

**Selecting comparators for drugs with multiple
indications and complex treatment patterns:**

***Example selecting comparators for daratumumab in
multiple myeloma***

SUPPLEMENTAL INFORMATION FOR OHDSI SYMPOSIUM 2019

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1 BACKGROUND

1.1 Selecting a comparator

To conduct a comparative study, an active comparator treatment/drug is selected to compare outcomes in patients receiving the target drug to those in a similar population. Comparator drugs should be recommended in guidelines for the same treatment line or populations with similar risks for the outcome as the target population to ensure that confounding by indication, confounding by severity, and channeling bias are controlled for appropriately.¹

Selecting comparator drugs for comparative studies can be a challenge when the target treatment is indicated for multiple treatment lines or subpopulations, when different combinations of treatment are given in the regimens with the target drug, when varying patterns of treatment could have been received prior to the patient receiving the target drug, and when different populations are indicated for the drug at different lines of treatment. In these complex treatment situations, researchers often try to select a comparator with the exact prior treatment lines and concurrent drugs in the regimen as are received in the target regimen. However, this can lead to extreme restriction in analytic population sizes, especially when the condition being treated is rare, when there are multiple options for each treatment line, and when analytical methods such as propensity score matching are used (Fig 1).

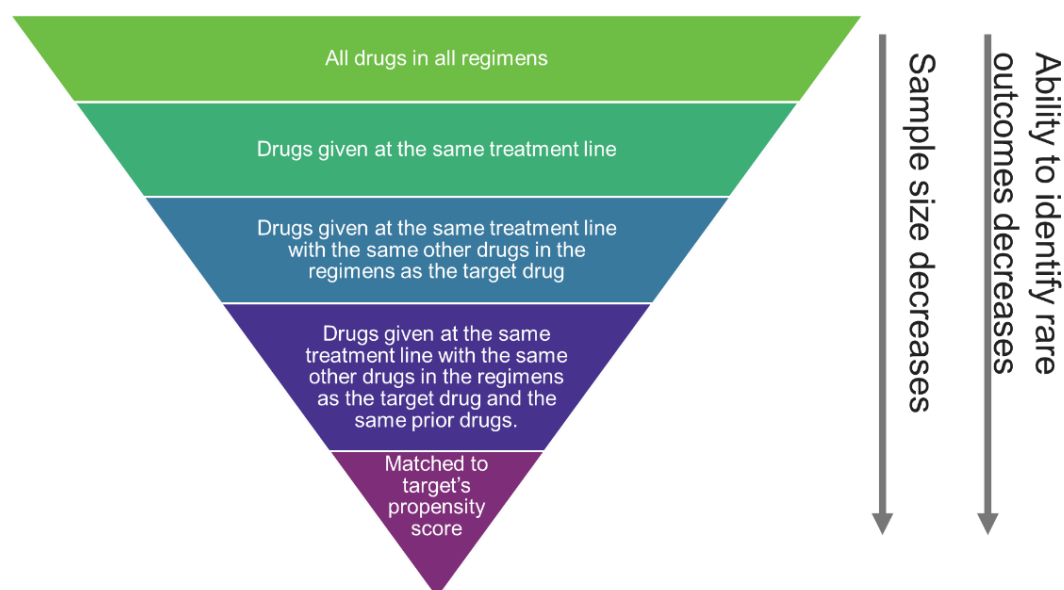


Figure 1. Illustration of how restriction and analytical methods can impact sample size of a comparator drug.

Instead of using restriction, comparator drugs can be selected by ensuring that the population receiving the comparator drug has a similar: (1) probability of receiving the

treatment based on prior characteristics and (2) prevalence of baseline characteristics as the population receiving the target drug of interest.

There are two potential ways of assessing whether the target and comparator drug new user populations look the same at the index date.

One tool for assessing the comparability of a target and comparator drug is by using preference scores. Preference scores are propensity scores (predicted values of a regression of all prior covariates on the choice of receiving the target or comparator drug) that are standardized by the treatment prevalence.³ This score attempts to diminish concerns about confounding by indication by balancing preferences of individual physicians across all physicians. When >50% of patients fall within preference scores in the range of 0.3-0.7, then the comparison of the target and comparator drugs are considered to be in clinical equipoise when there is a high degree of overlap in physician choice between two drugs. Equipoise represents a balance of opinion in the clinical community about the best treatment for patients.

Another method for ensuring that confounding by indication is at a minimum is by assessing the absolute standardized difference in the prevalence of prior covariates from patients who are new users of the target versus the comparator drug. If the difference is high (benchmark of 0.1 used in the literature)⁴, then the two groups do not have a similar balance in the prevalence of a covariate in the data, and that imbalance could lead to influential confounding of the treatment effect. Two ways to measure imbalance in baseline covariate balance are the maximum standardized difference and the percent of covariates that exceed the benchmark of 0.1.

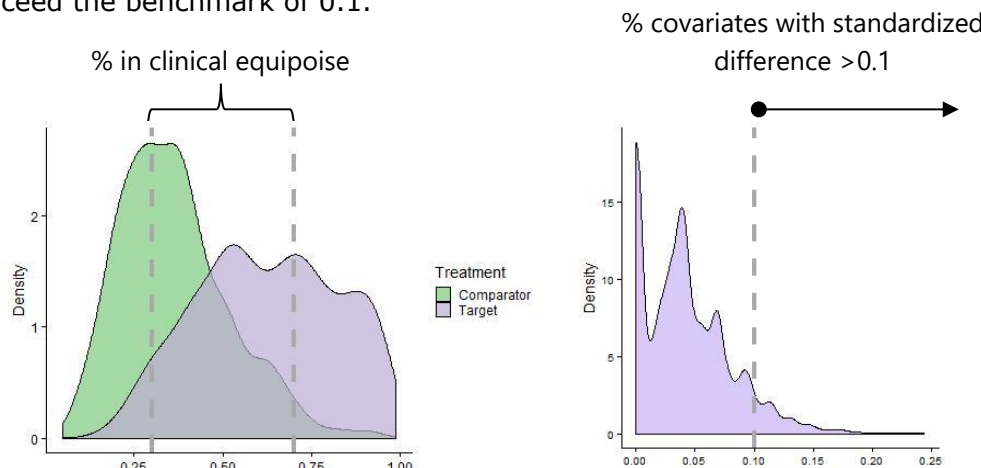


Figure 2. (Left) Illustration of the percent of patients in clinical equipoise using two overlapping preference score distributions for treatment and comparator drugs and (Right) Illustration of the percent of baseline covariates where the standardized difference in the prevalence differs by more than 0.1 between the patients initiating the target and comparator drug.

A third factor that should be considered when selecting a comparator is the sample size. While small sample sizes don't necessarily affect confounding, they do impact the precision of the treatment effect and the probability of identifying rare outcomes. Bias and precision should both be considered when identifying appropriate comparators.

1.2 Applying the comparator selection method for the multiple myeloma drug, daratumumab

Selecting comparators for cancer drugs can be particularly challenging given the complex treatment guidelines for these conditions. These guidelines usually have multiple regimens which contain different combinations of drugs recommended at different stages of disease. In particular, multiple myeloma (MM) has incredibly complex treatment guidelines that complicate selection of comparators to investigate drugs given for this disease.⁵

First-line treatment	
PRIMARY THERAPY FOR TRANSPLANT CANDIDATES	PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES
Preferred Regimens <ul style="list-style-type: none"> Bortezomib/lenalidomide/dexamethasone (category 1) Bortezomib/cyclophosphamide/dexamethasone Other Recommended Regimens <ul style="list-style-type: none"> Bortezomib/doxorubicin/dexamethasone (category 1) Carfilzomib^b/lenalidomide/dexamethasone Ixazomib/lenalidomide/dexamethasone (category 2B) Useful In Certain Circumstances <ul style="list-style-type: none"> Bortezomib/dexamethasone (category 1)^f Bortezomib/thalidomide/dexamethasone (category 1) Cyclophosphamide/lenalidomide/dexamethasone Lenalidomide/dexamethasone (category 1)^f Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE) 	Preferred Regimens <ul style="list-style-type: none"> Bortezomib/lenalidomide/dexamethasone (category 1) Lenalidomide/low-dose dexamethasone (category 1)^f Bortezomib/cyclophosphamide/dexamethasone Daratumumab^g/bortezomib/melphalan/prednisone (category 1) Other Recommended Regimens <ul style="list-style-type: none"> Carfilzomib^b/lenalidomide/dexamethasone Carfilzomib^b/cyclophosphamide/dexamethasone Ixazomib/lenalidomide/dexamethasone Useful In Certain Circumstances <ul style="list-style-type: none"> Bortezomib/dexamethasone Cyclophosphamide/lenalidomide/dexamethasone
	MAINTENANCE THERAPY
	Preferred Regimens <ul style="list-style-type: none"> Lenalidomide^e (category 1) Other Recommended Regimens <ul style="list-style-type: none"> Bortezomib
Additional lines of treatment	
THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA ^h	
Preferred Regimens <ul style="list-style-type: none"> Bortezomib/lenalidomide/dexamethasone Carfilzomib (twice weekly)^b/dexamethasone (category 1)^f Carfilzomib (weekly)^b/dexamethasone^f Carfilzomib^b/lenalidomide/dexamethasone (category 1)^g Other Recommended Regimens <ul style="list-style-type: none"> Bendamustine/bortezomib/dexamethasone Bendamustine/lenalidomide/dexamethasone Bortezomib/lenalidomide/dexamethasone (category 1) Bortezomib/cyclophosphamide/dexamethasone Carfilzomib^b/cyclophosphamide/dexamethasone Cyclophosphamide/lenalidomide/dexamethasone Useful In Certain Circumstances <ul style="list-style-type: none"> Bortezomib/dexamethasone (category 1)^f Daratumumab^g/pomalidomide^v/dexamethasone Elotuzumab/bortezomib/dexamethasone^v Elotuzumab/pomalidomide/dexamethasone^v Bendamustine Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)^k 	<ul style="list-style-type: none"> Daratumumab^g/bortezomib/dexamethasone (category 1) Daratumumab^g/lenalidomide/dexamethasone (category 1) Elotuzumab^g/lenalidomide/dexamethasone (category 1)^g Ixazomib^b/lenalidomide/dexamethasone (category 1)^g Ixazomib^b/dexamethasone^f Ixazomib/pomalidomide^v/dexamethasone Lenalidomide/dexamethasone^f (category 1)^f Panobinostat^u/bortezomib/dexamethasone (category 1) Panobinostat^u/carfilzomib^b^f Panobinostat^u/lenalidomide/dexamethasone Pomalidomide^v/cyclophosphamide/dexamethasone Pomalidomide^v/dexamethasone^f (category 1)^f Pomalidomide^v/bortezomib/dexamethasone Pomalidomide^v/carfilzomib^b/dexamethasone <ul style="list-style-type: none"> Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)^k ± bortezomib (VTD-PACE)^k High-dose cyclophosphamide

Figure 3. National Comprehensive Cancer Network guidelines for multiple myeloma treatment with daratumumab regimens outlined in red.

One MM drug is daratumumab, which is an anti-CD38 monoclonal antibody. Daratumumab has 4 MM indications, including in first-line treatment regimens for MM patients ineligible for stem cell transplant, with bortezomib or lenalidomide and dexamethasone after ≥ 1 prior MM treatment, with pomalidomide and dexamethasone after ≥ 2 prior MM treatment, or as a monotherapy ≥ 3 prior MM treatments.³ Selecting comparators for outcome studies of daratumumab is challenging given the drug's numerous indications, which can result in populations too small for analysis. Comparator selection is also difficult given the complex patterns of other MM treatments received prior to or with daratumumab. Confounding may occur if comparators are selected from populations with different prior treatment patterns or current regimens but restricting to populations with similar treatment patterns can also result in small analytic study sizes. Instead of requiring comparator drugs to have the exact indication and prior/concurrent drugs as the daratumumab cohort, this study explored a step-wise approach that used propensity score matching on subsequently restrictive populations of 4 potential comparator drugs to identify appropriate comparators in claims data based on clinical equipoise, covariate balance, and sample size.

These metrics can be compared side-by-side to assess the degree of imbalance between the target and comparator drug that remains after propensity score adjustment. If the two cohorts are quite different, then comparisons between the target and comparator drugs may be too confounded to make a reasonable inferences of treatment effect. This information is

important for selecting reasonable comparators, especially in situations where the best comparator is not clear.

2 OBJECTIVES

The main objective of the present study is:

- To explore an approach for selecting comparator drugs using clinical equipoise, covariate balance, and sample size in a setting where treatment guidelines are complex.

A secondary objective is:

- To identify potential comparator drugs for daratumumab in a population of multiple myeloma patients.

3 METHODS

3.1 Databases

Optum De-Identified Clinformatics® Data Mart Database (Optum) -Socioeconomic Status (SES)	
CDM Version ID	876
Database Start Date	2000-05-01
Database End Date	2018-03-01
Database Description	De-Identified Clinformatics® Data Mart Database (OptumInsight, Eden Prairie, MN) is an adjudicated administrative health claims database for members with private health insurance, who are fully insured in commercial plans or in administrative services only (ASOs), Legacy Medicare Choice Lives (prior to January 2006), and Medicare Advantage (Medicare Advantage Prescription Drug coverage starting January 2006). The population is primarily representative of US commercial claims patients (0-65 years old) with some Medicare (65+ years old) however ages are capped at 90 years. It includes data captured from administrative claims processed from inpatient and outpatient medical services and prescriptions as dispensed, as well as results for outpatient lab tests processed by large national lab vendors. Optum SES provides socio-economic status for members with both medical and pharmacy coverage and location information for patients it at the US Census Division.

3.2 Cohort Definitions

3.2.1 Daratumumab new users after January 2016

Event Index	<p>People having any of the following:</p> <ul style="list-style-type: none"> a drug exposure of daratumumab <ul style="list-style-type: none"> for the first time in the person's history occurrence start is on or after 2016-01-01 with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.2 Bortezomib new users after January 2016

Event Index	<p>A drug exposure of bortezomib</p> <ul style="list-style-type: none"> for the first time in the person's history occurrence start is on or after 2016-01-01 with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.3 Lenalidomide new users after January 2016

Event Index	<p>A drug exposure of lenalidomide</p> <ul style="list-style-type: none"> for the first time in the person's history occurrence start is on or after 2016-01-01 with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.4 Carfilzomib new users after January 2016

Event Index	<p>A drug exposure of carfilzomib</p> <ul style="list-style-type: none"> for the first time in the person's history occurrence start is on or after 2016-01-01 with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [597] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.5 Pomalidomide new users after January 2016

Event Index	<p>A drug exposure of pomalidomide</p> <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [597] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.6 Bortezomib new users with prior lenalidomide after January 2016

Event Index	<p>A drug exposure of bortezomib</p> <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.7 Bortezomib new users with concurrent lenalidomide after January 2016

Event Index	<p>A drug exposure of bortezomib</p> <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.8 Lenalidomide new users with prior bortezomib after January 2016

Event Index	<p>A drug exposure of bortezomib</p> <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 <p>with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.</p>
Inclusion Criteria	<p>Having all of the following criteria:</p> <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date <p>Limit cohort of initial events to: earliest event per person.</p>

3.2.9 Lenalidomide new users with prior proteasome inhibitor after Jan 2016

Event Index	<p>A drug exposure of bortezomib</p> <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01
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	<ul style="list-style-type: none"> ○ with age ≥ 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria: <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.

3.2.10 Carfilzomib new users with prior bortezomib after January 2016

Event Index	A drug exposure of bortezomib <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria: <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.

3.2.11 Carfilzomib new users with prior lenalidomide after January 2016

Event Index	A drug exposure of bortezomib <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria: <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.

3.2.12 Carfilzomib new users with concurrent lenalidomide after January 2016

Event Index	A drug exposure of bortezomib <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria: <ul style="list-style-type: none"> • at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.

3.2.13 Pomalidomide new users with prior bortezomib after January 2016

Event Index	A drug exposure of bortezomib <ul style="list-style-type: none"> ○ for the first time in the person's history ○ occurrence start is on or after 2016-01-01 ○ with age ≥ 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria:

	<ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.
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3.2.14 Pomalidomide new users with prior lenalidomide after January 2016

Event Index	A drug exposure of bortezomib <ul style="list-style-type: none"> for the first time in the person's history occurrence start is on or after 2016-01-01 with age >= 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria: <ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.

3.2.15 Pomalidomide new users with prior proteasome inhibitor after Jan 2016

Event Index	A drug exposure of bortezomib <ul style="list-style-type: none"> for the first time in the person's history occurrence start is on or after 2016-01-01 with age >= 18 with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.
Inclusion Criteria	Having all of the following criteria: <ul style="list-style-type: none"> at least 2 occurrences of a condition occurrence of [609] Multiple myeloma¹ where event starts between 180 days Before and 0 days Before index start date Limit cohort of initial events to: earliest event per person.

3.3 Analysis

3.3.1 Analysis entry requirements

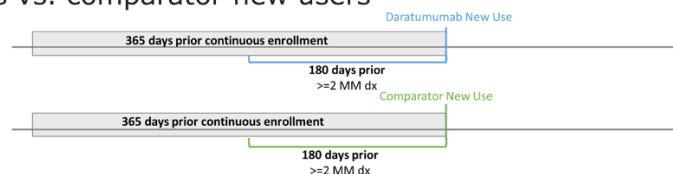
- Analysis 1: Allow patients to enter both the target and comparator drug new user cohorts
- Analysis 2: Only allow patients to enter either the target or comparator drug new user cohorts

3.3.2 Comparisons

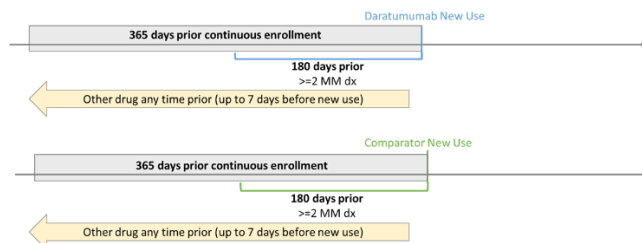
Target	Comparator
Daratumumab new users	Lenalidomide new users
Daratumumab new users	Bortezomib new users
Daratumumab new users	Carfilzomib new users
Daratumumab new users	Pomalidomide new users
Daratumumab new users – concurrent bortezomib	Bortezomib new users
Daratumumab new users – concurrent lenalidomide	Lenalidomide new users
Daratumumab new users – prior bortezomib	Lenalidomide new users – prior bortezomib
Daratumumab new users – prior bortezomib	Carfilzomib new users – prior bortezomib
Daratumumab new users – prior bortezomib	Pomalidomide new users – prior bortezomib
Daratumumab new users – prior lenalidomide	Bortezomib new users – prior lenalidomide
Daratumumab new users – prior lenalidomide	Carfilzomib new users – prior lenalidomide
Daratumumab new users – concurrent lenalidomide	Bortezomib new users – concurrent lenalidomide
Daratumumab new users – concurrent lenalidomide	Carfilzomib new users – concurrent lenalidomide
Daratumumab new users – prior proteasome inhibitor	Pomalidomide new users – prior proteasome inhibitor
Daratumumab new users – prior proteasome inhibitor	Lenalidomide new users – prior proteasome inhibitor

3.3.3 Comparison diagrams

Target new users vs. comparator new users

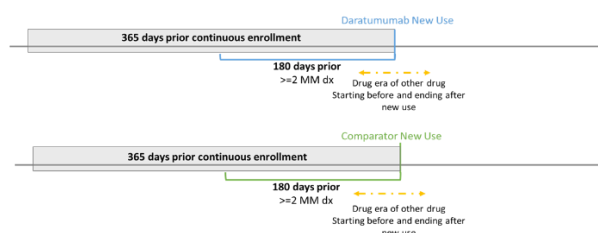


Target new users + prior other drug(s) vs. comparator new users + prior other drug(s)

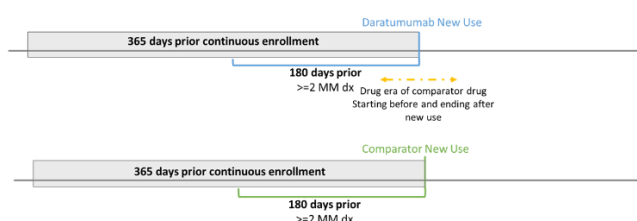


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Target new users + concurrent other drug vs. comparator new users + concurrent other drug



Target new users + concurrent comparator vs. comparator new users



3.3.4 Analysis Methods

3.3.4.1 Analysis #1: Propensity score matching the target and comparator cohorts and comparison of exchangeability metrics where patients can enter both cohorts AND daratumumab-specific administration methods or pre-/post-supportive care removed from PS model

Methods	<ul style="list-style-type: none"> Exposures restricted to the time both target and comparator cohorts are found. Patients can contribute to BOTH the target or comparator cohorts Remove all daratumumab-specific administration methods or pre/post-supportive care removed from PS model using clinical knowledge (List in Appendix 1) Set time at risk starting 1 day after cohort start date; 1 day minimum time at risk required. All drugs, conditions, procedures and measurements received in the 365 days before index date (inclusive) identified. Using baseline covariates, calculate propensity scores of target and comparator treatment receipt using a LASSO regularized logistic regression with LaPlace prior from 10 repetitions of 10-fold cross validation 1:1 matching on propensity score with a 0.2 of the standardized logit caliper for matching
Output	<ol style="list-style-type: none"> Preference score distributions for target and comparator cohorts and % in clinical equipoise Standardized difference in prevalence of baseline covariates in PS model before and after PS matching Top 10 covariates with the greatest difference in standardized difference between target and comparator cohorts before and after PS matching. Table with target/comparator cohort size, % in equipoise, maximum standardized difference between covariates and proportion of covariates with a >0.1 standardized difference between target and comparator cohorts.

3.3.4.2 Analysis #2: Propensity score matching the target and comparator cohorts and comparison of exchangeability metrics where patients can only have a first exposure to one or the other drug AND daratumumab-specific administration methods or pre-/post-supportive care removed from PS model

Methods	<ul style="list-style-type: none"> Exposures restricted to the time both target and comparator cohorts are found. Patients can contribute to ONLY the target or comparator cohorts (whichever comes first) Remove all daratumumab-specific administration methods or pre/post-supportive care removed from PS model (List in Appendix 1) Set time at risk starting 1 day after cohort start date and 1 day minimum time at risk required Propensity score calculated for the target and comparator cohorts using a LASSO regularized logistic regression with LaPlace prior from 10 repetitions of 10-fold cross validation 1:1 matching on propensity score with a 0.2 of the standardized logit caliper for matching
Output	<ol style="list-style-type: none"> Propensity score distributions for target and comparator cohorts Scatterplot of prevalence of all covariates in PS model before and after PS matching Top 10 covariates with the greatest difference in standardized difference between target and comparator cohorts before and after PS matching. Table with target/comparator cohort size, % in equipoise, maximum standardized difference between covariates and proportion of covariates with a >0.1 standardized difference between target and comparator cohorts.

4 RESULTS – FOR ANALYSIS 1¹

4.1 Table of target comparator cohort sizes and metrics for covariate balance and equipoise

Table 1. Size, percent in clinical equipoise, and maximum standardized difference (std diff) for daratumumab/comparator pairs for patients without pre-/post-treatment variables in the propensity score among patients allowed to enter both the target and comparator cohorts

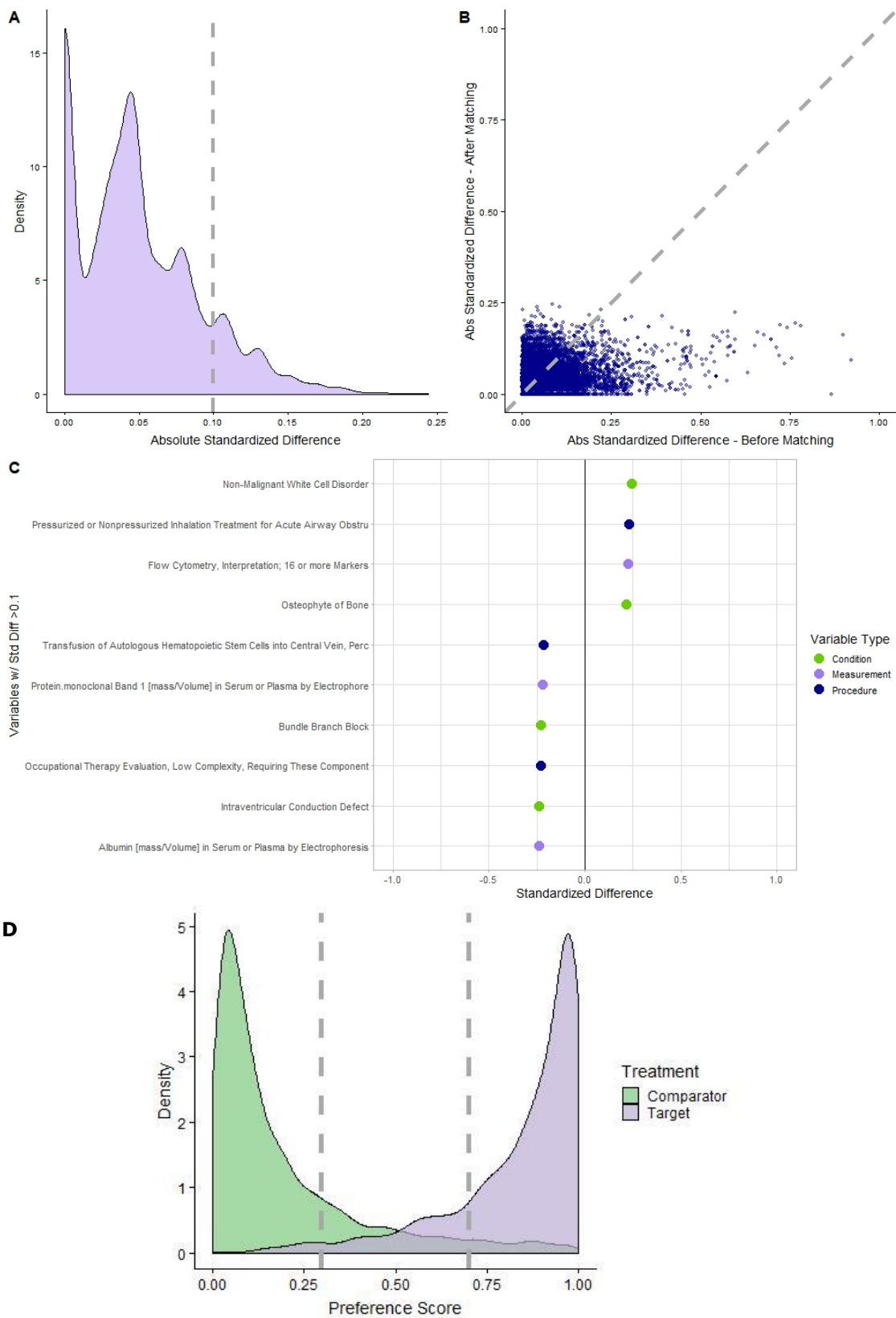
Target	Comparator	Before Matching		After Matching		Equipoise %	Max Std Diff Covariate Prop	% covariates Std Diff >0.1
		Target size	Comparator size	Target size	Comparator size			
Daratumumab new users	Bortezomib new users	1081	2881	323	323	20.9	0.24	3.1
Daratumumab new users	Lenalidomide new users	1081	2965	297	297	20.9	0.31	3.3
Daratumumab new users	Carfilzomib new users	1081	807	426	426	70.1	0.24	2.0
Daratumumab new users	Pomalidomide new users	1081	927	438	438	59.3	0.24	1.6
Daratumumab new users – concurrent bortezomib	Bortezomib new users	214	2881	154	154	40.3	0.34	5.7
Daratumumab new users – concurrent lenalidomide	Lenalidomide new users	115	2965	47	47	24.5	0.74	12.3
Daratumumab new users – prior bortezomib	Lenalidomide new users – prior bortezomib	549	362	75	75	30.3	0.53	7.9
Daratumumab new users – prior bortezomib	Carfilzomib new users – prior bortezomib	549	420	316	316	88.5	0.27	4.7
Daratumumab new users – prior bortezomib	Pomalidomide new users – prior bortezomib	549	395	259	259	73.3	0.30	4.5
Daratumumab new users – prior lenalidomide	Bortezomib new users – prior lenalidomide	512	194	138	138	67.7	0.40	8.8
Daratumumab new users – concurrent lenalidomide	Bortezomib new users – concurrent lenalidomide	115	697	22	22	22.1	0.74	13.4
Daratumumab new users – prior lenalidomide	Carfilzomib new users – prior lenalidomide	512	267	214	214	82.2	0.33	5.0
Daratumumab new users – concurrent lenalidomide	Carfilzomib new users – concurrent lenalidomide	115	159	30	30	63.2	0.86	13.3
Daratumumab new users – prior proteasome inhibitor	Pomalidomide new users – prior proteasome inhibitor	865	531	363	363	70.5	0.26	3.3
Daratumumab new users – prior proteasome inhibitor	Lenalidomide new users – prior proteasome inhibitor	865	599	160	160	34.3	0.35	7.1

¹ Results for Analysis 2 in Appendix 2. Diagnostic plots available upon request

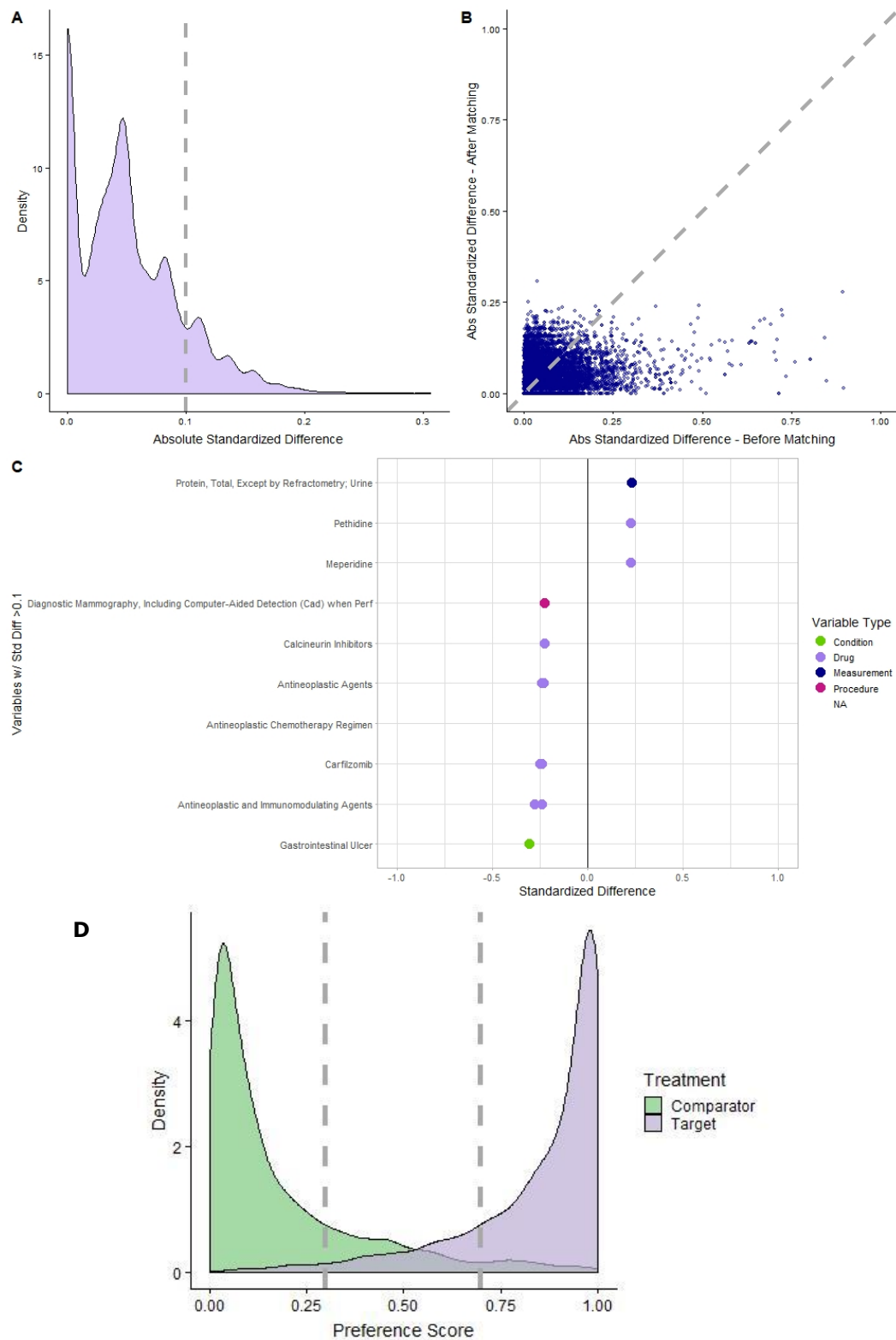
4.2 Diagnostic plots

Proportion of covariates with a standardized difference in covariates prevalence between the target and comparator >0.1; (B) Scatterplot of standardized differences in covariate prevalence before and after matching; (C) Top 10 imbalanced covariates after propensity score matching by variable class type [positive= greater prevalence in target]; (D) Preference score distribution with area of clinical equipoise noted between the dashed lines.

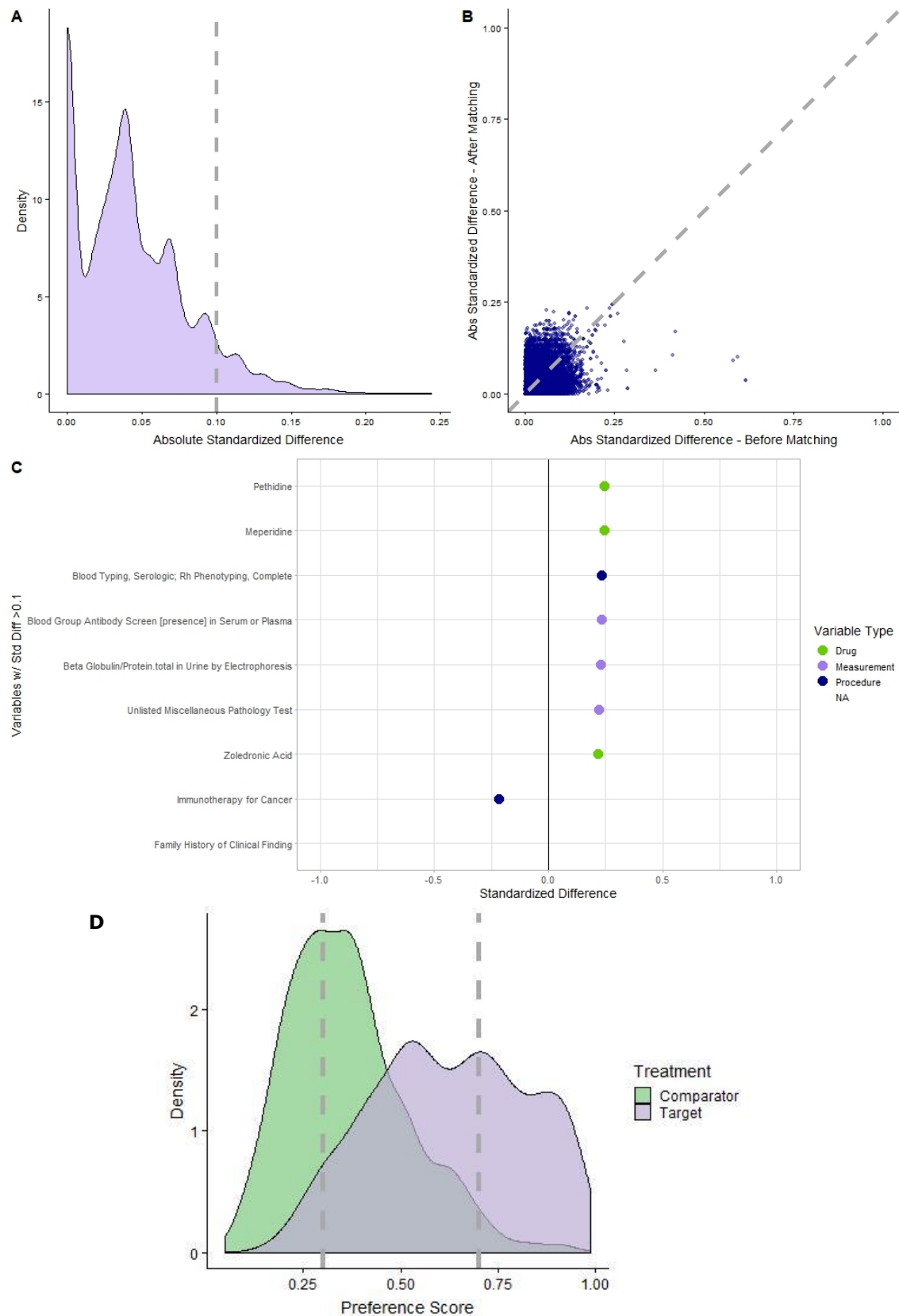
4.2.1 Daratumumab new users (Target) vs. Bortezomib new users (Comparator)



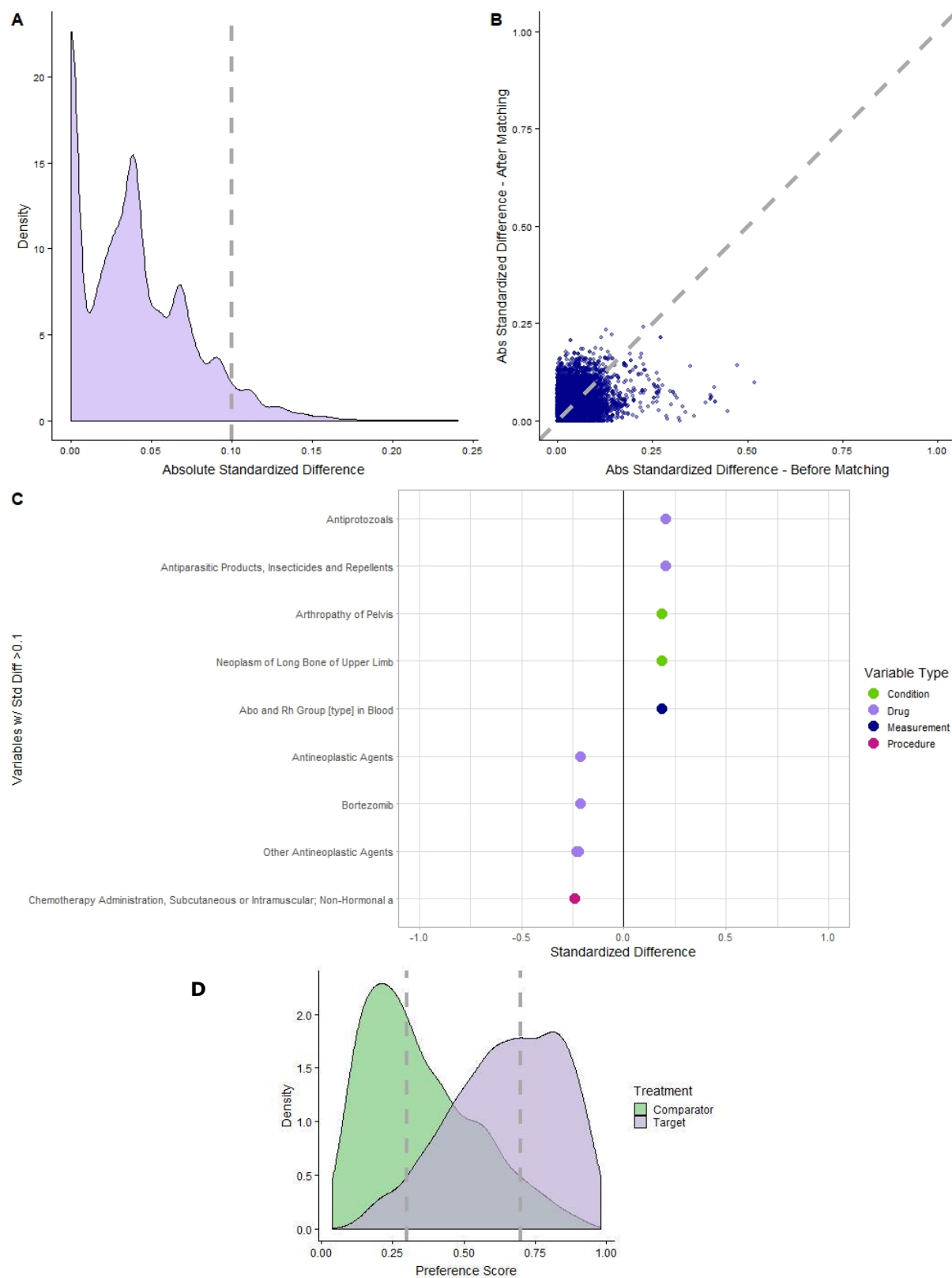
4.2.2 Daratumumab new users (Target) vs. Lenalidomide new users (Comparator)



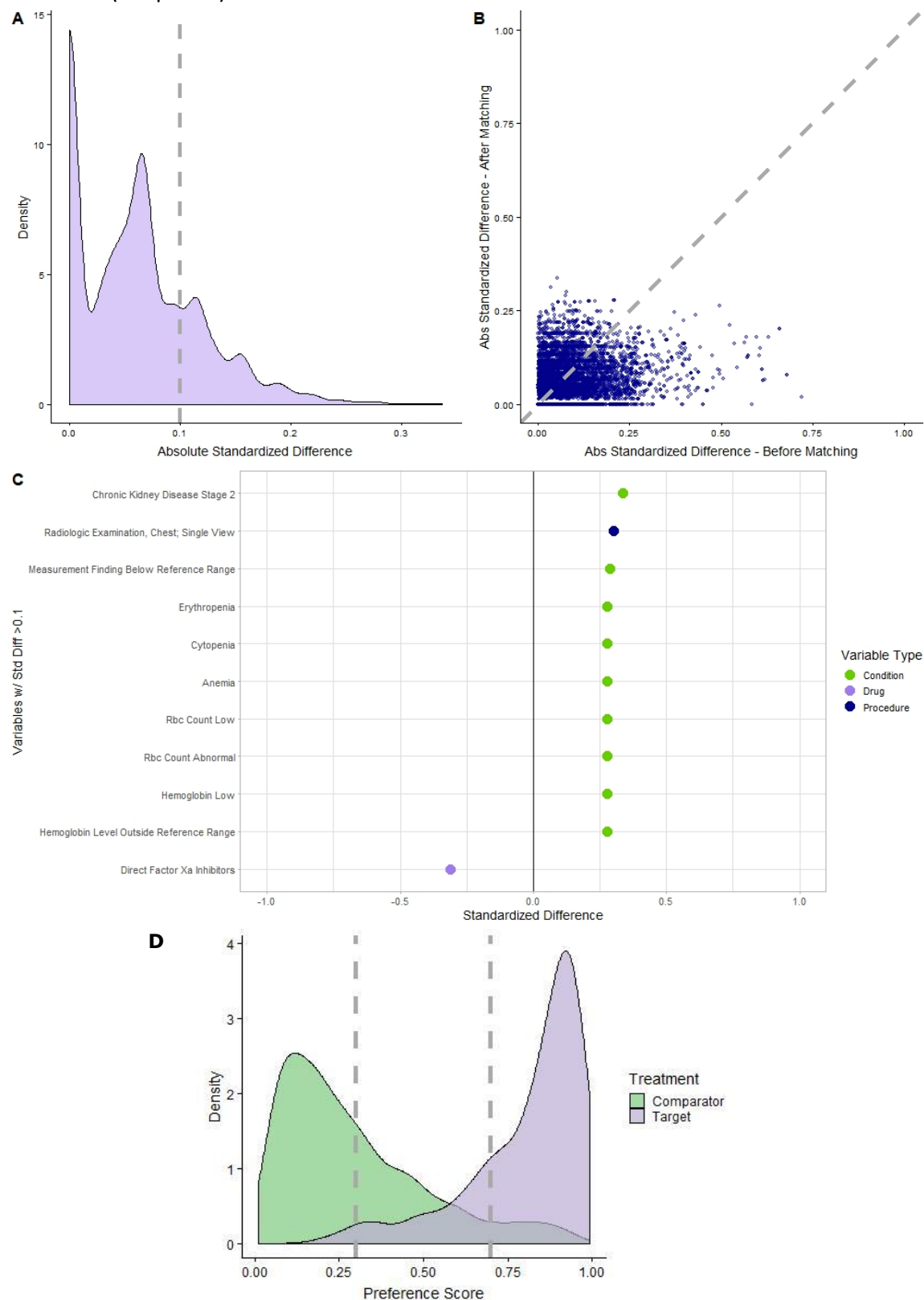
4.2.3 Daratumumab new users (Target) vs. Carfilzomib new users (Comparator)



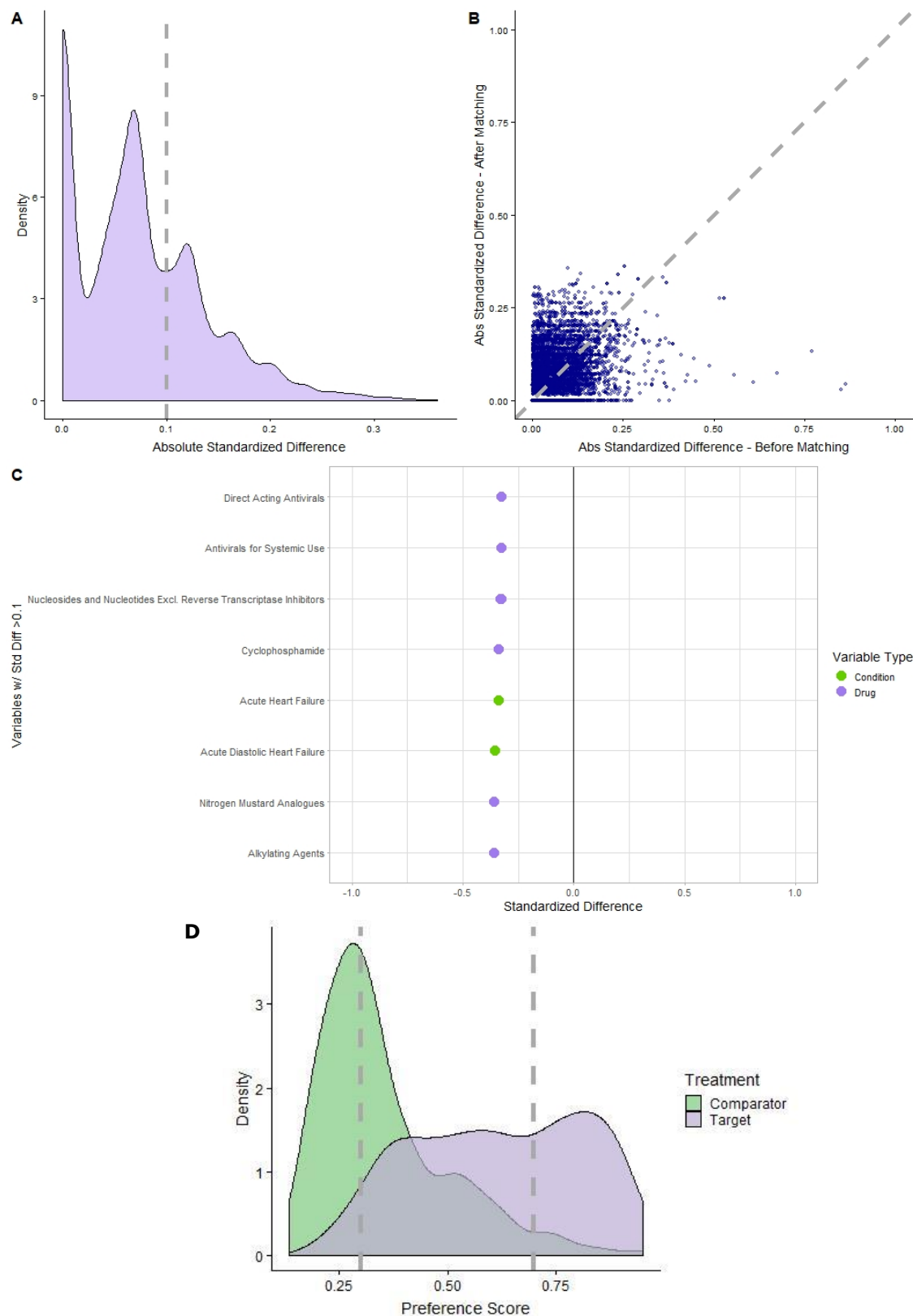
4.2.4 Daratumumab new users (Target) vs. Pomalidomide new users (Comparator)



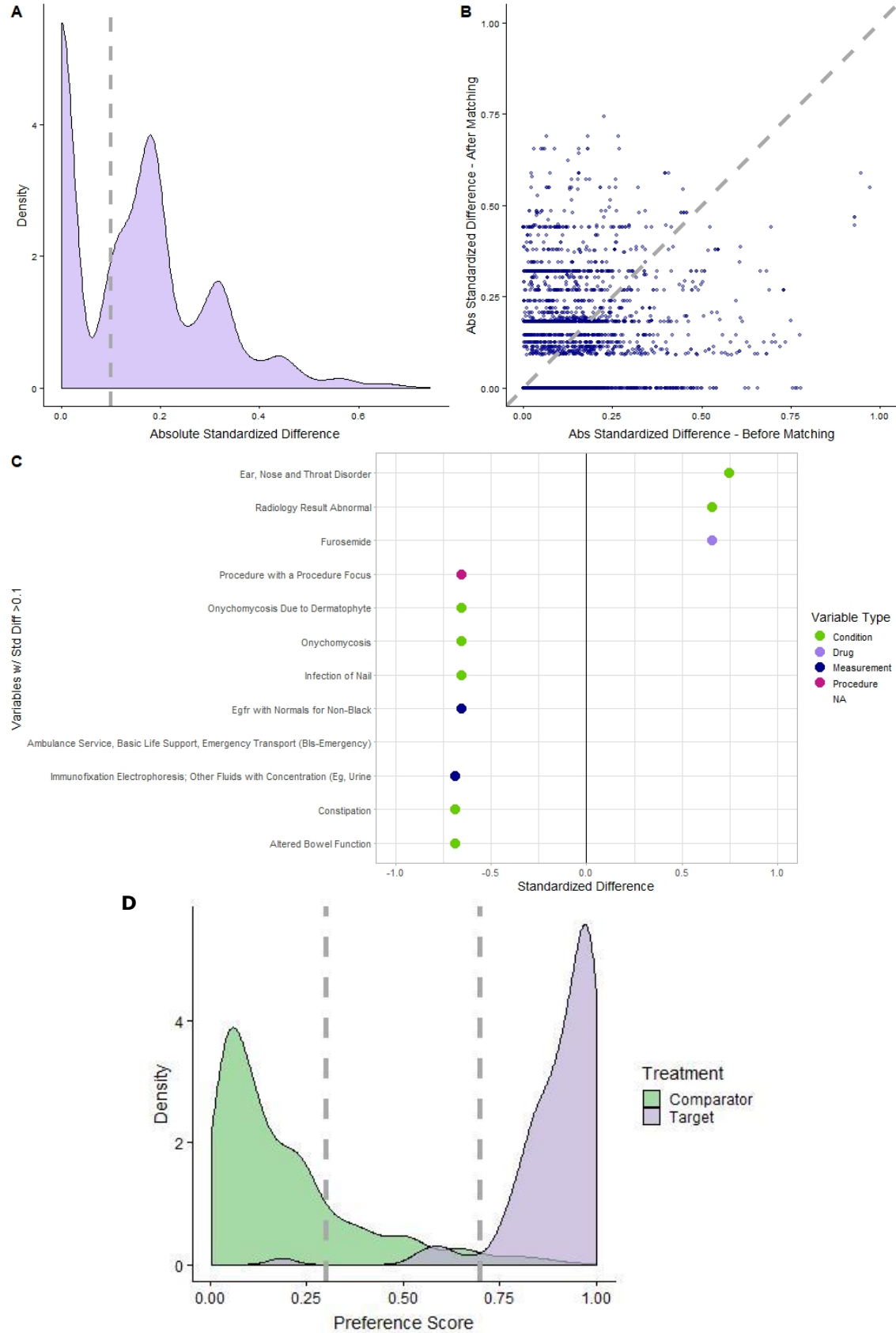
4.2.5 Daratumumab new users with concurrent bortezomib (Target) vs. Bortezomib new users (Comparator)



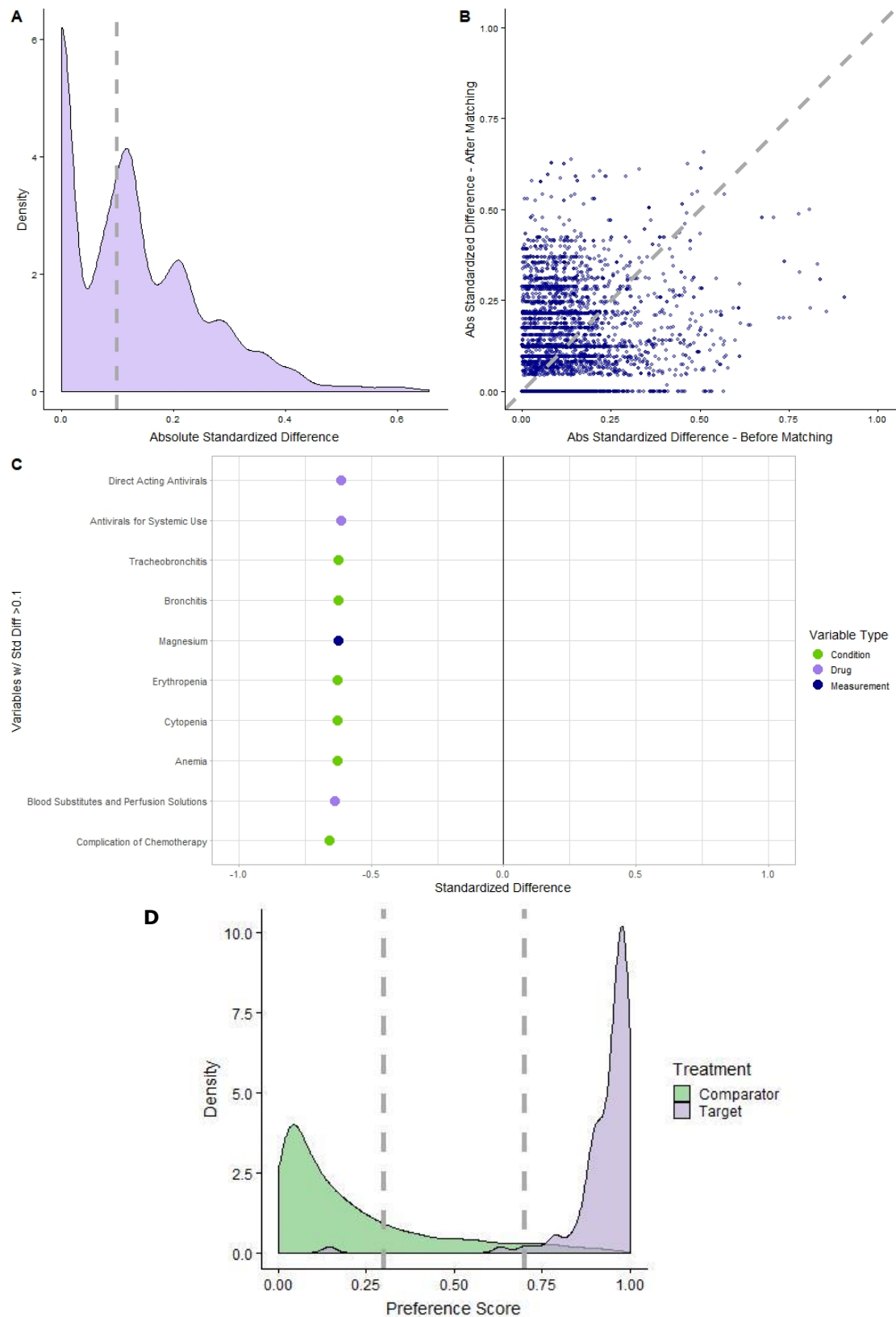
4.2.6 Daratumumab new users with prior lenalidomide (Target) vs Bortezomib new users with prior lenalidomide (Comparator)



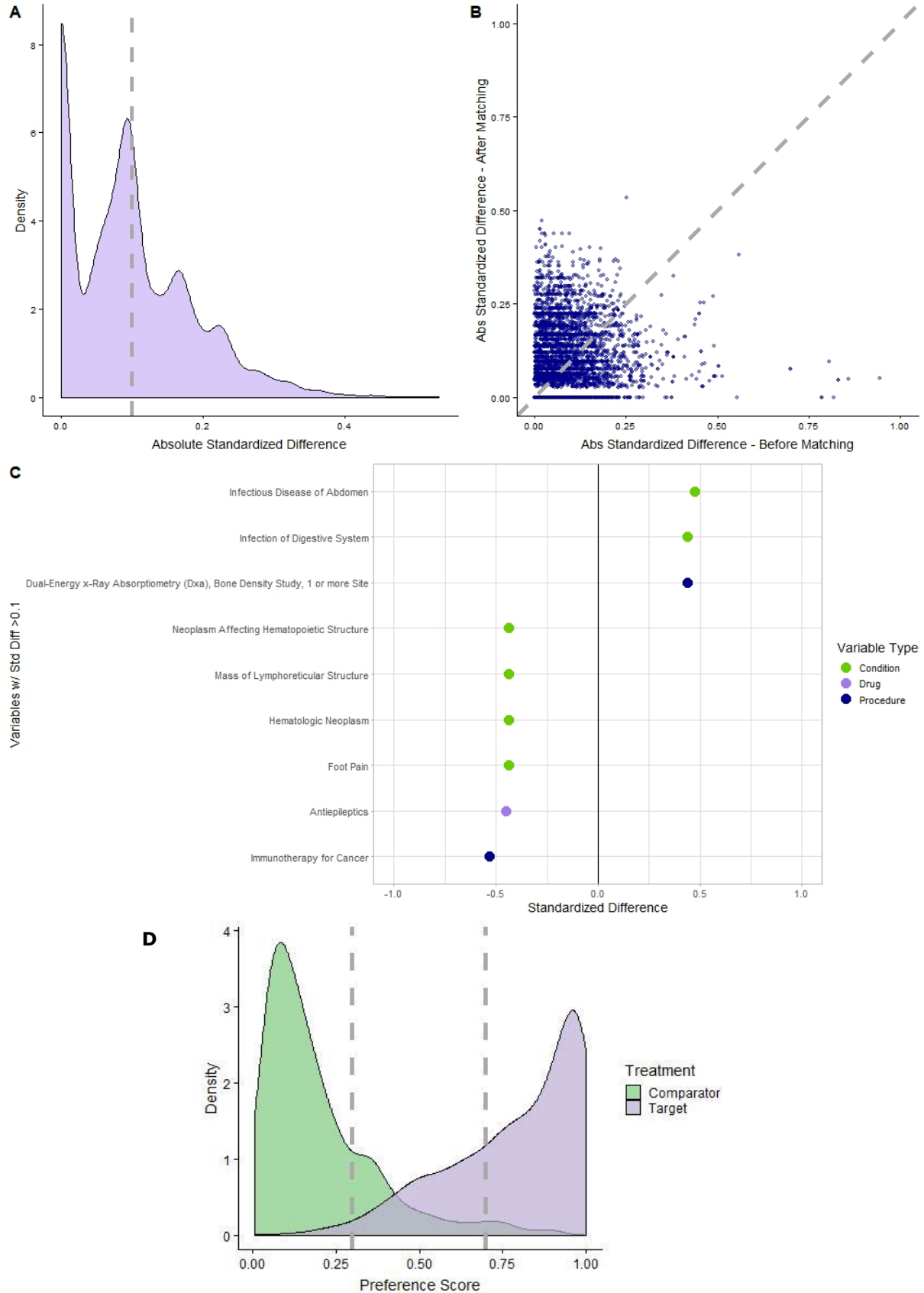
4.2.7 Daratumumab new users with concurrent lenalidomide (Target) vs Bortezomib new users with concurrent lenalidomide (Comparator)



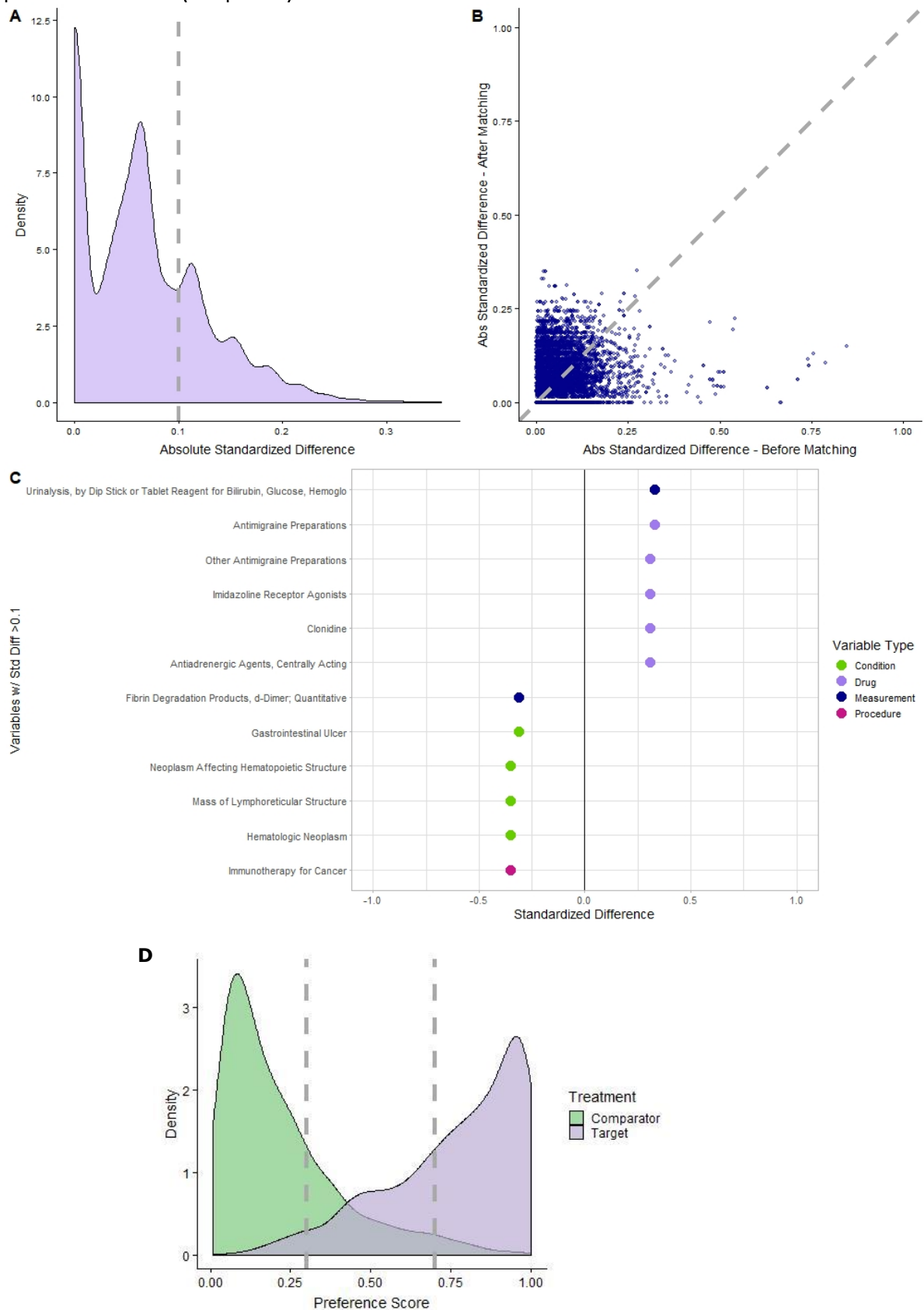
4.2.8 Daratumumab new users with concurrent lenalidomide (Target) vs Lenalidomide new users (Comparator)



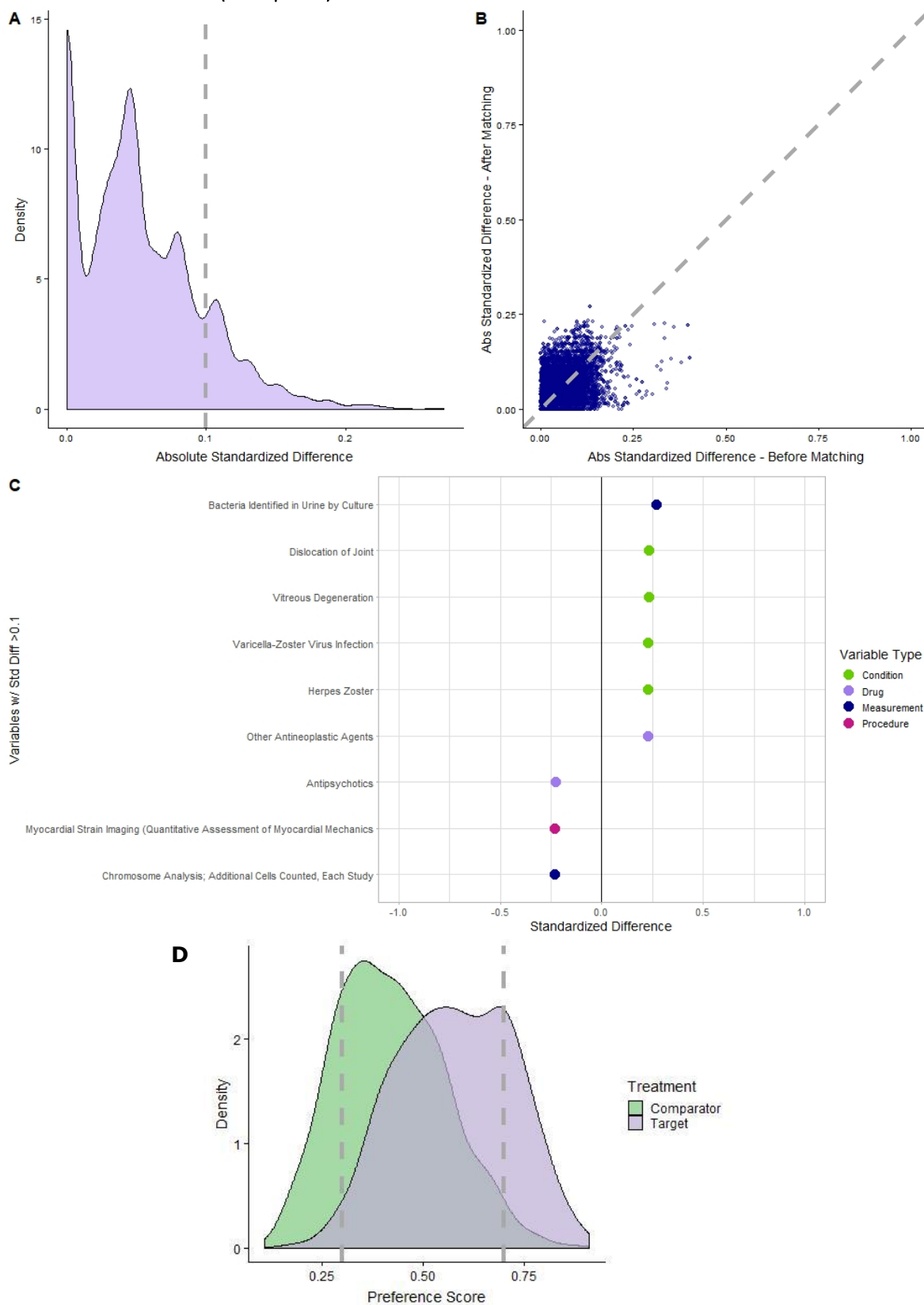
4.2.9 Daratumumab new users with prior bortezomib (Target) vs. Lenalidomide new users with prior bortezomib (Comparator)



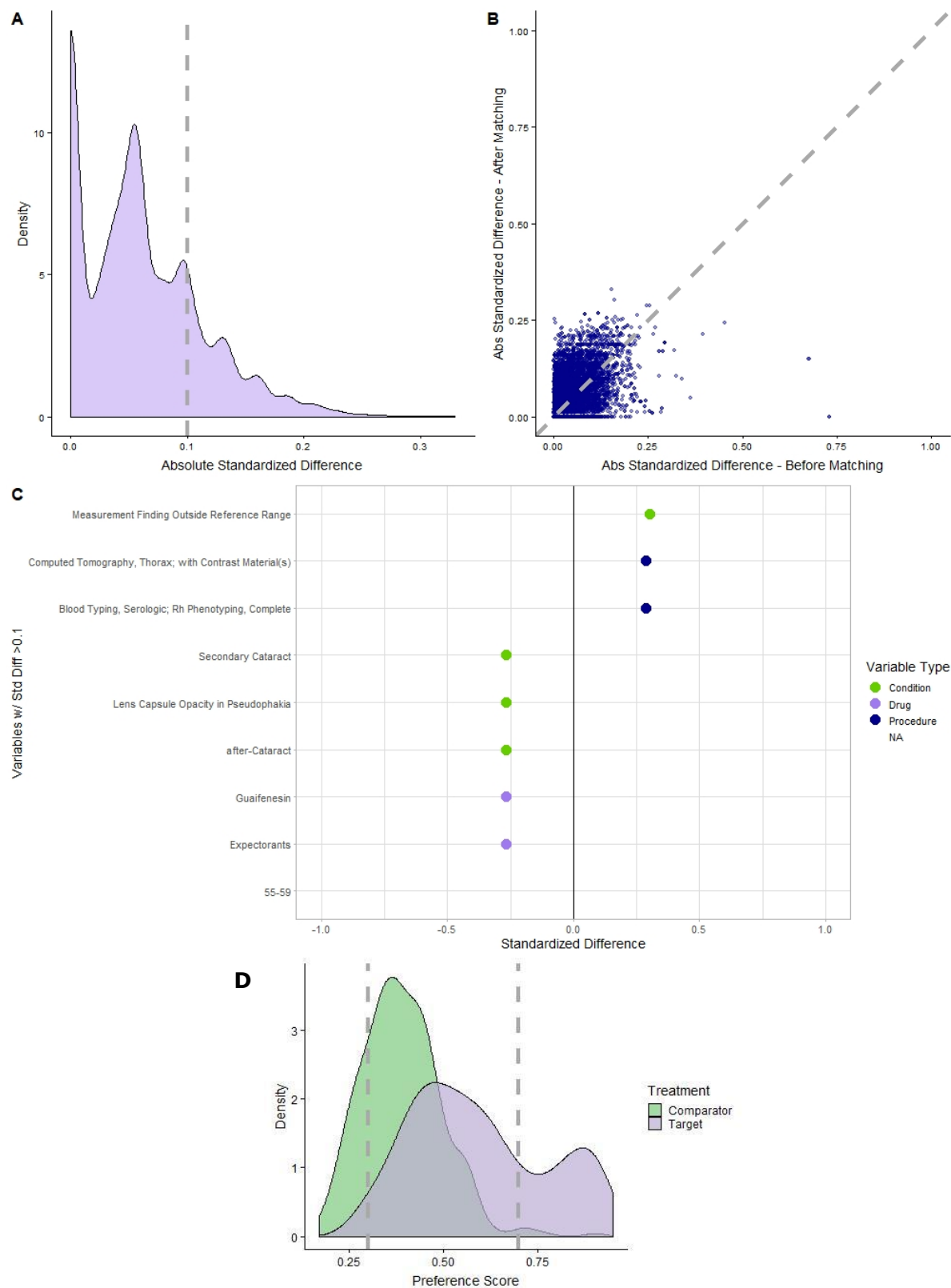
4.2.10 Daratumumab new users with prior proteasome inhibitor (Target) vs. Lenalidomide new users with prior proteasome inhibitor (Comparator)



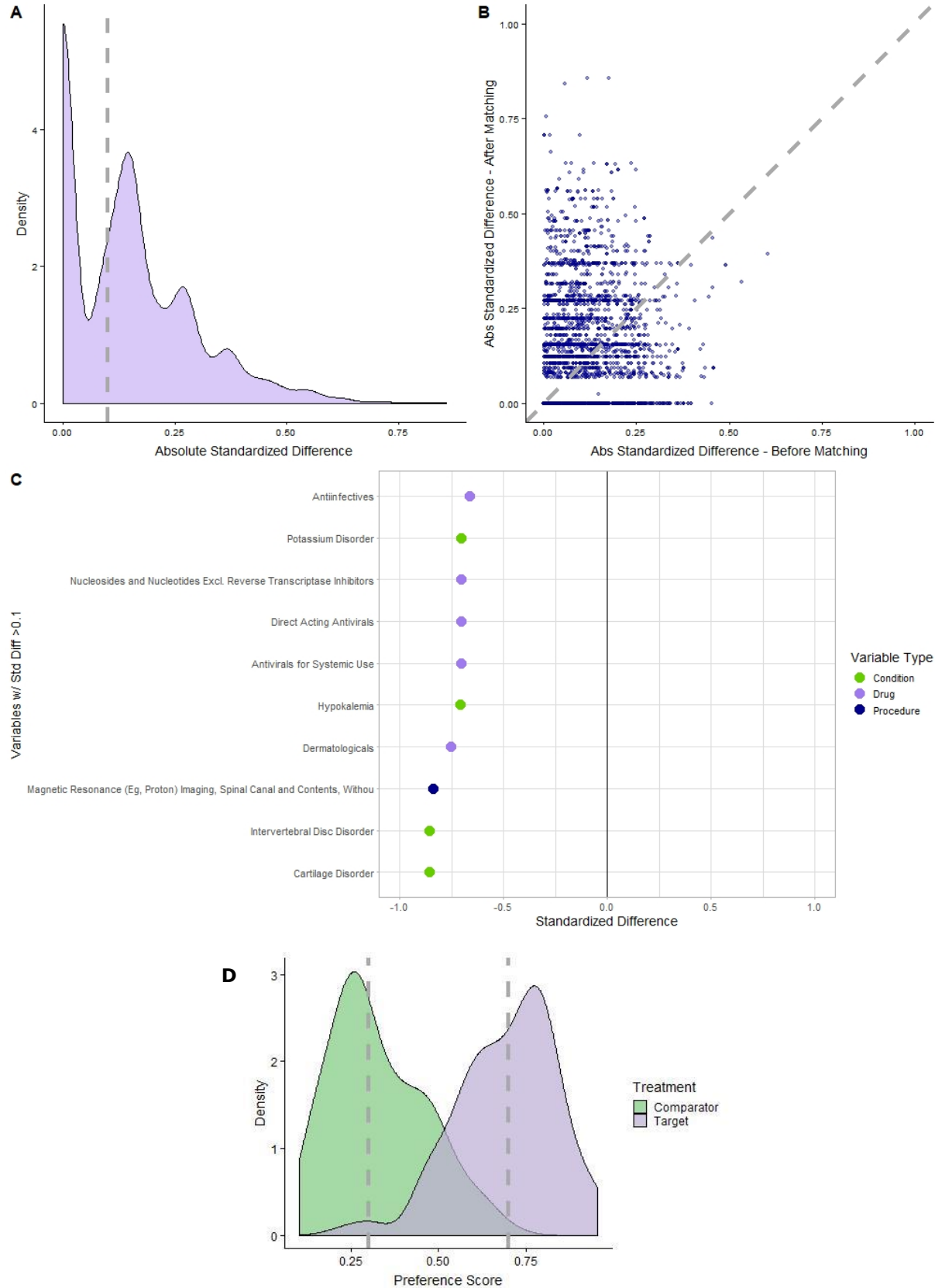
4.2.11 Daratumumab new users with prior bortezomib (Target) vs. Carfilzomib new users with prior bortezomib (Comaprator)



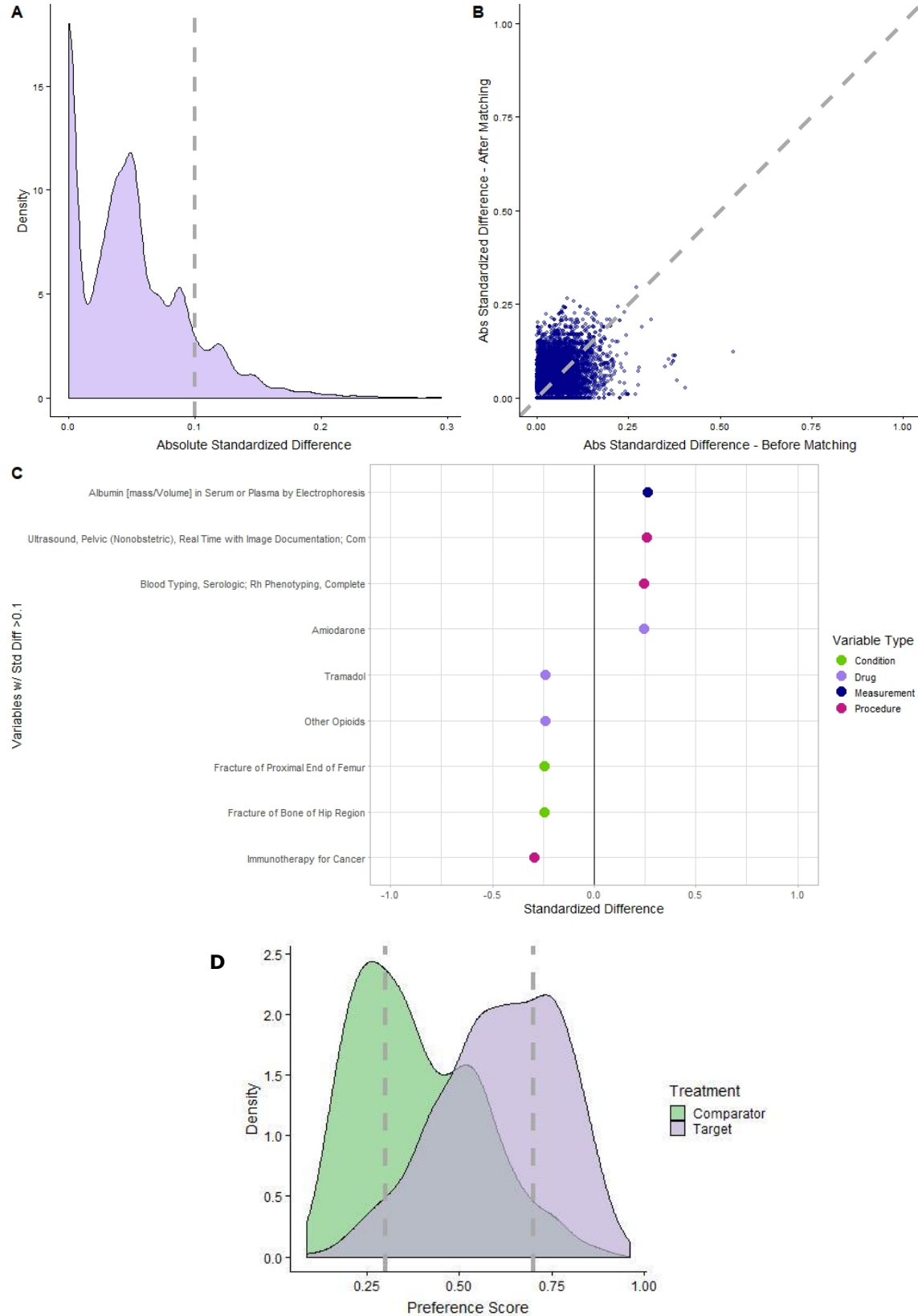
4.2.12 Daratumumab new users with prior lenalidomide (Target) vs. Carfilzomib new users with prior lenalidomide (Comparator)



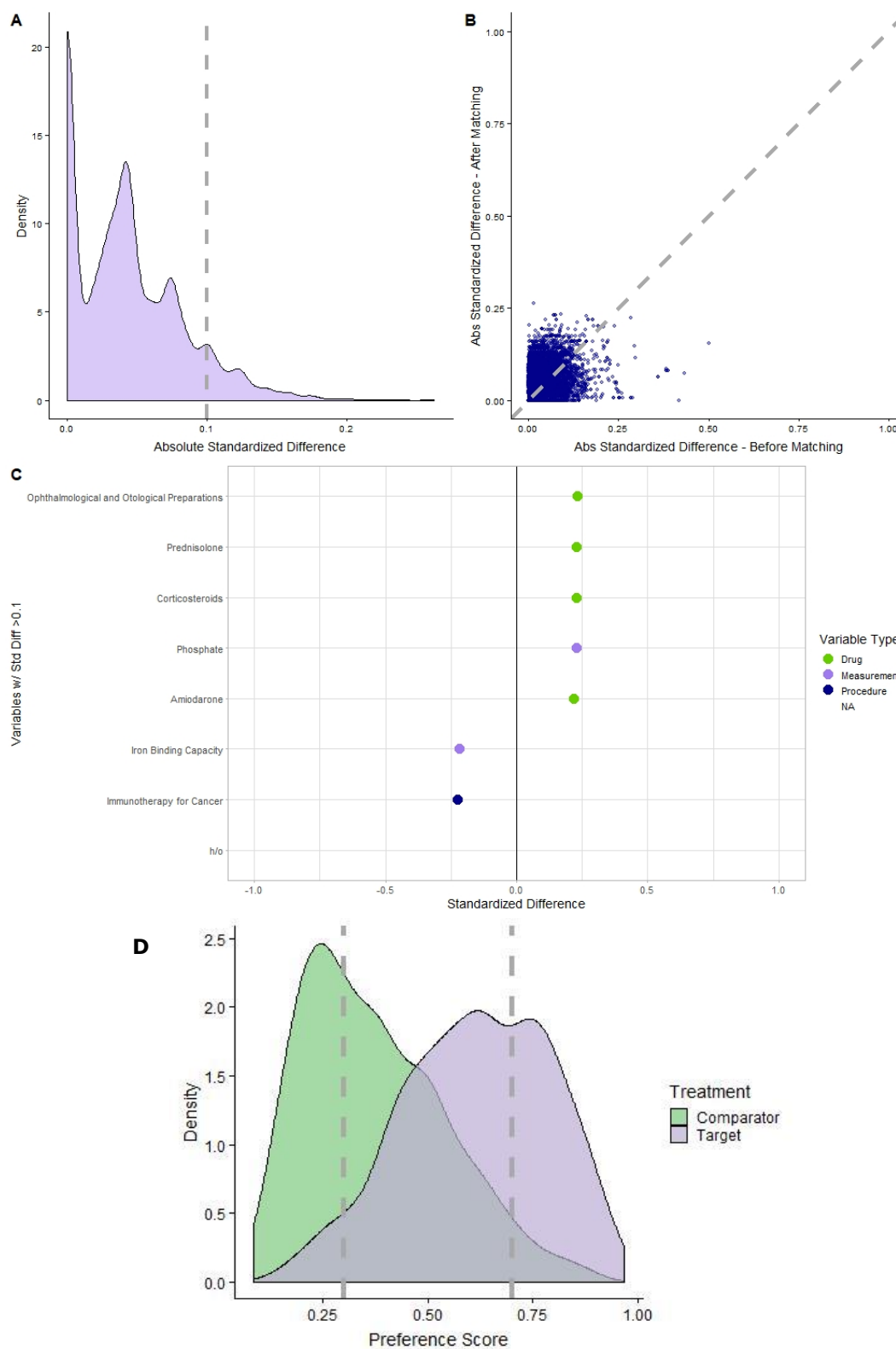
4.2.13 Daratumumab new users with concurrent lenalidomide (Target) vs. Carfilzomib new users with concurrent lenalidomide (Comparator)



4.2.14 Daratumumab new users with prior bortezomib (Target) vs. Pomalidomide new users with prior bortezomib (Comparator)



4.2.15 Daratumumab new users with prior proteasome inhibitor (Target) vs. Pomalidomide new users with prior proteasome inhibitor (Comparator)



5 DISCUSSION AND CONCLUSIONS

Selecting the best comparator requires a balance of equipoise >50%, a low max standardized difference (preferably <0.1), a low percentage of covariates with a standardized difference <0.1, and a large enough sample size to identify rare outcomes and have adequate precision to estimate the effect. Given these requirements, analyses of outcomes for daratumumab in the Optum SES database, there are no strong comparators for daratumumab.

The following comparators should be explored in more depth to explore whether the variables with a standardized difference >0.1 would bias the estimate:

Target	Comparator	Before Matching		After Matching		Equipoise %	Max Std Diff Covariate Prop	% covariates Std Diff >0.1
		Target size	Comparator size	Target size	Comparator size			
Daratumumab new users	Carfilzomib new users	1081	807	426	426	70.1	0.24	2.0
Daratumumab new users	Pomalidomide new users	1081	927	438	438	59.3	0.24	1.6
Daratumumab new users - prior bortezomib	Carfilzomib new users - prior bortezomib	549	420	316	316	88.5	0.27	4.7
Daratumumab new users - prior bortezomib	Pomalidomide new users - prior bortezomib	549	395	259	259	73.3	0.30	4.5
Daratumumab new users - prior lenalidomide	Carfilzomib new users - prior lenalidomide	512	267	214	214	82.2	0.33	5.0
Daratumumab new users - prior proteasome inhibitor	Pomalidomide new users - prior proteasome inhibitor	865	531	363	363	70.5	0.26	3.3

Future analyses should explore how comparator benchmarks change when all patients are retained in a PS model using stratification for adjustment.

6 APPENDIX 1 – CONCEPTS EXCLUDED FROM PS MODEL

6.1 Concepts removed from the propensity score that include administration methods specific to daratumumab or supportive care specifically given before or after daratumumab administration



conceptset-8104.zip

7 APPENDIX 2 – RESULTS FOR ANALYSIS 2

7.1 Table of target comparator cohort sizes and metrics for covariate balance and equipoise

Table A1. Size, percent in clinical equipoise, and maximum standardized difference (std diff) for daratumumab/comparator pairs for patients without pre-/post-treatment variables in the propensity score among patients entering only one cohort.

Target	Comparator	Before Matching		After Matching		Equipoise %	Max Std Diff Covariate Prop	% covariates Std Diff >0.1
		Target size	Comparator size	Target size	Comparator size			
Daratumumab new users	Bortezomib new users	1081	2881	322	322	20.9	0.27	3.2
Daratumumab new users	Lenalidomide new users	1081	2965	292	292	20.6	0.25	3.3
Daratumumab new users	Carfilzomib new users	1081	807	430	430	71.1	0.27	2.0
Daratumumab new users	Pomalidomide new users	1081	927	435	435	59.0	0.24	1.7
Daratumumab new users concurrent bortezomib	Bortezomib new users	214	2881	154	154	40.3	0.38	7.7
Daratumumab new users – concurrent lenalidomide	Lenalidomide new users	115	2965	50	50	20.9	0.63	10.2
Daratumumab new users – prior bortezomib	Lenalidomide new users – prior bortezomib	549	362	78	78	30.4	0.60	8.7
Daratumumab new users – prior bortezomib	Carfilzomib new users prior bortezomib	549	420	316	316	89.4	0.26	4.1

Daratumumab new users - prior bortezomib	Pomalidomide new users - prior bortezomib	549	395	256	256	73.6	0.36	3.9
Daratumumab new users - prior lenalidomide	Bortezomib new users - prior lenalidomide	512	194	139	139	68.5	0.40	9.3
Daratumumab new users - concurrent lenalidomide	Bortezomib new users - concurrent lenalidomide	115	697	24	24	22.7	0.83	13.8
Daratumumab new users - prior lenalidomide	Carfilzomib new users - prior lenalidomide	512	267	213	213	82.1	0.37	4.6
Daratumumab new users - concurrent lenalidomide	Carfilzomib new users - concurrent lenalidomide	115	159	40	40	76.6	0.63	15.8
Daratumumab new users - prior proteasome inhibitor	Pomalidomide new users - prior proteasome inhibitor	865	531	362	362	70.5	0.29	3.7
Daratumumab new users - prior proteasome inhibitor	Lenalidomide new users - prior proteasome inhibitor	865	599	161	161	34.6	0.36	6.5

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