Comparative Effectiveness of Immune Checkpoint Inhibitors vs Chemotherapy by Tumor Mutational Burden in Metastatic Castration-Resistant Prostate Cancer

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Abstract

**IMPORTANCE** The most useful biomarkers for clinical decision-making identify patients likely to have improved outcomes with one treatment vs another.

**OBJECTIVE** To evaluate treatment class-specific outcomes of patients receiving immune checkpoint inhibitor (ICI) vs taxane chemotherapy by tumor mutational burden (TMB).

**DESIGN, SETTING, AND PARTICIPANTS** This comparative effectiveness analysis of clinical variables and outcomes used prospectively defined biomarker-stratified genomic data from a deidentified clinicogenomic database. Data included men with previously treated metastatic castration-resistant prostate cancer (mCRPC) receiving ICI or single-agent taxane chemotherapy from January 2011 to April 2021 at approximately 280 US academic or community-based cancer clinics (approximately 800 sites of care). Data were analyzed from July to August 2021.

**EXPOSURES** Single-agent ICI or single-agent taxanes. Treatments were assigned at discretion of physician and patient without randomization. Imbalances of known factors between treatment groups were adjusted with propensity weighting.

**MAIN OUTCOMES AND MEASURES** Prostate-specific antigen (PSA) response, time to next therapy (TTNT), and overall survival (OS).

**RESULTS** A total of 741 men (median [IQR], 70 [64-76] years) with mCRPC received comprehensive genomic profiling and were treated with ICI or single-agent taxane therapy. At baseline, the median (IQR) PSA level was 79.4 (19.0-254) ng/mL, 108 men (18.8%) had Eastern Cooperative Oncology Group Performance Status scores of 2 or greater, and 644 men (86.9%) had received prior systemic treatments for mCRPC. A total of 45 patients (6.1%) received ICI therapy and 696 patients (93.9%) received taxane therapy. Among patients with TMB of fewer than 10 mutations per megabase (mt/Mb) receiving ICI, compared with those receiving taxanes, had worse TTNT (median [IQR], 2.4 [1.1-3.2] months vs 4.1 [2.2-6.3] months; hazard ratio [HR], 2.65; 95% CI, 1.78-3.95; P < .001). In contrast, for patients with TMB of 10 mt/Mb or greater, use of ICIs, compared with use taxanes, was associated with more favorable TTNT (median [IQR], 8.0 [3.4 to unknown] months vs 2.4 [2.4-7.3] months; HR, 0.37; 95% CI, 0.15-0.87; P = .02) and OS (median 19.9 [8.0-6 to unknown] months vs 4.2 [2.69 – 6.12] months; HR, 0.23; 95% CI, 0.10-0.57; P = .001). Among all 741 patients, 44 (5.9%) had TMB of 10 mt/Mb or greater, 22 (3.0%) had high microsatellite instability, and 20 (2.7%) had both. Treatment interactions with TMB of 10 mt/Mb or greater (TTNT: HR, 0.10; 95% CI, 0.32-0.31; P < .001; OS: HR, 0.25; 95% CI, 0.076-0.81; P = .02) were stronger than high microsatellite instability alone (TTNT: HR, 0.12; 95% CI, 0.03-0.51; P = .004; OS: HR, 0.38; 95% CI, 0.13-1.12; P = .08).

Key Points

**Question** What is the comparative effectiveness of single-agent immune checkpoint inhibitors (ICIs) vs taxane chemotherapy in populations of patients with metastatic castration-resistant prostate cancer (mCRPC) defined by levels of tumor mutational burden (TMB)?

**Findings** In this comparative effectiveness study of 741 patients with mCRPC, patients with TMB of 10 mutations per megabase (mt/Mb) or greater had significantly longer time to next treatment and overall survival with ICIs vs taxanes.

**Meaning** These findings suggest that in scenarios where taxane use is considered, ICIs are a viable alternate treatment option for patients with mCRPC and TMB of 10 mt/Mb or greater.

(continued)
CONCLUSIONS AND RELEVANCE In this comparative effectiveness study, ICIs were more effective than taxanes in patients with mCRPC when TMB was 10 mt/Mb or greater but not when TMB was fewer than 10 mt/Mb. The results add validity to the existing TMB cutoff of 10 mt/Mb for ICI use in later lines of therapy, and suggest that ICIs may be a viable alternative to taxane chemotherapy for patients with mCRPC with high TMB.

Introduction

Immune checkpoint inhibitors (ICI) can enable deep responses and durable benefit in some patients with metastatic cancer who have received many prior treatments. However, the rate of clinical benefit differs considerably by tumor type. Unfortunately, for patients with metastatic castration-resistant prostate cancer (mCRPC) the objective response rate for ICI treatments has been reported as 3% for patients with tumors without programmed cell death ligand 1 (PD-L1) expression and 5% for those with PD-L1-expressing tumors. For this reason, interest has developed in other biomarkers that might identify patients with mCRPC likely to receive greater clinical benefit from ICIs than alternate treatments. Pembrolizumab, an anti-programmed cell death 1 (PD1) drug, has received pantumor US Food and Drug Administration (FDA) approvals for patients with clinically advanced solid tumors who have progressed after prior treatment, have no satisfactory alternative treatment options, and have tumors with high microsatellite instability (MSI-H) (ie, mismatch repair deficient) and patients with high tumor mutational burden (TMB) of at least 10 mutations per megabase (mt/Mb). These approvals were significantly influenced by the KEYNOTE-016 and KEYNOTE-158 studies. KEYNOTE-016 enrolled only 2 patients with prostate cancer with MSI-H, observing stable disease and a partial response. KEYNOTE-158 observed objective responses in 30 of 102 patients in the group with TMB of 10 mt/Mb or greater and 43 patients of 688 patients in the group with TMB of fewer than 10 mt/Mb. While this included a wide range of tumor types, there were no patients with prostate cancer in the TMB of 10 mt/Mb or greater group.

To our knowledge, the largest single study to date evaluating outcomes among patients with MSI-H or mismatch repair deficient mCRPC receiving anti-PD-1 or anti-PD-L1 therapy reported declines of prostate-specific antigen (PSA) levels of 50% or more in 6 of 11 patients in a retrospective single-center study. Evaluating outcomes on a combination of ipilimumab plus nivolumab, a recent evaluation of the CheckMate-650 study reported an objective response rate of 19 of 33 patients (58%) with TMB of 10 mt/Mb or greater. Recently published supplemental data submitted to the FDA outside of KEYNOTE-158 supporting the pantumor TMB label (using a whole exome sequencing assay with high TMB calibrated to the existing companion diagnostic assay) reported prostate cancer objective responses in 1 of 11 patients (9%) in the high TMB and 7 of 115 patients (6%) in the low TMB group. Notably, patients with mCRPC frequently have diffuse bone-predominant metastatic deposits, making many patients ineligible for objective response assessments. Owing to this caveat, the KEYNOTE-199 trial included a cohort of patients with bone-predominant disease, and a trend for superior PFS and OS was observed in this cohort compared with those assessable for both response evaluation criteria in solid tumors and PD-L1.

While response rates are valuable surrogate outcomes for assessing efficacy, treatment decisions are always made in the context of an alternate path, such as drug A vs drug B. In the case of mCRPC, the alternative to ICI for most contexts of use is taxane chemotherapy (often as a rechallenge with limited clinical benefit) or palliative care. To our knowledge, there are no studies, prospective or retrospective, comparing outcomes of ICI vs an alternate drug class in mCRPC using established statistical criteria or evaluating overall survival (OS). In this study, we sought to compare clinical outcomes of patients receiving ICIs vs taxane chemotherapy in cohorts of patients with
mCRPC with comparable characteristics and prior treatments and adjusted for known imbalances in treatment assignment and prognostic factors.

Methods

This comparative effectiveness study was approved by the Western Institutional Review Board, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization. This study followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) reporting guideline.

Study Design and Patient Selection

The study cohort included patients with confirmed diagnosis of mCRPC included in the US-wide Flatiron Health and Foundation Medicine deidentified clinicogenic database between January 2011 and April 2021 who underwent genomic testing using Foundation Medicine comprehensive genomic profiling (CGP) assays.

The deidentified data originated from approximately 280 US cancer clinics (approximately 800 sites of care). Retrospective longitudinal clinical data were derived from electronic health record data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction of clinical notes and radiology or pathology reports, and were linked to CGP data by deidentified, deterministic matching. Clinical data included demographics, clinical features, therapy exposure (with start and stop dates for each therapy line), and survival.

The clinicogenic database contains multiple lines of therapy (LOT) per patient. Patients were included in this study if they received a single-agent anti–PD-1 axis therapy or single-agent taxane in the mCRPC setting and had TMB assessed via tissue biopsy. Some patients received a taxane and ICI on separate LOT; for these, the ICI LOT was chosen owing to less common ICI use. Some patients had more than 1 line of taxane given; for these patients, the latter-most taxane LOT was chosen to help mimic the FDA label for pembrolizumab and restrict to patient populations that may be more homogeneous in their baseline characteristics, reducing potential bias in estimates. The patient selection flowchart is presented in Figure 1.

Comprehensive Genomic Profiling

The FoundationOne or FoundationOne CDx hybrid capture-based next-generation sequencing assays were performed on patient tumor biopsies in a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited laboratory (Foundation Medicine). Samples were evaluated for alterations as previously described. TMB was determined on up to 1.1 Mb of sequenced DNA. MSI was determined on 95 to 114 loci, as previously described.

PSA Response Assessment

A LOT was eligible for PSA response assessment if a PSA result was available within 60 days prior to LOT, and a separate PSA result was available 1 to 180 days after. If multiple results were available, respective values most proximal to treatment initiation, and 12 weeks of receiving treatment were used. PSA response was calculated as \( \frac{(receiving \ treatment \ PSA - baseline \ PSA)}{\text{baseline PSA} + 0.01} \)

Statistical Analysis

An a priori statistical analysis plan was developed and executed. The inclusion criteria, exclusion criteria, potential biases, primary outcome measures, exploratory outcome measures, handling of missing data, and all statistical methods were specified prior to analysis execution. The prespecified analysis compared the effectiveness of ICI vs taxane chemotherapy in patients stratified by TMB of fewer than 10 mt/Mb and TMB of 10 mt/Mb or greater by evaluating PSA response, time to next therapy (TTNT), and OS in concert. Stratification by MSI status was included as an exploratory
analysis. Stratification by additional biomarkers was not prespecified. The statistical analysis plan also outlined a case-crossover analysis that was deemed not feasible owing to small sample size. We used χ² tests and Wilcoxon rank sum tests to assess differences between cohorts of categorical and continuous variables, respectively. Missing values were imputed with the expected values based on observed covariates using random forests with R statistical software version 3.6.3 (R Project for Statistical Computing) package missForest, with imputed values treated identically to measured values in subsequent analysis. TTNT was calculated from start of treatment to start of next treatment, or last clinic visit if they had not yet reached next treatment. Patients were right-censored if they had not yet reached next treatment or died. OS was calculated from start of treatment to death from any cause, and patients with no record of mortality were right censored at the date of last clinic visit. Electronic health record OS data derivation has been previously described. Differences in time-to-event outcomes were assessed with the log-rank test and Cox proportional hazard models. Multiple comparison adjustments were not performed. P values are reported to quantify the strength of association for biomarker and each respective outcome, not for null hypothesis significance testing. Two-sided tests were used throughout. Results were interpreted considering all outcome measures collectively (PSA response, TTNT, and OS) rather than outcome measures standing on their own.

Propensity analyses are frequently used in observational data-heavy fields, such as epidemiology, economics, and the social sciences, as a best practice to adjust for subgroup imbalances. Propensity scores made use of the full matching technique (R package MatchIt) without caliper restrictions, resulting in no patient exclusions but taxane treatments receiving

Figure 1. Patient Recruitment Flowchart

CGP indicates comprehensive genomic profiling; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ICI, immune checkpoint inhibitor; LOT, lines of therapy; mCRPC, metastatic castration-resistant prostate cancer; NHT, novel hormonal therapy; PD-1, programmed cell death 1; PSA, prostate-specific antigen; TMB, tumor mutational burden; and TTNT, time to next treatment.
weights. Among patients receiving taxanes, those with characteristics most similar to the patients receiving ICIs were weighted more, and those less like the patients receiving ICIs weighted less. These weights were included in all Kaplan-Meier visualizations and Cox proportional hazard models. The features included for adjustment in the propensity model were age at time of treatment initiation, pretherapy PSA level, hemoglobin, alkaline phosphatase, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, TMB, mCRPC treatment line, prior novel hormonal therapy (NHT; yes vs no), and prior taxane (yes vs no). Full matching made use of a generalized linear model, and weights were truncated at 10 equivalents to limit influence per observation. Standardized mean difference (SMD) was used to assess balance, and within 10% was considered acceptable.15

Owing to focus on the 10 mt/Mb TMB threshold, propensity weights were created separately for the group with TMB of 10 mt/Mb or greater and the group with TMB of fewer than 10 mt/Mb for best possible within-group balance. For analyses evaluating MSI-H vs microsatellite stable (MSS), propensity weights were similarly created separately per group.

Propensity weighting
Despite favorable overall cohort balance prior to propensity weighting, 6 of 9 features had greater than 10% SMD. After weighting, only TMB had greater than 10% SMD, with patients receiving ICI having higher values (eFigure 1 in the Supplement). The main source of this remaining imbalance was the subgroup with TMB of 10 mt/Mb or greater, as the subgroup with TMB of 10 mt/Mb or fewer had less of an imbalance (eFigure 1 in the Supplement). The subgroup with TMB of 10 mt/Mb or greater additionally had residual imbalance of higher ECOG PS scores for the ICI group. TMB was not significantly associated with TTNT or OS among patients receiving taxane chemotherapy (eFigure 2 in the Supplement).

Results
After LOT selection, the cohort include 741 treatment exposures from 741 unique patients (median [IQR] age, 70 [64-76] years) (Figure 1 and Table), with baseline median (IQR) pretreatment PSA levels of 79.4 (19.0-254) ng/mL (to convert to micrograms per liter, multiply by 1.0). A total of 108 patients (18.8%) had tumors with ECOG PS scores of 2 or greater and 644 patients (86.9%) had received prior systemic treatments for mCRPC. A total of 45 patients (6.1%) received ICIs, and 741 patients (93.9%) received taxanes. There were no significant differences between patients who received ICIs vs those who received taxanes in age, pretherapy PSA levels, ECOG PS score, practice setting (community vs academic), prior NHT use, prior prescribed opioid use, and biopsy site. However, patients receiving ICIs, compared with those receiving taxane, had higher TMB (median [IQR], 3.5 [1.7-15.0] mt/Mb vs 2.5 [1.3-3.8] mt/Mb; P < .001).

PSA response was evaluable in 607 patients (81.9%) (Figure 1). The most common reason for unevaluable PSA response was lack of baseline PSA value (eTable 1 in the Supplement). For 14 patients with TMB of 10 mt/Mb or greater who received ICI, only 9 had evaluable PSA responses. Of these, 4 patients had PSA declines of greater than 50% from baseline. Of 31 patients with TMB of 10 mt/Mb or fewer who received an ICI, 24 were evaluable for PSA responses, and none had PSA declines of greater than 50% from baseline (Figure 2A). For patients receiving taxanes, TMB level was not associated with PSA response (Figure 2B).
Outcomes by Therapy Class and TMB of 10 mt/Mb or Greater

The propensity-adjusted TTNT and OS by drug class was stratified by whether patients had TMB of fewer than 10 mt/Mb or 10 mt/Mb or greater, the FDA-approved cutoff indicated on the pantumor label of pembrolizumab. Patients with TMB of fewer than 10 mt/Mb receiving ICIs, compared with those receiving taxanes, had worse TTNT (median [IQR], 2.4 [1.1-3.2] months vs 4.1 [2.2-6.3] months; HR, 2.65, 95% CI, 1.78-3.85; \( P < .001 \)), while the trend was reversed for patients with TMB of 10 mt/Mb or greater, with observed improved TTNT (median [IQR], 8.0 [3.4 to unknown] months vs 2.4 [2.43-7.33] months; HR, 0.37; 95% CI, 0.15-0.87; \( P = .02 \)) (Figure 3). There was no significant difference between patients with TMB of fewer than 10 mt/Mb receiving ICIs vs those receiving taxanes in OS (median [IQR], 4.2 [2.1-8.1] months vs 6.0 [3.1-9.7] months; HR, 1.08; 95% CI, 0.68-1.74; \( P = .73 \)), but for patients with TMB of 10 mt/Mb or greater, those receiving ICIs had better OS (median [IQR], 19.9 [8.1 to unknown] months vs 4.2 [2.69-6.12] months; HR, 0.23, 95% CI, 0.10-0.57; \( P = .001 \)).

Table. Patient Characteristics by Line of Treatment Among Patients with Metastatic Castration-Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>P value</th>
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<tr>
<td></td>
<td>ICI (n = 45)</td>
<td>Taxane (n = 696)</td>
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<tr>
<td>Age, median (IQR), y</td>
<td>72.0 (64.0-76.0)</td>
<td>70.0 (64.0-76.0)</td>
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<tr>
<td>TMB, median (IQR), mt/Mb</td>
<td>3.5 (1.7-15.0)</td>
<td>2.5 (1.3-3.8)</td>
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<td>ECOG PS*</td>
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<tr>
<td>0</td>
<td>5 (13.9)</td>
<td>158 (29.4)</td>
</tr>
<tr>
<td>1</td>
<td>20 (55.6)</td>
<td>283 (52.6)</td>
</tr>
<tr>
<td>≥2</td>
<td>11 (30.6)</td>
<td>97 (18.0)</td>
</tr>
<tr>
<td>PSA, median (IQR), ng/mL</td>
<td>63.9 (10.8-183.2)</td>
<td>80.8 (19.4-256.1)</td>
</tr>
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<td>Hemoglobin, median (IQR), g/dL</td>
<td>10.8 (9.5-11.9)</td>
<td>11.2 (9.8-12.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase, median (IQR), IU/L</td>
<td>91.0 (77.0-145.0)</td>
<td>110.0 (77.0-186.0)</td>
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<td>Treatment line</td>
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<tr>
<td>First</td>
<td>5 (11.1)</td>
<td>92 (13.2)</td>
</tr>
<tr>
<td>Second</td>
<td>5 (11.1)</td>
<td>167 (24.0)</td>
</tr>
<tr>
<td>Third</td>
<td>9 (20.0)</td>
<td>167 (24.0)</td>
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<td>Prior opioid use</td>
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<tr>
<td>Atezolizumab</td>
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Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; mt/Mb, mutations per megabase; NHT, novel hormonal therapy; PSA, prostate-specific antigen; TMB, tumor mutational burden.

SI conversion factor: To convert alkaline phosphatase to microkatal per liter, multiply by 0.0167; hemoglobin to grams per liter, multiply by 10; prostate-specific antigen to micrograms per liter, multiply by 1.

* Among 574 patients with data.
Treatment interactions with TMB were observed for both TTNT (HR, 0.10; 95% CI, 0.03-0.31; \( P < .001 \)) and OS (HR, 0.25; 95% CI, 0.08-0.81; \( P = .02 \)). As a sensitivity analysis, TTNT and OS analyses were additionally conducted without propensity adjustments, with similar results observed (eFigure 3 in the Supplement). As an additional sensitivity analysis, the prognoses of patients with tumors having TMB of less than 10 mt/Mb or TMB of 10 mt/Mb or greater and receiving ICI or taxanes were compared (eFigure 4 in the Supplement), with TMB being highly prognostic of TTNT and OS for patients receiving ICI but not taxanes, unadjusted and adjusted for potential confounding factors, such as ECOG PS score, PSA level, and prior treatments (eTable 2 in the Supplement).

**TMB, MSI, and Treatment Interactions**

The association between TMB and MSI was additionally explored. Of all 741 patients, 2 (<1%) had MSI-H and TMB of fewer than 10 mt/Mb, 20 (2.7%) had MSI-H and TMB of 10 mt/Mb or greater, 24 (3.2%) had MSS and TMB of 10 mt/Mb or greater, 601 (81%) had MSS and TMB of fewer than 10 mt/Mb, and 94 (12.7%) had TMB of fewer than 10 mt/Mb and had unknown or indeterminate microsatellite status (eTable 4 in the Supplement). Comparing outcomes of ICI vs taxanes in the MSI-H group, those receiving ICI had more favorable TTNT (HR, 0.38; 95% CI, 0.15-0.94; \( P = .04 \)) (Figure 4A), but there was no significant difference in OS (HR, 0.44; 95% CI, 0.15-1.27; \( P = .13 \)) (Figure 4B). Patients with TMB of 10 mt/Mb or greater receiving ICI had better OS and TTNT (Figure 3B, 3D, Figure 4A, 4B; eFigure 5 and eFigure 6 in the Supplement) with weaker treatment interactions (Figure 4A, 4B).

However, only 15 total patients had TMB of 10 mt/Mb or greater and/or MSI-H and received ICI (Figure 4C; eTable 5 in the Supplement). The only patient with MSI-H and TMB of fewer than 10 mt/Mb who received an ICI had a PSA increase of 210%, TTNT of 4.8 months, and OS of 5.1 months.

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**Figure 2. Prostate-Specific Antigen (PSA) Response by Drug Class**

**A** Single-agent anti–PD-1 axis therapy

Waterfall plots indicate the relative change in PSA from baseline to approximately 12 weeks of therapy for patients receiving (A) single-agent anti-programmed cell death 1 (PD-1) axis therapies and (B) single-agent taxanes. A total of 134 patients did not have evaluable PSA response, and are not represented in these plots, including 5 patients with tumor mutational burden (TMB) of 10 mutations per megabase (mt/Mb) who received single-agent anti–PD-1 axis therapy. Patients with more than 100% PSA gain are capped at 100.
Of 3 patients in the TMB of 10 mt/Mb or greater but MSS subgroup, 1 had a PSA increase of 20% and was still receiving an ICI after 1.3 months, 1 was unevaluable for PSA response and had TTNT of 4.1 months and OS of 8.1 months, and 1 had a PSA reduction of 78% and had not initiated a new treatment nor died at 13.1 months after treatment initiation at time of data lock.

While the etiology of TMB levels was not a focus of this study, among 24 patients who had TMB of 10 mt/Mb or greater without MSI-H, 10 had a deleterious alteration in a known MMR gene and 14 did not (eTable 6 in the Supplement). While the FDA label for TMB is not dependent upon the etiology of TMB levels, we included subgroup analyses of patients with MSS and TMB of 10 mt/Mb or greater with respect to TTNT and OS (eTable 7 in the Supplement). Because there were 3 patients in this group receiving ICIs, and only 1 patient had a TTNT or OS event, the point estimates for TTNT (HR, 0.44; 95% CI, 0.04-4.67) and OS (HR, 0.50; 95% CI, 0.10-2.65), while numerically consistent with the broader TMB of 10 mt/Mb or greater subgroup, must be interpreted in the context of these caveats.

Discussion

This comparative effectiveness study evaluating a cohort of patients treated with ICIs or taxanes found improved TTNT and OS in patients with high TMB treated with ICIs vs taxanes. Treatment

Figure 3. Time to Next Treatment (TTNT) and Overall Survival (OS) by Therapy Class

Overall survival estimates are left truncated with at-risk tables adjusted accordingly. Numerical summary and treatment interaction tests can be found in eTable 3 in the Supplement. HR indicates hazard ratio; mt/Mb, mutations per megabase; PD-1, programmed cell death 1; TMB, tumor mutational burden.
decisions are always dependent on multiple courses of action. The most useful biomarkers are those that can identify patients who are anticipated to have differing outcomes on different viable treatment paths, such as 2 different FDA-approved drugs.

In practice, the decision to use ICI vs taxanes will also weigh nonbiomarker considerations, such as patient frailty, cost, and tolerability. While there exists no head-to-head comparison of adverse events (AEs) of ICIs vs taxanes, both the KEYNOTE-199 and CARD studies were conducted in the post-NHT, postdocetaxel mCRPC setting. KEYNOTE-199 reported AEs for pembrolizumab in 60% of patients, with 15% having grade 3 to 5 AEs.1 The cabazitaxel group of the CARD study reported AEs in 98% of patients, with 56% of patients experiencing grade 3 to 5 AEs.16

When a treatment is working well for a patient, their TTNT will be prolonged. However, a potential source of bias for TTNT assessments is when 1 regimen has more AEs than the other; patients with very poor benefit might need additional time to recover after their treatment discontinuation from a less tolerable regimen. For these reasons, TTNT values for taxanes relative to ICIs taken at face value might result in an inflated evaluation of taxane benefit relative to ICIs.

Within the subgroup of patients with TMB of 10 mt/Mb or greater, there were residual imbalances after weighting indicating higher TMB and higher ECOG PS scores for the patients receiving ICIs. While higher TMB was not associated with poorer survival in patients receiving taxanes in this study or across non-ICI treatments in many cancer types,17 poor performance status is a negative prognostic marker in mCRPC.18 The residual known imbalances in the subgroup with TMB of 10 mt/Mb or greater would potentially result in a relative penalty toward ICI outcomes relative to taxanes in this subgroup, even after adjustment.

Figure 4. Time to Next Treatment (TTNT) and Overall Survival (OS) by Therapy Class, Tumor Mutational Burden (TMB), and Microsatellite Instability (MSI) Status

(A) TTNT and (B) OS is shown by biomarker. (C) Graphical matrix focusing on intersection of TMB of 10 mutations per megabase (mt/Mb) or greater and high microsatellite instability (MSI-H) for patients receiving an immune checkpoint inhibitor (ICI). Numerical values for panels A and B can be found in eTable 3 in the Supplement. Breakdown of all patients by treatment, TMB, and MSI can be found in eTable 4 in the Supplement. Additional patient characteristics of patients in panel C can be found in eTable 5 in the Supplement. MSS indicates microsatellite stable.
Patients in clinical settings often differ from those enrolled in the randomized clinical trials. We evaluated the outcomes of ICIs vs taxanes in a heavily pretreated cohort, in which 79.2% of patients had received prior NHT and 54.9% of patients had received prior taxanes. Among those treated with taxanes, only few had PSA declines of 50% or greater, and less than half had any PSA decline. This context of use calls into question the true utility of systemic cytotoxic therapy in this setting. Comparisons of ICIs vs taxanes in this setting could be influenced by clinical practices particular to this context for use, and care must be taken for extrapolation of our results outside of this context. However, given this context, and carefully considering biases and imbalances, our results are consistent with the hypothesis that ICIs are a superior option to taxanes for patients with TMB of 10 mt/Mb or greater. Whether an ICI might be a superior option to other treatment modalities, such as second generation NHTs, for patients with TMB of 10 mt/Mb or greater in earlier LOT remains unevaluated. In our cohort, most patients with TMB of 10 mt/Mb or greater who received ICIs also had MSI-H. Among 3 patients with TMB of 10 mt/Mb or greater MSS in this group, 2 had greater than median TTNT for patients with TMB of 10 mt/Mb or greater receiving taxanes, and the third had only 1.3 months of follow-up without a treatment switch, making interpretations challenging.

While to our knowledge, our study is the most rigorous analysis to date comparing ICI and taxane effectiveness in biomarker groups consistent with FDA labels, prospective randomized evaluation would add precision and granularity to comparative efficacy estimates for ICIs vs taxanes for patients with high TMB, potentially stratified by MSI status, MMR gene alterations, and, in earlier lines of therapy.

The evaluation of TMB is dependent on sequencing breadth, depth, and characteristics of bioinformatic germline filtering, on top of the degree of platform analytical validity and demonstrated rigor and robustness of measurement. For these reasons, the clinical validity (associations with patient outcomes, such as in the American Society of Clinical Oncology and College of American Pathologists guideline) cannot be assumed to transfer from platform to platform. It is very important that the biomarker platform evaluated for outcome associations be the one used in practice to guide therapy. A strength of the study is the use of the platform supporting the only existing FDA-approved TMB companion diagnostic.

Rigorous genomics-centered comparative effectiveness studies of standard of care patient populations are likely to become increasingly important in the coming years, as the systemic treatment landscape for many cancer types will continue to diversify. Considering mCRPC as an example, recent FDA approvals have resulted in Poly (ADP-ribose) polymerase inhibitors and ICIs being added alongside the existing standard of care therapies of NHT and taxane chemotherapy. In the near future, anti–prostate-specific membrane antigen radionuclides are likely to be approved, while other treatment modalities, such as AKT inhibitors and androgen receptor degraders, show promise. It will not be possible for control groups of future registrational trials to rigorously assess all alternatives in a diversified landscape. The use of clinical data, especially linked to biomarkers, can help fill knowledge gaps to aid in decision-making in a wide variety of clinical scenarios.

**Limitations**

This study has some limitations. This is not a randomized clinical trial. Treatment assignments were at the discretion of the clinician, and while biases were carefully considered and known imbalances adjusted, unknown imbalances likely remain. The number of patients with mCRPC receiving ICI was relatively small. Patients were not restricted by timing of biopsy (archival vs contemporaneous) and higher TMB is more common in contemporaneous biopsies. Additionally, 40.9% of the cohort specimens were from prostate anatomical origin, and it is possible that there may exist false negatives with respect to TMB threshold assessments.
Conclusions

The findings of this comparative effectiveness study add validity to the existing FDA-approved TMB cutoff of 10 mt/Mb. These results suggest that ICI may be a viable alternative to taxane chemotherapy in later lines of therapy for patients with mCRPC with high TMB.

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