

Original Investigation

SUPPLEMENTAL MATERIALS

Effectiveness of Sipuleucel-T on Overall Survival in Medicare Beneficiaries Treated for Advanced Prostate Cancer

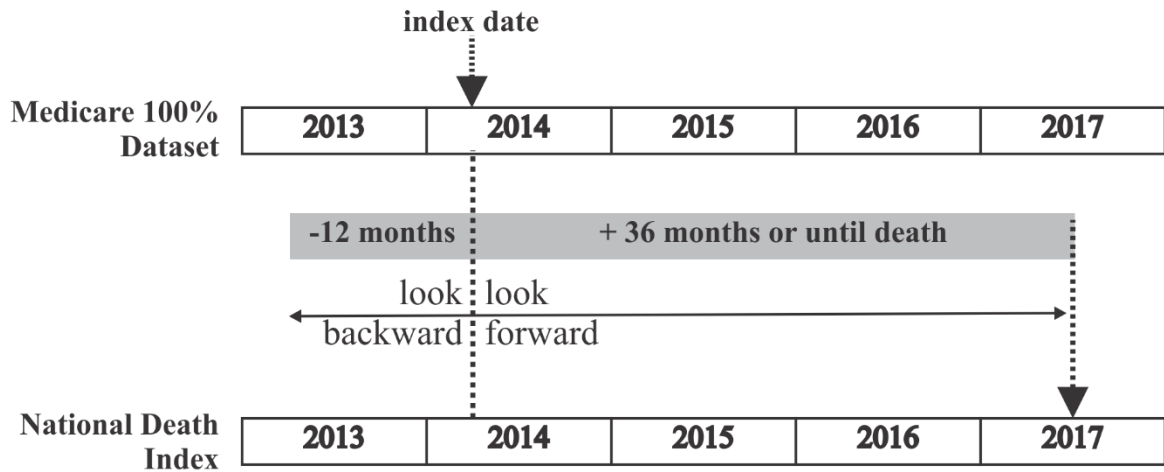
Authors: McKay RR, Hafron J, Ferro C, Wilfehrt HM, Fitch K, Flanders SL, Fabrizio M, Schweizer M

This supplement contains materials referred to in the main paper as well as additional details regarding the model.

CONTENTS (In order of mention)	Page
Supplemental Figure 1. Diagram of How Eligible Patients Were Identified	2
Supplemental Figure 2. Univariate Kaplan-Meier Survival Curves	3
Supplemental Figure 3. Exploratory Analyses by Line of Treatment: Univariate Kaplan Meier Curves with 95% Hall-Wellner Bands	4
Supplemental Table 1. Patient Characteristics by Cohort: Initial Population Explored During Model Development	5
Supplemental Table 2. Summary of Initial Models Generated During Stepwise Process to Create Multivariable Model	7
Supplemental Table 3. Prespecified List of Covariates Used During Model Development	8
Supplemental Table 4. Description of Covariates Used in the Final Multivariate Model	10
Supplemental Table 5. Patient Characteristics by Cohort: Testing Population Used During Model Development	12

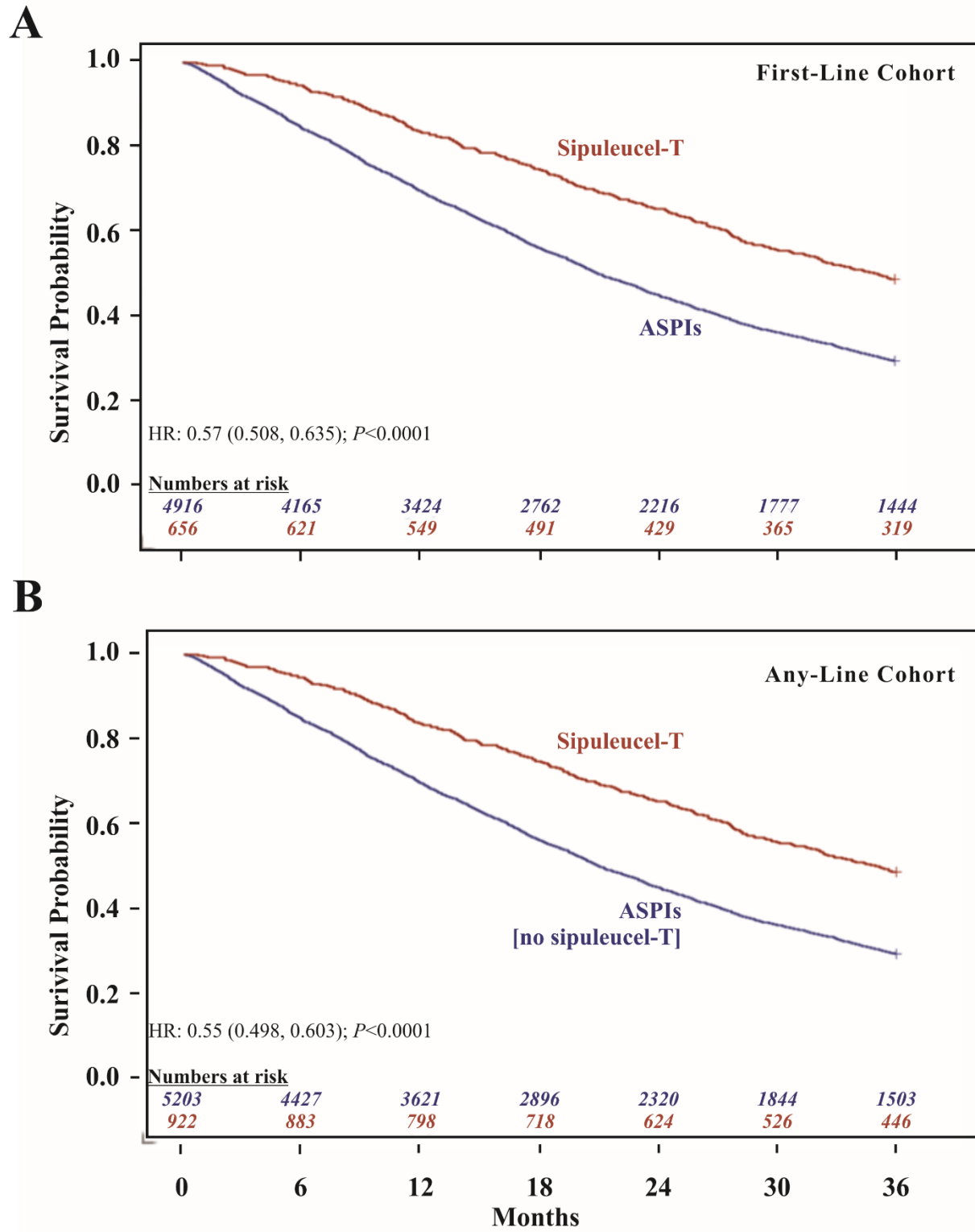
Supplemental Figure 1. Diagram of How Eligible Patients Were Identified

A patient's data was reviewed to identify the first claim for prostate cancer treatment in 2014. Next, data from the previous 12 months was reviewed for any other claims for treatments for metastatic prostate cancer. If no other claims were identified, the date of the first claim in 2014 was identified as the index date. Afterwards, the data for up to the first 36 months (through 2017) or death, whichever came first, was analyzed. Details regarding death came from the link to the National Death Index²². This procedure was repeated for each patient.

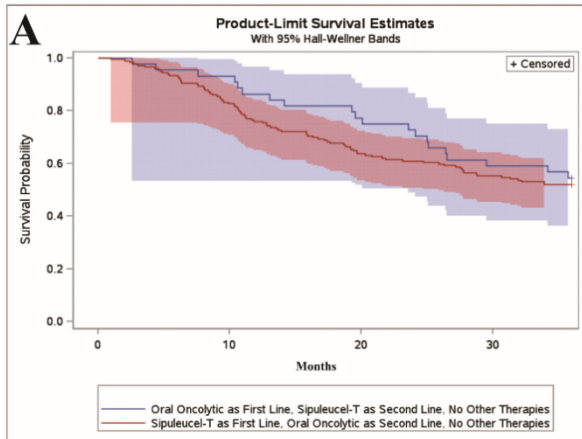


Supplemental Figure 2. Univariate Kaplan-Meier Survival Curves

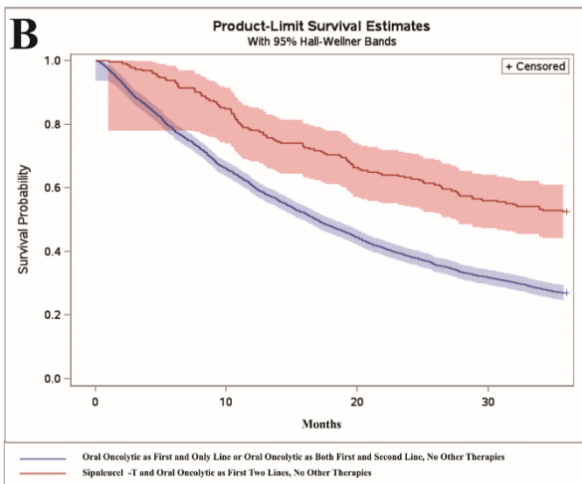
A. Illustration of the curve for the first-line cohort. **B.** Illustration of the curve for the any-line cohort.
Adapted from McKay et al 2020²¹



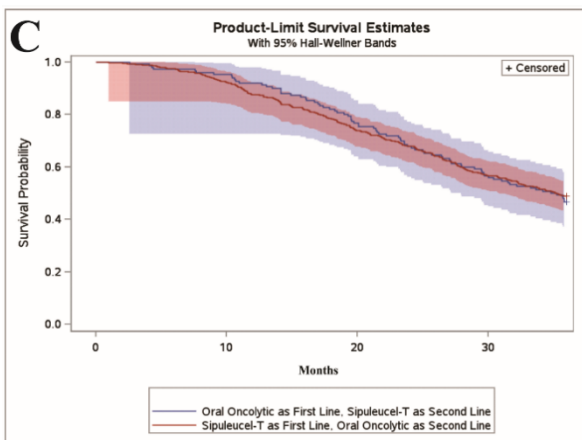
Supplemental Figure 3. Exploratory Analyses by Line of Treatment: Univariate Kaplan Meier Curves with 95% Hall-Wellner Bands.



A. (red) first-line sipuleucel-T and second-line APSIs with no other therapies vs first-line APSIs and second-line sip-T with no other therapies (Hazard Ratio [HR], 1.1726 [95% Wald Confidence Limits: 0.7368, 1.9608]; P = 0.5213).



B. (red) sipuleucel-T and APSIs with no other therapies vs (blue) first- and only line APSIs or first- and second-line APSIs with no other therapies (HR, 0.4845 [0.3964, 0.5853]; P < 0.0001).



C. Describes outcomes with (red) first-line sipuleucel-T and second-line APSIs vs (blue line) first-line APSIs and second-line sipuleucel-T. Abbreviations: ASPI, androgen signaling pathway inhibitors (HR, 0.9744 [0.7622, 1.2600]; P = 0.8396).

Supplemental Table 1. Patient Characteristics by Cohort: Initial Population Explored During Model Development

Characteristic	First-line Cohort		Any-line Cohort	
	Sipuleucel-T (n=449)	ASPI (n=3,240)	Sipuleucel-T (n=614)	ASPI (Never Sipuleucel-T) (n=3,439)
No. (%) of patients by age group				
< 65 years old	--	53 (2%)	11 (2%)	89 (3%)
65–69 years old	71 (16%)	325 (10%)	103 (17%)	354 (10%)
70–74 years old	144 (32%)	654 (20%)	188 (31%)	714 (21%)
75–79 years old	106 (24%)	742 (23%)	163 (27%)	789 (23%)
80–84 years old	76 (17%)	682 (21%)	97 (16%)	709 (21%)
85–89 years old	39 (9%)	552 (17%)	46 (7%)	544 (16%)
90+ years old	--	232 (7%)	--	240 (7%)
Average Age, years	75.3	78.6	75.2	78.2
Median Age, years	74.0	79.0	75.0	78.0
No. (%) of patients by race				
Black	34 (8%)	333 (10%)	45 (7%)	383 (11%)
White	391 (87%)	2,743 (85%)	542 (88%)	2,871 (83%)
Other	24 (5%)	164 (5%)	27 (4%)	185 (5%)
No. (%) of patients with weighted Charlson Comorbidity Index score ^a within stated range				
0–3	37 (8%)	366 (11%)	52 (8%)	363 (11%)
4–7	30 (7%)	349 (11%)	43 (7%)	340 (10%)
8–11	299 (67%)	1,872 (58%)	434 (71%)	2,035 (59%)
12–15	76 (17%)	566 (17%)	82 (13%)	601 (17%)
16–19	--	82 (3%)	--	97 (3%)
20–24	0 (0%)	--	0 (0%)	--
Median Score	9.0	9.0	9.0	9.0
No. (%) of patients by type of eligibility				
Both Medicare and Medicaid	35 (8%)	462 (14%)	41 (7%)	499 (15%)
One or the other	414 (92%)	2,778 (86%)	573 (93%)	2,940 (85%)
No. (%) of patients with specified numbers of mCRPC lines of therapy				
One	70 (16%)	1,460 (45%)	65 (11%)	1,468 (43%)
Two	131 (29%)	977 (30%)	161 (26%)	1,097 (32%)
Three	125 (28%)	470 (15%)	183 (30%)	554 (16%)
Four	75 (17%)	267 (8%)	126 (21%)	261 (8%)
Five	43 (10%)	62 (2%)	63 (10%)	59 (2%)
Six	--	--	16 (3%)	0 (0%)
Median time to 2nd line (mon)	4.8	9.2	5.3	8.8
Opioid utilization around index ^b				
Chronic Use	37 (8%)	556 (17%)	59 (10%)	624 (18%)
No Chronic Use	412 (92%)	2,684 (83%)	555 (90%)	2,815 (82%)

No. (%) of patients having multiple metastasis sites ^c				
Yes	86 (19%)	726 (22%)	118 (19%)	822 (24%)
No	363 (81%)	2,514 (78%)	496 (81%)	2,617 (76%)
No. (%) of patients having ≥ 1 SRE ^d around index date				
Yes	62 (14%)	703 (22%)	95 (15%)	750 (22%)
No	387 (86%)	2,537 (78%)	519 (85%)	2,689 (78%)
No. (%) of patients by number of days of corticosteroid use within 6 months after index date ^e				
< 60 Days	445 (99%)	3,186 (98%)	604 (98%)	3,346 (97%)
≥ 60 Days	--	54 (2%)	--	93 (3%)
No. (%) of patients by corticosteroid PDC ^f within 6 months after index date ^e				
< 0.2	440 (98%)	3,150 (97%)	598 (97%)	3,297 (96%)
0.2–0.4	--	29 (1%)	--	40 (1%)
0.4–0.6	--	27 (1%)	--	26 (1%)
0.6–0.8	--	11 (0%)	--	21 (1%)
> 0.8	0 (0%)	23 (1%)	--	55 (2%)

Abbreviation: ASPI, androgen signaling pathway inhibitor; CI, confidence interval; coeff, coefficient; cov, covariate; PDC, proportion of days covered; ref, reference; v., versus; na=not applicable; --=indicates cell was suppressed due to insufficient numbers of patients available

^a Charlson comorbidity index score was assigned based on claims in year before the index date. A score of 0 indicates that no comorbidities were found; worse comorbidity was indicated by higher scores, with a maximum score possible of 33.

^b Chronic opioid use defined as two or more 30-day scripts within 60 days before or after the index date

^c 1+ claims in year before the index date

^d 1+ claims in the 90 days before until 90 days after the index date

^e Corticosteroid-use related variables shown here do not include abiraterone users receiving corticosteroid as per abiraterone label.

^f PDC=Proportion of Days Covered refers to the numbers of day supply of corticosteroids divided by the difference of total days alive in the study minus the number of days spent in inpatient or skilled nursing facility care.

Supplemental Table 2. Summary of Initial Models Generated During Stepwise Process to Create Multivariable Model

Model	36-Month Observation Period			
	HR (95% CL)	P-value	AIC	SBC
First-line Cohort				
<i>Significance level=0.05</i>				
Forward selection model	0.5472 (0.4705, 0.6337)	<0.001	36551.5	36708.2
Backward selection model	0.5472 (0.4705, 0.6337)	<0.001	36551.5	36708.2
Stepwise selection model	0.5472 (0.4705, 0.6337)	<0.001	36551.5	36708.2
<i>Significance level=0.01</i>				
Forward selection model	0.5457 (0.4692, 0.6320)	<0.001	36557.5	36702.6
Backward selection model	0.5457 (0.4692, 0.6320)	<0.001	36557.5	36702.6
Stepwise selection model	0.5457 (0.4692, 0.6320)	<0.001	36557.5	36702.6
Any-line Cohort				
<i>Significance level=0.05</i>				
Forward selection model	0.6027 (0.5272, 0.6868)	<0.001	40436.9	40572.4
Backward selection model	0.6036 (0.5280, 0.6879)	<0.001	40435.9	40577.3
Stepwise selection model	0.6027 (0.5272, 0.6868)	<0.001	40436.9	40572.4
<i>Significance level=0.01</i>				
Forward selection model	0.6027 (0.5272, 0.6868)	<0.001	40436.9	40572.4
Backward selection model	0.6036 (0.5280, 0.6879)	<0.001	40435.9	40577.3
Stepwise selection model	0.6027 (0.5272, 0.6868)	<0.001	40436.9	40572.4

Abbreviation: AIC, Akaike Information Criterion; CL, confidence limits; HR, hazard ratio; SBC, Schwarz Bayes Criterion.

The bold text indicates the model moved forward for final testing and use.

Supplemental Table 3. Prespecified List of Covariates Used During Model Development

Prespecified Covariates
Age
Race
CDC Region ¹
Urban/Rural – Type of region
Dual/Non-Dual – Both Medicare and Medicaid Eligible / Eligible for only one
mCRPC Lines of Therapy
Time to mCRPC Second Line Therapy
Charlson Comorbidity Index ²
Opioid Utilization Around Index ³
SRE Around Index - Radiation Therapy ⁵
SRE Around Index - Bone Fracture ⁶
SRE Around Index - Spinal Cord Compression ⁶
SRE Around Index - Bone Surgery ⁶
SRE Around Index - Any
60+ days of corticosteroid coverage within 6 months after index date
60+ days corticosteroid coverage at any time after index date
60+ days of corticosteroid coverage within 6 months after index date, not including use by Abi patients
60+ days corticosteroid coverage at any time after index date, not including use by Abi patients
Corticosteroid PDC ⁷ within 6 months after index date, not including use by Abi patients
HCC Community Score ⁸
Median Household Income ⁹
Metastases ⁴ - Any
Metastases ⁴ - Multiple
Metastases ⁴ - Bone Only
Metastases ⁴ - Liver Only
Metastases ⁴ - Lung Only
Metastases ⁴ - Lymph Only
Metastases ⁴ - Visceral Only
Metastases ⁴ - Other Only
Metastases ⁴ - Bone + Liver
Metastases ⁴ - Bone + Lung
Metastases ⁴ - Bone + Lymph
Metastases ⁴ - Bone + Visceral
Metastases ⁴ - Bone + Other
Metastases ⁴ - Liver + Lung

Metastases⁴ - Liver + Lymph
Metastases⁴ - Liver + Visceral
Metastases⁴ - Liver + Other
Metastases⁴ - Lung + Lymph
Metastases⁴ - Lung + Visceral
Metastases⁴ - Lung + Other
Metastases⁴ - Lymph + Visceral
Metastases⁴ - Lymph + Other
Metastases⁴ - Visceral + Other

Abbreviations: ACS, American Community Survey; CDC, Centers for Disease Control; HCC, Hierarchical Condition Category; mCRPC, metastatic castration-resistant prostate cancer; PDC, proportion of Days Covered; SRE, skeletal-related events

¹ <https://www.cdc.gov/coordinatedchronic/docs/NCCDPHP-Regions-Map.pdf>

² Charlson comorbidity index score was assigned based on claims in year before the index date. A score of 0 indicates that no comorbidities were found, level of comorbidity indicated by higher scores, maximum score possible is 33

² Chronic opioid use defined as two or more 30-day scripts within 60 days before or after the index date

⁴ 1+ claims in year before the index date

⁵ 1+ claims in the 60 days before until 60 days after the index date

⁶ 1+ claims in the 90 days before until 90 days after the index date

⁷ Proportion of Days Covered refers to the numbers of day supply of corticosteroids divided by the total days alive in the study less the number of days spent in inpatient or skilled nursing facility care

⁸ HCC community score is assigned based on claims in year before the index date and patients' sex, date of birth, original reason for entitlement to Medicare, and Medicaid-status. The score was produced using version 22, model year 2014, of the CMS-HCC Risk Adjustment Model

⁹ Median household income is derived from the 2014 ACS median household Income data and the patients' zip code of residence during the index year

Supplemental Table 4. Description of Covariates Used in the Final Multivariate Model

Covariate	Description	How Identified
Treatment	Primary covariate <i>Model 1:</i> First-line mCRPC therapy sipuleucel-T vs. first-line ASPI <i>Model 2:</i> Any-line sipuleucel-T use vs. any-line ASPI without use of sipuleucel-T	NDC codes
< 60 vs 60+ days of corticosteroid coverage within 6 months following index date (categorical)	Indication of 60+ days of oral corticosteroid utilization in the 6 months following index therapy; this excludes use of corticosteroids when used concomitantly in patients receiving abiraterone	NDC codes
Age (continuous variable)	Age at time of index therapy (based on actual date of birth)	Identifiers in reviewed claims
Charlson Comorbidity Index (continuous variable)	Increased comorbidity indicated by higher scores, (range, 0 to 33)	A selection of ICD-9-CM codes ¹²
Proportion of Days Covered (PDC) for patients with corticosteroid use within 6 months following index date	Proportion of days covered by corticosteroid prescriptions in the 6 months following index therapy (the number of days in inpatient or skilled nursing facility not included in 6-month denominator); this excludes use of corticosteroids when used concomitantly with abiraterone. Proportion of Days Covered refers to the supply of corticosteroids (in terms of days) divided by the total days alive in the study minus the number of days spent in inpatient or skilled nursing facility care (range, 0 to 1)	NDC codes
Dual vs Non-Dual Eligibility (categorical)	Indication of full or partial dual eligibility in both Medicare and Medicaid or only Medicare. Dual eligibility typically is a flag for worse status.	
mCRPC Lines of Therapy (continuous)	Number of mCRPC therapies received by the patient during the analysis period (range, 1 to 6)	NDC codes
Having multiple metastasis sites (yes or no)	Identified by reviewing diagnosis codes for indication of multiple sites of metastasis in the year before index date	Number of claims with ICD-9-CM diagnosis codes indicating such were present during the year before index date (2013-2014)
Opioid Utilization Around Index (yes or no)	Indication of chronic opioid utilization within 60 days before or after index therapy, with chronic use defined as 2+ scripts of 30 days within 60 days before and after index date	NDC codes
Race (categorical)	Race of patient: White, Black, Other	Identifiers in examined claims

Covariate	Description	How Identified
Any Skeletal Related Events (SRE) Around Index (yes or no)	Indication of whether an SRE incurred around time off index therapy, with SRE including ≥ 1 occurrence of radiation therapy, bone fracture, spinal cord compression, or bone surgery	claims for bone fracture, bone surgery, or spinal cord compression in the 90-day window before or after the index date and/or radiation therapy within a 60-day window
Time to mCRPC Second Line Therapy (categorical)	Number of months (30 day increments) from the time of index therapy to the second mCRPC therapy: 'No Second Line Therapy' '0 to 3 months,' '3 to 6 months,' '6 to 9 months,' '9 to 12 months,' '12 to 15 months,' and 'Greater than 15 months'	Calculation and categorization of the time between treatments

Supplemental Table 5. Patient Characteristics by Cohort: Testing Population Used During Model Development

Characteristic	First-line Cohort		Any-line Cohort	
	Sipuleucel-T (n=198)	ASPI (n=1,570)	Sipuleucel-T (n=292)	ASPI (Never Sipuleucel-T) (n=1,653)
No. (%) of patients by age group				
< 65 years old	--	44 (3%)	--	32 (2%)
65–69 years old	30 (15%)	163 (10%)	47 (16%)	184 (11%)
70–74 years old	50 (25%)	283 (18%)	93 (32%)	321 (19%)
75–79 years old	58 (29%)	372 (24%)	73 (25%)	373 (23%)
80–84 years old	32 (16%)	332 (21%)	41 (14%)	358 (22%)
85–89 years old	18 (9%)	268 (17%)	25 (9%)	285 (17%)
90+ years old	--	108 (7%)	--	100 (6%)
Average age, years	75.9	78.5	75.3	78.4
Median age, years	76.0	78.0	74.0	78.0
No. (%) of patients by race				
Black	13 (7%)	175 (11%)	18 (6%)	177 (11%)
White	175 (88%)	1,313 (84%)	260 (89%)	1,397 (85%)
Other	--	82 (5%)	14 (5%)	79 (5%)
No. (%) of patients with weighted Charlson Comorbidity Index score ^a within stated range				
0–3	18 (9%)	175 (11%)	33 (11%)	172 (10%)
4–7	12 (6%)	146 (9%)	22 (8%)	162 (10%)
8–11	146 (74%)	913 (58%)	194 (66%)	968 (59%)
12–15	19 (10%)	300 (19%)	36 (12%)	316 (19%)
16–19	--	35 (2%)	--	32 (2%)
20–24	0 (0%)	--	0 (0%)	--
Median Score	9.0	9.0	9.0	9.0
No. (%) of patients by type of eligibility				
Both Medicare and Medicaid	--	214 (14%)	22 (8%)	234 (14%)
One or the other	188 (95%)	1,356 (86%)	270 (92%)	1,419 (86%)
No. (%) of patients with specified numbers of mCRPC lines of therapy				
One	26 (13%)	734 (47%)	31 (11%)	726 (44%)
Two	55 (28%)	439 (28%)	70 (24%)	525 (32%)
Three	61 (31%)	250 (16%)	90 (31%)	250 (15%)
Four	32 (16%)	109 (7%)	53 (18%)	132 (8%)
Five	16 (8%)	33 (2%)	37 (13%)	20 (1%)
Six	--	--	11 (4%)	0 (0%)
Median time to mCRPC second line therapy (months)	4.4	9.2	5.2	9.3
Opioid utilization around index ^b				
Chronic use	19 (10%)	274 (17%)	24 (8%)	304 (18%)
No chronic use	179 (90%)	1,296 (83%)	268 (92%)	1,349 (82%)

No. (%) of patients having multiple metastasis sites ^c				
Yes	39 (20%)	373 (24%)	55 (19%)	419 (25%)
No	159 (80%)	1,197 (76%)	237 (81%)	1,234 (75%)
No. (%) of patients having ≥ 1 SRE ^d around index date				
Yes	26 (13%)	335 (21%)	30 (10%)	369 (22%)
No	172 (87%)	1,235 (79%)	262 (90%)	1,284 (78%)
No. (%) of patients by number of days of corticosteroid use within 6 months after index date ^e				
< 60 Days	193 (97%)	1,533 (98%)	287 (98%)	1,601 (97%)
≥ 60 Days	--	37 (2%)	--	52 (3%)
No. (%) of patients by corticosteroid PDC ^f within 6 months after index date ^e				
< 0.2	193 (97%)	1,517 (97%)	286 (98%)	1,579 (96%)
0.2–0.4	0 (0%)	--	--	19 (1%)
0.4–0.6	--	--	--	19 (1%)
0.6–0.8	--	--	--	--
> 0.8	--	30 (2%)	0 (0%)	29 (2%)

Abbreviation: ASPI, androgen signaling pathway inhibitor; CI, confidence interval; coeff, coefficient; cov, covariate; PDC, proportion of days covered; ref, reference; v., versus; na=not applicable; --=indicates cell was suppressed due to insufficient numbers of patients available

^a Charlson comorbidity index score was assigned based on claims in year before the index date. A score of 0 indicates that no comorbidities were found; worse comorbidity was indicated by higher scores, with a maximum score possible of 33

^b Chronic opioid use defined as two or more 30-day scripts within 60 days before or after the index date

^c 1+ claims in year before the index date

^d 1+ claims in the 90 days before until 90 days after the index date

^e PDC=Proportion of Days Covered refers to the numbers of day supply of corticosteroids divided by the difference of total days alive in the study minus the number of days spent in inpatient or skilled nursing facility care.

^f Corticosteroid-use related variables shown here do not include abiraterone users receiving corticosteroid as per abiraterone label.