

Supplementary Material

Data

We defined a cohort of men who received treatment for advanced prostate cancer, based on receiving one of six focus medications known to have a survival benefit in men with advanced prostate cancer (abiraterone, enzalutamide, sipuleucel-T, docetaxel, cabazitaxel, radium-223) from January 2010 through June 2016 from the Clinformatics TM Data Mart Insurance Claims Database. The initial cohort included any patient over the age of 18 with a diagnosis of malignant neoplasm of the prostate, coded as “185” in ICD-9 and “C61” in ICD-10. We restricted our final cohort to include patients that were continuously enrolled in the plan for the 180 days before the first medication claim. Finally, we wished to compare first-line therapies between patients where first-line treatment was defined as the first medication given of the six focus medications. We only kept those whose first focus claim was abiraterone, enzalutamide, docetaxel, and sipuleucel-T, as the other two medications were rarely first-line, and then categorized patients given abiraterone or enzalutamide as a common oral therapy group. Thus, there are three final first-line treatment groups: 1) Immunotherapy, 2) Oral Therapy, and 3) Chemotherapy.

Binary Outcome

We defined a binary outcome to be whether the patient had any emergency room (ER) visit within 60 days of the first pharmacy claim of the focus medications. ER visits were identified using both the provider and facility definition. The provider definition uses Current Procedural Technology (CPT) codes 99281-99285, and the facility definition uses revenue center codes 0450-0459, 098. To account for duplicate records for the same ER visit, claims for the same patient with the same date were removed. ATE is defined on the odds ratio scale.

Count Outcome

Using the previously defined ER visits, we counted the number of ER visits each patient had within 180 days from the first pharmacy claim as a count outcome. ATE is defined on the rate ratio scale

Time to Event Outcomes

We were also interested in the overall survival of patients; however, exact death dates were unavailable with this version of the data. We thus considered two other time to event outcomes as possible surrogates: time on treatment and time in database. Time on treatment was defined as the time from start of first medication to the last claim of any of the six focus medications, thus the event is stopping all focus treatment permanently. Time in database was defined as the time from start of the first medication to the last claim for that subject within the Clinformatics TM Data Mart Database for any medical-related issue. The last claim was identified by extracting the latest claim from each dataset, removing those after the enrollment end-date, and taking the maximum of those remaining. This definition of time in database could

be considered a censored surrogate for death because we expect most patients to have medical needs until shortly before death. These two endpoints differ in that some individuals may have stopped treatment from a focus medication, yet still used medical services and managed pain beyond ending treatment, while others may have been treated continuously right up until death. Patients would be expected to have less total time on treatment if they had a highly resistant cancer that would not respond to any treatments (and thus treatments would not be continued if they were ineffective), or if they had severe toxicities to treatment that did not allow for continuation. Also, these endpoints differed across treatment groups, with those on oral therapy continuing treatment near the end of enrollment, whereas chemotherapy patients may stop a year or more before ending enrollment. ATE was defined as the mean difference in time, restricting to five years of follow-up. Results for time in database outcome are shown in Supplementary Table 1 (S1)

Longitudinally Varying Outcome

For the final longitudinal varying repeated measures outcome, we used opioid usage over time, calculated using prescription drug pharmacy claims. Common opioid drug types were identified and were converted into morphine milligram equivalents (MME) according to the Center for Disease Control conversion factors.[73] The total (MME) supply prescribed was calculated in 30-day periods, starting with the 30 days before the first-line of treatment, which was used as a baseline, and continuing at 30-day intervals for the duration of claims data available. Many patients with metastatic prostate cancer have pain from their disease that require opiates for pain control. Therefore, the level of MMEs may be a surrogate measure for disease burden, and disease response to treatment. ATE is defined as the mean difference in opioids prescribed at three specified time points: treatment start, 3 months after treatment start, and 6 months after treatment start.

Confounders:

Potential confounders were identified using previous research explored factors associated with treatment and our outcomes of interest Age of the patient at the time of receipt of first-line treatment and patient sociodemographic variables were identified through enrollment records included in the OptumInsight database. A demographic-based analytical model is used by OptumInsight to derive many of the sociodemographic variables. The major data syndicator used is Knowledge-Based Marketing Solutions (KBM, Richardson, TX). Race was classified as white, black, Hispanic, or Asian. Geographic region of the patient was originally determined by their ZIP; however, this view of the data was encrypted so only a broader geographic region could be identified.

Diabetes, hypertension, cardiac arrhythmias, congestive heart failure (CHF), and osteoporosis, were the pre-existing comorbid diseases we included in our analysis. To identify a pre-existing comorbid disease rather than a comorbid condition that may have resulted from treatment, the presence of a pre-existing comorbid disease was defined as at least two diagnosis codes within the two years before receipt of the first-line drug. The list of ICD-9 (2008-2015) and ICD-10 (2015-2016) codes that describe the comorbid conditions are from Elixhauser Comorbidity Index and Clinical Classification Software.

Stratification by Propensity Score

Another method not discussed at length in the main manuscript is propensity score stratification. Once the propensity score is calculated, the data can be stratified based on specified quantiles of the propensity score distribution. Researchers suggest 5 strata is often sufficient (Rubin, 2005). Balance diagnostics can then be checked within each stratum. If sufficient balance is achieved, estimates from each stratum can be estimated and then combined using Mantel-Haenszel's method of meta-analysis, weighting each group inversely by the variance. Supplemental Table 2 (S2) shows an example using the binary outcome.

Reduced Sample sizes for matched datasets:

Binary Outcome: Oral 1424, Immunotherapy 455;
 Chemotherapy 1287, Immunotherapy 326
 Count Outcome: Oral 1097, Immunotherapy 381;
 Chemotherapy 1063, Immunotherapy 269
 Time on to Event-Time on Treatment: Oral 1536, Immunotherapy 491;
 Chemotherapy 1345 Immunotherapy 341
 Time on to Event-Time on Treatment: Oral 1536, Immunotherapy 491;
 Chemotherapy 1345 Immunotherapy 341
 Longitudinally Varying Repeated Measures Opioids Prescribed:
 Oral 877, Immunotherapy 263; Chemotherapy 764, Immunotherapy 193

Supplemental Table 1 (S1) Time in Database Outcome Results

	Immunotherapy (n=504)		Chemotherapy (n=2,214)		Oral Therapy (n=2,747)	
	Median	(q1,q2)	Median	(q1,q2)	Median	(q1,q2)
Time in Database (days)	414	(183,785)	256	(105,541)	291	(125,541)
Total Time in Database Model Estimates – Difference in mean Days on Treatment from Immunotherapy (restricted to 5 year follow-up)						
Oral Therapy	-146 (-184, -109)	-130 (-169, -90)	-125 (-164, -96)	-107 (-125, -90)	-116 (134, -98)	-124* (-226, -22)
Chemotherapy	-147 (-186, -108)	-172 (-200, -125)	-177 (-224, -131)	-186 (-207, -164)	-155 (-176, -134)	-147* (-194, -101)

S1 Legend: Descriptive characteristics and model estimates for time in database outcome. All methods mirror the time on treatment outcome, however this outcome is also considered as a potential surrogate endpoint for death.

*Adjustment covariates limited to age and race due to computational issues with full covariate set.

Supplementary Table 2 (S2)

Stratification by Propensity Score: Binary Outcome (ER Visit)

	Strata				
	1	2	3	4	5
Oral Therapy (N)	357	454	488	513	551
Immunotherapy (N)	210	116	75	54	16
Total (N)	567	570	563	567	567
Odds Ratio Estimate	0.63 (0.23, 1.45)	2.90 (0.67, 12.52)	0.41 (0.13, 1.32)	0.80 (0.23, 2.75)	0.33 (0.04, 2.74)
Final Mantel-Haenszel Estimate	0.82 (0.49, 1.37)				

S2 Legend:

Stratified datasets based on propensity score quintiles. Total counts for each therapy group (N) and total (N) are shown, as well as stratum specific odds ratios and final Mantel-Haenszel estimate.

Additional References

Rubin, D. B. (2005). Causal Inference Using Potential Outcomes: Design, Modeling, Decisions. <https://doi.org/10.1198/016214504000001880>