD) Median (range) Age group, years, n (%) < 65 65 to 75 ≥ 75	 66.6 (9.1) 68.0 (36 to 83) 54 (35.1) 68 (44.2) 32 (20.8)	 65.2 (9.5) 66.0 (41 to 86) 70 (45.8) 54 (35.3) 29 (19.0)
Gender, n (%) Male Female	 89 (57.8) 65 (42.2)	 70 (45.8) 83 (54.2)
Race, n (%) White Asian Black or African American Native Hawaiian or Other Pacific Island Missing/NR	 118 (76.6) 21 (13.6) 1 (0.6) 2 (1.3) 12 (7.8)	 126 (82.4) 15 (9.8) 3 (2.0) 1 (0.7) 8 (5.2)
ECOG PS, n (%) 0 1 2	 55 (35.7) 83 (53.9) 16 (10.4)	 69 (45.1) 68 (44.4) 16 (10.5)
Geographic region, n (%) Western Europe Eastern Europe North America Asia Other Countries	 55 (35.7) 28 (18.2) 7 (4.5) 21 (13.6) 43 (27.9)	 76 (49.7) 20 (13.1) 5 (3.3) 15 (9.8) 37 (24.2)
Initial diagnosis of MM, n (%)	154 (100)	153 (100)
Time from initial diagnosis of MM, years Mean (StdD) Median (range)	 5.23 (3.24) 4.46 (0.6 to 18.4)	 5.29 (3.69) 4.09 (0.5 to 20.5)
ISS stage at initial diagnosis, n (%)		

Baseline Demographics and Characteristics	IsaPd (n=154)	Pd (n=153)
Stage I	36 (23.4)	41 (26.8)
Stage II	49 (31.8)	48 (31.4)
Stage III	42 (27.3)	44 (28.8)
Unknown	27 (17.5)	20 (13.1)
ISS stage at study entry, n (%)		
Stage I	64 (41.6)	51 (33.3)
Stage II	53 (34.4)	56 (36.6)
Stage III	34 (22.1)	43 (28.1)
Unknown	3 (1.9)	3 (2.0)
R-ISS stage at study entry, n (%)		
Stage I	39 (25.3)	31 (20.3)
Stage II	99 (64.3)	98 (64.1)
Stage III	16 (10.4)	24 (15.7)
Unknown	0	0
Cytogenic risk at baseline, n (%)		
High CA	24 (15.6)	36 (23.5)
Standard CA	103 (66.9)	78 (51.0)
Unknown or missing	27 (17.5)	39 (25.5)
Prior anti-myeloma treatment, n(%)		
Alkylating agents	139 (90.3)	148 (96.7)
Proteasome inhibitors	154 (100)	153 (100)
Immunomodulators	154 (100)	153 (100)
Lenalidomide	154 (100)	153 (100)
Monoclonal antibodies	2 (1.3)	2 (1.3)
Daratumumab	1 (0.6)	0
Elotuzumab	1 (0.6)	2 (1.3)
Refractory status, n (%)		
Relapsed and refractory	154 (100)	153 (100)
Patients refractory to, n (%)		
IMiD	147 (95.5)	144 (94.1)
Lenalidomide	144 (93.5)	140 (91.5)
PI	118 (76.6)	115 (75.2)
IMiD + PI	113 (73.4)	110 (71.9)
Refractory to last regimen	150 (97.4)	151 (98.7)
Refractory to lenalidomide at last regimen	93 (60.4)	88 (57.5)
Patients intolerant to, n (%)		
Lenalidomide	10 (6.5)	12 (7.8)
PI	19 (12.3)	21 (13.7)
Lenalidomide +PI	4 (2.6)	4 (2.6)
Number of prior lines*		
Mean (StdD)	3.52 (1.73)	3.33 (1.39)
Median (range)	3.0 (2.0 to 11.0)	3.0 (2.0 to 10.0)
Number of lines, n (%):		
2	45 (29.2)	45 (29.4)
3	52 (33.8)	58 (37.9)

Baseline Demographics and Characteristics	IsaPd (n=154)	Pd (n=153)
4	32 (20.8)	28 (18.3)
5	7 (4.5)	8 (5.2)
6	6 (3.9)	10 (6.5)
7	7 (4.5)	2 (1.3)
≥8	5 (3.2)	2 (1.3)
Patients with ≥ 1 transplant, n (%)	83 (53.9)	90 (58.8)
Allogenic transplant	2 (1.3)	2 (1.3)
Autologous transplant	83 (53.9)	90 (58.8)
Patients with ≥ 2 transplants, n (%)	27 (17.5)	22 (14.4)
Autologous transplant only	25 (16.2)	20 (13.1)
Autologous/allogeneic transplant	2 (1.3)	2 (1.3)

CA = chromosomal abnormalities; ECOG PS = European Cooperative Oncology Group Performance Status; IMiD = immunomodulator; IRT = interactive response technology; IsaPd = isatuximab plus pomalidomide plus dexamethasone; ISS = International Staging System; ITT = intention-to-treat; MM = multiple myeloma; NR = not reported; PI = proteasome inhibitor; Pd = pomalidomide plus dexamethasone; R-ISS = Revised International Staging System; StdD = standard deviation.
* based on eCRF, rather than IRT as also displayed at the top of the table
‡ other countries include Australia, New Zealand, Turkey, and Russia
Source: Attal et al., 2019;[2] Checkpoint Meeting Materials, October 28, 2020 (Sanofi-Genzyme);[3] EPAR;[5] Clinical Study Report;[6] CADTH Submission, Clinical Summary[7]

Table 13: Refractory Status to Prior Anti-Myeloma Therapies

Refractory Status	IsaPd (n=154)	Pd (n=153)	Total (n=307)
Refractory to IMiD, n (%)	147 (95.5)	144 (94.1)	291 (94.8)
Refractory to lenalidomide	144 (93.5)	140 (91.5)	284 (92.5)
Refractory to PI, n (%)	118 (76.6)	115 (75.2)	233 (75.9)
Refractory to bortezomib	95 (61.7)	89 (58.2)	184 (59.9)
Refractory to carfilzomib	28 (18.2)	40 (26.1)	68 (22.1)
Refractory to ixazomib	17 (11.0)	13 (8.5)	30 (9.8)
Refractory to IMiD and PI, n (%)	113 (73.4)	110 (71.9)	223 (72.6)
Refractory to lenalidomide and bortezomib	89 (57.8)	82 (53.6)	171 (55.7)
Refractory to lenalidomide and carfilzomib	26 (16.9)	39 (25.5)	65 (21.2)
Refractory to lenalidomide and ixazomib	17 (11.0)	11 (7.2)	28 (9.1)
Refractory to lenalidomide, bortezomib, carfilzomib and ixazomib	0	0	0
Refractory to last line of therapy, n (%)	150 (97.4)	151 (98.7)	301 (98.0)
Lenalidomide	93 (60.4)	88 (57.5)	181 (59.0)
Bortezomib	88 (57.1)	83 (54.2)	171 (55.7)
Carfilzomib	28 (18.2)	40 (26.1)	68 (22.1)
Lenalidomide and bortezomib	81 (52.6)	76 (49.7)	157 (51.1)
Lenalidomide and carfilzomib	26 (16.9)	39 (25.5)	65 (21.2)

IMiD = immunomodulator; IsaPd = isatuximab plus pomalidomide plus dexamethasone; Pd = pomalidomide plus dexamethasone, PI = proteasome inhibitor.
Source: Attal et al., 2019;[2] Clinical Study Report;[6] Checkpoint Meeting Materials, October 28, 2020 (Sanofi-Genzyme)[3]

Comparison Between Treatment Groups

The number of previous lines of therapy, class of drug(s) received, and refractory status to prior treatment were generally balanced between treatment groups. Overall, baseline characteristics and demographics were also balanced, though there were some differences between the two treatment groups. Table 14 summarizes the differences noted in patients randomized to the IsaPd group compared to the Pd group.

Table 14: Imbalanced Baseline Characteristics in the ICARIA-MM trial, ITT population

Baseline Demographics and Characteristics	IsaPd (n=154)	Pd (n=153)
Age < 65 years	54 (35.1%)	70 (45.8%)
Age 65 to 74 years of age	68 (44.2%)	54 (35.3%)
Male	89 (57.8%)	70 (45.8%)
Female	65 (42.2%)	83 (54.2%)
ECOG PS of 0	55 (35.7%)	69 (45.1%)
ECOG PS of 1	83 (53.9%)	68 (44.4%)
Geographical region – Western Europe	55 (35.7%)	69 (45.1%)
ISS Stage I disease at study entry	64 (41.6%)	51 (33.3%)
ISS Stage III disease at study entry	34 (22.1%)	43 (28.1%)
High risk cytogenetic abnormalities at baseline*	24 (15.6%)	36 (23.5%)
Received prior carfilzomib	34 (22.1%)	44 (28.8%)
Renal impairment, CrCl < 60 mL/min/1.73m^2 (MDRD formula)	55 of 142 (38.7%)	49 of 145 (33.8%)

CrCl = creatinine clearance; ECOG PS = European Cooperative Oncology Group performance status; IsaPd = isatuximab plus pomalidomide plus dexamethasone; ISS = International Staging system; Pd = pomalidomide plus dexamethasone; R-ISS = Revised International Staging System.
* most frequent cytogenetic abnormalities were del(17) and t(4;14)
Source: EPAR;[5] FDA Multi-disciplinary Review[4]

Imbalances in prognostic factors such as ISS stage of disease and cytogenetic abnormalities may have favoured the IsaPd group, while differences in ECOG PS and age appeared to have favoured the Pd group. These differences should be considered when interpreting results, though according to the CGP, key baseline characteristics were balanced between the two treatment groups.

c) Interventions

Patients were randomized in a 1:1 ratio to one of two treatment groups, both administered in 28-day cycles. Treatment was administered until disease progression or major toxicity. Diagnosis of disease progression based on laboratory criteria required confirmation with two consecutive measures.[2] Table 15 outlines the dosing and administration schedule of the intervention in each treatment group, as well as a summary of dosing modification guidelines and treatment exposure in the ICARIA-MM trial. Details on concurrent therapies are outlined below the table. The subsequent anti-cancer therapies received by patients are discussed in Section 6.3.2.2 Detailed Outcome Data and Summary of Outcomes.

Table 15: Treatment Details in the ICARIA-MM trial, Safety Population

Detail	Isatuximab plus pomalidomide plus dexamethasone (IsaPd)	Pomalidomide plus dexamethasone (Pd)
Treated	N = 152	N = 149
Cycle length	28-days	28-days

Dose	• **Isatuximab** 10 mg/kg IV infusion
	  ○ Cycle 1: once weekly (Days 1, 8, 15, and 22), then
	  ○ Cycle 2 and beyond: every two weeks (Days 1 and 15)
	• **Pomalidomide** 4 mg PO daily for three weeks (Days 1 to 21)*
	• **Dexamethasone** 40 mg PO or IV once weekly (Days 1, 8, 15, 22)‡
	  ○ 20 mg in patients 75 years of age or older
		• **Pomalidomide** 4 mg PO daily for three weeks (Days 1 to 21)*
		• **Dexamethasone** 40 mg PO or IV once weekly (Days 1, 8, 15, 22)‡
		  ○ 20 mg in patients 75 years of age or older

Premedication	Isatuximab: Routine medications were given with at least the first four administrations to reduce the risk and severity of infusion-related reactions. The following combination† was administered 15 to 30 minutes (maximum 60 minutes) prior to isatuximab infusion in the following order, except dexamethasone:
	• Acetaminophen 650 to 1000 mg PO
	• Ranitidine 50 mg IV
	• Diphenhydramine 25 to 50 mg IV
	• Dexamethasone 40 mg PO or IV
	  ○ 20 mg in patients ≥75 years
	  ○ PO: administered as the first of premedications
	  ○ IV: administered as last of the premedications
		• None

Dosing modification - key details	Details on the recommended action for different AEs, re-initiation of cycles after recovery from an AE, and management of isatuximab infusion-related reactions were outlined in the protocol. In general:	

Detail	Isatuximab plus pomalidomide plus dexamethasone (IsaPd)	Pomalidomide plus dexamethasone (Pd)
	• In the event of toxicity, delay of treatment cycle (i.e., of all treatments within a cycle) was permitted for isatuximab, pomalidomide, and dexamethasone. Dose omission within a cycle was also permitted if the patient had not recovered from toxicity before the day of next planned administration. • Dose reductions were not permitted for isatuximab. Dose reductions were permitted for pomalidomide and dexamethasone; however, once a dose reduction occurred, titration back to the previous dose of pomalidomide or dexamethasone was not permitted. • Study treatment was discontinued if the AE persisted despite dose modifications, or as deemed warranted by the investigator. If one component of the combination treatment was prematurely discontinued, the remaining agents were permitted to continue until disease progression, unacceptable toxicity, or patient withdrawal from study treatment. Details on the number of patients who had a dose modification or delay are discussed in detail under Section 6.3.2.2 (Detailed Outcome Data and Summary of Outcomes; Harms Outcomes – Treatment Modification or Discontinuation Due to Adverse Event).	
Treatment compliance	Isatuximab was administered under the supervision of study centre staff or investigator. For pomalidomide and oral dexamethasone, compliance was measured and documented via a patient diary. • One patient in the study (in the IsaPd group) discontinued treatment due to noncompliance.	

Treatment exposure	Median cycles initiated: 10 cycles (range 1.0 to 19.0)
	
	Median duration of treatment:
	• Overall, 41 weeks (range 1.3 to 76.7; IQR 19.1 to 52.3)
	  ○ Isatuximab 40.93 weeks (range 1 to 75.1)
	  ○ Pomalidomide 40.36 weeks (range 1.3 to 75.1)
	  ○ Dexamethasone 40.86 weeks (range 1.0 to 76.7)
	
	Median relative dose intensities:
	• Isatuximab 92.3% (range 19.7 to 111.1)
	• Pomalidomide 85.1% (range 22.9 to 103.7)
	• Dexamethasone 87.8% (range 15.9 to 130.0)
		Median cycles initiated: 6 cycles (range 1.0 to 18.0)
		
		Median duration of treatment:
		• Overall, 24 weeks (range 1.0 to 73.7; IQR 11.1 to 48.0)
		  ○ Pomalidomide 24.0 weeks (range 0.9 to 73.7)
		  ○ Dexamethasone 24.0 weeks (range 1.0 to 73.7)
		
		Median relative dose intensities:
		• Pomalidomide 93.3% (range 37.2 to 118.5)
		• Dexamethasone 96.3% (range 30.3 to 300.0)

AE = adverse event; IQR = interquartile range; IsaPd = isatuximab plus pomalidomide plus dexamethasone; IV = intravenous; Pd = pomalidomide plus dexamethasone; PO = orally

* Pomalidomide administration notes:
- Day 1 of each cycle: administered 30 minutes to 1 hour prior to isatuximab
- Other days of isatuximab infusion (Cycle 1, Day 8 and 15; Cycle 2 and beyond, Day 15): administered after isatuximab infusion at a time convenient for patient, preferably at the same time as the previous dose.

‡ Dexamethasone administration notes:
- Administered 15 to 30 minutes prior to isatuximab
- PO route preferred; however, if that was not possible, dose was given IV
- Depending on route, administered either at the beginning or end of isatuximab premedications

† Premedication combination administration notes: After four administrations of isatuximab, requirement for subsequent premedications could be reconsidered in patients who had not experienced an infusion-related reaction.
- Diphenhydramine
  - Alternatives: cetirizine, promethazine, dexchlorpheniramine
  - IV route preferred for at least first four infusions
- Ranitidine

- Alternatives: other approved histamine H2-receptor antagonists or proton pump inhibitors
- Dexamethasone
  - On the days of isatuximab administration, dexamethasone was only administered once, such that it was considered as part of both premedication and treatment combination.
  - Methylprednisone was given instead if a patient was intolerant to dexamethasone

Source: Attal et al., 2019;[2] FDA Multi-disciplinary Review;[4] Checkpoint Meeting Materials, October 28, 2020 (Sanofi-Genzyme)[3]

Concomitant Treatment

All patients received a prophylactic antithrombotic agent, unless there was an excess risk of bleeding. An assessment of risk factors for venous thromboembolism was performed; risk factors included history of prior venous thromboembolism, concomitant use of an erythropoiesis-stimulating agent, or immobility. Patients with standard risk were recommended aspirin, whereas patients with at least one risk factor were recommended low molecular weight heparin.[2]

Granulocyte colony-stimulating factor prophylaxis in patients experiencing recurrent neutropenia, or treatment in patients experiencing serious neutropenic complications could be considered especially during the first three cycles in patients with extensive bone marrow involvement or reduced neutrophil count at baseline.[2] Supportive G-CSF was also permitted beyond the first three cycles at the discretion of the investigators.[3] G-CSF was used more often in the IsaPd group (69.1%, n=105) compared to patients randomized to Pd (53.0%, n=79).[2] The rate of prophylactic G-CSF administration was similar between the two treatment groups (37.1%, 39/105 treated with IsaPd vs. 39.2%, 31/79 treated with Pd); more patients in the IsaPd group (93.3%, 98/105) received therapeutic G-CSF compared to patients in the Pd group (84.4%, 67/79).[3]

Antimicrobial agents were administered concomitantly in a higher number of patients in the IsaPd group. Specifically, systemic antibacterial agents were administered in 91.4% (n=139) compared to 84.6% (n=126) of IsaPd and Pd patients, respectively. Therapeutic antibacterial regimens were administered to 80.9% (n=123) of patients in the IsaPd group and 66.4% (n=99) of patients the Pd group, and antibacterial prophylaxis was administered to 63.2% (n=96) patients who received IsaPd and 57.7% (n=86) patients who received Pd. Antiviral agents were administered in 79.6% (n=121) vs. 75.2% (n=112) of patients in the IsaPd and Pd groups, respectively, with most prescribed as a prophylactic regimen (72.4% IsaPd vs. 68.5% Pd).[3] Blood transfusions and erythropoietin were administered similarly between the two treatment groups.[4]

Although concurrent treatment with other anti-myeloma therapy was prohibited, palliative radiotherapy to control pain was permitted. The irradiated area was to be 20% or less of the bone marrow in any given three-week timeframe and could not be used for response assessment.[2]

d) Patient Disposition

Two cut-off dates were specified in the study. The cut-off date for PFS and all efficacy analyses was October 11, 2018, whereas the cutoff-date for other analyses (e.g., safety, demographics, and baseline characteristics) was November 22, 2018.[4] The earlier cut-off date of October 11, 2018 was determined based on PFS events that occurred (i.e., 162 events for planned analysis was reached).[5] The latter date of November 22, 2018 was to include data (e.g., assessment to confirm disease progression, determine survival status) that were collected after the cut-off date and based on the last patient last visit date.[6]

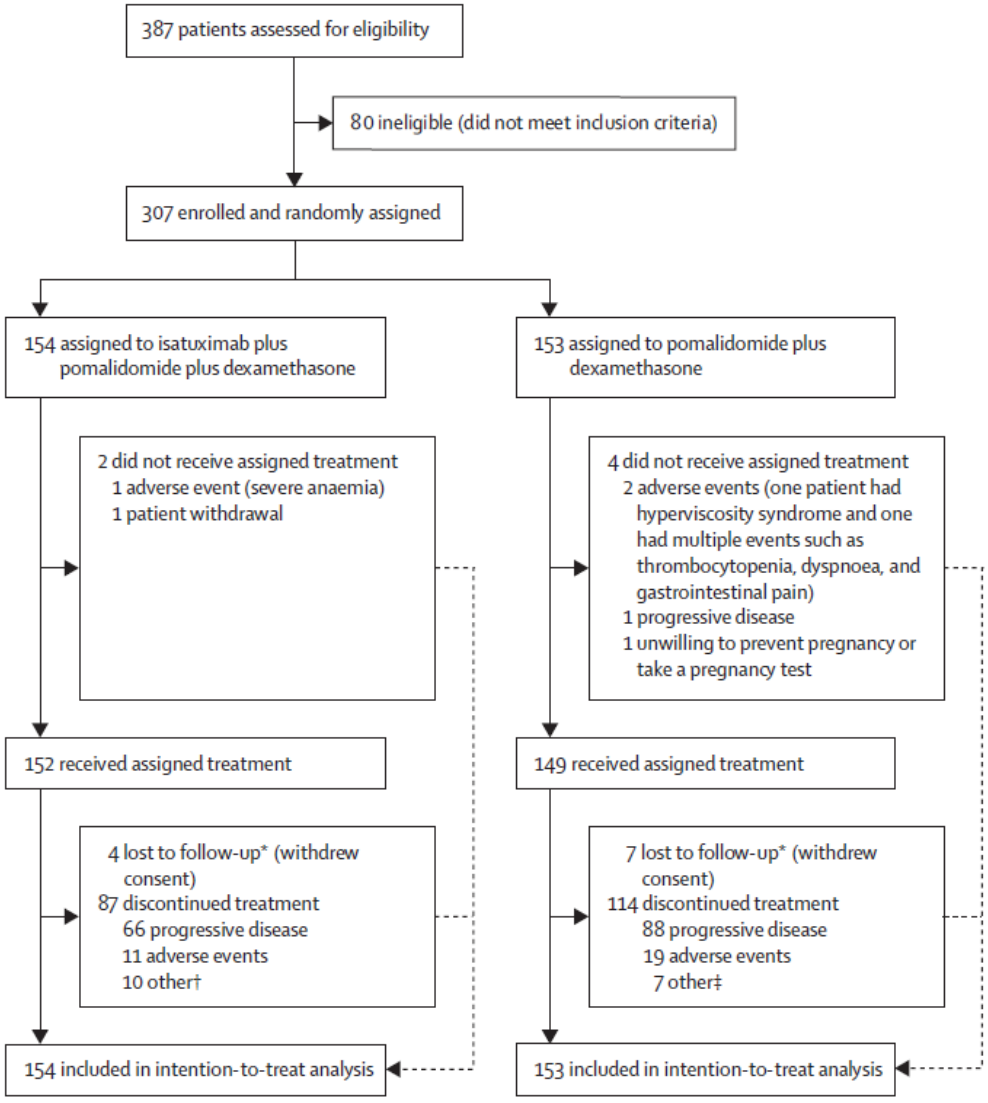
The disposition of patients through the ICARIA-MM study is depicted in Figure 4. A total of 387 patients were screened and 80 were excluded due to not meeting eligibility criteria; ultimately 307 patients were randomly assigned to either IsaPd (n=154) or Pd (n=153). The most common reasons for screening failure were due to not meeting the following inclusion criteria: lenalidomide and PI treatment failure (n=31), documented diagnosis of MM with measurable disease (n=24), and progressing within 60 days after the end of previous therapy (i.e., refractory to last line of treatment, n=13).[54] Two patients in the IsaPd group and four patients in the Pd group did not receive treatment, resulting in a safety population of 301 patients: 152 patients in the IsaPd group and 149 patients in the Pd group.[2]

At the primary data cut-off date of October 11, 2018, 65 patients (42.2%) randomized to IsaPd were still receiving study treatment, whereas 87 patients (56.5%) had discontinued treatment and two patients (1.30%) had not received IsaPd. Of the 87 patients who were off study treatment, 40 patients (26.0%) were in still in the follow-up phase of the trial and 47 patients (30.5%) had discontinued from the study completely. Treatment/study discontinuation was due to death in 43 patients (27.9%).[2,3]

In the control group, 35 patients (22.9%) randomized to Pd were still receiving study treatment, whereas 114 patients (74.5%) had discontinued treatment and four patients (2.6%) had not received Pd. Of the 114 patients who were off study treatment, 51 patients (33.3%) were in study follow-up, and 63 patients (41.2%) had discontinued from the study completely. Treatment/study discontinuation was due to death in 56 patients (36.6%).[2,3]

Disease progression was the main reason for treatment discontinuation in both treatment groups, accounting for 66 patients (42.9%) randomized to IsaPd and 88 patients (57.5%) randomized to Pd.[2,3]

Figure 4: Summary of Patient Disposition



*Greater than 8 weeks between last contact and analysis cutoff date. †Five patient decision to withdraw; one poor compliance to protocol; four principal investigator decision (one to switch treatment to daratumumab plus pomalidomide plus dexamethasone; three discontinued because of increase in serum free light chain concentrations). ‡Six patient decision to withdraw; one physician decision to withdraw the patient.

Note: Although the figure shows four patients in the IsaPd group and seven patients in the Pd group as lost to follow-up separately from those who discontinued treatment, these patients are also counted in the 87 patients and 114 patients who had discontinued IsaPd and Pd, respectively. Thus, the total number of patients who discontinued treatment remains as 87 for the IsaPd group and 114 for the Pd group.[3]

Source of figure: Reprinted from Attal et al. The Lancet. 394(10214):2096-2107. Copyright 2019, with permission from Elsevier.[2]

Protocol Deviations

Major protocol deviations, as defined in the trial, did not occur in a significant number of patients (<5%). Reported major deviations were mainly related to the inclusion and exclusion criteria, randomization (i.e., wrong strata), assessments/procedures, or prohibited

concomitant treatments (i.e., inappropriate use of thromboprophylaxis). Overall, protocol deviations were generally balanced between the two treatment groups and were not deemed to significantly bias or affect the integrity of the trial results.[4,5]

Notable minor protocol deviations involving included deviations from the inclusion criteria occurred in 22 patients (12 in IsaPd vs. 10 in the Pd group). Although these patients had received prior treatment with lenalidomide and a PI, they had not failed treatment on both (whether given together or separately). However, these deviations were considered minor as they were consistent with the approved indication of Pd in the US and EU.[4]

e) Limitations/Sources of Bias

Overall, the ICARIA-MM trial was well-designed, though there were some concerns with the conduct of the trial that could limit the interpretation and generalizability of the results. In terms of strengths, the measured outcomes were clinically important and relevant to patients with RRMM. The randomization method and sample size were adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. Eligibility criteria were well defined and appropriate. The study population characteristics overall reflect a heavily pre-treated patient population who would be eligible for treatment with IsaPd or Pd in Canada. The populations used for analyses were appropriate, with the key efficacy analyses conducted according to the ITT principle. The study protocol was approved by institutional review boards and/or ethics committees at each study center and the trial was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.[4] An independent review committee periodically reviewed unmasked safety data.[2] However, there are a few key limitations and potential sources of bias that were noted by the CADTH Methods Team, as outlined below.

Trial design and statistical analysis

- The study design was open label, which is susceptible to reporting, performance, detection, and selection biases as patients and investigators are not blinded to study treatment allocation. However, due to the different modes of administration of the study treatments investigated in the trial, the use of this design was considered justified. It is possible that reporting biases by both investigators and patients may have influenced the assessment of more subjective outcomes including safety and patient-reported symptoms and outcomes. For example, investigators may have assessed AEs at a lower grade or unrelated to study drug in the experimental treatment group and patients may have overreported or underreported specific AEs if they believed they were or were not related to the study drug(s). Since patients were aware of their assigned treatment, they may have indicated more favourable responses to HRQoL assessments if they perceived the treatment to be superior, which results in the potential for performance bias. The primary endpoint, IRC-assessed PFS, and secondary endpoints, including IRC-assessed ORR, were unlikely influenced by the study design as the IRC was masked to study treatment. Specifically, the radiological and laboratory assessments for disease response and progression were measured by a central IRC who were blinded to the treatment allocation details.[2]
- The study permitted enrolment of patients who had received prior anti-CD38 monoclonal antibody treatment, as long as they had not become refractory to the therapeutic agent.[2] Thus, results of this trial cannot be generalized to patients who are refractory to anti-CD38 monoclonal antibodies, such as daratumumab. Also, only one patient (in the IsaPd group) had received prior daratumumab treatment.[4] Thus, the efficacy of IsaPd in daratumumab-exposed patients is unknown.
- To account for interim analyses as well as key secondary endpoints, the overall type 1 error rate was appropriately controlled using a closed test procedure. Only the primary and key secondary endpoints, specifically ORR and OS, were adjusted to account for multiple comparison testing. Other secondary and exploratory endpoints, including PROs and HRQoL measures, were not controlled for type 1 error; as the trial was not powered to test specific hypotheses in these endpoints, the results of these analyses should be interpreted as exploratory in nature.[2,4]

Study treatment

- The median duration of treatment was 41 weeks for the IsaPd group and 24 weeks for the Pd group. A median of 10 cycles in the IsaPd group and 6 cycles in the Pd group were initiated.[2] Given higher rates of disease progression and discontinuation of treatment in the Pd group, this difference is expected.The potential biases introduced by the differences in the length of treatment between the two groups should be considered, particularly when interpreting AE or HRQoL data that may be related to

length of exposure, though this may be reflective of the real world. Other factors contributing to HRQoL, for example additional burden of hospital visits for administration of isatuximab IV infusion compared to the oral Pd regimen, should also be considered.

Study endpoints

- Sensitivity and subgroup analyses were mostly prespecified, though an additional sensitivity analysis for PFS and two covariates in the subgroup analysis were included in an amendment to the statistical analysis plan after the data cut-off date.[2] Results of sensitivity and subgroup analyses, including those added as part of the amendment, were generally consistent with the primary analysis. Subgroups for the primary endpoint of PFS were generally consistent with the ITT population, with point estimates for HRs favouring treatment with IsaPd, except for patients from North America, where results favoured treatment with Pd (HR 1.132; 95% CI 0.19 to 6.85).[5] However, very small sample size and wide confidence intervals needs to be considered, and subgroup analyses were not adjusted for multiple comparison testing to control for Type 1 error. The trial was also not powered to test specific hypotheses in these subgroups; thus, results should be interpreted as exploratory in nature.
- Disease progression in the ICARIA-MM trial was measured using the IMWG criteria, which is often used in clinical trials and is an appropriate measure of response in MM; however, it has inherent limitations in fully capturing progressive disease. In the ICARIA-MM trial, symptomatic deterioration was not considered as an indicator of progression.[2] Thus, in the trial, biochemical progression that occured in the absence of clinical progression was counted as a PFS event, but not vice versa. According to the CGP, disease progression for MM in clinical practice is assessed based on trends observed in both biochemical and clinical progression, within the context of overall patient status. Athough biochemical and clinical progression generally occur in parallel, there may be some instances where treatment decisions (i.e., to switch or continue treatment) are based on a patient's overall clinical status and not solely on biochemical progression. Nevertheless, the CGP believe the trial data remain generalizable to patients treated for MM in the Canadian clinical setting.
- The final analysis of OS, a key secondary outcome, was scheduled for after 220 deaths which have yet to occur (99 deaths had occurred by data cut-off date, corresponding with 45% information fraction). Median survival was also not reached in either treatment group.[5] Although there was a trend towards longer OS in patients randomized to IsaPd, current OS data are immature and reflect the interim analysis; therefore, longer follow-up of survival data is required to appropriately characterize the long-term effects of adding isatuximab to pomalidomide and dexamethasone. In RRMM, OS is regarded as the most robust endpoint; however, according to the CGP, PFS is also accepted as a clinically relelvant endpoint and the HR of 0.596 in the ICARIA-MM trial supports prolonged survival benefit from IsaPd treatment.
- Although prespecified and a secondary endpoint of the trial, PRO measures were not adjusted for multiplicity and no statistical testing was done to compare within or between group differences; thus, results should be considered only as descriptive and exploratory.[2] Compliance with completing the questionnares was similar across all three PRO scales; rates were high at baseline and remained at 90% or greater between Cycle 2 to Cycle 10. At the end of treatment (30 days after last dose of study treamtent), compliance was 81.3% in the IsaPd group and 81.1% in the Pd group; at 60 day follow-up, compliance decreased to 46.2% in the IsaPd group and 53.4% in the Pd group across all three PRO questionnaires. Compliance was measured relative to the number of patients treated at a given timepoint. Thus, it did not consider HRQoL in patients who missed treatment, for example due to an AE, and may not fully reflect a patient's experience with the assigned treatment. Also, less than half of the patients randomized received treatment beyond Cycle 10 in the IsaPd group and Cycle 6 in the Pd group; those remaining on treatment beyond these timepoints reflect the quality of life of those remaining on treatment.[3] These PROs may not be representative of the ITT population (i.e., those who are remaining are likley healthier than all patients randomized in the trial) and thus not generalizable to the broader patient population. Finally, due to the open-label study design and exploratory nature of the endpoint, it is difficult to fully appreciate the adverse effect of treatment on QoL and results should be interpreted with caution.

Patient population

- The characteristics of the ICARIA-MM study population reflect a heavily pretreated patient population, and according to the CGP, is generally representative of patients who would be eligible for IsaPd in Canada. Several risk factors have been recognized for MM, including advanced age, male gender, family history, and obesity. People with African ancestry have also been shown to be disproportionately affected by this cancer.[55,56] Although detailed Canadian statistics are lacking, data from the US have shown that the incidence rate of MM is approximately twice as high in the African-American population compared to

non-Hispanic white Americans.[57] Participation in MM clinical trials also varies and was shown to be lower amongst minority group patients, for example non-Hispanic black or Hispanic Americans, compared to non-Hispanic White Americans.[58] According to the International Myeloma Foundation, African Americans account for 20% of patients with myeloma in the US, but for only 6% of all patients in clinical trials.[59] The majority of patients enrolled in the ICARIA-MM trial were White (79.5%), whereas 11.7% were Asian and 1.3% were Black or African American.[2] While various factors may contribute to these disparities, the CGP acknowledged the importance of racial equity in clinical trials and the underrepresentation of minority groups. Despite this observation, the CGP consider the results of the ICARIA-MM study remain generalizable to the overall Canadian population. In a retrospective analysis of clinical trials in newly diagnosed MM, similar outcomes were seen across different racial-ethnic groups when provided with the same treatment.[60]

- There were some imbalances in baseline disease characteristics between the treatment groups, particularly in age, performance status, baseline renal function and cytogenetic abnormalities (See Table 14 under Section b) Populations). Imbalances in baseline prognostic factors, such as ISS stage of disease and cytogenetic abnormalities may have given advantage to the IsaPd group, and differences in ECOG PS and age may reflect a favourable prognosis for the Pd group. Accordingly, these differences between the groups may have influenced efficacy outcomes, although the exact direction and magnitude are unknown. Potential confounding from differences in disease or demographic characteristics was identified in a multivariate analysis of PFS that adjusted for several such covariates; a lower adjusted HR was observed, which suggests that certain covariates may have influenced the treatment effect in favour of Pd.[4] However, the CGP noted that key baseline characteristics were generally balanced between the two groups; thus, it was unlikely that the observed imbalances would significantly influence the efficacy results or the interpretation of outcomes in the trial.

Adverse events

- Hematologic abnormalities, such as neutropenia and thrombocytopenia, were captured as both laboratory results as well as reports from investigators; however, only serious hematologic AEs or those which led to study treatment modification or discontinuation were documented as an AE (i.e., only those deemed clinically significant by the investigators). Similarly, abnormal serum chemistry values were only recorded as an AE if they were serious or led to modification or discontinuation of study treatment.[2,4] Investigator bias may result in underreporting of these AEs (i.e., investigator-assessed rates may be underestimated).
- The protocol for pre-treatment in patients receiving IsaPd was specified and reasonable to reduce risk of infusion-related reactions. Infusion reactions were diagnosed and reported by investigators, based on events that occurred wthin 24 hours of isatuximab administration. A precise diagnostic term for an infusion reaction was not predefined, and only diagnoses according to investigator judgement were included in the TEAE analysis, which could include various clinical diagnoses (e.g., infusion-related reaction, cytokine release syndrome, hypersensitivity, anaphylactic reaction).[4] Invidual symptoms were recorded separately. Thus, infusion-related reactions that occurred beyond 24 hours after isatuximab administration were not captured (i.e., potentially leading to underestimation of events), and there may have been a lack of consistentency in identifing reactions that were counted as a TEAE. Most of the diagnoses of infusion reactions made in the 58 patients were infusion-related reactions (n=56), with only two patients diagnosed with cytokine release syndrome, and one diagnosed with drug hypersensitivity.

Subsequent treatment

- During the study follow-up period, patients were permitted to receive subsequent treatment for RRMM. The decision to administer subsequent treatment after disease progression and the choice of treatment was up to the investigator's discretion.[2] In an unblinded trial setting, the choice of subsequent therapy may be influenced by the treatment received in the study. The impact of such bias is unknown. Overall, a higher proportion of patients randomized to Pd received subsequent therapy (n= 60, 39.0% IsaPd vs. n=83, 54.2% Pd), includuding daratumumab, which was given to 6 patients (3.9%) randomized to IsaPd and 45 patients (29.4%) randomized Pd. This can confound the assessment of OS by prolonging survival beyond what would have occurred with frontline treatment alone. In particular, the higher proportion of patients receiving subsequent treatment with daratumumab was higher in the Pd group (29.4%), compared to the IsaPd group (3.9%).[2,5] This would also be expected to favour the Pd group and underestimate the OS benefit associated with the experimental group.

- Patients who started a subsequent anti-cancer therapy prior to a PFS event were censored from the primary efficacy analysis, which may have biased results through informative censoring. This does not provide an accurate estimate of all events that could occur during a course of treatment. Patients who started a new therapy may have discontinued treatment with study drug(s) due to reasons such as intolerance or toxicities related to the study drug(s); therefore, censoring of these patients could overestimate clinical efficacy in both treatment groups. However, the number of patients censored for this reason was fairly low (5.8% IsaPd vs. 10.5% Pd) and a sensitivity analysis without censoring for subsequent therapy was conducted. The results of this analysis were highly consistent with the primary results (HR 0.599; 95% CI, 0.45 to 0.80); thus, the impact of this bias is considered minimal.[4]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the ITT population, which included all patients randomized to treatment and analyzed according to the treatment group they were assigned, regardless of whether the study treatment was actually received.[2]

As previously mentioned, the cut-off date for efficacy analyses was October 11, 2018, at which time, the median duration of follow-up was 11.6 months (IQR, 10.1 to 13.9); the median duration of follow-up was 11.56 months in the IsaPd group and 11.73 months in the Pd group.[2,4]

Primary Endpoint – Progression-free Survival (PFS)

As of the efficacy analysis data cut-off date, 73 events had occurred in patients randomized to IsaPd (47.4%) compared to 89 events in the Pd group (58.2%). The median PFS according to IRC assessment was 11.53 months (95% CI, 8.94 to 13.90) in the IsaPd group compared to 6.47 months (95% CI, 4.47 to 8.28) in the Pd group. The stratified HR for progression or death was 0.596 (95% CI, 0.44 to 0.81; p=0.001).[4] The K-M curve for PFS based on IRC assessment is shown below in Figure 5A.

Figure 5: K-M Analysis for PFS and OS, ITT population

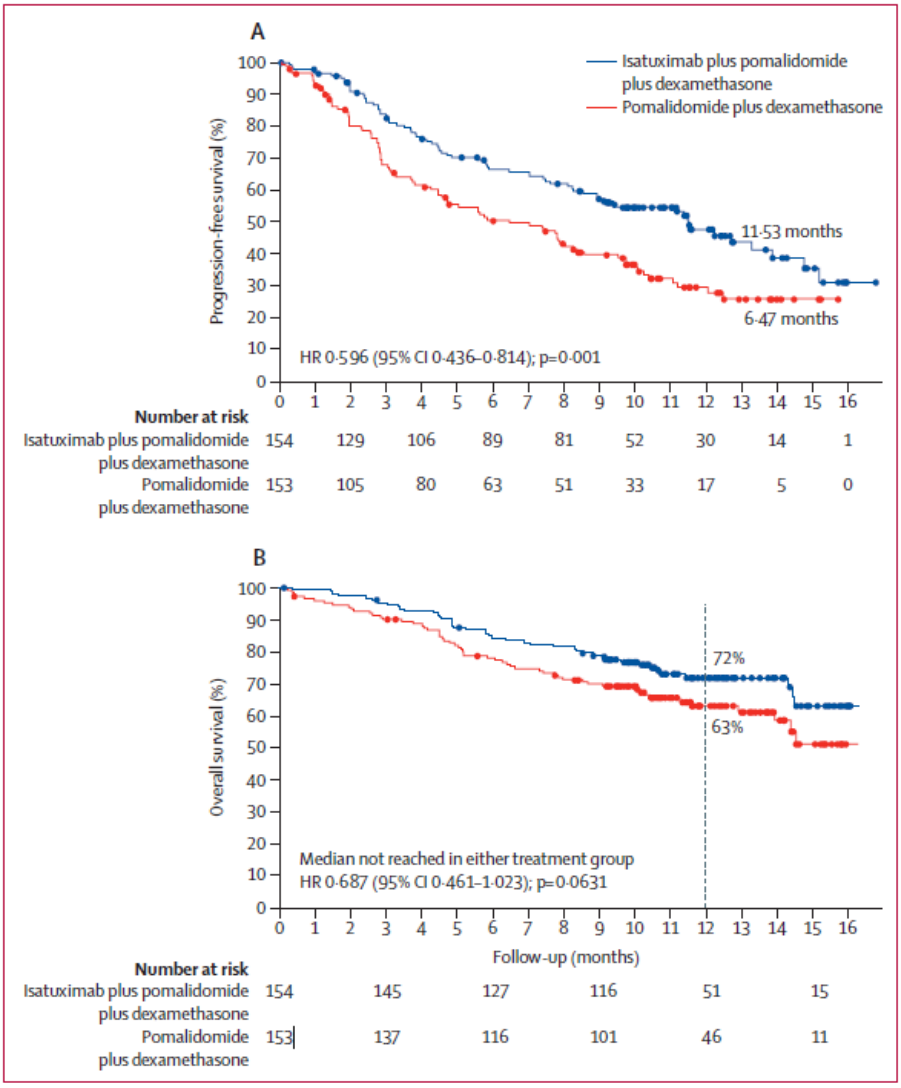


***Figure 2:* Progression-free survival and overall survival**
(A) Kaplan-Meier analysis of progression-free survival in the intention-to-treat population (ie, all patients who were randomly assigned to treatment (regardless of treatment received), as assessed by an independent response review committee. Hazard ratio (HR) and corresponding 95% CIs are from a Cox proportional hazard model stratified by age and number of previous lines of therapy. One-sided p value was derived from a log-rank test. (B) Overall survival was compared using a one-sided log-rank test in the intention-to-treat population at the time of the primary analysis on progression-free survival. Patients remaining alive at their last contact were censored at the last date known to be alive or the cutoff date, whichever was earlier.
Source: Reprinted from Attal et al. The Lancet. 394(10214):2096-2107. Copyright 2019, with permission from Elsevier.[2]

Sensitivity and Subgroup Analyses

Sensitivity analyses of PFS showed results that were consistent with the primary analysis (Table 16), with the HRs ranging from 0.568 to 0.602. Consistent results were seen for sensitivity analyses that were prespecified as well as those added after the data cut-off date (i.e., PFS#2). For example, investigator assessed PFS including symptomatic deterioration as an event (i.e., PFS#3), showed a HR of 0.580 (95% CI, 0.43 to 0.78). For the scenario where IRC-assessed PFS was not censored for further anti-myeloma treatment (i.e., PFS#1), the HR was 0.599 (95% CI, 0.45 to 0.80).[5]

Table 16: PFS Sensitivity Analyses

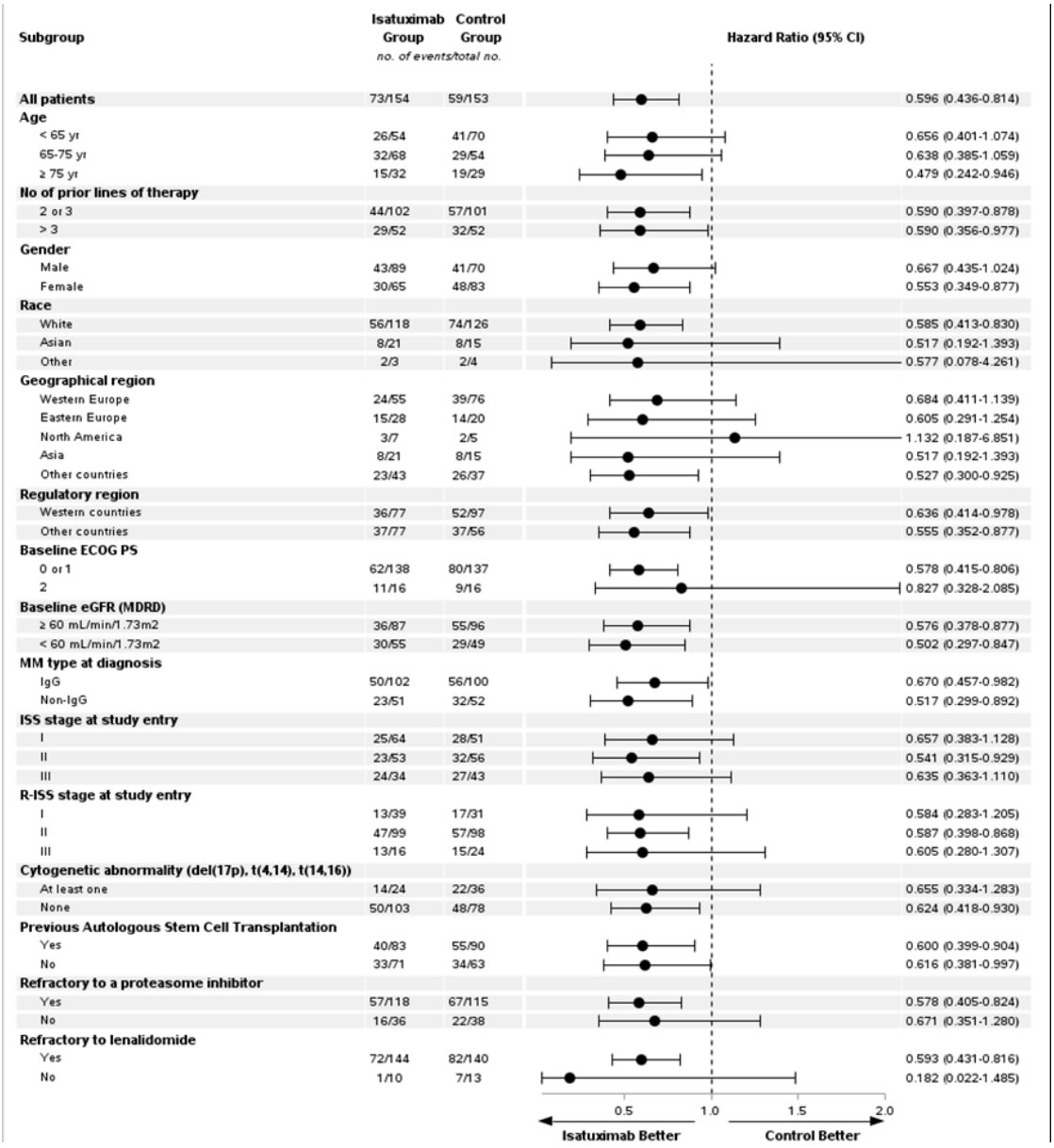
	Pd		IPd			
	N(%) of Events	Median (Months) (95% CI)	N(%) of Events	Median (Months) (95% CI)	Hazard Ratio (95% CI) vs Pd	P-value[a]
Main analysis: PFS as per IRC, stratified by stratification factors as entered in the IRT	89 (58.2)	6.47 (4.468 to 8.279)	73 (47.4)	11.53 (8.936 to 13.897)	0.596 (0.436 to 0.814)	0.0010
PFS as per IRC, stratified by stratification factors as entered in the eCRF	89 (58.2)	6.47 (4.468 to 8.279)	73 (47.4)	11.53 (8.936 to 13.897)	0.568 (0.414 to 0.779)	0.0004
PFS #1: PFS as per IRC without censoring for further anti-myeloma treatment	105 (68.6)	5.85 (4.468 to 7.819)	82 (53.2)	11.20 (8.246 to 13.306)	0.599 (0.447 to 0.801)	0.0005
PFS #2: PFS as per investigator (ignoring symptomatic deterioration)	96 (62.7)	6.54 (4.468 to 7.885)	76 (49.4)	11.14 (7.491 to 14.784)	0.602 (0.444 to 0.816)	0.0009
PFS #3: PFS as per investigator including symptomatic deterioration as an event	103 (67.3)	5.59 (4.041 to 7.491)	78 (50.6)	11.14 (7.425 to 14.784)	0.580 (0.431 to 0.780)	0.0003
PFS #4: PFS as per IRC including initiation of further anti-myeloma treatment as an event	114 (74.5)	4.60 (3.055 to 5.848)	90 (58.4)	8.97 (7.228 to 11.565)	0.591 (0.447 to 0.781)	0.0002

CI: Confidence interval
Cutoff date = 11OCT2018
[a] One-sided significance level is 0.025
Source: FDA Multi-disciplinary Review[4]

When PFS was adjusted for potential confounding due to imbalances in demographics and baseline characteristics in a multivariate analysis, the analysis produced an HR of 0.484 (95% CI, 0.33 to 0.70) that was lower than the primary analysis. This suggests that there may have been confounding factors among analyzed covariates that influenced the primary analysis, with the treatment effect favouring the Pd arm.[4]

Analysis of subgroups showed an overall consistent PFS benefit with IsaPd compared to Pd (Figure 6). Both prespecified subgroups as well as those added after the data cut-off date supported the results of the PFS primary analysis (ITT population). All subgroup treatment effect estimates favoured treatment with IsaPd, with the exception of the North America region, which favoured treatment with Pd. However, for this subgroup (n=12), as well as several others (e.g., Asian or Other race, ECOG PS of 2, R-ISS stage III at study entry, non-refractory status to lenalidomide, etc.), the sample sizes were small, and CIs were wide and crossed the line of unity (1.0). The treatment effect estimates in these subgroups are more uncertain, and therefore the results should be interpreted with caution.[5]

Figure 6: Subgroup Analysis of PFS, ITT population



Source: EPAR[5]

Key Secondary Endpoints

Overall Response Rate (ORR)

The ORR (i.e., PR or better as BOR) according to IRC using IMWG response criteria was higher in patients who were randomized to IsaPd (60.4%, n=93) compared to patients in the Pd group (35.3%, n=54). The stratified CMH p-value was < 0.0001 indicating a significant difference between the two groups that favoured IsaPd.[5] A summary of the BOR achieved in each treatment group can be found in Table 17.

Table 17: Summary of Overall Response per Independent Response Committee, ITT Population

	IsaPd (n=154)	Pd (n=153)
Best overall response, n (%)		
Stringent Complete Response (sCR)	0 (0)	1 (0.7)
Complete Response (CR)	7 (4.5)	2 (1.3)
Very Good Partial Response (VGPR)	42 (27.3)	10 (6.5)
Biochemical CR but missing bone marrow[a]	9 (5.8)	2 (1.3)
Near-CR[b]	24 (15.6)	5 (3.3)
Partial Response (PR)	44 (28.6)	41 (26.8)
Minimal Response (MR)	10 (6.5)	17 (11.1)
Stable Disease	33 (21.4)	45 (29.4)
Non-Progressive Disease (Non-PD)	4 (2.6)	3 (2.0)
Progressive Disease (PD)	6 (3.9)	14 (9.2)
Unconfirmed PD	1 (0.6)	4 (2.6)
Not evaluable/Not assessed	7 (4.5)	16 (10.5)
Overall response		
Responders (sCR, CR, VGPR, or PR), n (%)	93 (60.4)	54 (35.3)
95% CI[c]	0.5220; 0.6817	0.2775; 0.4342
Stratified CMH test *P*-value[d]	<0.0001	
VGPR or better		
n (%)	49 (31.8)	13 (8.5)
95% CI[c]	0.2455; 0.3980	0.0460; 0.1409
Stratified CMH test *P*-value[d]	<0.0001	
Clinical benefit		
Responders (MR or better)	103 (66.9)	71 (46.4)
95% CI[c]	0.5885; 0.7425	0.3832; 0.5464

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IRC = independent review committee; IsaPd = isatuximab plus pomalidomide and low-dose dexamethasone; ITT = intention-to-treat; Pd = pomalidomide and low-dose dexamethasone

[a] Two consecutive negative M-protein and negative immunofixation with missing bone marrow

[b] All criteria for a CR were met except that immunofixation remained positive

[c] Estimated using Clopper-Pearson method

[d] Stratified by age (< 75 years versus ≥ 75 years) and number of previous lines of therapy (2 or 3 versus > 3); one-sided significance level is 0.025

Source: ICARIA-MM Clinical Study Report[10]

Note: Data cut-off: October 11, 2018

Source: CADTH Submission, Clinical Summary[7]

Overall Survival (OS)

At the time of the efficacy data cut-off date (interim OS analysis), OS data were still immature at 45% information fraction. Overall, 99 deaths had occurred in total, with 43 deaths (27.9%) in the IsaPd group and 56 deaths (36.6%) in the Pd group. The median OS had not been reached in either treatment group. Although not statistically significant, there was a trend towards longer OS in patients randomized to IsaPd, with a stratified HR of 0.687 (95% CI, 0.46 to 1.02; p=0.0631, one-sided significance level of 0.0008). The significance threshold for superior efficacy, based on 99 deaths, was not met. The estimated probability of survival at 12 months was 72% and 63% in the IsaPd and Pd groups, respectively.[5] The K-M curves for OS is presented above in Figure 5B.

Secondary Endpoints Relevant to Current Review

Time to Progression (TTP)

At the efficacy data cut-off date, 62 patients (40.3%) in the IsaPd group and 78 patients (51.0%) in the Pd group had experienced disease progression and TTP, as assessed by IRC, was longer with the addition of isatuximab. The median TTP was 12.71 months (95% CI, 11.20 to 15.21) in the IsaPd group and 7.75 months (95% CI, 5.03 to 9.76) in the Pd group.[5,7]

Duration of Response (DOR)

Duration of response, as determined by IRC, was assessed in patients who achieved a response of PR or better (i.e., same population as ORR); 93 patients in the IsaPd group and 54 patients in the Pd group were included in this analysis. Of patients responding to treatment, a similar proportion of patients in each group experienced disease progression or death, seen in 34% (32 of 93) in the IsaPd group and 35% (19 of 54) in Pd group.[4] The median DOR was 13.27 months (95% CI, 10.61 to not calculable [NC]) in the IsaPd group and 11.07 months (95% CI, 8.54 to NC) in the Pd group.[5]

Exploratory and Other Endpoints Relevant to Current Review

Minimal Residual Disease (MRD)

Minimal residual disease was evaluable in 16 enrolled patients: 14 patients in the IsaPd group and two patients in the Pd group. In patients randomized to IsaPd, 10 were MRD negative at the sensitivity level of 10^{-4} (6.5%), 8 were negative at 10^{-5} (5.2%) and two were negative at 10^{-6} (1.3%). Of the patients randomized to Pd, neither of the two evaluable patients were MRD negative at any sensitivity level.[5]

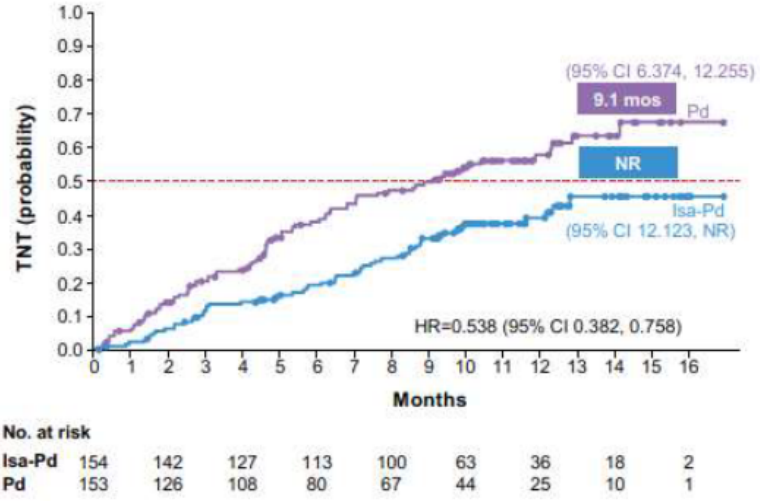
Time to Next Treatment (TTNT)

The median TTNT was not reached in the IsaPd group (range, 12.12 months to not reached), and was 9.10 months (range 6.37 to 12.23) in the Pd group. The HR was 0.538 (95% CI, 0.38 to 0.77), suggesting that the addition of isatuximab delayed the need for subsequent anti-myeloma treatment.[5]

After disease progression and treatment discontinuation, the decision to administer subsequent anti-myeloma treatment and the choice of treatment was made according to the investigator's discretion.[2] According to the sponsor, the study captured all subsequent systemic anti-myeloma treatment together and included treatments given in all subsequent lines of therapy after discontinuing study treatment and throughout study follow-up. Thus, the information collected in the study reflect subsequent systemic anti-myeloma treatment regardless of whether patients received a single or multiple lines of subsequent therapy.[3]

Subsequent systemic anti-myeloma treatment was administered to 39.0% (n=60) of patients in the IsaPd group and 54.2% (n=83) of patients in the Pd group at the data cut-off date of November 22, 2018. Overall, there was a difference between the two groups in the proportion of patients who received an alkylating agent (more patients in the IsaPd group) or daratumumab (more patients in the Pd group) as subsequent therapy. The most significant difference was seen with daratumumab, which was administered in 3.9% of patients (6 of 154) randomized to IsaPd compared to 29.4% (45 of 153) randomized to Pd. Most patients randomized to IsaPd received alkylating agents (25.9%; 40 of 154) as subsequent therapy; PIs were also prescribed, in particular bortezomib (11.7%; 18 of 154) and carfilzomib (13.6%; 21 of 154). Lenalidomide was also given to seven patients (4.5%). In patients randomized to Pd, the most common category of subsequent treatment was daratumumab. PIs were also given to a similar proportion of patients, mostly bortezomib (13.7%; 21 of 153) and carfilzomib (12.4%; 19 of 153). Alkylating agents were given as subsequent therapy to 33 patients (21.6%) randomized to Pd, and six patients received lenalidomide (3.9%).[5] Details of subsequent anti-myeloma treatment given to patients after disease progression can be found in Table 18.

Table 18: TTNT and Subsequent Anti-Myeloma Treatment Given Post-Progression, ITT



Data cut-off: 11 October 2018
Median follow-up time: 11.6 months (IQR 10.2, 14.1) isatuximab; 11.7 months (IQR 10.0, 13.9) control

CI, confidence interval; d, dexamethasone; HR, Hazard ratio; Isa, isatuximab; m, median; mo, months; NR, not reached; P, pomalidomide; TNT, time to next treatment, IQR, Interquartile range

Patients with further anti-myeloma treatment, n (%)	Isa-Pd (n=60/154; 39.0%)	Pd (n=83/153; 54.2%)
Alkylating agents	40 (66.7)	33 (39.8)
PIs	34 (56.7)	39 (47.0)
Bortezomib	18 (30.0)	21 (25.3)
Carfilzomib	21 (35.0)	19 (22.9)
Ixazomib	0	3 (3.6)
IMiDs	14 (23.3)	19 (22.9)
Lenalidomide	7 (11.7)	6 (7.2)
Pomalidomide	5 (8.3)	11 (13.3)
Thalidomide	3 (5.0)	3 (3.6)
mAbs (Daratumumab)	6 (10.0)	45 (54.2)
Other (Atezolizumab)	0	2 (2.4)

d, dexamethasone; IMiD: immunomodulatory drug; Isa, isatuximab; mAb, monoclonal antibody; PI, proteasome inhibitor; P, pomalidomide

Note – percentages in the table are calculated based on number of patients who received further treatment (i.e., 60 for IsaPd, 83 for Pd) as the denominator, and not relative to the ITT population. In the text above, percentages are calculated using the ITT population (i.e., 154 for IsaPd and 153 for Pd in the denominator).
Source: Reprinted from Attal et al. The Lancet. 394(10214):2096-2107. Copyright 2019, with permission from Elsevier.[2]

Health-Related Quality of Life

Patient compliance for completing PRO questionnaires was measured by dividing the number of fully complete questionnaires received by the number of patients treated at a given timepoint. Overall, compliance was similar across all three PRO questionnaires; rates were high at baseline and remained at 90% or greater between Cycle 2 and Cycle 10. Less than half of the safety population

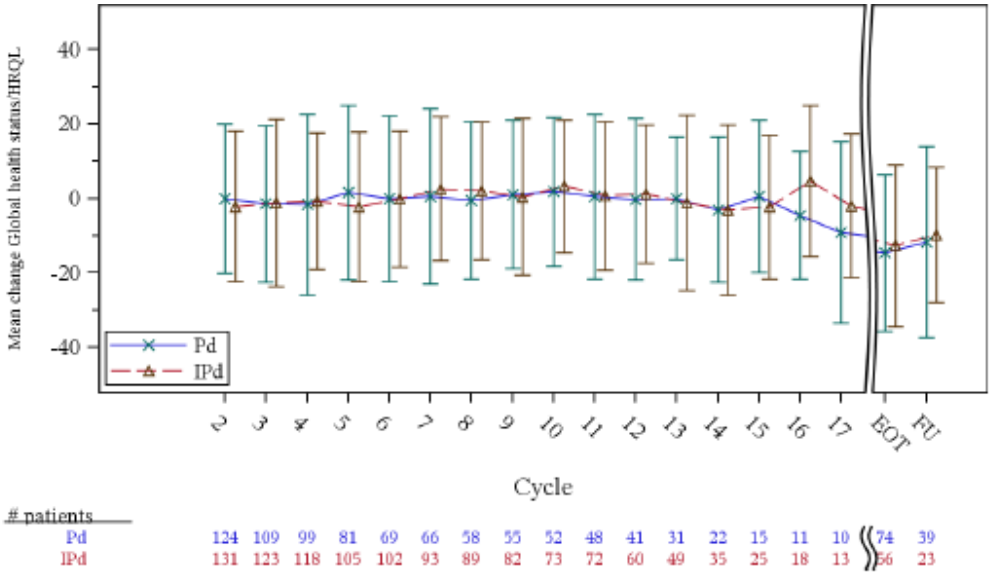
remained and received treatment beyond Cycle 6 in the Pd group and Cycle 10 in the IsaPd group.[3] Results for each questionnaire were provided for the treatment period only.

EORTC QLQ-C30

Compliance for the EORTC QLQ-C30 questionnaire was 92.8% and 95.3% at baseline in the IsaPd and Pd groups, respectively. Between Cycle 2 to Cycle 10, compliance ranged from 93.4% to 100% in the IsaPd group and 89.9% to 99.1% in the Pd group. Compliance at end of treatment (30 days after administration of last study treatment) was 81.3% versus 81.1% for patients in the IsaPd and Pd groups, respectively.[3]

Overall, HRQoL as measured by the GHS/QoL scores of EORTC-QLQ-C30 was maintained in both treatment groups, as indicated by change in scores from baseline not meeting the MCID threshold in either treatment group.[4]

Figure 7: Global Health Status Score Over Time (Mean Change from Baseline and Standard Deviation) – Evaluable Safety Population



A higher score represents a better level of quality of life.
EOT: End of treatment, FU: Follow-up
End of treatment: 30 days after last study treatment administration, Follow-up: 60 days after last study treatment administration
Note: Cycles with less than 20 patients overall are not presented.
Safety population evaluable for quality of life assessment: patients from the safety population who have completed the baseline and at least 1 post baseline assessment.
PGM=PRODOPS/SAR650984/EFC14335/CIR/REPORT/PGM/eff_qlq_c30_line_s_f.sas
OUT=REPORT/OUTPUT/eff_qlq_c30_line_glb_chg_s_f_x rtf (19FEB2019 21:09)
Source: FDA Multi-disciplinary Review[4]

Functioning, as measured by the EORTC QLQ-C30 was maintained in both treatment groups during the treatment period. The MCID was not met in scores for physical, role, cognitive, emotional, or social functioning in either treatment group. Similarly, symptom burden was overall maintained for both groups during treatment. Changes from baseline also did not meet the MCID threshold in the EORTC QLQ-C30 scores for symptoms of fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. There were isolated changes in symptom scores by +/- 10 points or more near the end of the treatment period (when sample sizes were small) for both groups; however, no consistent or clear pattern was identified.[6]

EORTC QLQ-MY20

Compliance for the EORTC QLQ-MY20 questionnaire was 91.4% and 93.3% at baseline in the IsaPd and Pd groups, respectively. Between Cycle 2 and Cycle 10, compliance ranged from 93.4% to 100% in the IsaPd group and 89.9% to 99.1% in the Pd group. Compliance at end of treatment was 81.3% and 81.1% for patients in the IsaPd and Pd groups, respectively.

Changes in scores from baseline did not meet the prespecified MCID for EORTC QLQ-MY20 assessments in either treatment groups. Subscale scores for body image, future perspective, disease symptoms, and side effects were maintained overall during the treatment period for both groups.[6]

EQ-5D-5L

Compliance for the EQ-5D-5L questionnaire was 93.4% and 95.3% at baseline in the IsaPd and Pd groups, respectively. Between Cycle 2 and Cycle 10, compliance ranged from 93.4% to 100% in the IsaPd group and 89.9% to 99.1% in the Pd group. Compliance at end of treatment was 81.3% and 81.1% for patients in the IsaPd and Pd groups, respectively.[3]

Similar to the other PROs assessed, health state utility values and health status (VAS scores) were overall maintained during the treatment period. There were isolated changes in scores from baseline beyond the threshold of the MCID near the end of the treatment period, but sample sizes at these timepoints were small.[6]

Post-hoc analysis of HRQoL

The HRQoL results from the ICARIA-MM trial were supported by the results of a post-hoc analysis, published as an abstract, which investigated the overall rate of change in patient-reported HRQoL associated with the addition of isatuximab to Pd. To estimate the true predicated rate of change over time in the EORTC QLQ-C30 domains of GHS/QoL, physical function, pain, and fatigue, a modelling approach (i.e., flexible longitudinal analysis) was used to estimate the true mean rate of change in each treatment group using all data from all patients at each timepoint simultaneously. Baseline ECOG PS, age, number of prior lines of therapy, death, and disease progression were controlled in the model. The focus of the analyses was to identify the overall trend over time in each treatment group for each scale, rather than the change in scores between specific timepoints.[52]

The results showed that none of the observed changes in each scale, in either treatment group, reached the MCID of 10-points; however, according to the authors, there was an overall trend of no significant changes in scores in the IsaPd group and worsening of scores in the Pd group. Specifically, the mean change at each cycle (standard deviation) was as follows:

- GHS / QoL: +0.18 (0.03) points for IsaPd vs. -0.50 (0.05) for Pd
- Physical functioning: -0.27 (0.05) points for IsaPd vs. -0.75 (0.05) points for Pd
- Pain: -0.12 (0.10) points for IsaPd vs. +0.44 (0.06) points for Pd
- Fatigue: +0.04 (0.01) points for IsaPd vs. +0.49 (0.07) points for Pd[52]

The authors reported that changes in pain and physical functioning scores predicted changes in GHS/QoL in both treatment groups; however, changes in fatigue significantly predicted changes in GHS/QoL only in the Pd group. Overall, the authors concluded that the addition of isatuximab to Pd preserved (maintained) HRQoL in patients with RRMM. The preservation of QoL was attributed in part to management of pain and the delay of physical functioning.[52]

Harms Outcomes

Treatment-Emergent Adverse Events (TEAEs)

Treatment-Emergent Adverse Events were defined as AEs that developed, worsened, or became serious during the treatment period (i.e., time from administration of first dose to the last dose of study treatment, plus 30 days). Treatment-emergent adverse events were evaluated in the safety population, comprised of 152 patients in the IsaPd group and 149 patients in the Pd group.[5] The data cut-off date for the safety evaluation was November 22, 2018.[4] Although the addition of isatuximab to pomalidomide and dexamethasone led to greater severe (≥ Grade 3) and serious TEAEs, this did not lead to increased discontinuation of study treatment or deaths. Most TEAEs were reported as manageable and reversible.[5] An overview of TEAEs occurring in the ICARIA-MM study can be found in Table 19.

It should be noted that reported infusion reactions were documented as a collective of different clinical diagnoses (e.g., infusion-related reaction, cytokine release syndrome, hypersensitivity, anaphylactic reaction), according to investigator assessment. Individual symptoms were captured on a separate form.[2] Infusion reactions were defined as those which typically occurred within 24 hours since the start of the isatuximab infusion; however, a precise diagnostic term for an infusion reaction was not predefined. The diagnosis of infusion-related reactions according to investigator judgement were part of the TEAE analysis, whereas the individual symptoms were not (and thus, were analyzed separately).[4]

Hematologic abnormalities, such as neutropenia and thrombocytopenia, were captured as both laboratory results as well as reports from investigators; however, only serious hematologic AEs or those which led to study treatment modification or discontinuation were documented as an AE. Since only those deemed clinically significant by the investigators were captured as a TEAE, discrepancies were seen between the two different methods of AE identification. Similarly, abnormal serum chemistry values were only recorded as an AE if they were serious or led to modification or discontinuation of study treatment.[2]

Table 19: Overview of Treatment-Emergent Adverse Events, Safety Population

Adverse Event, n (%)	IsaPd (n=152)	Pd (n=149)
Patients with any TEAEs (any grade)	151 (99.3)	146 (98.0)
Patients with any Grade ≥ 3 TEAE	132 (86.8)	105 (70.5)
Patients with any serious TEAE	94 (61.8)	80 (53.7)
Patients with any treatment-related TEAE (any grade)*	138 (90.8)	119 (79.9)
Patients with any treatment-related Grade ≥ 3 TEAE*	109 (71.7)	71 (47.7)
Patients with any serious treatment-related TEAE‡	54 (35.5)	24 (16.1)
Patients with any AESI†	10 (6.6)	1 (0.7)
Patients with any infusion reaction of grade ≥ 3	4 (2.6)	0 (0)
Patients with any TEAE leading to definitive treatment discontinuation	11 (7.2)	19 (12.8)
Patients with any TEAE leading to premature discontinuation of isatuximab	4 (2.6)	NA
Patients with any TEAE leading to premature discontinuation of pomalidomide	8 (5.3)	0 (0)
Patients with any TEAE leading to premature discontinuation of dexamethasone	2 (1.3)	2 (1.3)
Total number of patients with Grade 5 AE during study	16 (10.5)	17 (11.4)
Patients with any Grade 5 TEAE with fatal outcome during the treatment period§	11 (7.2)	13 (8.7)
Death due to progressive disease	6 (3.9)	5 (3.4)
Death due to adverse event¶	3 (2.0)	6 (4.0)
Death due to other reasons	2 (1.3)	2 (1.3)
Patients with any TEAE with fatal outcome during the post-treatment period#	5 (3.3)	4 (2.7)
Deaths due to drug-related adverse event	1 (0.7)	2 (1.3)

AE = adverse event; AESI = adverse events of special interest; IsaPd = isatuximab plus pomalidomide plus dexamethasone; NA = not applicable; Pd = pomalidomide plus dexamethasone; TEAE = treatment-emergent adverse event.
* Treatment-related TEAE are TEAEs related to at least one drug of the combination
‡ TEAEs with a start date before the operational cut-off date and becoming serious after the operational cut-off date were excluded from this analysis
† AESI includes infusion reactions of Grade 3 or 4, pregnancy, overdose, and second primary malignancy
§ According to the sponsors, a Grade 5 TEAE is an adverse event that occurred or worsened during treatment period and led to death during the treatment period, regardless of cause. The number of patients with Grade 5 TEAE include all who died during the treatment period, whatever the cause, and had a TEAE is reported in the electronic case report form.
¶ Includes adverse events that may or may not be related study drug.

[#] TEAE that worsened to Grade 5 during the post-treatment period.
Source: FDA Multi-disciplinary Review;[4] Checkpoint Meeting Materials, October 28, 2020 (Sanofi-Genzyme);[3] CADTH Submission, Clinical Summary[7]

A TEAE of any grade was reported in 151 (99.3%) and 146 (98.0%) of patients in the IsaPd and Pd groups, respectively. When adjusted for the longer duration of treatment exposure in patients who received IsaPd, the incidence rate per patient-years was 3.17 in the IsaPd group and 2.29 in the Pd group.[3] A greater proportion of patients treated with IsaPd experienced severe TEAEs of grade ≥ 3 (86.8%, n=132 vs. 70.5%, n=105 Pd), and serious TEAEs (61.8%, n=94 vs. 53.7%, n=80 Pd). However, the exposure-adjusted incidence rate per patient-years for serious TEAEs was similar between the two groups (1.36 for IsaPd vs. 1.30 for Pd).[5]

The most common TEAEs, reported in at least 5% of patients for all grades and at least 2% for grade ≥ 3, are shown in Table 20. Notably, the following TEAEs of any grade were reported at an incidence of 10% or greater, and more frequently (i.e., ≥ 5%) in patients treated with IsaPd compared to Pd: neutropenia (46.7% vs. 33.6%), infusion-related reaction (36.8% vs. 1.3%), upper respiratory tract infection (28.3% vs. 17.4%), diarrhea (25.7% vs. 19.5%), bronchitis (23.7% vs. 8.7%), dyspnea (15.1% vs. 10.1%), nausea (15.1% vs. 9.4%), vomiting (11.8% vs. 3.4%) and febrile neutropenia (11.8% vs. 2.0%). Grade ≥ 3 TEAEs reported in at least 10% of patients and more frequently (i.e., ≥ 5%) in the IsaPd group, compared to the Pd group, were neutropenia (46.1% vs. 32.2%) and febrile neutropenia (11.8% vs. 2.0%). There were no TEAEs reported (of any grade or grade ≥ 3) with an incidence of 5% or higher in the Pd group, compared to patients treated with IsaPd.[4]

Table 20: Most Common TEAEs with an Incidence of ≥5% (All Grades) or ≥2% (Grade ≥3) in Either Treatment Group, Safety Population

Preferred Term	IsaPd (n=152)		Pd (n=149)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any event	**151 (99.3)**	**132 (86.8)**	**146 (98.0)**	**105 (70.5)**
Neutropenia	71 (46.7)	70 (46.1)	50 (33.6)	48 (32.2)
Infusion-related reaction	56 (36.8)	4 (2.6)	2 (1.3)*	0
Upper respiratory tract infection	43 (28.3)	5 (3.3)	26 (17.4)	1 (0.7)
Diarrhea	39 (25.7)	3 (2.0)	29 (19.5)	1 (0.7)
Bronchitis	36 (23.7)	5 (3.3)	13 (8.7)	1 (0.7)
Pneumonia	31 (20.4)	25 (16.4)	26 (17.4)	23 (15.4)
Fatigue	26 (17.1)	6 (3.9)	32 (21.5)	0
Back pain	25 (16.4)	3 (2.0)	22 (14.8)	2 (1.3)
Constipation	24 (15.8)	0	26 (17.4)	0
Asthenia	23 (15.1)	5 (3.3)	27 (18.1)	4 (2.7)
Dyspnea	23 (15.1)	6 (3.9)	15 (10.1)	2 (1.3)
Nausea	23 (15.1)	0	14 (9.4)	0
Pyrexia	22 (14.5)	2 (1.3)	21 (14.1)	2 (1.3)
Peripheral edema	20 (13.2)	1 (0.7)	16 (10.7)	0
Thrombocytopenia	19 (12.5)	18 (11.8)	18 (12.1)	18 (12.1)
Febrile neutropenia	18 (11.8)	18 (11.8)	3 (2.0)	3 (2.0)
Vomiting	18 (11.8)	2 (1.3)	5 (3.4)	0
Arthralgia	16 (10.5)	4 (2.6)	13 (8.7)	1 (0.7)

Preferred Term	IsaPd (n=152)		Pd (n=149)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Decreased appetite	15 (9.9)	2 (1.3)	7 (4.7)	1 (0.7)
Headache	15 (9.9)	0	8 (5.4)	0
Urinary tract infection	15 (9.9)	7 (4.6)	14 (9.4)	2 (1.3)
Cough	14 (9.2)	0	11 (7.4)	1 (0.7)
Muscle spasms	14 (9.2)	0	15 (10.1)	0
Nasopharyngitis	14 (9.2)	0	7 (4.7)	0
Insomnia	13 (8.6)	1 (0.7)	12 (8.1)	1 (0.7)
Musculoskeletal chest pain	13 (8.6)	0	7 (4.7)	0
Bone pain	12 (7.9)	1 (0.7)	8 (5.4)	2 (1.3)
Tremor	12 (7.9)	3 (2.0)	6 (4.0)	0
Muscular weakness	11 (7.2)	1 (0.7)	7 (4.7)	0
Peripheral sensory neuropathy	11 (7.2)	1 (0.7)	9 (6.0)	0
Myalgia	10 (6.6)	0	5 (3.4)	0
Stomatitis	10 (6.6)	1 (0.7)	4 (2.7)	0
Weight decreased	10 (6.6)	0	2 (1.3)	0
Influenza	9 (5.9)	4 (2.6)	8 (5.4)	1 (0.7)
Pathological fracture	9 (5.9)	3 (2.0)	8 (5.4)	3 (2.0)
Disease progression	8 (5.3)	8 (5.3)	8 (5.4)	8 (5.4)
Dizziness	8 (5.3)	0	4 (2.7)	0
Fall	8 (5.3)	0	8 (5.4)	1 (0.7)
Lower respiratory tract infection	8 (5.3)	5 (3.3)	8 (5.4)	4 (2.7)
Oropharyngeal pain	8 (5.3)	0	3 (2.0)	0
Acute kidney injury	7 (4.6)	4 (2.6)	8 (5.4)	6 (4.0)
Atrial fibrillation	7 (4.6)	3 (2.0)	3 (2.0)	1 (0.7)
Hypertension	7 (4.6)	2 (1.3)	8 (5.4)	3 (2.0)
Anemia	6 (3.9)	5 (3.3)	2 (1.3)	1 (0.7)
Syncope	6 (3.9)	5 (3.3)	3 (2.0)	3 (2.0)
Hyperglycemia	5 (3.3)	4 (2.6)	1 (0.7)	0
Rash	5 (3.3)	0	8 (5.4)	0
Sepsis	4 (2.6)	4 (2.6)	2 (1.3)	2 (1.3)
Pulmonary embolism	3 (2.0)	3 (2.0)	3 (2.0)	3 (2.0)

IsaPd = isatuximab plus pomalidomide and dexamethasone; Pd = pomalidomide plus dexamethasone
Note: Percentages are calculated using the number of patients treated as denominator.

Note: Table sorted by decreasing frequency of PTs (all grades) in the IsaPd treatment group.
* Infusion-related reactions reported in the Pd group were attributed to daratumumab given after study drug discontinuation. The infusion-related reactions had occurred within 30 days of discontinuing assigned study treatment.
Source: FDA Multi-disciplinary Review[4]

The most common serious TEAEs (of all grades), reported in at least 3% of patients, and with a higher incidence in the IsaPd group were: urinary tract infections (3.9% vs. 1.3%), neutropenia (3.3% vs. 1.3%), febrile neutropenia (6.6% vs. 2.0%), pathological fracture (3.3% vs. 2.0%), and infusion-related reactions (3.9% vs. 0.7%). Serious TEAEs that were reported at a higher incidence in the Pd group were: pneumonia (15.1% vs. 15.4%), disease progression (4.6% vs. 4.7%) and acute kidney injury (3.3% vs. 4.0%). The difference in the incidence of various serious TEAEs between treatment groups did not exceed 5%.[4] Serious TEAEs lead to hospitalizations in 60.5% of patients in the IsaPd group and 51.7% of patients in the Pd group.[3]

When grouped by SOC in the MedDRA Hierarchy, TEAEs with the following etiologies were reported with the greatest difference between the two treatments (≥ 10%): 'Nervous system disorders', 'Cardiac disorders', 'Injury, poisoning and procedural complications (infusion reactions)', 'Infections and infestations', and 'Blood and lymphatic system disorders' including thrombocytopenia and neutropenia. Key details are discussed under the section *Specific AEs of Interest* below.

Most of the frequently reported TEAEs had resolved by the time of data cut-off. The median duration to resolution was longer in the Pd group for dyspnea (16 vs. 10 days) and nausea (24 vs. 8 days). Upper respiratory tract infections resolved after a similar duration (median 11 days for IsaPd vs. 13 days for Pd). Duration of the most frequently reported grade ≥3 TEAE was also similar between the two treatment groups. Although the incidence was low, of the most common severe TEAEs, the main difference in duration to resolution was seen in pathological fractures; the median time to resolution in the IsaPd group was 28 days compared to 110 days in the Pd group.[5]

Treatment-related TEAEs

Treatment-related TEAEs were defined as AEs that were reasonably thought to be caused by at least one of the study drug treatments, according to investigators.[4] Treatment-related TEAEs of any grade were higher in the IsaPd group (90.8%, n=138) compared to the Pd group (79.9%, n=119). Of TEAEs deemed related to treatment, the most commonly reported (i.e., ≥ 10%) and with a higher incidence (i.e., ≥ 5%) in the IsaPd group were: neutropenia (42.8% vs. 32.2%), infusion related reaction (36.2% vs. 0.0%), upper respiratory tract infection (9.9% vs. 4.4%), and febrile neutropenia (10.5% vs. 2.0%).[5]

The incidence of treatment-related TEAEs of grade ≥ 3 in severity were also higher in patients treated with IsaPd (71.7%, n=109) than Pd (47.4%, n=71). Of grade ≥ 3 TEAEs deemed related to treatment, the most commonly reported (i.e., ≥ 5%) and with an incidence of 5% or higher in the IsaPd group were: neutropenia (42.1% vs. 30.9%) and febrile neutropenia (10.5% vs. 2.0%).[5] None of the treatment-related TEAEs in the Pd group occurred at an incidence of 5% or higher than the IsaPd group (for all grades reported in ≥ 10% of patients or Grade ≥ 3 reported in ≥ 5% of patients).[5]

Serious treatment-related TEAEs also occurred in a greater proportion of patients treated with IsaPd (35.5%, n=54) than with Pd (16.1%, n=24).[5] Serious treatment-related TEAEs, reported in 2% or more patients in the IsaPd group, were: pneumonia (9.9%), febrile neutropenia (6.6%), infusion related reaction (3.9%), neutropenia (2.0%), pulmonary embolism (2.0%), and thrombocytopenia (2.0%). Treatment-related serious TEAEs reported in at least 2% of patients in the Pd group were: pneumonia (5.4%) and febrile neutropenia (2.0%).[6]

Treatment Modification or Discontinuation Due to AEs

More patients randomized to IsaPd had a delay in treatment cycle (57.9% vs. 43.0% for Pd) and a treatment cycle delay of longer than seven days (34.9% vs. 17.4%). Out of the treatment cycles administered, 13.1% in the IsaPd group and 10.9% in the Pd group were delayed.[5]

There were greater number of patients who had dose reductions of pomalidomide and dexamethasone in the IsaPd group compared to the Pd group. In patients who received IsaPd, the dose of pomalidomide was reduced in 42.8% of patients (n=65) and dose of dexamethasone was reduced in 32.9% of patients (n=50). Dose reductions of isatuximab were not permitted according to the protocol. In the Pd group, pomalidomide dose was reduced in 24.2% (n=36) patients and dexamethasone dose was reduced in 25.5% (n=38) patients. Dose reductions in both treatment groups were mainly due to neutropenia and infections.[2]

At least one dose of isatuximab was omitted in 52.0% of patients, and a dose delay occurred in 10.5% of patients; however, the median relative dose intensity remained at >90%.[6] A dose modification of isatuximab (i.e., dose delay, dose interruption, or dose omission) reported in at least 10% of patients, were due the following TEAEs of any grade: neutropenia (33.6%), infusion-related reactions (28.3%), pneumonia (13.2%), and upper respiratory tract infections (10.5%)[5]. Isatuximab infusion was interrupted in 34.9% of patients (n=53), with interruptions occurring during the first infusion in 50 patients; and infusions were interrupted due to TEAEs in 30.9% of patients (n=47). The most frequently reported TEAE that lead to interruption of isatuximab administration was infusion-related reaction, seen in 28.9% of patients.[4] A greater number of patients in the IsaPd group had a dose of pomalidomide omitted (82.9% vs. 63.1% Pd).[5] Similarly, a greater number of patients treated with IsaPd had a dose of dexamethasone omitted (58.6% vs. 32.2% Pd).[6]

Individual agents in the assigned treatment combination were discontinued due to a TEAE in more patients in the IsaPd group overall. Premature discontinuation of at least one component of the combination occurred in 14 patients (9.2%) in the IsaPd group and 3 patients (2.0%) in the Pd group. In the IsaPd group, isatuximab was prematurely discontinued due to a TEAE in 2.6% (n=4; all infusion-related reactions), pomalidomide in 5.3% (n=8), and dexamethasone in 1.3% (n=2) of patients. In the Pd group, no patients prematurely discontinued pomalidomide due to an TEAE, and 1.3% (n=2) prematurely discontinued dexamethasone.[4]

TEAEs led to definitive discontinuation, defined as discontinuation of all study treatment or of the last ongoing study drug, occurred in 7.2% (n=11) of patients treated with IsaPd and 12.8% (n=19) of patients treated with Pd. The most frequently reported TEAEs (SOCs) which led to discontinuation of IsaPd included infections and infestations (2.6% IsaPd vs. 5.4% Pd group), as well as blood and lymphatic system disorders (0.7% IsaPd vs. 4.7% Pd). Specifically, TEAEs which led to definitive treatment discontinuation in two or more patients were death in the IsaPd group (n=2), and thrombocytopenia (n=7), pneumonia (n=3), neutropenia (n=2), and septic shock (n=2) in the Pd group.[4]

Deaths Due to an AE

At the time of the safety data cut-off of November 22, 2018, there were a total of 102 deaths; 24 deaths occurred during the study treatment period (within 30 days of last treatment dose), and 78 deaths occurred during the post-treatment period, regardless of cause.[4]

A summary of deaths related to a TEAE can be found in Table 19 above. According to the sponsor, a grade 5 TEAE includes patients who died during the treatment period and had a TEAE reported in the electronic case report form, regardless of the cause of death. In other words, counts of grade 5 TEAEs included all patients who died during the treatment period, whatever the cause, and could have included disease progression.[3] A grade 5 TEAE occurred in a total of 24 patients (8.0%) during the treatment period. By treatment group, 11 patients (7.2%) who received IsaPd and 13 patients (8.7%) who received Pd experienced a grade 5 TEAE during the treatment period. Death was thought to be due to disease progression in six patients (3.9%) in the IsaPd group and five patients (3.4%) in the Pd group. A specific TEAE was thought to be the cause of death (and unrelated to disease progression) in a total of nine patients; three patients (2.0%) in the IsaPd group and six patients (4.0%) in the Pd group.[4] The most common causes of death were infections; other causes included intracranial hemorrhage and hepatic failure.[6] Two patients (1.3%) in each treatment group had died due to other causes, categorized as death or sudden death of unknown cause.[4]

Additionally, nine patients who experienced a TEAE had died during the post-treatment period (i.e., worsened to grade 5); five patients (3.4%) in the IsaPd group and four patients (2.6%) in the Pd group. In total, 33 patients (11.0%) had died due to a grade 5 TEAE during the study prior to the data cut-off date (i.e., treatment and post-treatment period), including 16 patients (10.5%) in the IsaPd group and 17 patients (11.4%) in the Pd group.[3]

Death which was thought to be related to an AE from study treatment was reported in one patient (0.7%) treated with IsaPd and in two patients (1.3%) treated with Pd. The drug-related fatal TEAE in the IsaPd group was due to sepsis, and the two patients in the Pd group died from pneumonia and urinary tract infection, deemed related to treatment by the investigators.[4]

Specific AEs of Interest as Highlighted in the ICARIA-MM Trial

Nervous system disorders

Nervous system disorders were reported at a higher incidence in patients treated with IsaPd (40.8% vs. 28.9% Pd). Specifically, the following TEAEs fell under this category and had a 2% or greater incidence in the IsaPd group (and reported in ≥ 5% for all grades): headache (9.9% vs. 5.4%), tremor (7.9% vs. 4.0%), and dizziness (5.3% vs. 2.7%). All incidences were non-serious and unrelated to treatment. Nervous system disorders also did not lead to definitive discontinuation of treatment.[5]

Cardiac disorders

More patients treated with IsaPd experienced cardiac disorders as a TEAE (14.5% vs. 4.0% Pd), with the majority of events categorized as grades 1 or 2. The most commonly reported TEAE in the IsaPd group that fell under this category was cardiac arrhythmias (11.2% and 2.0%), of which atrial fibrillation was the most frequently reported type (4.6%; n=7 IsaPd vs. 2.0%; n=3 Pd).[5]

Infusion Reactions

Infusion reactions of any grade, including clinical diagnoses such as infusion-related reactions and cytokine release syndrome, occurred in 38.2% of patients (n=58) in the IsaPd group overall. Specific diagnoses included infusion-related reactions in 36.8% (n=56), cytokine release syndrome in 1.3% (n=2) and drug hypersensitivity in 0.7% (n=1) of patients. Most infusion reactions were grade 1 (3.9%) or 2 (31.6%); and grade 3 or 4 reactions were experienced in 1.3% of patients (in each category), and no patients experienced a grade 5 infusion reaction. Most patients experienced a single episode, with reactions occurring generally during the first infusion and on the same day. No delayed infusion-reactions (reported within 24 hours) occurred. Most reactions were managed with infusion interruption and/or with treatment. All infusion reactions had resolved within a day and without further sequalae. Interruption of a dose of isatuximab due to an infusion reaction was required in 28.9% of patients, and discontinuation of isatuximab treatment due to an infusion reaction occurred in 2.6% (n=4) of patients as a result of a grade 3 or 4 reaction which occurred during the first infusion.[4]

The most frequently reported symptoms of infusion reactions were dyspnea (15.1%), cough (6.6%), nausea (5.9%), and chills (5.3%). Grade 3 symptoms occurred in seven (4.6%) patients and included hypertension in three patients, and in one patient each: dyspnea, bronchospasm, hypoxia, acute pulmonary edema, hypotension, tachycardia, syncope, and hyperglycemia. Grade 4 symptoms occurred in one patient and were reported as dyspnea and wheezing. It should be noted that the severity grading for infusion reactions was not directly linked to the severity grading of the individual symptoms; rather they were defined by specific NCI-CTCAE criteria.[4]

Infusion-related reactions were reported in two patients (1.3%) in the Pd group; however, both were attributed to daratumumab given after study drug discontinuation. In both patients the infusion-related reaction occurred within 30 days of discontinuing assigned study treatment.[4]

Infections

Infections of any grade were reported in 80.9% of patients treated with IsaPd compared to 64.4% treated with Pd. Of TEAEs categorized under this category, the most frequently reported AEs that contributed to this imbalance were upper respiratory tract infection (28.3% vs. 17.4%) and bronchitis (23.7% vs. 8.7%). Of opportunistic infections, there was a difference in the incidence of herpes virus (9.9% vs. 2.7%). No reactivation of HBV or HCV was reported.[5]

Infections of ≥ grade 3 severity occurred in 42.8% compared to 30.2% of patients treated with IsaPd and Pd, respectively. Pneumonia was the most common infection of grade 3 or 4 severity; it was reported in 25% of patients in the IsaPd group compared to 18.8% of patients treated with Pd. Treatment was discontinued due to infections in 2.6% and 5.4% of patients treated with IsaPd and Pd, respectively. Infections led to death in 3.3% of patients treated with IsaPd and 4.0% of patients treated with Pd.[5]

Respiratory Tract Infections

Respiratory tract infections were reported in 74.3% of patients in the IsaPd group compared to 53.0% of patients in the Pd group; and grade ≥ 3 infections were reported in 36.2% vs. 24.2% in patients treated with IsaPd vs. Pd, respectively. Upper respiratory tract infection, pneumonia, bronchitis, and nasopharyngitis had contributed most significantly to the imbalance observed between the two treatment groups. During the study, lower respiratory tract infections (LRTIs) were reported in 36.8% of patients treated with IsaPd

compared to 25.5% of patients treated with Pd. The incidence of LRTIs ≥ grade 3 were also higher in the IsaPd group (7.9% vs. 3.4%) where dyspnea and productive cough contributed most to this imbalance.[5]

Hematologic Abnormalities

Laboratory-measured neutropenia of grade 3-4 severity was reported in 84.8% of patients in the IsaPd group compared to 70.1% of patients in the IsaPd group. Notably, Grade 4 neutropenia occurred in 60.5% of patients treated with IsaPd compared to 31.3% of patients treated with Pd. The incidence of neutropenia reported as an AE (i.e., clinically significant according to investigators) was lower, with grade ≥ 3 TEAEs recorded in 46.1% of patients in the IsaPd group and 32.2% of patients in the Pd group.

Febrile neutropenia of grade ≥ 3 severity was reported in 11.8% of patients in the IsaPd group and 2.0% of patients in the Pd group; and the incidence of neutropenic infections was 25.0% and 19.5% of patients in the IsaPd and Pd groups, respectively, with grade ≥ 3 neutropenic infections occurring in 13.2% of patients treated with IsaPd compared to 9.4% of patients treated with Pd. Neutropenic complications led to permanent discontinuation of treatment in 1.3% and 3.4% of patients in the IsaPd and Pd groups respectively. One patient in the IsaPd group died due to neutropenic complications (i.e., influenza pneumonia plus concurrent grade 4 neutropenia). In the Pd group, three patients died due to neutropenic complications. One of the deaths in the Pd group was due to pneumonia with concurrent grade 3 neutropenia and was deemed to be treatment-related.[4]

Grade 3-4 laboratory measured thrombocytopenia was reported in 30.9% of patients in the IsaPd group, compared to 24.5% of patients in the Pd group. According to investigators, thrombocytopenia was reported as a grade ≥3 TEAE in 12.1% of patients in the IsaPd group and 11.8% of patients in the Pd group. Hemorrhage of all grades occurred in 8.6% of patients treated with IsaPd and 11.4% of patients treated with Pd.[4]

Second Primary Malignancies

A total of seven patients developed second primary malignancies after starting study treatment, including six patients (3.9%) in the IsaPd group and one patient in the Pd group (0.7%). In the IsaPd group, four patients were diagnosed with squamous cell carcinoma; breast angiosarcoma and myelodysplastic syndrome were diagnosed in one patient each. The patient in the Pd group developed squamous cell carcinoma. Most patients did not discontinue treatment due to a secondary primary malignancy. One patient treated with IsaPd, who had developed myelodysplastic syndrome which transformed to acute myeloid leukemia, discontinued study treatment.[4]

6.4 Ongoing Trials

No ongoing trials meeting our systematic review selection criteria were found.

7 Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of IsaPd in RRMM who have received at least two prior therapies (including lenalidomide and a PI):

- Summary and critical appraisal of a sponsor-submitted indirect ITC comparing efficacy data (OS and PFS) for IsaPd to Kd. The ITC is based on a subgroup of patients receiving Kd in the ENDEAVOR trial who were refractory to lenalidomide.[7]

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Sponsor-Submitted Indirect Treatment Comparison

7.1.1 Objective

The objective of this section is to summarize and critically appraise the methods and findings of the sponsor-submitted ITC estimating the comparative efficacy of IsaPd to Kd in the treatment of patients with RRMM. The available clinical trial did not include all relevant comparators for the economic model and analysis supporting this submission, specifically the combination of Kd, which was identified by the CGP as well as the PAG and registered clinician Input. The sponsor supplied an ITC including this relevant comparator in response to feedback they received from clinicians, who indicated Kd may be used as treatment for patients with RRMM who have been previously exposed to two prior therapies.[7]

7.1.2 Findings

The ITC was based on results from two trials, ICARIA-MM[2] and ENDEAVOR.[61-63] Due to differences in key treatment effect modifiers, an unadjusted and unanchored ITC was performed for the outcomes of PFS and OS. The sponsors indicated that a robust ITC was not possible due to the key differences in baseline characteristics between patients enrolled in the two trials which would lead to biased results. Also, due to the lack of an anchor, a network meta-analysis could not be performed. No systematic review of the literature was provided or performed in preparation of this ITC. The sponsor submitted the details as an ITC report, and the contents have not been published. Results of the ITC informed the sponsor's cost-effectiveness modelling for IsaPd compared to Kd.[7]

Trial and Patient Characteristics

The report highlighted the key differences between patients enrolled in the ICARIA-MM and ENDEAVOR trials that were included in the ITC; however, comprehensive information on the characteristics of the overall patient population in each trial was not reported. Further, no details related to study design and administered treatment were provided.

Two important treatment effect modifiers were identified by the sponsors: refractoriness to lenalidomide and number of prior lines of therapy. According to the sponsor, there were substantial differences in the inclusion criteria of the trials that preclude an appropriate comparison of patient populations. Specifically, the authors noted that the ICARIA-MM trial required patients to have received and failed at least two consecutive cycles of lenalidomide and a PI (i.e., bortezomib, carfilzomib, ixazomib) that were given alone or in combination, whereas the ENDEAVOR trial did not require patients to have received lenalidomide and a PI. Notably, only 34.0% (n=158) of patients who received Kd in the ENDEAVOR trial had received prior treatment with both an IMiD, such as lenalidomide, and bortezomib.[7]

Differences in the patients enrolled in the trials were noted in regard to treatment history. In the ICARIA-MM trial, all patients had received at least two prior lines of therapy, whereas half of the patients in the ENDEAVOR trial had received only one prior line of treatment. In the ICARIA-MM trial, 94.0% of patients were refractory to lenalidomide, and 72.0% were refractory to both lenalidomide and a PI. In the ENDEAVOR trial, 24.4% of patients were refractory to prior lenalidomide treatment and 3.2% were refractory to bortezomib; the proportion of patients who were refractory to both lenalidomide and a PI (i.e., double refractory) was not reported. Overall, patients in the ENDEAVOR trial were not as heavily treated prior to study enrolment as patients in the ICARIA-MM trial.[7]

Methods for Indirect Treatment Comparison

As discussed above, the differences in inclusion criteria between the two trials and the resulting discrepancies in treatment effect modifiers precluded matching of patient populations; thus, it was deemed by the sponsor that a robust, adjusted ITC could not be performed. In the submitted report, an unadjusted and unanchored ITC was conducted. Data for the IsaPd group were taken from patients randomized to this treatment (n=154) in the ITT population of the ICARIA-MM trial. Data for the Kd population was obtained from the subgroup of patients in the ENDEAVOR trial who were refractory to lenalidomide (n=113) as it was considered the most appropriate group of patients for comparison in the ITC.[7]

Overall Survival

Kaplan Meier curves in the ENDEAVOR trial publication were digitized to obtain OS data for lenalidomide-refractory patients who received Kd.[61] Individual patient-level data were reconstructed by combining the number of patients at risk with the K-M curves for the Kd arm. Patient-level data for the IsaPd group were used from the ITT population of the ICARIA-MM trial. K-M estimates of OS were generated for pairwise comparisons of IsaPd versus Kd, and HRs were generated using Cox proportional hazards regression analysis with a single covariate for treatment. Schoenfeld residuals were also tested for linearity.[7]

Progression-Free Survival

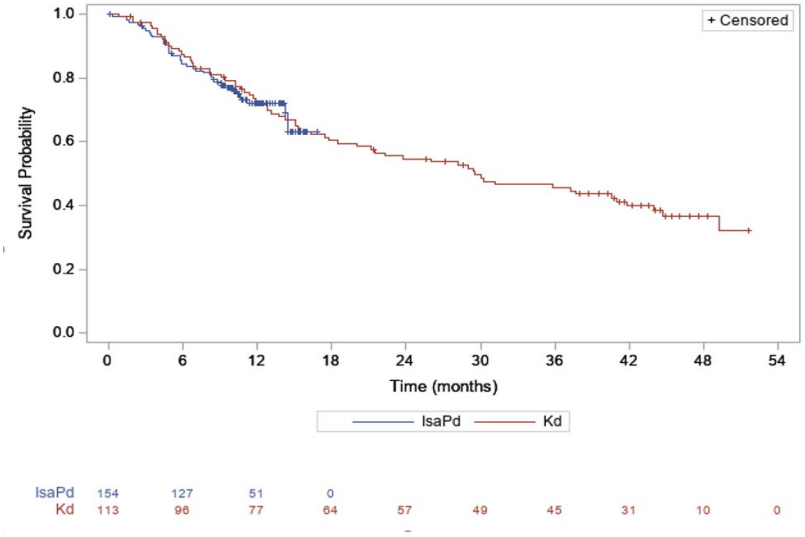
A K-M curve for the subgroup of interest was not available in the ENDEAVOR publication. The HR for PFS was calculated by dividing the median PFS reported for lenalidomide-refractory patients treated with Kd by the median PFS for patients treated with IsaPd, using the assumptions for a constant proportional hazard (i.e., distributions are approximately exponential or Weibull with the same shape parameters). Since a CI was not reported for the median PFS estimate for lenalidomide-refractory patents in the ENDEAVOR trial, the CI for the HR was calculated using several assumptions surrounding standard error for the log(HR).[7]

Results

Overall Survival

The estimated HR for OS was 1.0 (95% CI, 0.67 to 1.62; P=0.848), and the K-M curve of OS for patients treated with IsaPd versus lenalidomide-refractory patients treated with Kd is provided in Figure 8. The test for linearity of the Schoenfeld residuals was not statistically significant, suggesting that there is no evidence that the proportional hazards assumption was violated (correlation of -0.0432, p=0.6557).[7]

Figure 8: K-M curve for OS, IsaPd versus Kd (lenalidomide-refractory)



Source: CADTH Submission, Indirect Treatment Comparison[7]

Progression-Free Survival (PFS)

The estimated HR for PFS was 0.75 (95% CI, 0.52 to 1.07; P=0.11), as calculated from the median PFS data reported in the two trials. In the ENDEAVOR trial, the median PFS was 8.6 months (95% CI, not available) whereas the median PFS in the ICARIA-MM trial was 11.53 months (95% CI, 8.94 to 13.90 months).[63] The standard error of the ln(HR) for IsaPd compared to lenalidomide-refractory Kd patients was 0.1845.[7]

Critical Appraisal

An unadjusted and unanchored ITC was performed and submitted by the sponsor. A robust method of ITC was deemed not possible due to the differences in key treatment effect modifiers and insufficient data available for the subgroup of lenalidomide-refractory patients who received Kd. Due to limitations in methodology for ITCs of this nature, it is not recommended to derive definitive conclusions from the comparative treatment effect estimates that were generated from the ITC.

The authors chose the comparator and patient population based on feedback from clinicians who treat RRMM. The sponsor did not describe whether any literature search had been performed to identify additional data or studies for inclusion, and thus the completeness of the available evidence cannot be evaluated. Nonetheless, the chosen comparator (Kd) was identified by the CGP and in the PAG and registered clinician input received by CADTH and is therefore relevant to Canadian clinical practice.

There are several significant limitations of the methodology used for the submitted ITC, which were acknowledged in the ITC report. Overall, the sponsor concluded that the ITC results should be interpreted with caution due to differences in important treatment effect modifiers. Further, they also provided reasons for why a more robust ITC approach would be biased with an unknown magnitude. The ICARIA-MM and ENDEAVOR trials differed quite substantially with respect to important treatment effect modifiers that include prior treatment with lenalidomide and a PI, refractory status to prior lenalidomide, and number of lines of prior treatment received. The authors also stated that a population adjusted approach to ITC, such as a match-adjusted indirect comparison or simulated treatment comparisons, were also not feasible due to insufficient data available for the subgroup of lenalidomide-refractory patients who received Kd. A network meta-analyses was also deemed not possible due to the lack of a common comparator to anchor comparisons. Additionally, the authors acknowledge that selecting the subgroup of lenalidomide-refractory patients from the ENDEAVOR trial does not adjust for the known differences in other treatment effect modifiers, such as number of lines of prior treatment, which has the potential to bias the results in favour of Kd.[7]

In addition to the limitations identified by the sponsor, a few others should also be considered when interpreting the results of the unanchored ITC. The authors focused on three treatment effect modifiers, two of which (i.e., refractoriness to lenalidomide and number of prior lines of treatment) were deemed important according to the clinical experts they consulted for the ITC. The sponsor did not mention whether there were any differences in prognostic factors between the trials, which also is a source of clinical heterogeneity that has the potential to bias results due to the fact that the comparison was unanchored. In such comparisons, within-study randomization is not preserved and can result in imbalances in the baseline characteristics, both measured and unmeasured, which were not discussed by the authors. Furthermore, patients in the Kd group (lenalidomide-refractory) represent a subgroup of the main ENDEAVOR trial population. Important information on the trials and the specific subgroup in terms of treatment exposure, the median duration of follow-up for OS and PFS outcomes, outcome definitions, and assessment (e.g., blinded versus investigator) were also not reported. Differences in these aspects of trial conduct also have the potential to bias the results.

Overall, the differences between trials in terms of eligibility criteria resulted in heterogeneity in important treatment effect modifiers, which introduces a high level of uncertainty in determining the true comparative efficacy between IsaPd and Kd. Additionally, randomization within each study was lost due to the unanchored comparison, and results could also be biased by differences in prognostic factors since the comparison was unadjusted. Therefore, no clinical conclusions can be drawn from these results due to these limitations. Outcomes related to other relevant efficacy endpoints (e.g., ORR), safety, and HRQoL were not analyzed, and therefore no conclusions can be drawn in comparing IsaPd to Kd for these outcomes.

7.1.3 Summary

In the absence of direct evidence comparing IsaPd and Kd for the treatment of RRMM who have been exposed to two prior therapies (including lenalidomide and a PI), the sponsor submitted an unadjusted and unanchored ITC comparing the two treatments in this patient population. Two trials were included in the ITC: the ICARIA-MM trial provided individual patient-level data for IsaPd and the ENDEAVOR trial provided aggregate data for treatment with Kd in the analysis of OS. Published median values were used in the analysis of PFS.[7] Although statistical comparisons between the treatments were provided for these key outcomes, inherent limitations to the unanchored and unadjusted approach used in the ITC leads to a high level of uncertainty in the results. The heterogeneity in the patient populations of the two trials, particularly surrounding important treatment effect modifiers relating to prior treatment history (i.e., number and types of prior lines of therapy received) and prognostic factors have the potential to severely bias and limit the generalizability of the results. As such, no conclusions can be made regarding the comparative efficacy of IsaPd and Kd based on the submitted ITC, and its results should be interpreted with caution.

8 Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Myeloma CGP and supported by the CADTH Methods Team. This document is intended to advise the pERC regarding the clinical evidence available on IsaPd in RRMM. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

Literature Search Methods

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2020, Embase 1974 to 2020 September 03 , Ovid MEDLINE(R) ALL 1946 to September 03, 2020
Search Strategy:

#	Searches	Results
1	(Sarclisa* or isatuximab or SAR 650984 or SAR650984 or Hu 38SB19 or Hu38SB19 or R30772KCU0).ti,ab,ot,kf,kw,hw,nm,rn.	494
2	1 use medall	76
3	limit 2 to english language	72
4	1 use cctr	59
5	*isatuximab/ or (Sarclisa* or isatuximab or SAR 650984 or SAR650984 or Hu 38SB19 or Hu38SB19).ti,ab,kw,dq.	340
6	5 use oemezd	209
7	limit 6 to english language	207
8	7 not conference abstract.pt.	86
9	3 or 4 or 8	217
10	remove duplicates from 9	147
11	7 and conference abstract.pt.	121
12	limit 11 to yr="2015 -Current"	103
13	10 or 12	250

2. Cochrane Central Register of Controlled Trials (CENTRAL)
   (searched via Ovid)
3. Grey literature search via:

   Clinical trials registries:

   US National Library of Medicine. ClinicalTrials.gov
   https://clinicaltrials.gov/

   World Health Organization
   http://apps.who.int/trialsearch/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Sarclisa/isatuximab, multiple myeloma

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Sarclisa/isatuximab, multiple myeloma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Sarclisa/isatuximab, multiple myeloma - last 5 years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[64]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Sarclisa/isatuximab.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of December 24, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[65] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trials registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the American Society of Hematology were searched manually for conference years not available in Embase. Searches were supplemented through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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