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A novel approach to assess real-world efficacy of cancer therapy in metastatic prostate cancer. Analysis of national data on Veterans treated with abiraterone and enzalutamide

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ABSTRACT

Background: With 1.3 million new cases in 2018 worldwide, prostate cancer remains a challenge. Development of novel therapies targeting the androgen pathway followed recognition of the continued importance of androgens in castrate-resistant prostate cancer. To assess abiraterone and enzalutamide efficacy we analyzed data from US Veterans Administration Medical Centers (VAMCs).
Methods: We used a novel method independent of assessment intervals and ideal for real-world analysis to estimate ***rates*** of tumor growth (***g***) and regression (***d***).
Findings: Using the VA Informatics and Computing Infrastructure, we collected data from 5,116 Veterans with castrate-resistant prostate cancer prescribed abiraterone, enzalutamide or both. We estimated values for ***g*** and ***d*** and demonstrated a correlation of ***g*** with overall survival ($P < .0001$). Abiraterone and enzalutamide slowed growth rates across age groups and across the entire VAMC system, although less so in Veterans previously treated with a taxane and those with Gleason grade group 5 tumors. Abiraterone and enzalutamide efficacy in first-line were comparable although abiraterone in first-line slowed growth rates significantly more in African Americans than in Caucasians; enzalutamide was a better salvage therapy. When abiraterone was first-line and ***g*** was low, switching to enzalutamide was associated with a faster ***g*** in 67%.
Interpretation: In the real-world ***g*** can be estimated using a novel analysis method indifferent to assessment intervals that correlates highly with OS. While we show excellent real-world outcomes with abiraterone and enzalutamide, 2 effective and tolerable therapies, our results in VAMCs suggest enzalutamide should follow abiraterone. Changing therapies may be detrimental and consideration should be given to continue monitoring of growth rates over time.
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Introduction

With 31,620 deaths projected in 2019 [1], prostate cancer (PC) is the second leading cause of cancer-related death in men in the United States. Worldwide in 2018, 1.3 million men had a new diagnosis of PC, with the 20 countries with the highest incidences evenly divided between developed and developing countries [2]. Although a majority of men initially benefit from androgen

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deprivation therapy, in most, progression to "castrate-resistant" prostate cancer (CRPC) occurs. Approvals of the androgen synthesis inhibitor abiraterone acetate and the selective androgen receptor inhibitors enzalutamide and apalutamide by the US food and Drug Administration and the European Medicines Agency (EMA) changed treatment options for metastatic CRPC (mCRPC) [3-8]. While level I evidence has demonstrated an overall survival (OS) benefit when these agents are used with androgen deprivation therapy [5,6], the choice of first-line treatment for mCRPC remains provider dependent. Challenges remaining include identification of patients more likely to benefit from abiraterone or enzalutamide and the optimal treatment sequence.

Considered the gold standard for clinical research and drug authorization, randomized controlled trials enrol carefully selected patients so as to clearly answer a narrowly framed research question with predetermined assessment intervals that must be strictly adhered to. While “fit for purpose”, their limited endpoint assessment intervals and often narrow eligibility criteria raises questions about the applicability of the study findings in the read-world setting where intervals of assessment vary greatly [9]. The US food and Drug Administration, the EMA, as well as heads of 3 national EU agencies, and academia, payer, and the Organization for Economic Co-operation and Development have recognized the potential of use of real-world evidence to complement randomized trials and have started building frameworks to implement judicial and methodical use of the real-world evidence [10,11].

We assessed treatment efficacy with an approach previously validated with clinical trial data [12-17] and now, with real-world data from Veterans Administration Medical Centers (VAMCs) with the oldest and largest repository of data. [19] Our goals using this real-world data were to demonstrate the potential value of the **rates** of tumor growth (**g**) as a metric of efficacy in the real-world while comparing the efficacy of abiraterone and enzalutamide in CRPC.

Methods

Patient cohort

We collected data from Veterans with a diagnosis of PC from the VA **C**orporate **D**ata **W**arehouse (**CDW**) using the **V**A **In**formatics and **C**omputing **I**nfrastructure (**VINCI**). Veterans with PC diagnosed between January 2001 and January 2015 were identified based on relevant ICD-9/ICD-10 codes shown as a highly sensitive method of case identification within these data. We then confirmed PC diagnosis using CDW oncology data from individual cancer registrars and searched the CDW pharmacy database to identify Veterans prescribed abiraterone, enzalutamide or both. During a systematic and exhaustive search of the CDW we identified more than 1500 different labels for PSA samples used in different VAMCs across the USA.

Outcome

Our primary outcome of interest was OS; cancer-specific mortality was not available. Death dates were collected from VA Vital Status files. We calculated survival times by determining differences between the (start date) and either death date or March 2018.

Covariates

We collected demographics (age, race, ethnicity, geography), serial PSA values, and Gleason grade group from CDW files. Use of abiraterone and/or enzalutamide and dates of administration were collected from VA pharmacy data.

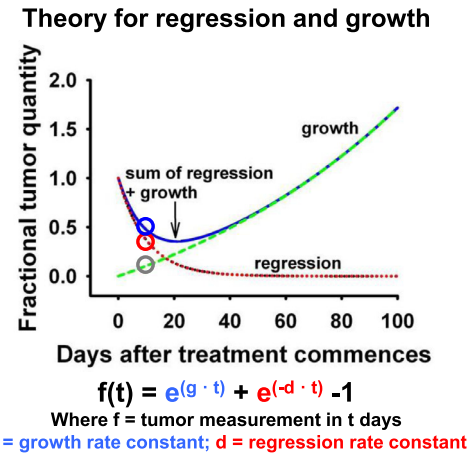

Fig. 1. Description of the theory. The blue line is observed in the clinic in the overwhelming majority of patients with a solid tumor. An initial regression of tumor, unfortunately followed by progression/growth. But it is actually a result of 2 simultaneous processes occurring in a tumor as a patient is treated: exponential regression of the sensitive fraction of the tumor, depicted by the red dotted line and exponential growth of the resistant or relatively resistant fraction of the tumor depicted by the green dotted line. The fraction that is regressing will not cause any long-term harm as it will die and never recur; while the growing fraction is responsible for the eventual death of the patient. Although this happens simultaneously one can mathematically estimate both a regression rate and a growth rate. Actually, we estimate a regression rate constant and a growth rate constant as these are constants that do not change. The regression rate represents the rate at which the sensitive fraction of the tumor disappears; the growth rates, the rate at which the resistant/relatively resistant fraction is growing. Importantly, even as total tumor quantity is falling these 2 processes are occurring simultaneously and one can estimate both rates, including the growth rate, although it appears to the clinician the tumor is continuing to respond. Indeed, even as the total tumor quantity falls, one can ascertain the rate of growth of the “as yet clinically undetected” gowning tumor. (Color version of figure is available online.)

Data analysis

The rates of tumor growth [***g***] and regression [***d***] were calculated using serial PSA values and the TUMGr package for R, that uses a novel set of equations validated in in >20,000 patients [12-18]. We have previously confirmed that data from most patients fit 1 of 4 equations below. The regression-growth models used assumes tumor quantity changes during therapy result from simultaneous exponential decay/regression, termed ***d***, and exponential growth/regrowth of the tumor, termed ***g*** (Fig. 1). This mathematical model is labeled ***gd***:

$$f(t) = \exp(-d * t) + \exp(g * t) - 1$$

Where *f(t)* is the tumor burden, quantitated as PSA level, at time t in days normalized to the PSA level at time $t = 0$; and ***g*** is the constant that defines the rate of growth.

In cases where data show a continuous decrease from the start of treatment, ***g*** is eliminated and the decay rate estimated using the ***dx*** equation:

$$f(t) = \exp(-d * t)$$

Patients whose data was best fit by the ***dx*** model, only had regression of the tumor. This meant their ***g*** was essentially zero but to be able to capture all such patients for calculation, we imputed a very low fixed value of 0.0001 for ***g*** in patients whose data was best fit by ***dx***.

Similarly, in cases where the data show continuous growth from the start of treatment, ***d*** is eliminated and the growth rate estimated using the ***gx*** equation:

$$f(t) = \exp(g * t)$$

Table 1
Summary of data for Veterans who received both abiraterone and enzalutamide or only one agent.

	Both agents N (%)	Abiraterone Only N (%)	Enzalutamide Only N (%)
Total	1344	3321	451
Caucasian	903 (67)	2308 (69)	302 (67)
African American	316 (24)	695 (21)	105 (23)
American Indian or Alaska native	1 (0)	21 (1)	1 (0)
Asian	3 (0)	13 (0)	1 (0)
Native Hawaiian	10 (1)	23 (1)	2 (0)
Null/unknown/declined to answer	112 (8)	280 (8)	40 (8)
Median age at start of medication (years)	73	78	77
Prior taxane	469 (35)	796 (24)	73 (16)
Abiraterone first	1279 (95)	N/A	N/A
Enzalutamide first	65 (5)		
Median PSA when 1st agent started	48.7	48.4	45.8
Median PSA when 2nd agent started	74.5	N/A	N/A
Median abiraterone use (days)	206	164	N/A
Median enzalutamide use (days)	96	N/A	92
Did not refill abiraterone [2]	66 (5)	433 (13)	N/A
Did not refill enzalutamide[2]	198 (15)	N/A	87 (19)
Did not refill either[2]	11 (1)	N/A	N/A
Total death in cohort	1278 (95)	2839 (85)	371 (82)
Median time to death after last refill (days)	214	216	276

A fourth model shown below and labeled ***gdØ*** contains an additional parameter, **Ø**, representing the proportion of tumor cells sensitive to a therapy. In this model, ***d*** represents the rate of regression or **d**ecay of the sensitive tumor fraction, **Ø**, while ***g*** describes the rate of growth of the fraction of tumor resistant to therapy (**1 – Ø**):

$$f(t) = \phi \exp(-d * t) + (1 - \phi) \exp(g * t) - 1$$

The tumgr package in R provides *P* values for fits to all 4 equations and selects the model best fitting the data for further analysis. In cases where all parameters were significant predictors of tumor quantity in more than one model with a specified cut-off *P* value of .10, the model selected is that which best minimizes the Akaike Information Criterion. Patient datasets with insufficient data (no or only one PSA value) were not analyzed and excluded. Datasets with sufficient data were analyzed and either included, with the selected model indicated, or were excluded if no model converged ('not fit') or if there were only 2 data points differing by <20%. Comparisons of the distribution of ***g*** based on specific therapy or other variables were made using nonparametric *t* tests, either 2-sided Mann-Whitney test (where groups analyzed = 2) or Kruskal-Wallis test (where groups analyzed >2) followed by a Dunn's test for pairwise difference where there was an overall difference for unmatched samples, or a Wilcoxon test for matched samples. The Kaplan-Meier method was used to estimate OS. Log-rank test and Gehan-Breslow-Wilcoxon tests were used to assess differences between Kaplan-Meier curves generated for estimation of OS. Landmark analyses of OS were done using landmarks of 4 and 6 months. The programs used for analysis were R studio (RStudio Team (2016), RStudio: Integrated Development for R. (RStudio, Inc., Boston, MA http://www.rstudio.com), GraphPad Prism version 7.0 for Mac (GraphPad Software, La Jolla California USA, www.graphpad.com) and JMP® version 14 (SAS institute Inc., Cary NC)

We identified start dates and harvested PSA values with collection dates to estimate ***g*** and ***d***. Unlike clinical trials that adhere to prespecified assessment intervals, "real world" assessments are performed at widely varying intervals. While the lack of common intervals would present a challenge to conventional efficacy assessments, the kinetic equations incorporate time as a variable rendering differences in assessment intervals inconsequential.

Results

Data were retrieved for 5,116 Veterans with a diagnosis of mCRPC prescribed either abiraterone, enzalutamide or both sequentially (Tables 1–3). Values for either ***g*** or ***d*** or both could be estimated in 81% (3,420 of 4,246) and 80% (1,210 of 1,519) of Veterans with 2 or more PSA values who received abiraterone and enzalutamide, respectively (Table 2). In the abiraterone cohort, the data was best fit by the ***gd*** (845, 16%), ***gx*** (1363, 25%), ***dx*** (813, 15%), or ***gdØ*** (399, 7%) models. For patients receiving enzalutamide, the data was best fit by the ***gd*** (334, 16%), ***gx*** (570, 27%), ***dx*** (222, 11%), or ***gdØ*** (84, 4%) models. We could not estimate ***g*** nor ***d*** values in 688 (13%) and 236 (11%) Veterans treated with abiraterone or enzalutamide, respectively, because their data did not fit any equation; and we did not attempt to estimate ***g*** nor ***d*** values in 138 (3%) and 73 (3%) receiving abiraterone and enzalutamide, respectively, for whom we had two PSA values with a difference of less than 20% (Table 2). In the latter, we did not estimate ***g*** or ***d***, recognizing small differences could be laboratory variations. This cutoff, defined prospectively before data inspection, has been constant in all our previous analyses, having been chosen based on RECIST cutoffs of 20% for stable disease. Table 3 summarizes the median values of ***g*** and ***d***. Examples of included cases are depicted in Fig. 2**A**. The fits of data for all Veterans are provided as **Supplemental PDFs**. As described in Methods, ***g*** and ***d*** were estimated only if the fit of the data had a *P* value <.1 although**,** *P* values for the overwhelming majority were <.01.

Central to our analyses is the observation that ***g*** is an excellent biomarker of OS, and hence a meaningful value. We demonstrate that in Fig. 2 showing the results examining data for all 3,595 Veterans who received either abiraterone or enzalutamide or both drugs. Quartiles of ***g*** compared to OS establish ***g*** as an excellent biomarker of OS. Kaplan-Meier plots of OS by quartile of the log ***g*** predictor are displayed. The quartile represented by the KM plot to the far right consists of those men whose tumors had the lowest ***g*** values; while the fourth quartile represented by the KM plot to the far left is comprised of those men whose tumors has the fastest ***g*** values. The second and third quartiles are intermediate. The entire data is used in the analysis in **2B**, with **2C** depicting results with the data landmarked at 4 months. The latter, used only PSA data obtained during the first 4 months of measurements and omits patients who died during these initial 4 months.

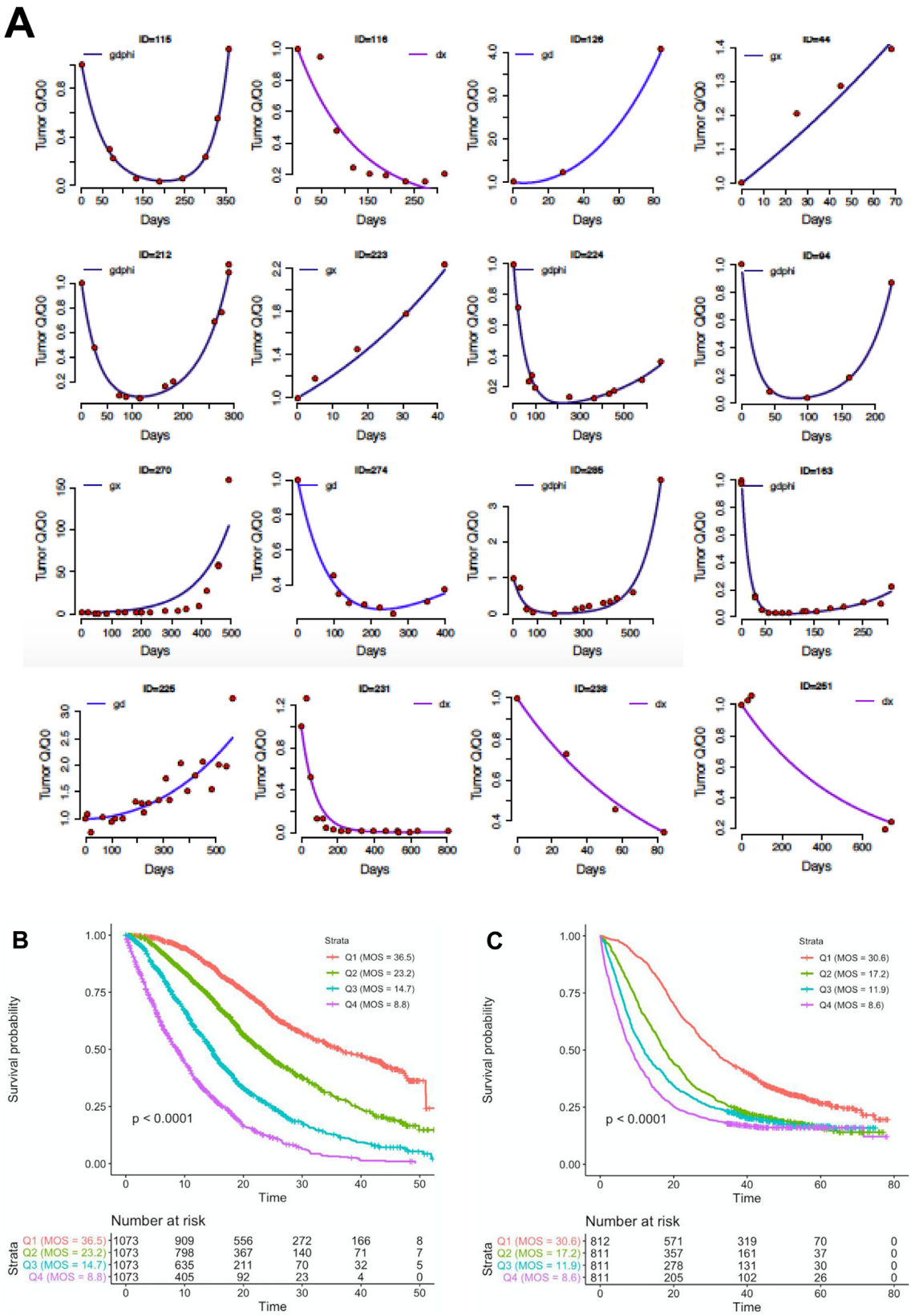

Fig. 2. [**A**] Examples of curve fits to the data. Note that the curves are not drawn to fit the data but rather *are described by the fixed rate constants for* ***g***, ***d*** *or both* that are estimated by an iterative process that assesses the fit of the data to each of the 4 basic equations. The fits of the data for 4630 Veterans are provided as **Supplementary PDFs**. [**B**] Quartiles of ***g*** compared to OS establish ***g*** as an excellent biomarker of OS. Kaplan-Meier plots of OS by quartile of the log ***g*** predictor are displayed for Veterans who received abiraterone, enzalutamide or both drugs. The first quartile [KM plot far right] consists of those men whose tumors had the lowest ***g*** values; while the fourth quartile [KM plot far left] is comprised of those men whose tumors has the fastest ***g*** values. The second and third quartiles are intermediate. The Kaplan-Meier method was used to describe OS. [**C**] The data was "landmarked" at 4 months and hence the numbers in the graph for the Veterans data will be less than the total analyzed in [**B**]. Log-rank test and Gehan-Breslow-Wilcoxon tests were used to assess differences between Kaplan-Meier curves generated for estimation of OS.

Table 2
Disposition of data.

Abiraterone				
Model [equation] fit	Analyzed	N (5,361)	Percent of all data	Percent of analyzed data
No PSA data in CDW (non-evaluable)	No	637	11.8	–
Erroneous values[a]	No	26	0.48	–
Only 1 value in CDW	No	452	8.43	–
2 values <20% difference[b]	No	138	2.57	–
Did not fit any model	Yes	688	12.83	16.74
dx	Yes	813	15.16	19.79
gd	Yes	845	15.76	20.56
gdphi	Yes	399	7.44	9.71
gx	Yes	1,363	25.42	33.17
Enzalutamide				
Model [equation] fit	Analyzed	N (2098)	Percent of all data	Percent of analyzed data
No PSA data in CDW (non-evaluable)	No	289	13.77	–
Erroneous values[a]	No	38	1.81	–
Only 1 value in CDW	No	252	12.01	–
2 values <20% difference[b]	No	73	3.47	–
Did not fit any model	Yes	236	11.24	16.32
dx	Yes	222	10.58	15.35
gd	Yes	334	15.91	23.09
gdphi	Yes	84	4.00	5.80
gx	Yes	570	27.16	39.41

[a] No units, units in % or units in % years.
[b] Where there were only 2 values <20% the data was not analyzed as it could not be certain this may have been an error in the measurement in the same way RECIST guidance scores as SD.

Table 3
Summary of *g* and *d* values.

	Median *g*	Median *d*		Median *g*	Median *d*
Abiraterone Acetate			Enzalutamide		
Full cohort	0.0025	0.014	Full cohort	0.0059	0.015
Treatment order					
Abiraterone only (full-combined)	0.0018	0.014	Enzalutamide only (full-combined)	0.0015	0.018
Abiraterone first	0.0032	0.014	Enzalutamide first	0.0030	0.014
Abiraterone second	0.0083	0.018	Enzalutamide second	0.0062	0.015
Patient Race					
Caucasian, full cohort	0.0026	0.014	Caucasian, full cohort	0.0056	0.015
African American, full cohort	0.0016	0.015	African American, full cohort	0.0047	0.018
Prior therapy					
Prior taxane, full cohort	0.0032	0.015	Prior taxane, full cohort	0.0063	0.015
No taxane, full cohort	0.0022	0.014	No taxane, full cohort	0.0050	0.015
Age					
<60 years	0.0031	0.013	<60 years	0.0066	0.019
60-69 years	0.0031	0.015	60-69 years	0.0061	0.014
70-79 years	0.0026	0.014	70-79 years	0.0061	0.016
80-89 years	0.0020	0.014	80-89 years	0.0043	0.015
>80 years	0.0020	0.014	>80 years	0.0042	0.015
>90 years	0.0022	0.012	>90 years	0.0038	0.021

A four-month landmark was chosen prospectively based on work with data from Project Data Sphere [17]. However, note that similar outcomes were observed using ***g*** values estimated with individual agents; and with data that was not landmarked or landmarked at 6 months. Such correlations are not seen with ***d*** (not shown).

In Fig 3**,** we compared ***d*** and ***g*** in the entire Veteran population receiving abiraterone and/or enzalutamide. Decay rates, ***d,*** were almost identical for abiraterone (***d*** = 0.0014/day) and enzalutamide (***d*** = 0.0015/day), and likely not biologically different, although statistically significantly different ($P = .003$), enzalutamide's effect on PSA synthesis likely exaggerates its impact on ***d***) (**3A**). Because both the current and prior analyses in PC demonstrated ***g*** correlates with survival and ***d*** does not [17], we focused the remaining analyses on ***g***. In contrast, to values of ***d***, median estimated ***g*** values for abiraterone (***g*** = 0.0025/day) were slower than for enzalutamide (***g*** = 0.0055/day) ($P < .0001$) (**not shown**). However, the data indicates that VAMC physicians usually begin with abiraterone, reflecting the general preference for an abiraterone-first strategy, and this could impact the analyses. Consequently, we re-analyzed the data (**3B**) considering the order of drug administration and compared ***g*** in Veterans receiving abiraterone first (***g*** = 0.0024/day) or enzalutamide first (***g*** = 0.0021/day) and found ***g*** indistinguishable ($P = .29$). However, in second line (**3C, 3D**), enzalutamide (***g*** = 0.0062/day) achieved a modestly slower growth rate ($P = 0.03$) than abiraterone (***g*** = 0.0083/day) as shown in both dot plots and the cumulative distribution plots. Furthermore, as shown in panels **3E/F**, both abiraterone and enzalutamide are more effective when administered as the first than as the second agent underscoring incremental loss of efficacy with successive lines of therapy.

To further support the hypothesis that incremental loss of efficacy reflects gradual emergence of more treatment-refractory disease we examined whether similar results could be demonstrated in Veterans who previously received a taxane for mCRPC. In Fig. 3**G/H** we compare ***g*** values on abiraterone and enzalutamide in Veterans who had or had not been previously treated with a

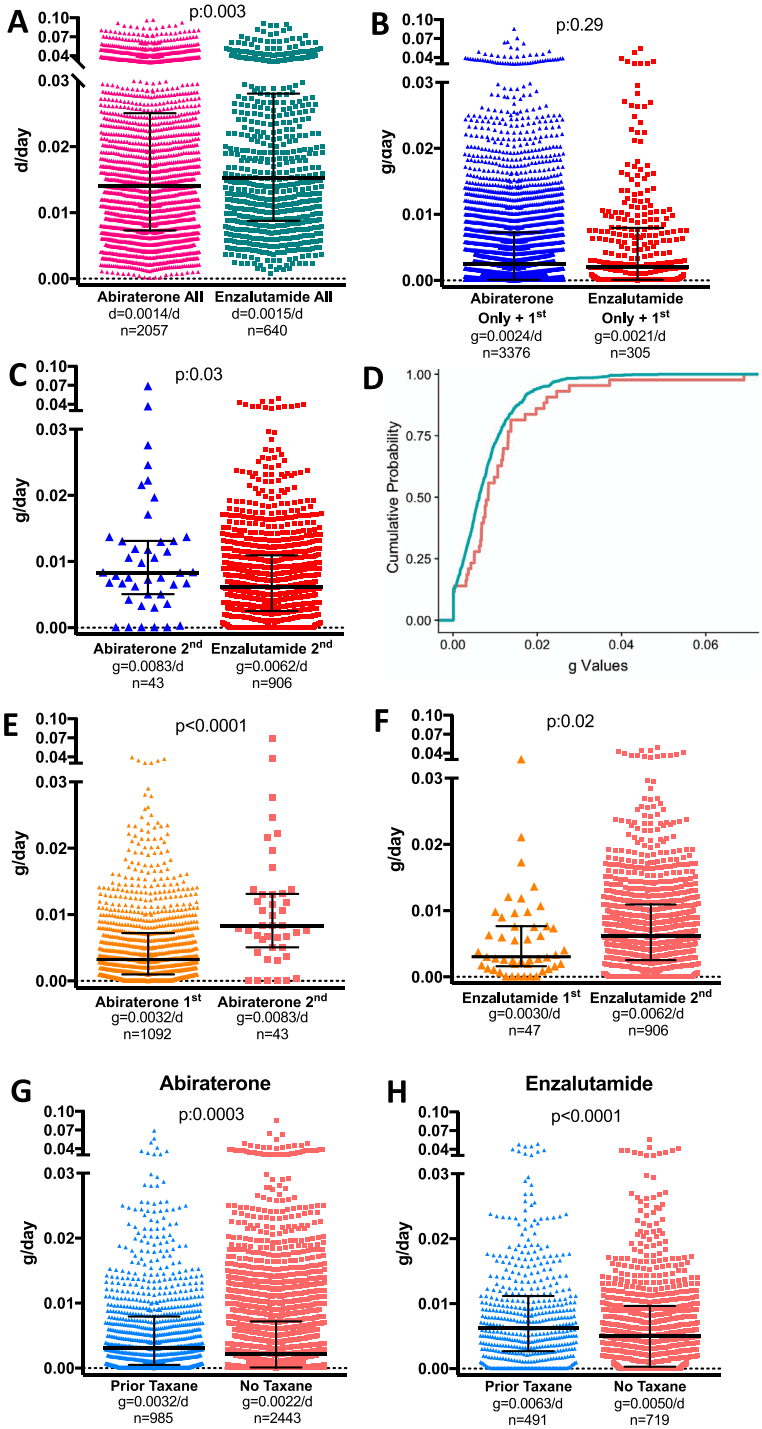

Fig. 3. Dot-plots comparing ***d*** and ***g*** values in all or in subsets of Veterans. [**A**] The rate of decay, ***d***, was slower [$P = .0031$] with abiraterone [$\boldsymbol{d} = 0.0014$/day] than with enzalutamide [$\boldsymbol{d} = 0.0015$/day]. Abiraterone, administered first in the majority of Veterans appears in an unclassified comparison superior to enzalutamide ($P < .0001$) as evidenced by a greater reduction in ***g*** with abiraterone ($\boldsymbol{g} = 0.0025$/day) than with enzalutamide ($\boldsymbol{g} = 0.0055$/day). [**B**] However, a comparison of abiraterone ($\boldsymbol{g} = 0.0024$/day) and enzalutamide ($\boldsymbol{g} = 0.0021$/day), when each was administered first shows comparable efficacy at reducing the rate of tumor growth ($P = .29$); [**C/D**] whereas enzalutamide is superior [$P = .02$] when the administration of abiraterone [$\boldsymbol{g} = 0.0083$/day] and enzalutamide [$\boldsymbol{g} = 0.0062$/day] second is compared; **2C** shows dot plot while **2D** shows the distribution plot. [**E/F**] Importantly, both abiraterone [**E,** $\boldsymbol{g} = 0.038$/day v $\boldsymbol{g} = 0.0091$/day; $P < .001$] and enzalutamide [**F**, $\boldsymbol{g} = 0.040$/day v $\boldsymbol{g} = 0.0071$/day; $P = .005$) were more effective when administered first versus second with greater slowing of ***g*** with each drug when administered first demonstrating each prior line of therapy diminishes the efficacy of an ensuing treatment. [**G/H**] Growth rates of tumors in Veterans who had received a prior taxane were faster while being treated with both abiraterone [**G**] ($\boldsymbol{g} = 0.0032$/day if had received prior taxane v $\boldsymbol{g} = 0.0022$/day for taxane naive, $P = .0003$) and enzalutamide [**H**] ($\boldsymbol{g} = 0.0063$/day if had received prior taxane v $\boldsymbol{g} = 0.0050$/day for taxane naive, $P < .0001$). Figures show median values and interquartile ranges. Comparisons of the distribution of ***g*** based were made using a 2-sided Mann-Whitney test followed by a Dunn's test for pairwise difference.

Note: Similar outcomes were observed when the analyses were confined to Veterans whose tumors were "taxane-naïve".

Note: Mann-Whitney test established that the difference in ***d***, while small, was nevertheless statistically significant. This conclusion was reinforced by a comparison that looked at those who received *only* either drug and not both – with rates of decay on enzalutamide ($\boldsymbol{d} = 0.0018$/day), again statistically faster ($P = 0.0012$) than on abiraterone ($\boldsymbol{d} = 0.0014$/day) (not shown). Extensive prior data and the results from this analysis have found a lack of correlation between ***g*** and ***d*** and no correlation between ***d*** and overall survival [not shown].

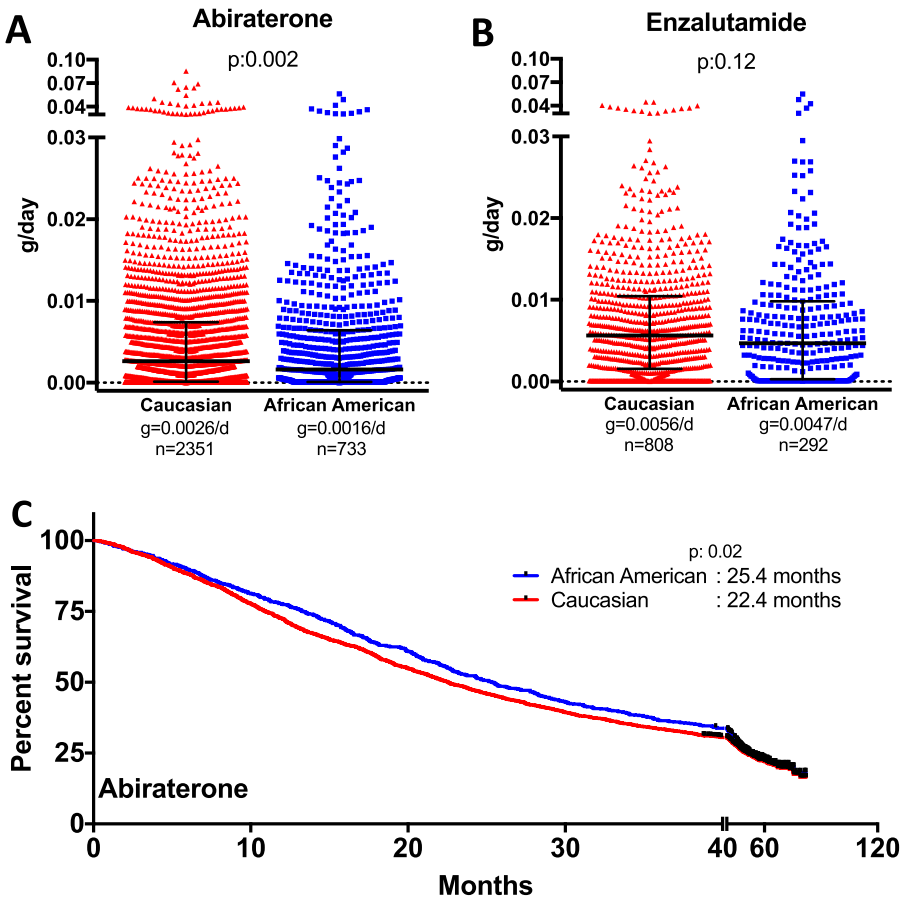

Fig. 4. **[A/B]** The distribution of ***g*** by treatment is displayed graphically in the upper panels for both abiraterone and enzalutamide. Abiraterone slowed ***g*** to a greater extent in African American compared to Caucasian Veterans whereas such a difference was not seen with enzalutamide. [**C**] Furthermore, the overall survival of African American Veterans treated only with abiraterone or with abiraterone followed by enzalutamide was superior compared with similarly managed Caucasian Veterans. Data analysis is as described in Figs. 1 and 2.

taxane. Amongst Veterans treated with abiraterone, 26% had previously received a taxane compared to 37% of enzalutamide recipients. For these Veterans, abiraterone was generally their second and enzalutamide their third line for mCRPC. As seen in **3G/H**, ***g*** was significantly faster in Veterans previously treated with a taxane than in those who were "taxane-naïve", for both abiraterone (***g*** = 0.0032/day v ***g***= 0.0022/day, $P = .0003$) and enzalutamide (***g*** = 0.0063/day v ***g*** = 0.0050/day, $P < .0001$), reflecting reduced abiraterone and enzalutamide efficacy in tumors previously treated with a taxane. Finally, survival from the start of either abiraterone or enzalutamide for Veterans previously treated with a taxane was shorter than for those who had not received a prior taxane (**not shown**).

The VHA is an egalitarian system with fewer socioeconomic forces affecting access to health care and outcomes. With data on 1100 African-American (AA) Veterans, this data represents an invaluable resource to assess the impact of race on the biology and responsiveness to therapy. Fig. 4. shows such a comparison. Most notably, as shown in **4A**, when assessing abiraterone efficacy, the median ***g*** in AA Veterans (***g*** = 0.0016/day) is seen to be 60% ($P = .002$) that of Caucasian Veterans (***g*** = 0.0026). The OS data depicted in **4C** further demonstrate the statistically superior survival ($P = .02$) of AA Veterans treated with abiraterone (only) or with abiraterone followed by enzalutamide (abiraterone first) compared with similarly managed Caucasian Veterans. These differences were unaffected by prior taxane exposure (not shown).

The Veteran population treated with abiraterone and/or enzalutamide included men under 60 to as old as 101 years. Fig. 5 compares growth rates across age groups, with ***g*** values comparable across all age groups for both abiraterone (**5A**) and enzalutamide (**5B**), although slightly slower in those over 80. In contrast, both abiraterone and enzalutamide were statistically inferior in Veterans whose tumors at diagnosis were Gleason grade group 5, compared to those with a grade group 1–4, with the latter 4 indistinguishable (**5C**). This is ratified by the Kaplan-Meier plots in **5D** showing inferior OS from start of therapy with either abiraterone or enzalutamide for patients with grade group 5 tumors. We also examined outcomes in different geographic locales. Comparable efficacy could be demonstrated for abiraterone (**5E**) and enzalutamide (**5F**) across 18 US regions, designated Veterans Integrated Service Networks .

Finally, we examined outcomes upon transitioning from one drug to the other. This is seen in Fig. 6, where ***g*** values while receiving abiraterone and enzalutamide are depicted for 766 Veterans who received both and in whom ***g*** values could be calculated while they received each drug. The median PSA when abiraterone treatment began was ~50, and was ~75 when abiraterone was discontinued, suggesting a transition when a threshold close to 1.5X the start of treatment value is reached. However, the consequences of such a transition were not uniformly favorable. In a majority of Veterans, *especially those with slower* ***g*** *values on abiraterone*, ***g*** increased after the change to enzalutamide and sometimes markedly so. An average 4.3-fold increase in ***g*** was observed in 515 Veterans, a 67% majority, from a median ***g*** = 0.0019/day to ***g*** = 0.0081/day. In contrast, a reduction in ***g*** occurred in 251 (33%) Veterans, notably those with a faster ***g*** on abiraterone – a median

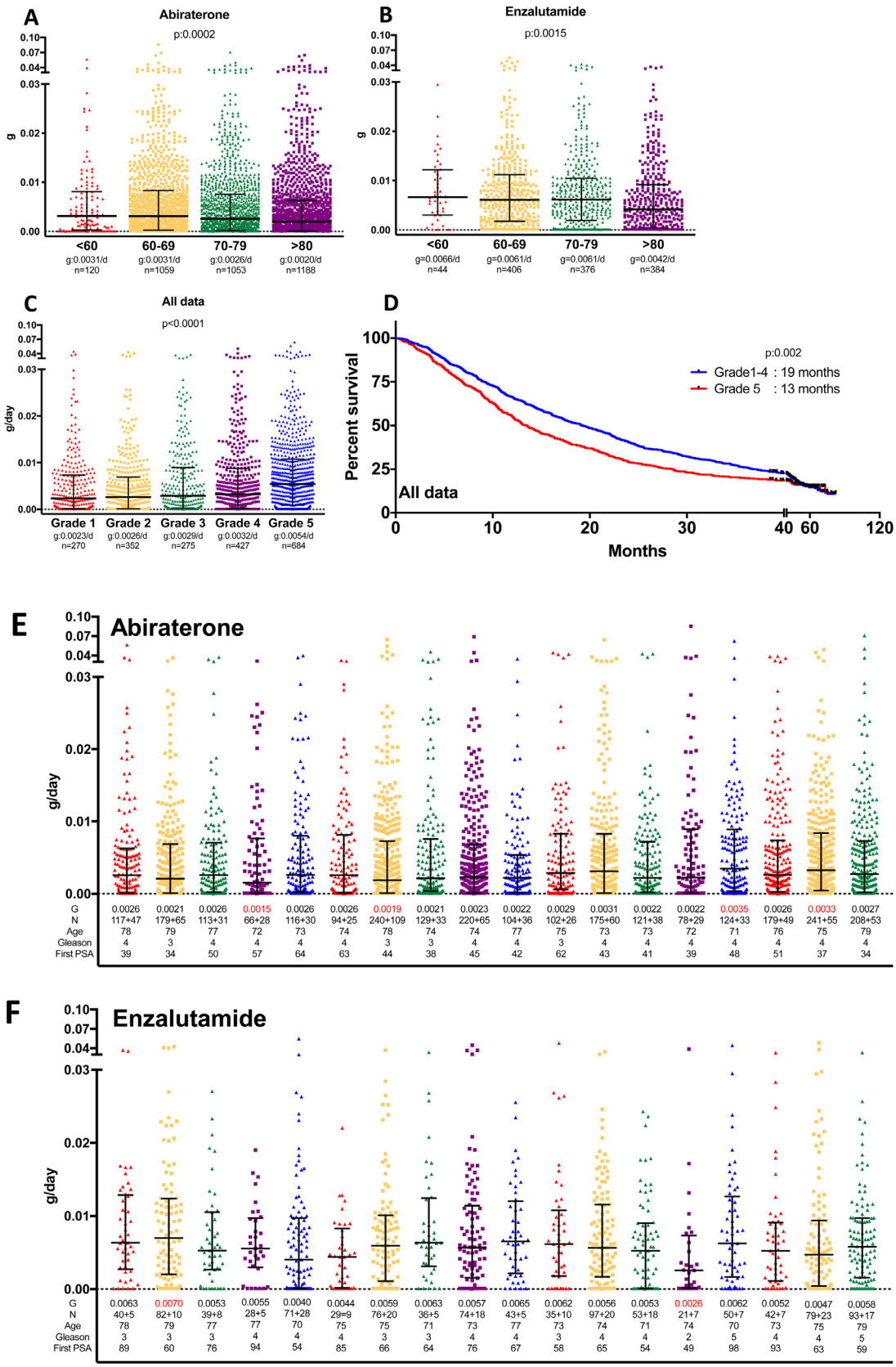

Fig. 5. [**A/B**] Comparison of abiraterone [**A**] and enzalutamide [**B**] efficacy across age groups. Outcomes were nearly comparable across all age groups; better outcomes in those over 80, possibly reflect the often more indolent biology of PC in older patients. [**C**] Efficacy of abiraterone and enzalutamide administered first or only according to Gleason grade group. ***g*** values for tumors with Gleason grade group 5 were faster than for tumors with grade groups 1–4, with the latter indistinguishable (not shown). [**D**] Kaplan-Meier plots comparing OS from the start of either abiraterone or enzalutamide as a function of Gleason grade groups. [**E/F**] Dot plots demonstrating comparable efficacy for abiraterone and enzalutamide across VA regions. No region was superior or inferior in terms of treatment efficacy. Data analysis as in Figs. **3 and 4**. Comparisons of the distribution of ***g*** based on abiraterone across the VA regions relied on Kruskal-Wallis test.

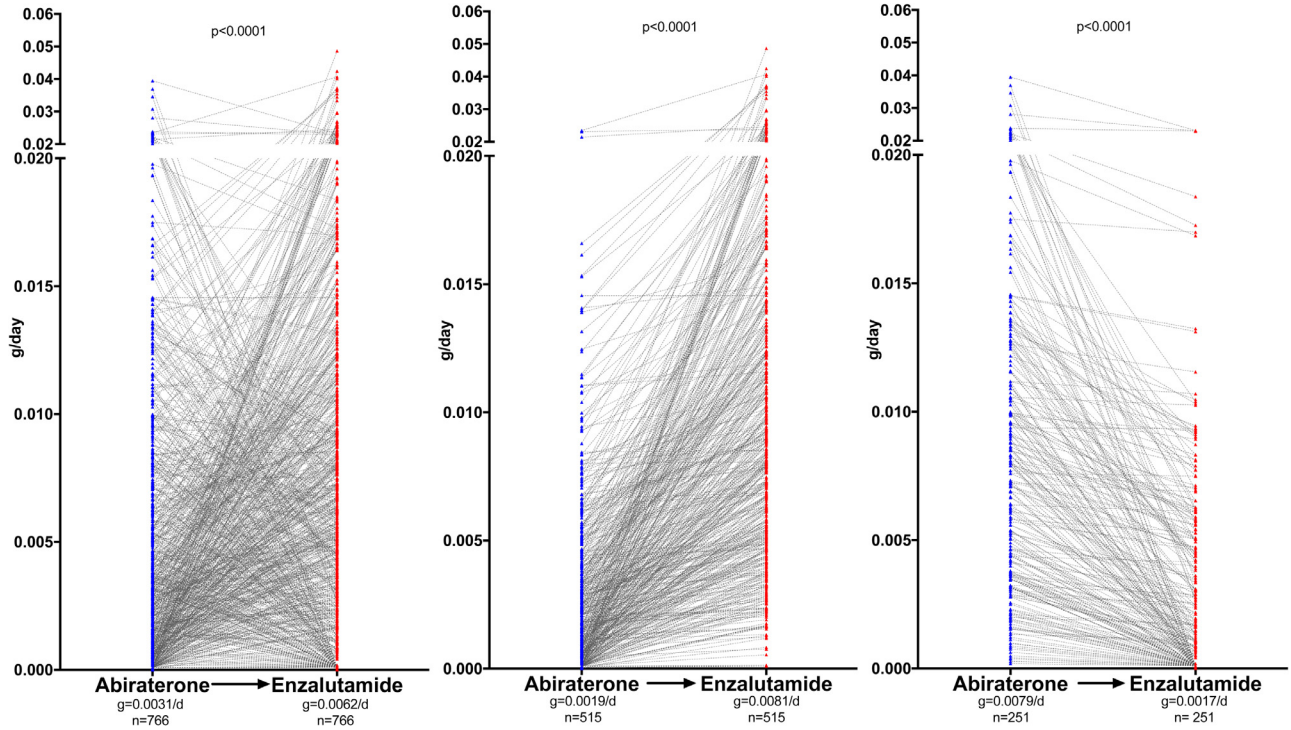

Fig. 6. Summary of ***g*** values on abiraterone and after transitioning to enzalutamide. The panel on the left is a composite that shows what happened with the 766 Veterans who received both therapies (abiraterone first), with enzalutamide treatment commencing within 3 months of discontinuing abiraterone and in whom the rates of tumor growth could be calculated while they received each drug. One can see more upward than downward trajectories. The middle and left panels show the trajectories of the 515 and 251 Veterans whose tumors either had an increase (4.3-fold) or a decrease (4.2-fold) in median ***g*** values, respectively, as they transitioned from abiraterone to enzalutamide. Middle panel median ***g*** values of 0.0019/day to 0.0081/day; right panel median ***g*** values 0.0079/day to 0.0018/day.

4.2-fold decrease in ***g*** on enzalutamide, after abiraterone – from a median $g = 0.0079$/day to $g = 0.0017$/day.

Discussion

Using real-world PSA data from 5,116 US military Veterans cared for at VAMCs across the US, we have estimated the rates of growth of PC in men treated with abiraterone, enzalutamide or both sequentially. Unlike PSA doubling time and PSA velocity, metrics used when only growth is occurring, our method of analysis estimates rates of growth (***g***) even as treatment leads to initial regression, and total tumor quantity falls [12-18]. As previously shown with clinical trial data [17] and extended in the current manuscript, ***g*** is an excellent biomarker for OS, despite death often occurring many years after PSA values were obtained and therapy discontinued. Additionally, in this real-world analysis with drugs shown effective and tolerable in clinical trials, we find uniform results in VAMCs across the US, and across age groups. Our results ratify the method of analysis described here as ideal for the real-world where, unlike clinical trials, timing of efficacy assessments often varies greatly. With time as one variable in all equations, the timing of assessment is rendered inconsequential, a highly desirable attribute in real-world efficacy analyses.

We previously validated the tumor kinetic equations utilized in this study in >3000 patients with PC treated on clinical trials, and reported ***g*** as a biomarker for OS using ***only*** PSA data obtained while patients receive therapy [17]. In the present study, we extend the results and again demonstrate ***g*** is an ideal biomarker of OS in a real-world setting. That a ***g*** value estimated from PSA data collected while patients receive drug serves as a biomarker for OS years later during which time other therapies were likely given, strongly suggests ***g*** is influenced by *both* inherent tumor biology and sensitivity/resistance to the drug administered. Note that ***g*** values obtained while these men received abiraterone as the first of both drugs predicts OS even though many subsequently received enzalutamide. Thus, these findings offer an approach for estimating an efficacy metric that is an excellent biomarker for OS in both clinical trials and the real-world.

We first compared ***g*** values on abiraterone with those on enzalutamide and found abiraterone more effective (not shown). However, because 95% of Veterans received abiraterone first, the higher ***g*** values with enzalutamide reflected its use second, confirmed by demonstrating ***g*** values on enzalutamide given first comparable to abiraterone first. This comparison was possible because the small enzalutamide dataset was benchmarked against the large abiraterone dataset. We also compared both agents used second, this time benchmarking the smaller abiraterone second dataset against the larger enzalutamide second dataset, and found enzalutamide administered second modestly superior to abiraterone second. This ratifies prevailing thought amongst PC specialists, who think enzalutamide a better salvage therapy [20-22].

Having this large dataset as reference now allows anyone to benchmark smaller datasets, and examine *any combination* with abiraterone or enzalutamide and read out efficacy with statistical confidence in a small number of patients, recognizing that the growth rate on treatment is influenced by the biology of the tumors as well as the drug's efficacy. Additionally, it can help inform efficacy in groups of patients, including those not normally enrolled in clinical trials. African American (AA) Veterans receiving abiraterone had a distribution of ***g*** values 1/3 less than Caucasian Veterans. Because no patient selection factor accounting for this is apparent, it supports the hypothesis that the tumors of AA men are more sensitive to abiraterone than those of Caucasian men. This observation using data from more than 1,100 AAs, is the first time efficacy of any therapy for PC has been assessed in such a large number of AAs, individuals under-represented in

clinical trials. The importance of the 3 month difference in overall survival for AA over Caucasian Veterans when using an abiraterone first strategy becomes apparent when considering that the overall survival for FDA approved cancer therapeutics in the last decade was only about 2 months.

The results underscore the immense value and importance of assessing treatment efficacy across the spectrum of real-world patients and across a health care system. While we found uniformity of care across the VAMC system, similar analyses could find differences and identify deficiencies in need of attention. Finally, we also found efficacy maintained across age groups with exception of slightly slower ***g*** values in the 80 and older age group, possibly reflecting more indolent biology. This gratifying result likely is a testament to the tolerability of both abiraterone and enzalutamide. Indeed, we found comparable OS for Veterans treated in VAMCs to that reported in the abiraterone registration trial for those who received prior chemotherapy [2] – median OS 17 and 15.8 months respectively – and similar ***g*** values (not shown).

What happened when abiraterone was discontinued and enzalutamide used as salvage therapy is important. A small fraction of men with faster ***g*** values on abiraterone had slower ***g*** values on enzalutamide suggesting their tumor's reduced sensitivity to abiraterone did not translate into reduced sensitivity to enzalutamide and benefit was achieved by switching. However, a large fraction of men whose tumors had low ***g*** values on abiraterone experienced a concerning increase in ***g*** values when switched to enzalutamide. The data do not indicate tumor growth ***rates*** were accelerating prior to the switch, an observation of stability we have made previously in other cancers [23]. Instead the data suggests a "personal physician threshold" was reached – PSA values ~1.5X higher than starting values – and the physician decided abiraterone was no longer bringing benefit requiring a change. But the present data argue that men whose tumors have very low, stable ***g*** values, should be considered for continuation of therapy with serial monitoring of ***g*** values for maximal benefit.

Although not a "prospective analysis" this study represents an example of a "prospective-retrospective" analysis [24] and satisfies all criteria for validity including (1) data on majority of subjects; (2) a valid test (ie, serum PSA); (3) an analytical method completely developed before its use; and (4) results validated in at least one or more similar data sets [12-17]. We acknowledge misclassification in Gleason score may have occurred and the limitation that the Gleason score in nearly all cases was determined at diagnosis. However, as the US FDA has noted, "real-world evidence can inform … patient care … and provide information on how factors such as clinical setting and provider and health-system characteristics influence treatment effects and outcomes, yielding answers relevant to broader populations of patients than would be possible in a specialized research environment" [9]. We believe that with this analysis we have moved beyond aspiration to reality by critically assessing and establishing the value of the methodology employed in a real-world setting.

In summary, in the real-world that is the VAMCs we have successfully estimated ***g*** values for abiraterone and enzalutamide and demonstrated ***g*** as an excellent biomarker of OS. We have successfully used this method of analysis with serial radiographic measurements, and also with CA19-9 in pancreatic cancer, serum chromogranin in neuroendocrine tumors, M-protein in multiple myeloma, calcitonin in medullary thyroid cancer, and circulating tumor DNA in CML and believe *the use of this metric in other settings should now be explored*. Beyond the value of our method as an assessment tool in the real-world, our observation that a majority of men fared worse when abiraterone was changed to enzalutamide highlight the possibility of using serial measurements of a tumor's growth rate to guide treatment decisions, a real-world example of "precision medicine" that leverages the individual patient's data to achieve maximum benefit and hopefully prolong survival. Finally, the results ratify the prevailing consensus that an abiraterone-first strategy is optimal. Unfortunately, as industry trials have moved this class of agents forward with new offerings [8,25-28], and the lack of patent protection has disincentivized abiraterone's upfront development, an abiraterone-first strategy is disappearing. This is evidenced in the US by the recommendations of guidelines such as those of the NCCN [29]. We would argue this is a serious error and that discarding an abiraterone-first strategy ignores a wealth of data to the detriment of patients with PC. Plans are underway to confirm the value of abiraterone as the first therapy in a trial to be conducted in VAMCs.

Conflicts of interest

The authors have no conflicts to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminoncol.2019.11.004.

References

[1] Siegel RL, Miller KD, Jemal A, et al. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[2] https://www.wcrf.org/dietandcancer/cancer-trends/prostate-cancer-statistics [last accessed 07JUL2019] .
[3] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[4] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48 Erratum in: N Engl J Med 2013; 368:584.
[5] Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152–60.
[6] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[7] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
[8] Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408–18.
[9] Sherman RE, Davies KM, Robb MA, Hunter NL, Califf RM. Accelerating development of scientific evidence for medical products within the existing US regulatory framework. Nat Rev Drug Discov 2017;16:297–8.
[10] Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, et al. Real-world evidence - what is it and what can it tell us? N Engl J Med. 2016;375:2293–7.
[11] Eichler HG, Bloechl-Daum B, Broich K, Kyrle PA, Oderkirk J, et al. Data rich, information poor: can we use electronic health records to create a learning healthcare system for pharmaceuticals? Clin Pharmacol Ther. 2019;105:912–22.
[12] Stein WD, Figg WD, Dahut W, et al. Tumor growth rates derived from data for patients in a clinical trial correlate strongly with patient survival: a novel strategy for evaluation of clinical trial data. Oncologist 2008;13:1046–54.
[13] Stein WD, Yang J, Bates SE, Fojo T, et al. Bevacizumab reduces the growth rate constants of renal carcinomas: a novel algorithm suggests early discontinuation of bevacizumab resulted in a lack of survival advantage. Oncologist 2008;13:1055–62.
[14] Stein WD, Huang H, Menefee M, et al. Other paradigms: growth rate constants and tumor burden determined using computed tomography data correlate strongly with the overall survival of patients with renal cell carcinoma. Cancer J 2009;15:441–7.

[15] Stein WD, Gulley JL, Schlom J, et al. Tumor regression and growth rates determined in five intramural NCI prostate cancer trials: the growth rate constant as an indicator of therapeutic efficacy. Clin Cancer Res 2011;17:907–17.
[16] Stein WD, Wilkerson J, Kim ST, et al. Analyzing the pivotal trial that compared sunitinib and IFN-alpha in renal cell carcinoma, using a method that assesses tumor regression and growth. Clin Cancer Res 2012;18:2374–81.
[17] Wilkerson J, Abdallah K, Hugh-Jones C, et al. Estimation of tumor regression and growth rates during treatment in patients with advanced prostate cancer: a retrospective analysis. Lancet Oncol 2017;18:143–54.
[18] Wilkerson J. (2015). tumgr: Tumor Growth Rate Analysis. R package version 0.0.3. http://CRAN.R-project.org/package=tumgr [last accessed 07JUL2019].
[19] https://www.ehrm.va.gov/about/history [last accessed 07JUL2019].
[20] Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807–12.
[21] Attard G, Borre M, Gurney H, et al. PLATO collaborators. abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. J Clin Oncol 2018;36:2639–46.
[22] de Bono JS, Chowdhury S, Feyerabend S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥24 weeks in Europe. Eur Urol 2018;74:37–45.
[23] Burotto M, Wilkerson J, Stein W, Motzer R, Bates S, Fojo T, et al. Continuing a cancer treatment despite tumor growth may be valuable: sunitinib in renal cell carcinoma as example. PLoS One 2014;9(5):e96316 Erratum in: PLoS One. 2014;9:e105179.
[24] Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 2009;101:1446–52.
[25] Smith MR, Saad F, Chowdhury S, et al. SPARTAN investigators. Apalutamide Treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408–18.
[26] Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2018;378:2465–74.
[27] Fizazi K, Tran N, Fein L, et al. LATITUDE investigators. abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377:352–60.
[28] James ND, de Bono JS, Spears MR, et al. STAMPEDE investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.
[29] https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf [last accessed 07JUL2019].