Assessment of PSA responses and changes in the rate of tumor growth (g-rate) with immune checkpoint inhibitors in US Veterans with prostate cancer

Harshraj Leuva (hleuva@unmc.edu)
University of Nebraska Medical Center  https://orcid.org/0000-0002-8860-1382

George Moran
Columbia University Herbert Irving Comprehensive Cancer Center

Nader Jammaleddine
SUNY Downstate Health Sciences University

Mina Maseeha
SUNY Downstate Health Sciences University

Mengxi Zhou
Columbia University Herbert Irving Comprehensive Cancer Center

Yunju Im
University of Nebraska Medical Center

Ta-Chueh Rosenberg
James J. Peters Bronx Veterans Affairs Medical Center

Carol Luhrs
SUNY Downstate Health Sciences University

Susan Bates
2Columbia University Herbert Irving Comprehensive Cancer Center

Yeun-Hee Park
James J. Peters Bronx Veterans Affairs Medical Center

Tito Fojo
Columbia University Herbert Irving Comprehensive Cancer Center

Izak Faiena
Columbia University Herbert Irving Comprehensive Cancer Center

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Abstract

Background:

The value of immune checkpoint inhibitors (PD1/PDL1 inhibitors; ICI) in treating prostate cancer (PC) is limited. We examined data from US Veterans with PC to assess disease response to ICIs as monotherapy or combined with abiraterone or enzalutamide. We compared results with reference datasets to assess ICI efficacy in the real-world.

Methods: We queried the VA corporate data warehouse (CDW) to identify Veterans with a diagnosis of PC who received ICI for any malignancy and had ≥1 PSA measurement while receiving ICI. To evaluate ICI monotherapy, we restricted analysis to Veterans who had not received LHRH agonists/antagonists, PC-directed medical therapy, or radiation/extirpative surgery of the bladder/prostate within and preceding the duration of ICI administration. For ICI combination analysis, we identified Veterans who received abiraterone or enzalutamide for PC while on ICI. We calculated rates of tumor (PSA) growth ($g$-rates), comparing them to a 1:2 matched reference cohort.

Results: We identified 787 Veterans with PC and ≥1 PSA measurement while receiving an ICI. The median duration of ICI therapy was 155 days. 223 Veterans received ICI monotherapy, with only 17(8%) having a reduction in PSA (median decline=43%). 12 (5%) had PSA declines >30% (PSA30) which included 6 (3%) who had PSA reductions greater than 50% (PSA50). Median $g$-rates for ICI plus abiraterone (n=20) or enzalutamide (n=31) were 0.000689/d$^{-1}$ and 0.002819/d$^{-1}$, respectively, and were statistically insignificant compared to $g$-rates of matched cohorts receiving abiraterone ($g$=0.000925/d$^{-1}$, p=0.73) or enzalutamide ($g$=0.001929/d$^{-1}$, p=0.58) alone.

Conclusion: Our data align with clinical trial data in PC, demonstrating limited benefit from ICI monotherapy and predicting no survival benefit from simultaneous administration of abiraterone or enzalutamide with an ICI using $g$-rate. We demonstrate the value of estimating $g$-rates and of our reference database in approaching challenging clinical questions and as aids in drug development.

INTRODUCTION

Though novel immunotherapies have fundamentally changed the treatment of several aggressive malignancies, this has not been the case in prostate cancer (PC). (1) Furthermore, despite recent therapeutic advances, the burden of advanced PC is high and may be rising. (2) Treatment with immune checkpoint inhibitors (ICIs), including monoclonal antibodies targeting PD-1, PD-L1, and CTLA-4 have led to durable clinical response for patients with several advanced cancers, including renal cell carcinoma and melanoma. The recognition of the prostate cancer microenvironment as a site of immunological dysregulation has encouraged investigators to seek similar benefits from ICIs.

Several clinical trials have recently investigated the use of ICIs in specific populations of patients with a diagnosis of metastatic prostate cancer (mPC). For instance, following promising results in patients with
tumors that were scored as PD-L1-positive, mismatch repair-deficient, and microsatellite instability-high 
(3, 4), the PD-1 antibody pembrolizumab was evaluated as monotherapy for patients with metastatic 
castrate-resistant prostate (mCRPC) in the phase 2 KEYNOTE-199 study. (5) While few patients 
demonstrated an objective response at interim analysis (3–6%), those responses that did occur were 
durable. (6) Data like this support the notion that ICIs, in their current formulations and combinations, 
benefit a specific subset of patients with advanced PC while providing little or no benefit to others. Most 
recently, the IMbassador250 trial, comparing the addition of atezolizumab to enzalutamide with 
enzalutamide alone, failed to meet its primary endpoint of improved overall survival. (7)

The US Veterans Health Administration (VHA) is the most extensive integrated healthcare system in the 
United States. All data is stored in the VA corporate data warehouse (CDW) and made available to 
researchers via a VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13–457. Since the 
COVID-19 pandemic, VINCI has been highlighted as one of the best sources of real-world data, given its 
ability to provide nationalized structured and unstructured data combined from various registries. This 
has allowed researchers to explore the impact of various underlying comorbidities on COVID-19 infection, 
assess vaccine effectiveness and not only emulate clinical trials but even conduct a virtual trial using the 
data. (8, 9)

Using VINCI, we have developed a reference database of more than 30,000 US Veterans with mPC 
receiving various therapies for mPC, including abiraterone, enzalutamide, darolutamide, apalutamide, 
docetaxel, cabazitaxel, and olaparib/rucaparib. We have also developed a g-rate method to calculate the 
rates of tumor (PSA) growth (g) and regression (d) using PSA values obtained while receiving any 
therapy. Using data from more than 10,000 patients with a diagnosis of mPC, including patients enrolled 
in clinical trials, and 5000 Veterans whose data were abstracted using VINCI, we have demonstrated that 
g-rates inversely correlate with overall survival and can be used to assess the efficacy of any therapeutic 
intervention. (10, 11)

The present observational study aimed to evaluate disease response in Veterans with a diagnosis of PC 
treated with ICIs for any advanced malignancy and report on the PSA responses to ICI monotherapy. 
Additionally, we sought to assess the value of using matched cohorts as reference arms for future studies 
by creating a matched cohort of Veterans who received abiraterone or enzalutamide alone as the 
comparator for the Veterans in our analysis who received either abiraterone or enzalutamide while 
receiving an ICI. We hypothesized that there would be no statistical difference in g-rates in the Veterans in 
our analysis who were treated with abiraterone or enzalutamide while also receiving an ICI when 
compared to the matched cohorts of Veterans treated with abiraterone or enzalutamide alone.

**METHODS**

Data were obtained from the VA CDW using VINCI to identify Veterans with PCa based on ICD-9/ICD-10 
codes. Data was cross-referenced with the CDW Oncology registry (VACCR) and VA Prostate Data Core to 
confirm the diagnosis. (12) Oral and intravenous (IV) medication dispensing details were then obtained
from the CDW pharmacy database. The diagnoses of other cancers were confirmed based on ICD-9/ICD-10 codes for the Veterans who received ICI. The project was approved by the James J Peters VA Medical Center Institutional Review Board (IRB).

**Patient cohort**

Our cohort was comprised of Veterans with a confirmed diagnosis of PCa who started a PD1/PD-L1 inhibitor – pembrolizumab, nivolumab, atezolizumab, durvalumab, or avelumab – for any malignancy between January 2015 and January 2021 and had ≥ 2 available PSA value while on ICI. We collected data regarding demographics (age, race/ethnicity) and PC-directed therapies – androgen deprivation therapy (ADT), novel hormonal therapies (NHT, abiraterone, enzalutamide), docetaxel, and cabazitaxel. Veterans with a decline in PSA while on ICI further underwent a comprehensive manual chart review for verification. This review included information on Gleason grade groups, PCa stage, prostate, bladder, or other extirpative surgeries, radiation, other chemotherapy or immunotherapies while on ICI, and cause of death when available.

To evaluate ICI monotherapy, we restricted our analysis to Veterans who had not received LHRH agonists or antagonists within six months, PCa-directed medical therapy within one month, or radiation or extirpative surgery of the bladder or prostate within two years of the ICI infusion.

To evaluate combination therapies of an ICI plus a NHT, we included Veterans who were receiving ICI and NHT — abiraterone or enzalutamide — concurrently.

**Data analysis**

**g-rate method**

The regression-growth models describe changes in tumor quantity during therapy resulting from simultaneous exponential decay/regression, termed d, and exponential growth/regrowth of the tumor, termed g. This basic mathematical model is:

\[
 f(t) = \exp(-d \times t) + \exp(g \times t) - 1
\]

At the time \(t\), the total tumor quantity/volume \(f\) is the sum of simultaneously occurring exponential growth \(g\) of the therapy-resistant part and the exponential regression/decay \(d\) of the therapy-sensitive part of the tumor. Using this theory, we iteratively estimate the growth rate \(g\)-rate)/day and decay rate\(d\)-rate)/day while on the therapy using the observed changes in tumor volume\(f\). (10, 11, 13–17)

The rates of tumor growth (g-rate) and regression (d-rate) are calculated using the TUMGr package for R using serial PSA values while on a drug (https://cran.r-
Iteratively, the package attempts to fit the individual patient data to one of four equations, designated $g_x$, $d_x$, $g_d$, and $g_d\Phi$, to provide $g$ and $d$ values. The value of this approach has been demonstrated in patients with mPCa using data from clinical trials and from VINCI. (10, 11, 15, 16)

**Matching**

Using VINCI data, we have developed a large reference cohort that includes 38,122 unique Veterans who received medications for mPCa through June 2022. This includes 12,328 and 9,529 Veterans who received abiraterone and enzalutamide, respectively, with estimable $g$-rate while on the medications. For this study, the aim was to identify two patients from the reference database per each patient from the study cohort, matched for race, age ±10 years, PSA value at the time of medication start (< 1, 1–50, > 50), prior lines of therapy (0, 1, ≥2), and Gleason score (< 8, ≥8).

**Outcome**

For ICI monotherapy analysis, we assessed PSA responses, including PSA30 and PSA50, defined as 30 and 50 percent reductions in PSA, respectively. For the analysis of ICI + NHT combinations, we used the $g$ value as an endpoint. We have previously shown and validated the inverse relationship of $g$ as a strong surrogate for overall survival in mPCa. (10, 11) This robust correlation is again demonstrated in our most recent expanded reference cohort of patients used for matching analysis. (Fig. 1)

**Statistical analysis**

The absolute and relative frequencies of the individual characteristics were calculated for the overall cohort and separately in groups with and with no PSA decline in patients who received ICI monotherapy. Similar statistics were also obtained for patients who received ICI with novel hormonal therapies and the corresponding matched cohort. A chi-square test was performed to compare the differences in the categorical variables between the two groups. For cells with an absolute count of less than 5, a Fisher's exact test was used. Continuous variables were compared using two-sided Wilcoxon test. Comparison of the distribution of the growth rates in the matching analysis was performed using paired two-sided Wilcoxon test. The Kaplan-Meier method was used to estimate the overall survival probability. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using R Statistical Software (version 4.2.2).

**RESULTS**

We identified 787 Veterans with a confirmed diagnosis of PC who were receiving a PD1/PD-L1 inhibitor – pembrolizumab, nivolumab, atezolizumab, durvalumab, or avelumab – for any malignancy and had ≥ 1 available PSA value while on ICI. The median age at onset of ICI therapy was 71 years. The cohort included 544 (69%) Caucasians and 200 (25%) Black American patients. 297(50%) received pembrolizumab, 327(42%) nivolumab, and 63 (8%) received atezolizumab. The median duration of ICI therapy was 155 days, with a median of six ICI infusions.
Evaluation of PSA response in Veterans with a diagnosis of prostate cancer receiving ICI monotherapy

For this analysis, we first excluded 411 Veterans with only one PSA value while on ICI, followed by exclusion of 154 patients who were found to have had either LHRH agonists/antagonists within six months or PC-directed medical therapy within one month. Of the remaining 263 Veterans, 57 had a decline in their PSA. These Veterans had stringent manual chart review, leading to the further exclusion of 40 Veterans. Reasons for exclusions were lack of confirmed tissues diagnosis in the EMR (n = 5), radiation or extirpative surgery of the bladder or prostate within two years of the ICI infusion (n = 10), other chemotherapy or targeted therapy while on ICI (n = 3) and LHRH agonists or antagonists within six months or PC-directed medical therapy administered at another institution in the previous one month (n = 22). (Fig. 2) The final cohort for evaluation of ICI monotherapy was comprised of 223 Veterans, including 155 (70%) Caucasians and 55 (25%) Black Americans. Eighty-two Veterans had a starting PSA $\geq 2$ during the administration of ICI. The most common reason for Veterans receiving ICI was lung cancer, in 62 (28%) patients, followed by other genitourinary cancers (bladder cancer and renal cell carcinoma) and skin cancers, with 37 (17%) and 35 (16%) Veterans, respectively. The median duration of ICI therapy was 231 days. (Table 1)
<table>
<thead>
<tr>
<th></th>
<th>ICI monotherapy</th>
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<th>P value</th>
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<tr>
<td>All (N = 223)</td>
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<td>72 (68–77)</td>
<td>72 (68–76)</td>
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<td>PSA decline (N = 17)</td>
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<td>no PSA decline (N = 206)</td>
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<td>14 (82)</td>
<td>141 (68)</td>
<td>0.5120</td>
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<td>2 (12)</td>
<td>53 (26)</td>
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<td>12 (71)</td>
<td>52 (25)</td>
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<td>3 + 4 (7)</td>
<td>57 (26)</td>
<td>4 (24)</td>
<td>53 (26)</td>
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<td>4 + 3 (7)</td>
<td>20 (9)</td>
<td>0 (0)</td>
<td>20 (10)</td>
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<tr>
<td>4 + 4 (8)</td>
<td>18 (8)</td>
<td>1 (6)</td>
<td>17 (8)</td>
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<tr>
<td>4 + 5 (9)</td>
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<td>10 (5)</td>
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<td>5 + 4 (9)</td>
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<td>3 (1)</td>
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<td>0 (0)</td>
<td>37 (18)</td>
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<td><strong>Clinical Stage (N, %)</strong></td>
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<td>I</td>
<td>28 (13)</td>
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<td>21 (10)</td>
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<td>II</td>
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<td>III</td>
<td>6 (3)</td>
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<td>6 (3)</td>
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<td>18 (8)</td>
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<td>18 (9)</td>
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<td>97 (43)</td>
<td>6 (35)</td>
<td>91 (44)</td>
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<td><strong>Cancer Treated with ICI (N, %)</strong></td>
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<td>Bladder</td>
<td>18 (8)</td>
<td>0 (0)</td>
<td>18 (9)</td>
<td>0.1309</td>
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Only 17 (8%) of the 223 Veterans experienced a decline in their PSA values. The median time to nadir PSA was 184 days. Twelve (5%) Veterans had PSA declines >30% (PSA30) which included six (3%) who had PSA reductions greater than 50% (PSA50) while receiving an ICI. Gleason scores of 3 + 3, 3 + 4, and 4 + 3 were seen in 3, 2 and 1 Veterans, respectively. Fourteen of the 17 responders had a starting PSA value of ≥ 2, of which nine (11% of 82) and three (4% of 82) Veterans reached PSA30 and PSA50 responses, respectively. All three Veterans with starting PSA values ≥ 2 and PSA50 responses had Gleason scores of 3 + 3.
Evaluation of the efficacy of combination ICI + NHT using g-rates

We identified 51 Veterans with mPCa who received a NHT (abiraterone or enzalutamide) and an ICI concurrently, including 20 Veterans who received abiraterone and 31 who received enzalutamide. Using all PSA values while on NHT + ICI, g-rates could be estimated in 12 and 22 Veterans while on abiraterone and enzalutamide, respectively. The median g-rates were 0.000689d$^{-1}$ and 0.002819d$^{-1}$ for abiraterone + ICI and enzalutamide + ICI, respectively. We performed an exact 1:2 match for all but two patients receiving NHT + ICI with a calculable g-rate (n = 34). We identified a matched cohort of 66 patients, of which 22 received abiraterone and 44 received enzalutamide alone without any known ICI administration. (Table 2) Median g values of the matched cohort were not statistically different for either abiraterone (0.000925d$^{-1}$, p = 0.73) or enzalutamide (0.001929d$^{-1}$, p = 0.58), predicting no benefit from the NHT + ICI combinations compared to NHT alone. (Fig. 3)
Table 2
Summary of patient characteristics of the ICI + NHT (ABI/ENZA) cohort and the matched* reference cohort (1:2 ratio)

<table>
<thead>
<tr>
<th></th>
<th>PD1 All (N = 51)</th>
<th>PD1 Evaluable† (N = 34)</th>
<th>Reference Cohort (N = 66£)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Age (years) median, IQR</strong></td>
<td>72 (70–78)</td>
<td>72 (70–78)</td>
<td>73 (69–76)</td>
<td>0.9100</td>
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<td><strong>Race (N,%)</strong></td>
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<tr>
<td>White</td>
<td>30 (59)</td>
<td>22 (65)</td>
<td>42 (64)</td>
<td>0.9999</td>
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<tr>
<td>Black</td>
<td>18 (35)</td>
<td>11 (32)</td>
<td>22 (33)</td>
<td></td>
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<td>3 (6)</td>
<td>1 (3)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Starting PSA median, IQR</strong></td>
<td>7.8 (0.9–81)</td>
<td>20 (1.9–87)</td>
<td>20 (2.6–93)</td>
<td>0.7378</td>
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<td><strong>Gleason Score (N, %)</strong></td>
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<tr>
<td>&lt;8</td>
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<td>5 (15)</td>
<td>10 (15)</td>
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<td><strong>Prior lines (N, %)</strong></td>
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<td>16 (47)</td>
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<td>14 (21)</td>
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<td>11 (32)</td>
<td>20 (30)</td>
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<td><strong>Treatment (N, %)</strong></td>
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<tr>
<td>Abiraterone</td>
<td>20 (39)</td>
<td>12 (35)</td>
<td>22 (33)</td>
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<tr>
<td>Enzalutamide</td>
<td>31 (61)</td>
<td>22 (65)</td>
<td>44 (67)</td>
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<td><strong>Treatment Duration (days)</strong></td>
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<td>Abiraterone</td>
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<td>185 (140–669)</td>
<td>231 (139–367)</td>
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<td>Enzalutamide</td>
<td>275 (162–636)</td>
<td>383 (179–631)</td>
<td>191 (116–494)</td>
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<td><strong>Model Fits (N, %)</strong></td>
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<td>PD1 All (N = 51)</td>
<td>PD1 Evaluable† (N = 34)</td>
<td>Reference Cohort (N = 66£)</td>
<td>p-value</td>
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<tr>
<td>gd</td>
<td>5 (10)</td>
<td>5 (15)</td>
<td>16 (24)</td>
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<td>gx</td>
<td>22 (43)</td>
<td>22 (65)</td>
<td>19 (29)</td>
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<tr>
<td>Not fit</td>
<td>4 (8)</td>
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</table>

*Matched on age +/- 10 years, race, starting PSA (<1, 1–50, >50), Gleason score (<8, >=8), number of prior lines, and treatment (ABI, ENZA)
†Those with calculable g values were considered evaluable
£Matches identified for all but 2 patients from the PD1 cohort

**Discussion**

We report on the effects of immune checkpoint inhibitors (ICI) on PSA levels in Veterans with prostate cancer (PC) using real-world data from the VA corporate data warehouse (CDW) via VINCI. We were able to identify Veterans with multiple concurrent cancers, which included PC. In this analysis, we 1) examined PSA responses while on ICI in Veterans with PC and 2) compared the efficacy of NHT + ICI combinations to that of matched cohort receiving NHT alone.

This analysis demonstrates the ability of the VHA database to address unique clinical questions, serve as a reference database and provide hypothesis-generating data. We successfully identified Veterans with PC and examined the PSA responses while on an ICI after identifying and eliminating known confounders. Interestingly, the PSA response of 8% noted in our study is similar to the 6% confirmed PSA response reported in the Keynote-199 study exploring pembrolizumab monotherapy in mCRPC. (5) For the NHT + ICI combination efficacy assessment, we identified two matches for all but two Veterans matched on five important variables to limit confounding in patient selection. The choices for matching were based on our previous analysis that found significant correlations with treatment efficacy for race, Gleason score, and prior lines of therapy but not for age, with the impact of starting PSA values not previously explored. (11) VA valuable source from which to construct cohorts for use as a reference exploratory analyses including clinical trials

We chose g-rates as an endpoint for the matched comparisons as g-rates serve as an excellent measure of the efficacy of PC therapy, given its robust inverse correlation with overall survival demonstrated using data from either clinical trials or the real-world *(Fig. 1)*. (10, 11, 14–16) Compared with conventional methods, estimates of g-rates are ideal for the analysis of real-world data given that all the underlying equations include time as a variable, allowing the use of PSA values obtained at differing time intervals rather than the stringent schedules required in clinical trials. This allows the inclusion of all patients as long as they have measurable PSA values during the period treatment is administered. Our study showed
no statistical difference in g-rate values when an ICI was added to a abiraterone or enzalutamide in Veterans with PC, indicating no improvement in the efficacy of the combination and predicting no gain in overall survival. These results closely resemble those from the IMbassador250 trial, in which the addition of atezolizumab to enzalutamide failed to improve overall survival when compared to enzalutamide alone (7); and those of Keynote-991, which was stopped at the interim analysis given pembrolizumab + enzalutamide + ADT did not improve overall survival or radiographic progression-free survival (rPFS), the trial's dual primary endpoints, when compared to enzalutamide + ADT in patients with metastatic hormone-sensitive PC. (19)

Our study has limitations common to observational registry-based studies, such as incorrectly entered diagnoses or data. To minimize this, we only included patients to whom medication was dispensed, not just prescribed, and also conducted additional in-depth chart reviews to ensure data accuracy. Given the study design, all patients have at least two cancers and can only provide g-rate estimates as a surrogate for overall survival prediction. Our large reference database has allowed us to match for known confounders but does not completely negate the effects of unknown confounders in the matched cohort. While smaller patient numbers and the study's observational nature can be only used for hypothesis generation, this provides an excellent example of the utilization of real-world data to provide important clinical insights.

In conclusion, we analyzed PSA responses in Veterans with PC receiving an ICI for another malignancy using real-world data from VA-CDW. We also assessed the efficacy of the combination of an ICI abiraterone or enzalutamide by comparing it to a matched reference cohort treated with abiraterone or enzalutamide alone using our novel g-rate method. We found no statistical difference in the efficacy of the combination, closely resembling clinical trial results. This demonstrates the robust ability of the reference database and the g-rate method to closely estimate important survival outcomes in veterans with PCa and its potential application as a reference/comparator for other treatments.

Declarations

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References


Figures
Figure 1

Deciles of $g$ compared to the overall survival (OS) establish $g$ as a robust biomarker of the OS. Kaplan-Meier plots of the log $g$ are shown for the Veterans in our reference database who had a calculable $g$-rate while receiving various medications – abiraterone, enzalutamide/apalutamide/darolutamide, docetaxel, cabazitaxel or olaparib/rucaparib – for metastatic prostate cancer. The first decile (red curve) consists of the Veterans with the slowest $g$-rates and the last decile (pink curve) consists of Veterans with the fastest.
Figure 2
Flow diagram for ICI monotherapy evaluation

ICI: Immune checkpoint inhibitor; PARP: poly(adenosine diphosphate-ribose) polymerase; LHRH: luteinizing hormone-releasing hormone; TKI: tyrosine kinase inhibitor

*There were no Veterans who underwent surgery for PC within 2 years of initiating an ICI
Figure 3

Distribution of $g$-rates in the current PD1 cohort, which includes Veterans who received abiraterone or enzalutamide (NHT) plus an ICI (n=34) and the matched reference cohort receiving abiraterone or enzalutamide alone (n=66). The combination therapy of a NHT plus an ICI did not have slower $g$-rates compared to NHT alone (0.0017 vs 0.0016 p=0.58), predicting no survival benefit of the combination therapy.