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Comparison of isatuximab-pomalidomide-dexamethasone *versus* elotuzumab-pomalidomide-dexamethasone in relapsed/refractory multiple myeloma patients: a target trial emulation using real-world data.

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AUTHOR CONTRIBUTIONS

E.A.M, A.P., M.G., F.D.R., V.D.S., N.B., G.T., A.N., F.M., M.T.P., and P.M. designed the study; G.T., A.P., M.G. and F.M. performed statistical analysis; D.D., E.R., P.S., S.M., E.Z., M.O., A.M.Q., R.D.P., G.B., E.B., C.C., C.D.M., V.B., A.M.C., A.M., N.S., G.M.C., O.A., A.R., R.F., E.V., A.B., A.A., A.Ci., A.G., V.B., V.A., P.S., S.T., S.P., R.B., M.B., F.L., M.A.F., C.Ce., C.Ca., R.Z., C.L., D.R., F.F., J.M., I.D.V., G.T., E.A., S.A., A.M., A.L., G.Be., A.F., A.M., P.B., L.D.P., G.Ba. and S.Mo. acquired, analyzed and interpreted data. E.A.M., A.P., G.T., M.G., and F.M. wrote the manuscript; all authors revised the manuscript and gave final approval; all authors agreed to be accountable for all aspects of the manuscript in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DISCLOSURE

Nothing to disclose.

DATA SHARING

Data are available upon reasonable request and submission of a research project proposal to the corresponding authors

ETHICS STATEMENT

The study protocol was reviewed and approved by the Institutional Ethics Committees in accordance with the principles of the Declaration of Helsinki.

COMPETING INTERESTS

Nothing to disclose

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Running title: IsaPd vs EloPd for RRMM patients: a target trial emulation

Advances in multiple myeloma (MM) treatment have significantly improved survival, yet most patients ultimately relapse and develop refractory disease. For those with relapsed/refractory MM (RRMM) after at least two prior therapies, two approved triplet regimens are available: Isatuximab-pomalidomide-dexamethasone (IsaPd) and Elotuzumab-pomalidomide-dexamethasone (EloPd) [1].

IsaPd and EloPd were evaluated in the ICARIA-MM [2,3] and ELOQUENT-3 [4,5] randomized controlled trials (RCTs), both demonstrating efficacy and safety. Real-world studies confirmed these findings [6-8], but the optimal choice remains unclear due to the lack of direct comparisons. To address this gap, we applied target trial emulation (TTE) [9,10], to compare the safety and efficacy of IsaPd and EloPd in two previously described real-world RRMM cohorts [6-8]. The study was approved by institutional ethics committees and conducted following the principles of the Declaration of Helsinki.

The cohorts were merged into a meta-database to emulate a target trial. TTE is a methodology designed to reduce biases in observational research, approximating randomized conditions [9,10]. Inverse probability of treatment weighting (IPTW) balanced baseline characteristics, creating a pseudo-randomized cohort [6-8]. Mann–Whitney and Chi-squared tests compared groups, while standardized mean differences (SMD) (>|0.1|) identified confounders for multivariable logistic regression and propensity score (PS) calculations. IPTW weights were "1/PS" for IsaPd and "[1/(1-PS)]" for EloPd. Weighted logistic regression assessed response, neutropenia, and infections, while Cox models evaluated PFS and OS. Effect modification by Daratumumab refractoriness was tested. Results were reported as ORs or HRs with 95% CIs. Analyses used R (Survival v4.2.3), SPSS (v29), and STATA (v16).

Of 596 eligible patients (Supplementary Table 1), 319 were excluded due to missing FISH data, leaving 277 for analysis. The median age was 69.9 years (IQR 63.4–75.7), and 54.9% were male (Table 1 Panel A). The EloPd group (n=130, 46.9%) and IsaPd group (n=147, 53.1%) were generally comparable, though EloPd patients were older, had higher Daratumumab refractoriness, and more high-risk FISH profiles. SMDs exceeded |0.1| for all except prior treatment lines and disease status. IPTW generated a balanced pseudo-population of 280 cases (130 EloPd, 150 IsaPd; all SMDs <0.07, Table 1 Panel B).

The overall response rate (ORR) was 66.8%, with IsaPd-treated patients showing a higher probability of response (76.9% vs. 55.4%; OR=2.68; P<0.001) (Supplementary Table 2). However, after IPTW, the ORR difference was not statistically significant (OR=1.51; P=0.093), nor in the fully adjusted model (OR=1.45; P=0.262). Factors independently associated with response included

ISS III (OR=0.41; P=0.027), Daratumumab refractoriness (OR=2.30; P=0.013), and high-risk FISH (OR=0.57; P=0.048).

Although in an unadjusted evaluation for treatment response, IsaPd was associated with a significantly higher rate of responders compared to EloPd, after adjusting for confounders through TTE, the difference in ORR between IsaPd and EloPd no longer reached statistical significance. In the multivariable logistic regression analysis, ISS III, Daratumumab refractoriness, and high-risk cytogenetic abnormalities independently impacted ORR. These findings underscore the importance of patient and disease-specific characteristics in predicting treatment response, suggesting that therapeutic decisions should consider individual baseline risk factors rather than solely focusing on the treatment regimen.

After a median follow-up of 21.7 months (95% CI 19.7–23.5), 168 patients progressed or died. Median PFS was 12.5 months (95% CI 9.53–16.7). Unadjusted analysis favored IsaPd (median 17.5 vs. 7.9 months; HR=0.55 [95% CI 0.41–0.75]; P=0.001) (Table 2 Panel A, Figure 1A), but after IPTW, the difference was not significant (IsaPd 10.1 vs. EloPd 8.9 months; HR=0.92 [95% CI 0.68–1.24]; P=0.59) (Table 2 Panel A, Figure 1B). Multivariable analysis confirmed no treatment effect on PFS (HR=0.92 [95% CI 0.61–1.38]; P=0.694). Independent PFS predictors were ISS II (HR=1.44; P=0.047), ISS III (HR=3.24; P<0.001), Daratumumab refractoriness (HR=0.51; P=0.001), prior ASCT (HR=0.68; P=0.045), and high-risk FISH (HR=1.75; P=0.001) (Table 2 Panel A).

Median OS was not reached for IsaPd and 22.9 months for EloPd. Unadjusted OS favored IsaPd (HR=0.57 [95% CI 0.38–0.85]; P=0.007) (Table 2 Panel B, Figure 1C), but after IPTW, the difference was not significant (IsaPd 25.6 vs. EloPd 22.9 months; HR=0.84 [95% CI 0.57–1.22]; P=0.35) (Table 2 Panel B, Figure 1D). Multivariable analysis confirmed no OS difference (HR=0.85 [95% CI 0.51–1.42]; P=0.54). Independent predictors of shorter OS were ISS II (HR=2.12; P=0.005), ISS III (HR=3.82; P<0.001), and elevated LDH (HR=1.79; P=0.009) (Table 2 Panel B). A trend was observed for Daratumumab refractoriness (HR=0.61; P=0.055) and high-risk FISH (HR=1.49; P=0.069).

This is the first hematology study to apply TTE for comparing outcomes and safety in two large RWD cohorts [6-8] of RRMM patients treated with EloPd and IsaPd. By emulating RCT design, TTE mitigates observational biases, balances baseline characteristics, controls for confounders, and strengthens causal inference in real-world settings [9,10]. Indeed, TTE applied to RWD offers a valuable approach for addressing clinical questions unresolved by RCTs, particularly in

underrepresented populations and specific subgroups. In our IsaPd-treated cohort [8], 29.3% had high-risk cytogenetics, a substantially higher proportion than in the ICARIA-MM [4,5], and ~20% were Daratumumab-refractory [11], a group excluded from ICARIA-MM [4,5]. Likewise, the real-world EloPd cohort had a higher prevalence of older patients (>75 years), severe renal impairment, advanced ISS stage, and high-risk cytogenetics compared to ELOQUENT-3 [2,3,6,7]. Moreover, our cohort included Daratumumab-refractory cases [12], a population absent in ELOQUENT-3 [2,3]. These findings underscore the critical role of RWD in evaluating treatment efficacy and safety across diverse populations often underrepresented in RCTs. By bridging the gap between RCT data and real-world clinical scenarios, TTE generates clinically relevant evidence to guide treatment decisions in these challenging settings [9,10].

In the original population, IsaPd was associated with a 45% lower risk of progression or death than EloPd, but this difference lost significance after IPTW adjustment, highlighting baseline imbalances. Independent predictors of worse PFS included ISS II/III, Daratumumab refractoriness, high-risk cytogenetics, and prior ASCT. OS predictors were similar, with elevated LDH as an additional risk factor, while prior ASCT had no negative impact in the fully adjusted model.

TTE performed in our study provides reasonable explanations regarding the difference in terms of PFS and OS that emerged from our previous real-world evidence (RWE) analysis. Indeed, PFS and OS registered in the IsaPd RWE study [8] were 17.5 months and not reached, respectively, while in the EloPd RWE study, these were 7.9 and 22.9 months, respectively [6,7]. One possible reason behind this discrepancy may rely on the fact that the two RWE studies effectively intercepted different populations in terms of patients and disease characteristics, with cases qualitatively more favorable being enrolled in IsaPd real-world analysis.

The findings of this study confirm prior observations from IsaPd RWE analysis, where ISS stage II-III, elevated LDH, and Daratumumab refractoriness were identified as independent prognostic factors for both PFS and OS [8,11]. These predictors also held significance in patients treated with EloPd, consistent with previous findings [6,7]. The impact of prior anti-CD38 monoclonal antibody therapy, such as Daratumumab, aligns with evidence of pronounced CD38+ NK cell depletion, potentially reducing Elotuzumab's efficacy, which relies on NK-mediated antibody-dependent cellular cytotoxicity [13].

Daratumumab refractoriness did not significantly modify the effect of IsaPd vs. EloPd on ORR (P=0.10), PFS (P=0.71), or OS (P=0.16), indicating consistent treatment effects regardless of prior exposure (P>0.10), confirming that the effectiveness of IsaPd versus EloPd was unaffected by

Daratumumab refractoriness. This finding is clinically relevant, as it challenges the theoretical concern that shared molecular targeting between Isatuximab and Daratumumab might compromise therapeutic outcomes in Daratumumab-exposed or potentially refractory patients. On the other hand, the results also imply that Elotuzumab, which operates via a distinct mechanism of action, does not confer a measurable advantage in this subset of patients, despite its independence from CD38-targeted pathways.

IsaPd had higher grade 3–4 hematological (neutropenia: 59.2% vs. 31.5%; P<0.001) and non-hematological (infections: 55.1% vs. 34.6%; P<0.001) toxicities, while gastrointestinal and fatigue rates were similar (Supplementary Table 3, Panel A). Discontinuation due to adverse events was rare and comparable (IsaPd 2.0% vs. EloPd 4.6%; P=0.228). Logistic regression confirmed a higher neutropenia risk with IsaPd (unadjusted OR=3.15; P<0.001; IPTW OR=2.09; P=0.024; fully adjusted OR=2.45; P=0.005) (Supplementary Table 3, Panel B). Daratumumab refractoriness (OR=2.21; P=0.012) and older age (OR=1.04; P=0.031) increased neutropenia risk, while prior ASCT was marginally protective (OR=0.55; P=0.053). IsaPd increased grade 3–4 infection risk (unadjusted OR=2.32; P<0.001), but significance was lost after adjustment (IPTW OR=1.50; P=0.2; fully adjusted OR=1.47; P=0.204) (Supplementary Table 3, Panel C). Daratumumab refractoriness increased infection risk (OR=1.92; P=0.035).

EloPd and IsaPd exhibit distinct safety profiles, particularly in hematologic toxicity. IsaPd had significantly higher grade 3–4 neutropenia rates (59.2% vs. 31.5%, P<0.001), persisting in adjusted analyses (logistic regression OR=2.09; multivariable analysis OR=2.45). This suggests that IsaPd requires closer monitoring and proactive management, such as growth factor support or dose adjustments.

Our findings can influence clinical practice by comparing IsaPd and EloPd in a real-world setting. As third-line treatments often yield transient responses, these regimens could serve as bridges to CAR-T therapy [14] or bispecific antibodies, such as Teclistamab [15], available from the fourth line. Both triplets exhibit comparable survival outcomes, with distinct toxicity profiles. EloPd potentially offers a lower infectious risk, which may be relevant for patient selection in cases where infection risk is a major concern. Nevertheless, Daratumumab refractoriness remains a dominant predictor of outcomes, representing an unmet clinical need.

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Table 1. Baseline characteristics of the cohorts.
Panel A. Baseline characteristics according to the treatment arm in the original cohorts, Panel B. Baseline characteristics according to treatment arm in the weighted cohorts.

Panel A.

	EloPd (n 130)	IsaPd (n 147)	All (n 277)	**P-value**	**SMD**
Age, mean (±SD), median (IQ)	70.2 (±8.6) 71.8 (64.1-76.9)	67.7 (±9.2) 68.7 (62.7-74.9)	68.9 (±9.0) 69.9 (63.4-75.7)	0.02	0.29
Gender, n (%)					
Male	75 (57.7)	77 (52.4)	152 (54.9)	0.38	0.107
Female	55 (42.3)	70 (47.6)	125 (45.1)		
Creatinine clearance mL/min, mean (±SD), median (IQ)	69.2 (±22.5) 70 (58.0-80.0)	71.8 (±24.6) 70 (54.7-90.0)	70.6 (±23.6) 70 (56.0-87.0)	0.36	0.111
International Staging System. n (%)					
I	50 (38.5)	70 (47.6)	120 (43.3)	0.12	0.25
II	51 (39.2)	57 (38.8)	108 (39)		
III	29 (22.3)	20 (13.6)	49 (17.7)		
Previous lines, mean (±SD), median (IQ)	2.5 (±1.0) 2 (2.0-3.0)	2.5 (±0.9) 2 (2.0-3.0)	2.5 (±0.9); 2 (2.0-3.0)	0.52	0.041
LDH. n (%)					
Normal	95 (73.1)	119 (81.0)	214 (77.3)	0.12	0.188
Elevated°	35 (26.9)	28 (19.0)	63 (22.7)		
Daratumumab refractoriness, n (%)					
Yes	99 (76.2)	28 (19.0)	127 (45.8)	<.001*	1.394
No	31 (23.8)	119 (81.0)	150 (54.2)		
Previous autologous stem cell transplantation, n (%)					
Yes	65 (50.0)	85 (57.8)	150 (54.2)	0.19	0.157
No	65 (50.0)	62 (42.2)	127 (45.8)		
Disease status, n (%)					
Biochemical relapse	26 (20.0)	30 (20.4)	56 (20.2)	0.81	0.078
Symtomatic relapse	56 (43.1)	68 (46.3)	124 (44.8)		
Refractory disease	48 (36.9)	49 (33.3)	97 (35.0)		
Cytogenetic analysis, n (%)					
Low risk	75 (57.7)	104 (70.7)	179 (64.6)	.023*	0.275
High risk*	55 (42.3)	43 (29.3)	98 (35.4)		

°Elevated=higher-than-normal LDH levels; *High Risk=patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; SMD=standardized mean differences; SD=standard deviation; IQ=interquartile.

Panel B.

	EloPd (n 130)	**IsaPd (n 150)**	**SMD**
Age, mean (±SD)	68.27 (9.3)	68.91 (9.1)	0.07
Gender Female, n (%)	60.40 (46.5)	68.9 (46.1)	0.008
Creatinine clearance mL/min, mean (±SD)	69.86 (25.2)	69.10 (27.9)	0.029
International Staging System, n (%)			
I	57.0 (43.9)	67.1 (44.9)	
II	50.7 (39.0)	55.1 (36.8)	0.047
III	22.3 (17.2)	27.4 (18.3)	
Elevated LDH°, n (%)	31.5 (24.2)	39.8 (26.6)	0.055

No Daratumumab refractoriness, n (%)	70.3 (54.1)	79.4 (53.1)	0.02
No previous autologous stem cell transplantation, n (%)	61.0 (46.9)	75.1 (50.2)	0.066
Cytogenetic analysis high risk*, n (%)	45.5 (35.0)	50.5 (33.8)	0.026

°Elevated= higher-than-normal LDH levels; *High Risk= patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; SMD=standardized mean differences; SD=standard deviation.

Table 2. Survival analyses.
Panel A: Univariate and multivariate Cox regression analyses of PFS, Panel B: Univariate and multivariate Cox regression analyses of OS.

Panel A.

	HR (95% CI)		
	Unadjusted model	IPWT model	Fully adjusted model
Therapy IsaPd *vs* EloPd	0.55 (0.41-0.75) p=0.001	0.92 (0.68-1.24) p=0.593	0.92 (0.61-1.38) p=0.694
Age			1.01 (0.99-1.04); p=0.210
Gender Female *vs* Male			1.21 (0.88-1.68); p=0.242
Creatinine clearance mL/min			1.00 (0.99-1.01); p=0.703
International Staging System I			1
International Staging System II			1.44 (1.00-2.06); p=0.047
International Staging System III			3.24 (1.98-5.29); p=0.000
LDH elevated° *vs* normal			1.33 (0.94-1.90). p=0.109
Daratumumab refractory no *vs* yes			0.51 (0.34-0.77); p=0.001
Previous autologous stem cell transplantation no *vs* yes			0.68 (0.47-0.99); p=0.045
Cytogenetic analysis high* *vs* low risk			1.75 (1.27-2.43); p=0.001

°Elevated=higher-than-normal LDH levels; *High Risk=patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; HR=hazard ratio; CI=confidence interval; IPWT= Inverse probability of treatment weighting

Panel B.

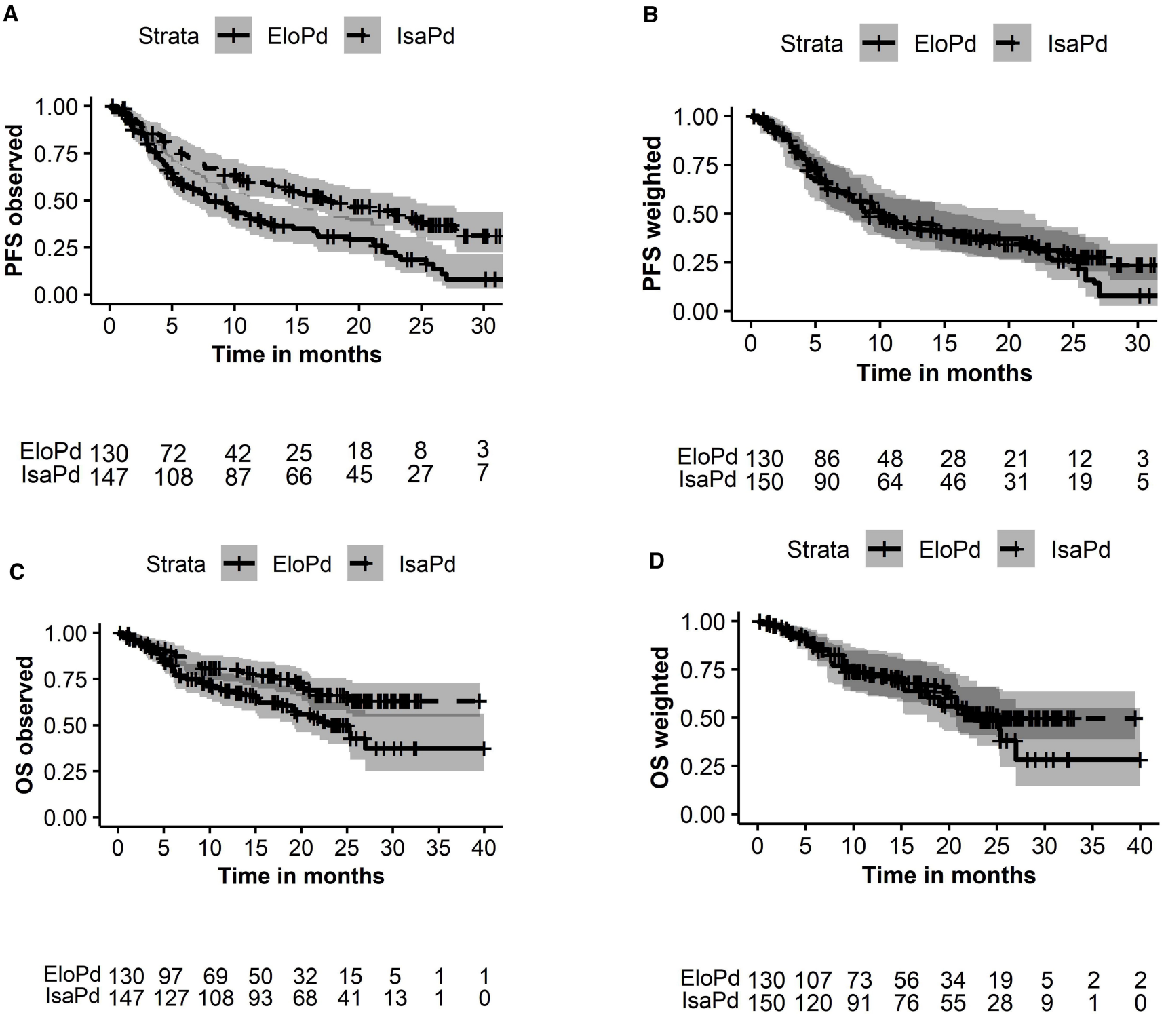
	HR (95% CI)		
	Unadjusted model	IPWT model	Fully adjusted model
Therapy IsaPd vs EloPd	0.57 (0.38-0.85) p=0.007	0.84 (0.57-1.22) p=0.35	0.85 (0.51-1.42) p=0.544
Age			1.01 (0.98-1.04); p=0.533
Gender Female vs Male			1.18 (0.76-1.81); p=0.465
Creatinine clearance mL/min			0.99 (0.98-1.00); p=0.230
International Staging System I			1
International Staging System II			2.12 (1.25-3.58); p=0.005
International Staging System III			3.82 (2.00-7.30); p=0.000
LDH elevated° vs normal			1.79 (1.16-2.78); p=0.009
Daratumumab refractory no vs yes			0.61 (0.36-1.01); p=0.055
Previous autologous stem cell transplantation no vs yes			0.73 (0.44-1.22); p=0.228
Cytogenetic analysis high* vs low risk			1.49 (0.97-2.30); p=0.069

°Elevated=higher-than-normal LDH levels; *High Risk=patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; HR=hazard ratio; CI=confidence interval; IPWT= Inverse probability of treatment weighting.

Figures legend

Figure 1. Kaplan Meier curves for all 596 relapsed/refractory multiple myeloma (RRMM) patients treated with isatuximab-pomalidomide-dexamethasone (IsaPd) or elotuzumab-pomalidomide-dexamethasone (EloPd). **Panel A**. Kaplan Meier curve of progression free survival (PFS) according treatment arm in the original cohort; **Panel B**. Kaplan Meier curve of PFS according treatment arm in the weighted cohort; **Panel C**. Kaplan Meier curve of overall survival (OS) according treatment arm in the original cohort; **Panel D**. Kaplan Meier curve of OS according treatment arm in the weighted cohort.


A
Strata EloPd IsaPd
PFS observed
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30
Time in months
EloPd 130 72 42 25 18 8 3
IsaPd 147 108 87 66 45 27 7
B
Strata EloPd IsaPd
PFS weighted
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30
Time in months
EloPd 130 86 48 28 21 12 3
IsaPd 150 90 64 46 31 19 5
C
Strata EloPd IsaPd
OS observed
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30 35 40
Time in months
EloPd 130 97 69 50 32 15 5 1 1
IsaPd 147 127 108 93 68 41 13 1 0
D
Strata EloPd IsaPd
OS weighted
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30 35 40
Time in months
EloPd 130 107 73 56 34 19 5 2 2
IsaPd 150 120 91 76 55 28 9 1 0

SUPPLEMENTARY APPENDIX CONTENTS

Comparison of isatuximab-pomalidomide-dexamethasone versus elotuzumab-pomalidomide-dexamethasone in relapsed/refractory multiple myeloma patients: a target trial emulation using real-world data.

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Competing interests: Nothing to disclose

Supplementary Tables

Supplementary Figure Legends

Supplementary Table 1. Description of a target trial to compare the efficacy of IsaPd vs EloPd for the treatment of relapsed/refractory multiple myeloma (RRMM) patients.

Protocol Element	Description	Target Trial	Emulation with Observational Data from the Swedish Renal Registry
Eligibility criteria	Who will be included in this study?	Individuals 18 year or older affected by multiple myeloma (MM) patients who received IsaPd or EloPd regimens according to marketing approval guidelines, outside the context of clinical trials	Same as target trial
Treatment strategies	Which precise treatment strategies or interventions will eligible individuals receive?	1. Initiate IsaPd 2. Initiate EloPd	Same as target trial (incidence users)
Treatment assignment	How will eligible individuals be assigned to the treatment strategies?	Randomization, no blinding	Eligible individuals are assigned at baseline to the treatment strategy that their data are consistent with. To emulate randomization, we consider the potential following baseline confounders: age, sex, creatinine clearance, International Staging System, LDH, previous line of therapies, previous autologous stem cell transplantation, previous daratumumab exposure, disease status (biochemical relapse, clinical relapse or refractory disease), cytogenetic risk. Variables with a standardized mean difference (SMD) >=|0.10| are considered as clinically relevant. Data adjustment is performed by inverse probability of treatment weighting (IPTW) in the pseudo-population as well as in a fully adjusted (no-IPTW) multivariable model.
Outcomes	What outcomes will be measured during follow-up?	1. Response to therapy 2. Progression free survival 3. Overall survival	Same as target trial
Causal estimand	Which causal estimand will be estimated with the observational data?	Intention-to-treat effect (effect of being randomized to treatment) Per protocol effect (effect of receiving treatment strategy as specified in protocol)	Per protocol effect (effect of receiving treatment strategy as specified in protocol)
Start and end of follow-up	When does follow-up start and when does it end?	Starts at therapy start and ends at occurrence of end point	Starts at medication initiation (filled prescription) and ends at occurrence of end point
Statistical analysis	Which statistical analyses will be used to estimate the causal estimand?	Intention-to-treat analysis, non-naïve per protocol analysis	Per protocol analysis: Hazard ratios are estimated using Cox regression while adjusting for baseline confounders with inverse probability of treatment weighting. Weighted cumulative incidence curves are estimated using the Aalen–Johansen estimator[a]

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; HR=hazard ratio; CI=confidence interval; IPWT= Inverse probability of treatment weighting.

Supplementary Table 2. Main characteristics of all 596 patients at the time of EloPd and IsaPd initiation.

	EloPd (N=321)	IsaPd (N=275)
	No. of patients (%)	**No. of patients (%)**
Age, (years)		
Median (range)	71.9 (38-89.4)	68.6 (38.6-87.6)
<70	138 (43)	163 (59.3)
≥70	183 (57)	112 (40.7)
Sex		
Male	177 (55.1)	150 (54.5)
Female	144 (44.9)	125 (45.5)
Paraproteins (isotype)		
Immunoglobulin G	184 (57.3)	162 (58.9)
Immunoglobulin A	73 (22.7)	58 (21.1)
Immunoglobulin D	3 (0.9)	2 (0.7)
Immunoglobulin M	3 (0.9)	1 (0.4)
Light chain only	58 (18.1)	52 (18.9)
Creatinine Clearance (mL/min)		
Median (range)	70 (5-161)	71 (3-172)
≥60	216 (67.3)	196 (71.3)
<60	105 (32.7)	79 (28.7)
International Staging System, (%)		
I	116 (36.1)	136 (49.5)
II	128 (39.9)	102 (37.1)
III	77 (24)	37 (13.5)
LDH serum level		
Median (range)	205 (43-1730)	197 (67-2508)
Normal	233 (72.6)	227 (82.5)
Elevated°	88 (27.4)	48 (17.5)
Previous lines of therapy		
Median (range)	2 (2-9)	2 (2-7)
2	183 (57)	172 (62.5)
3	85 (26.5)	70 (25.5)
≥4	53 (16.5)	33 (12.0)
Previous autologous stem cell transplantation		
No	161 (50.2)	107 (38.9)
Yes	160 (49.8)	168 (61.1)
Previous daratumumab		
No	74 (23.1)	224 (81.5)
Yes	247 (76.9)	51 (18.5)
Lenalidomide refractory		
No	13 (4)	7 (2.5)
Yes	308 (96)	268 (97.5)
Disease status		
Biochemical relapse	52 (16.2)	62 (22.5)
Symptomatic relapse	161 (50.2)	141 (51.3)
Refractory to last treatment	108 (33.6)	72 (26.2)
Cytogenetic analysis available (n= 130)		
Standard Risk	75 (57.7)	104 (70.7)
High Risk*	55 (42.3)	43 (29.3)

°Elevated= higher-than-normal LDH levels; *High Risk= patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone.

Supplementary Table 3. Serious adverse events.
Panel A: Incidence of serious adverse events according to the treatment arm in the original cohorts, Panel B: Univariate and multivariable logistic regressions in the original and weighted cohorts on the occurrence of grade 3-4 neutropenia, Panel C: Univariate and multivariable logistic regressions in the original and weighted cohorts on the occurrence of grade 3-4 infection.

Panel A.

	EloPd (N=130)	IsaPd (N=147)	All (N=277)	p-value
Grade 3/4 adverse events	No of cases (%)	No of cases (%)	No of cases (%)	
Hematological toxicities				
Anemia	13 (10)	24 (16.3)	37 (13.4)	0.122
Thrombocytopenia	11 (8.5)	22 (15)	33 (11.9)	0.095
Neutropenia	41 (31.5)	87 (59.2)	128 (46.2)	<.001
Non-hematological toxicities				
Infection	45 (34.6)	81 (55.1)	126 (45.5)	<.001
Gastrointestinal toxicity	6 (4.6)	7 (4.8)	13 (4.7)	0.954
Fatigue	29 (22.3)	27 (18.4)	56 (20.2)	0.415
Infusion reaction	0 (0)	2 (1.3)	2 (0.7)	0.7
Adverse event leading to discontinuation	6 (4.6)	3 (2)	9 (3.2)	0.228

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone.

Panel B.

	OR (95% CI)		
	Unadjusted model	IPWT model	Fully adjusted model
Therapy IsaPd vs EloPd	3.15 (1.93-5.2); p<0.001	2.09 (1.1-3.95); p=0.024	2.45 (1.32-4.58); p=0.005
Age			1.04 (1.00-1.08) p=0.031
Gender Female vs Male			1.48 (0.88-2.51) p=0.143
Creatinine clearance mL/min			1 (0.99-1.01) p=0.721
International Staging System I			1
International Staging System II			0.68 (0.37-1.22) p=0.198
International Staging System III			1.41 (0.64-3.12) p=0.392
LDH elevated° vs normal			1.3 (0,69-2.46) p=0.413
Daratumumab exposure no vs yes			2.21 (1.19-4.13) p=0.012
Previous autologous stem cell transplantation			

no vs yes			0.55 (0.3-1.00) p=0.053
Cytogenetic analysis high* vs low risk			1.3 (0.75-2.26) p=0.35

°Elevated= higher-than-normal LDH levels; *High Risk= patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; OR=Odds ratio; CI=confidence interval; IPWT= Inverse probability of treatment weighting

Panel C.

	OR (95% CI)		
	Unadjusted model	IPWT model	Fully adjusted model
Therapy IsaPd vs EloPd	2.32 (1.43-3.79) p<0.001	1.50 (0.81-2.8) p=0.2	1.47 (0.81-2.68) p=0.204
Age			0.99 (0.96-1.03) p=0.758
Gender Female vs Male			1.19 (0.72-1.98) p=0.495
Creatinine clearance			1 (0.99-1.01) p=0.871
International Staging System I			1
International Staging System II			0.9 (0.51-1.6) p=0.716
International Staging System III			0.98 (0.45-2.1) p=0.954
LDH elevated° vs normal			0.72 (0.39-1.32) p=0.294
Daratumumab exposure no vs yes			1.92 (1.05-3.52) p=0.035
Previous autologous stem cell transplantation no vs yes			0.92 (0.51-1.64) p=0.769
Cytogenetic analysis high* vs low risk			0.7 (0.41-1.18) p=0.186

°Elevated= higher-than-normal LDH levels; *High Risk= patients with the presence of either t(4;14), or t(14;16) or del(17p)

Abbreviations: EloPd=elotuzumab-pomalidomide-dexamethasone; IsaPd=isatuximab-pomalidomide-dexamethasone; OR=Odds ratio; CI=confidence interval; IPWT= Inverse probability of treatment weighting.