

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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SUPPLEMENTARY APPENDIX CONTENTS

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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) $\geq 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.