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Real-World Cabazitaxel Use and Outcomes in Metastatic Castrate-Resistant Prostate Cancer: The Impact of Response to First ARPI

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Keywords: CARD, Prostate, Sequencing, ARAT, Chemotherapy

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Abstract

In metastatic prostate cancer, optimal sequence of therapies is uncertain. We retrospectively analyzed the treatments and responses of 592 such patients, finding poor response to a first androgen receptor pathway inhibitor helped identify those who appear to derive more benefit from cabazitaxel chemotherapy. Clinicians underutilized cabazitaxel over the study period. These real-world results can support clinician therapeutic decision making.

Background: For post-docetaxel treatment of metastatic castrate-resistant prostate cancer (mCRPC), cabazitaxel has demonstrated superior third line PFS and OS compared to androgen receptor pathway inhibitors (ARPIs) in patients who progress within 12 months on first ARPI. The impact of first ARPI response, in particular responses beyond 12 months, on cabazitaxel outcomes in real-world populations is uncertain, as are other factors impacting cabazitaxel use. **Materials and Methods:** mCRPC patients in Alberta, Canada who received docetaxel from October 1, 2012 to December 31, 2017 were included. We reviewed mCRPC therapies, correlating cabazitaxel use with patient characteristics and TROPIC trial inclusion/exclusion criteria. OS and PFS were evaluated in patients who received cabazitaxel, stratified by time to progression on first ARPI $\leq$ 12 months (poor ARPI responders, PAR) or $>$12 months (strong ARPI responders, SAR), using the Kaplan-Meier method. **Results:** PAR patients had inferior OS compared to SAR patients (12.3 vs. 24.8 months, $P < .001$). OS was longer in PAR patients receiving cabazitaxel compared to those not treated with cabazitaxel (16.9 vs. 10.3 months, $P = .015$), but this benefit was not seen in the SAR group (17.1 vs. 32 months, $P = .084$). Cabazitaxel use was associated with reduced PFS first line post-docetaxel in SAR (3.5 vs. 14.7 months, $P < .001$) but not PAR patients. Of 592 patients, 170 (29%) received cabazitaxel post-docetaxel, compared to 280 (47%) and 250 (42%) for abiraterone and enzalutamide. 238 patients (40%) did not have a discussion of cabazitaxel documented. Cabazitaxel use was increased in patients who fit TROPIC trial criteria ($P < .001$). **Conclusions:** In a real-world mCRPC cohort, cabazitaxel use was associated with longer OS among PAR patients, but crucially not among strong ARPI responders. Cabazitaxel was used less frequently and later than ARPIs post-docetaxel. These data help support first ARPI progression time as a consideration in treatment sequencing.

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Abbreviations: ARPI, Androgen Receptor Pathway Inhibitor; PAR, Poor ARPI Responders less than or equal to 12 months; SAR, Strong ARPI Responders greater than 12 months.

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Introduction

The management of metastatic castrate-resistant prostate cancer (mCRPC) continues to evolve. Since 2010, six new systemic therapies have joined docetaxel in demonstrating improved overall survival (OS).[1-10] The androgen receptor pathway inhibitors (ARPIs) abiraterone and enzalutamide have proven benefit in the pre-docetaxel setting.[1-3] Post-docetaxel, in addition to both ARPIs, the second-generation taxane cabazitaxel demonstrated OS improvement in the TROPIC trial.[4-7] Other treatments have shown benefit in specific subtypes of mCRPC, including Radium-223 in patients with bone-only disease, olaparib in patients with DNA-damage repair defects, and lutetium-177-PSMA-617 in PSMA-positive patients.[8,10,11] The optimal sequence of these therapies is unknown, as direct comparisons have been limited.[12]

Anecdotally, post-docetaxel treatment sequencing in the context of prior ARPI exposure has been largely driven by perceptions of the tolerability and convenience of an alternative ARPI, compared to intravenous chemotherapy.[13] However, therapy sequencing can significantly impact treatment effectiveness due to overlapping resistance mechanisms.[14-19] In 2019, the CARD trial evaluated the use of third-line cabazitaxel in a more highly selected subgroup of mCRPC patients who had progressed on first ARPI within 12 months[14] and were hypothesized to be more resistant to a second ARPI.[14,20,21] There was clear benefit, both in progression-free survival (PFS) and OS, in those who received cabazitaxel over an alternate ARPI. These data are supported by prior studies suggesting cabazitaxel retains activity in patients who progressed on ARPIs[21] and may be more efficacious than ARPIs in those with poor-prognosis disease.[22] However, the overall ability of first ARPI response, in particular strong response, to predict cabazitaxel efficacy in clinical populations remains relatively unexplored.

The impact of systemic treatments may differ in real-world populations.[23] Most patients do not receive all life-prolonging therapies, due to factors such as disease progression, clinical ineligibility, funding and accessibility concerns, and patient preference.[24] Despite the evidence from CARD, there may be additional barriers to the optimal use of cabazitaxel in practice.

In this study, we examined post-docetaxel mCRPC treatments, with a focus on cabazitaxel, in a publicly funded health care system prior to the publication of the CARD trial. We first aimed to compare real-world cabazitaxel outcomes between patients based on response to first ARPI. Second, we evaluated mCRPC treatment sequencing, examining disease and patient factors correlating with cabazitaxel selection to identify barriers to optimal utilization.

Materials and Methods

Study cohort

Our study was a retrospective, population-based evaluation of patients with mCRPC who had received docetaxel, and were therefore potentially eligible for cabazitaxel, in the province of Alberta, Canada. Alberta has a publicly funded, universally accessible health care system. Docetaxel, enzalutamide, abiraterone, and cabazitaxel were publicly funded throughout the study period; lutetium-177-PSMA-617 and olaparib were not available during the study timeframe. Radium-223 was only accessible via clinical trial and was never publicly funded in Alberta. Cabazitaxel starting dose was 20 mg/m^2 in Alberta for the majority of the study period, with dose reductions per clinical protocols and clinician judgment, until progression or unacceptable toxicity.

After Research Ethics Board approval, patients diagnosed with prostate cancer who had received docetaxel chemotherapy from January 1st 2011 to December 31st 2017 were identified using the Alberta Cancer Registry and Cancer Pharmacy databases. Patients were included if they had mCRPC disease, progression after treatment with docetaxel, and received any active therapy after October 2012 (provincial date of cabazitaxel approval). Castrate resistance was defined per Prostate Cancer Working Group 2 criteria.[25]

Data classification

In depth chart reviews were conducted to obtain clinical information. Extracted data included demographics, vital statistics, PSA values, metastatic disease burden, therapies received over mCRPC disease course, and progression dates. Given that the degree of similarity between patients and trial populations is an important factor in clinician decision making, we recorded whether patients met individual inclusion/exclusion criteria from the seminal TROPIC trial (Table 1), which first demonstrated cabazitaxel benefit in mCRPC.[7] Where laboratory criteria were not specifically defined in TROPIC, values accepted in the CABACARE trial (outlined in Table 1) were employed.[26] Organ-specific serious comorbidities were not specifically defined in either trial, therefore we used a working definition of reference to a limiting comorbidity in clinical notes. Recorded first mention of cabazitaxel in clinic notes was classified as: prior to date of first post-docetaxel systemic therapy, later than first line, or no discussion documented.

Time to progression on first ARPI was noted, with poor response being defined as ≤12 months per the CARD trial; patients were divided into 'poor ARPI responders' (PAR) or 'strong ARPI responders' (SAR). To control for other prognostic variables, patients were also classified as having low or high volume disease, as per the CHAARTED clinical trial, defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 outside of the vertebral bodies and pelvis.[27] It should be noted this classification is best studied in castrate-sensitive settings.

Outcome measures

Our study evaluated survival outcomes with cabazitaxel use in PAR and SAR subgroups, comparing those exposed to cabazitaxel over their treatment course to those not exposed. The primary endpoint was OS, measured from the date of post-docetaxel therapy initiation until death, or censored at last follow-up. Censoring was at time of last healthcare contact, until December 15, 2020. Exploratory endpoints included PFS and PSA response rate (PSA decrease of ≥ 50% from baseline beyond 12 weeks) with subsequent cabazitaxel or an alternate

Table 1 Clinical Characteristics of mCRPC Patients Who Progressed After Docetaxel.

Characteristics	Total population (n = 592)	Poor ARPI Responders (n = 403)	Strong ARPI Responders (n = 189)
Median Age post-Docetaxel (25-75%)	70 (63-75)	70 (63-76)	69 (63-74)
PSA at post-Docetaxel therapy (25-75%)	60.3 (15.9-195.3)	72.1 (20.0-211.8)	34.9 (10.1-130.3)
High volume disease (%)	425 (72.0)	309 (76.7)	116 (61.4)
Visceral Metastasis (%)	57 (9.6)	34 (8.4)	23 (12.2)
>3 and/or non-axial bony metastasis (%)	397 (67.1)	295 (73.2)	102 (54.0)
Bone Targeted Therapy (%)	95 (16.0)	61 (15.1)	34 (18.0)
Docetaxel Setting (%) mCSPC mCRPC	 94 (15.9) 498 (84.1)	 47 (11.7) 356 (88.3)	 47 (24.9) 142 (75.1)
Cabazitaxel (%)	170 (28.7)	122 (30.3)	48 (25.4)
ECOG Post-DOC (%) [Not available] 0 1 2 3 4	 27 (4.6) 143 (24.2) 258 (43.6) 107 (18.1) 54 (9.1) 3 (0.5)	 9 (2.2) 87 (21.6) 192 (47.6) 73 (18.1) 40 (9.9) 2 (0.5)	 18 (9.5) 56 (29.6) 66 (34.9) 34 (18.0) 14 (9.0) 1 (0.5)
Intolerant of DOC <225mg/m^2 (%)	78 (13.2)	46 (11.4)	32 (17.0)
Serious comorbidity (%)	82 (13.9)	51 (12.7)	31 (16.4)
Cytopenias (%) Hgb <100 (%)	63 (10.6) 40 (6.8)	53 (13.2) 34 (8.4)	10 (5.3) 6 (3.2)
Abnormal Hepatic Function (%)	34 (5.7)	29 (7.2)	5 (2.6)
Neuropathy Gr 2 or higher (%)	35 (5.9)	26 (6.5)	9 (4.8)
Active other malignancy or prior malignancy disease-free <5yrs (%)	22 (3.7)	18 (4.5)	4 (2.1)
Cardiac dysfunction (%)	15 (2.5)	7 (1.7)	8 (4.2)
Renal dysfunction (%)	8 (1.4)	5 (1.2)	3 (1.6)
Total Trial Ineligible (%)	225 (38.0)	164 (41.0)	61 (32.3)

Patient counts and percentages shown as total population (left) and divided by response to first ARPI: longer then 12 months before progression (Strong ARPI Responder, SAR) or 12 months or less (Poor ARPI Responder, PAR). TROPIC trial (7) criteria shown, and CABACARE (26) laboratory values used to define cytopenias (absolute neutrophil count $<1.5 \times 109/L$, hemoglobin (hgb) <10g/dl, platelet count $<100 \times 109/L$), abnormal hepatic function (serum total bilirubin > upper limit normal (ULN), AST and/or ALT >1.5 times ULN), renal dysfunction (serum creatinine >1.5 ULN for age) where not expressly defined in TROPIC. Where criteria represent a single timepoint, values at time of first post-docetaxel therapy initiation are shown.

therapy post-docetaxel. These analyses were further divided based on the timing of cabazitaxel use, at first funded opportunity (progression on docetaxel, per TROPIC) or later, although later-line analyses were limited by sample size and adequate controls.

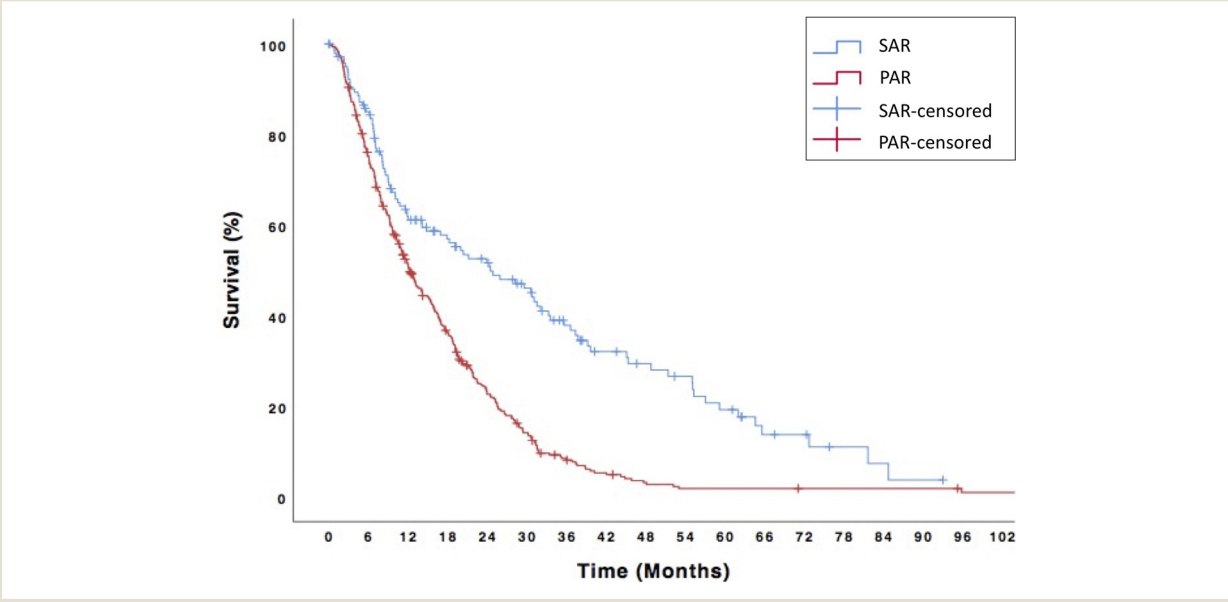
In the second part of our study, focusing on cabazitaxel clinical use, our primary endpoint was the relative frequency of ARPIs and cabazitaxel across lines of therapy. Secondary endpoints included the correlation between tumor characteristics (PSA, high volume disease) and patient factors (TROPIC inclusion/exclusion criteria, ARPI progression time) with cabazitaxel selection.

Statistics

Descriptive statistics were performed on all eligible patients to identify simple proportions and median values with inter-quartile ranges. Proportions of categorical variables were compared with Chi-square or Fisher's exact test, while continuous variables were compared with the Wilcoxon rank-sum test. Survival outcomes were assessed with Kaplan-Meier curves, and the log-rank test was used to compare groups. A stratified log-rank test was used to compare OS in patients who received cabazitaxel based on their ARPI response. Hazard ratios from cox-proportional hazards models were used to calculate interaction between ARPI and cabazitaxel effectiveness.

The sample size was based on all eligible patients treated in the province within the study period. For the primary outcome of OS, 592 patients would provide 80% power to detect a minimum hazard ratio of 1.28, using a 2-tailed alpha of 0.05, an accrual interval of 6 years, follow-up for up to 8 years, and a median time to failure of 15 months. All analyses were performed with SPSS 25th edition statistical software (IBM Corporation, Armonk, NY, USA). Sankey diagram was generated using the online Sankey Diagram Generator (Acquire Services, Brisbane, Australia).

Figure 1 Overall survival in mCRPC patients stratified by time to progression on first Androgen Receptor Pathway Inhibitor (ARPI), either less than or equal to 12 months (Poor ARPI Responders, PAR) or beyond 12 months (Strong ARPI Responders, SAR), log-rank p<0.001.



Results

Clinical Characteristics

3730 patients were identified with advanced prostate cancer over the study period, of which 592 patients had mCRPC and progressed after docetaxel therapy. Ninety-four (15.9%) of these patients received docetaxel for castrate sensitive disease. Table 1 shows the baseline characteristics of our cohort, overall and divided by response to first ARPI (PAR and SAR). Thirty-eight percent of patients either lacked an inclusion criteria, or had one or more exclusion criteria, from the TROPIC trial[7,14] as a surrogate marker for potential 'cabazitaxel ineligibility'. Two-thirds of patients (403, 68%) had disease progression within 12 months on first ARPI (PAR).

The majority of key clinical characteristics, including age, performance status and cabazitaxel exposure (30.3% in PAR, 25.4% in SAR patients), were comparable between the PAR and SAR groups (Table 1). Patients in the PAR group were more likely to have high volume disease ($P < .001$) and cytopenia than those in the SAR group ($P = .026$). There was a nonsignificant trend toward higher trial ineligibility in PAR patients ($P = .148$).

Survival Analysis and Treatment Response

The PAR group had a significantly shorter median OS post-docetaxel (Figure 1, 12.3 months vs. 24.8 months, $P < .001$). The presence of one or more exclusion criteria from the TROPIC trial did not significantly impact OS (11.8 months vs. 14.9 months, $P = .111$), however high-volume disease was associated with inferior OS (11.1 months vs. 25.4 months, $P < .001$).

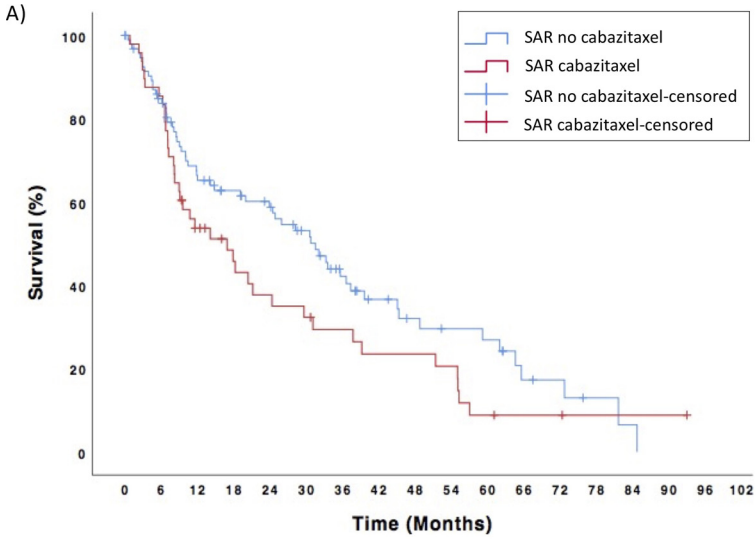
Among SAR patients, cabazitaxel use (as compared to clinician's choice of alternate funded therapies) was associated with a non-significant trend towards lower OS (Table 2 and Figure 2A, 17.1 months vs. 32.0 months, $P = .084$). Conversely, in those with PAR, cabazitaxel use was associated with significantly longer OS (Figure 2B, 16.9 months vs. 10.3 months, $P = .015$). *P*-interaction between first ARPI progression time and OS impact of cabazitaxel was significant by Cox-regression ($P = .004$).

There was no significant trend in PFS observed with or without cabazitaxel amongst PAR patients, either in the first line setting post-docetaxel (Table 2) or in subsequent lines of therapy. SAR patients demonstrated lower PFS with cabazitaxel used first line post-docetaxel (Table 2). No significant difference was seen in PSA response to cabazitaxel in either group.

Cabazitaxel Use and Treatment sequencing

One hundred thirty-four unique treatment sequences were represented in our cohort of 592 patients over their mCRPC disease course. As shown in Table 3, cabazitaxel was used later and less frequently then either ARPI. Patients who received cabazitaxel did so primarily in third or fourth line, with only 29% exposed over their treatment sequence compared to 73% receiving abiraterone (47% post-docetaxel) and 64% receiving enzalutamide (42% post-docetaxel). Supplementary Figure 1 demonstrates these treatment sequences in a Sankey diagram, showing the majority of patients who did not receive cabazitaxel were treated with alternate ARPI, or less frequently docetaxel rechallenge.

Figure 2 Overall survival in mCRPC patients with or without cabazitaxel therapy, either A) In patients with longer than 12 months progression-free on first Androgen Receptor Pathway Inhibitor (Strong ARPI Responders, SAR, log-rank p=0.084) or B) In patients who progressed within 12 months or less on first ARPI (Poor ARPI Responders, PAR, log rank p=0.015).



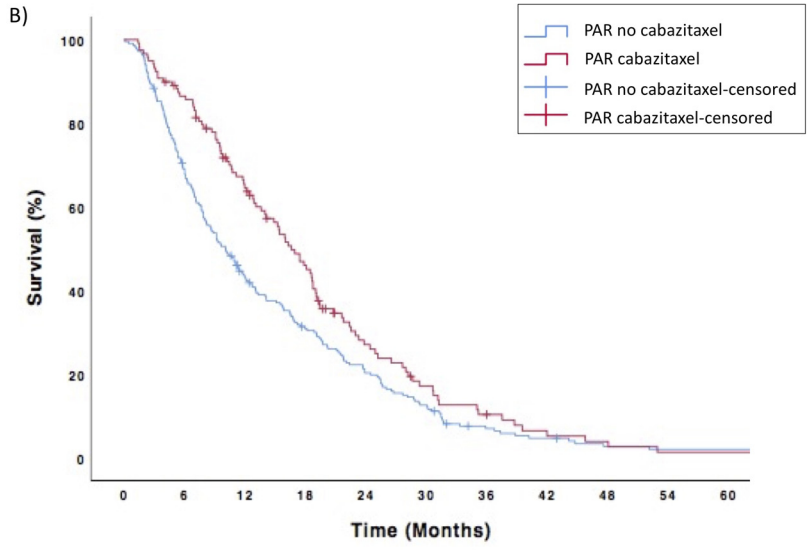


Table 2 Overall Survival, Progression Free Survival and PSA Response in mCRPC Patients Receiving Cabazitaxel, Segregated by First ARPI Response.

	Poor ARPI Responders			Strong ARPI Responders		
	Cabazitaxel	No Cabazitaxel	*P* Value	Cabazitaxel	No Cabazitaxel	*P* Value
Median Overall Survival (mo)	16.9 (14.2-19.6)	10.3 (8.4-12.1)	.015	17.1 (8.5-25.8)	32 (23.9-40.1)	$P = .084$
Progression Free Survival first line post-docetaxel[a] (mo)	3.4 (1.7-5.2)	3.3 (2.7-3.9)	$P = .777$	3.5 (3.0-4.0)	14.7 (8.8-20.6)	$P < .001$
Proportion of patients with PSA Response[b] first line post-docetaxel[a] (%)	8/32 (25)	98/362 (27)	$P = .8$	5/20 (25)	67/164 (41)	$P = .17$

[a] Note that treatment-line specific analyses focused on first cabazitaxel opportunity (after docetaxel progression) due to sample number and statistical limitations, see Methods and Materials.
[b] Includes patients with adequate PSA data.

Table 3 mCRPC Lines of Therapy in Alberta, Canada Among Those Receiving Docetaxel.

	Abiraterone	Enzalutamide	Docetaxel	Cabazitaxel	Other	Total Androgen Blockade	Total Population
Received First Line (% of line total)	167 (29)	133 (23)	178 (31)	1 (0.2)	33 (6)	71 (12)	***583***[a]
Received Second Line (% of line total)	135 (25)	76 (14)	256 (47)	29 (5)	44 (8)	2 (0.4)	***542***
Received Third Line (% of line total)	99 (25)	123 (31)	93 (23)	65 (16)	18 (5)	0 (0)	***398***
Received Forth Line (% of line total)	35 (19)	42 (22)	24 (13)	59 (31)	28 (15)	0 (0)	***188***
Received Fifth Line (% of line total)	9 (14)	11 (17)	11 (17)	19 (29)	13 (20)	2 (3)	***65***
Received Sixth Line (% of line total)	4 (17)	3 (13)	3 (13)	9 (39)	4 (17)	0 (0)	***23***
Total Individual Patients exposed to Agent while mCRPC[b] (% of 592)	433 (73)	377 (64)	565 (95)[c]	170 (29)	140 (24)	75 (13)	***592***

[a] 9 patients received only mCSPC docetaxel without further therapy.
[b] Note some patients received certain agents twice.
[c] Docetaxel in mCSPC setting not shown, and some patients received multiple docetaxel courses; all 592 patients included in cohort received docetaxel in mCSPC or mCRPC as study inclusion criteria

One hundred sixty-three patients (27.5%) had a documented discussion of cabazitaxel immediately post-docetaxel, while 238 patients (40%) did not have a discussion of cabazitaxel documented through their mCRPC course. In only 16% of documented discussions was patient preference the stated primary reason against cabazitaxel use.

Clinician-patient decision to utilize cabazitaxel was more likely in patients with higher performance status (1.2% vs. 13% ECOG greater than 2, $P < .001$) and less docetaxel intolerance (3.5% vs. 17.3%, $P < .001$) compared to patients receiving alternate therapies. 79.4% of those receiving cabazitaxel met TROPIC eligibility, compared to 48.1% among non-cabazitaxel treated patients ($P < .001$), however no relationship was seen between cabazitaxel use and first ARPI progression time ($P = .236$).

Discussion

In this retrospective, real-world study of patients with mCRPC treated with docetaxel, we observed a clear interaction between the duration of first ARPI response and cabazitaxel effectiveness. Patients who progressed within 12 months on first ARPI (poor ARPI responders) and were treated with cabazitaxel had significantly longer OS than similar patients not receiving cabazitaxel. Importantly, this interaction was not seen among strong responders to first ARPI, thus building upon the results of the CARD trial[14] in a real-world setting.

An increased benefit of cabazitaxel in those with faster ARPI progression may be explained by tumor heterogeneity. The mCRPC disease state likely represents a spectrum of tumor biology, with translational data beginning to uncover genome- and transcriptome-level differences based on ARPI sensitivity.[28-30] ARPI-insensitivity may enrich for a mCRPC subtype with poorer prognosis, yet in turn one more responsive to cytotoxic therapy. In these patients, the benefits of chemotherapy may outweigh any increased toxicity.[14,23]

Exposure to an ARPI likely also leads to iatrogenic, selective pressures that alter response to subsequent therapies. Poor responses to second ARPI have been noted in multiple trials,[31] particularly in the enzalutamide-abiraterone sequence.[14-16] Overlapping resistance mechanisms between ARPIs may further accentuate differences in outcomes.[18,21]

These findings corroborate the benefit of cabazitaxel observed in the CARD trial. CARD examined the third-line setting exclusively, while our analysis was unselected for timing of cabazitaxel. The observed longer OS with cabazitaxel in PAR patients was not accompanied by extended PFS or increased PSA response. Notably, even in early randomized settings, stronger trends for OS benefit than surrogate endpoints such as PFS have been reported with cabazitaxel.[22] Additionally, our secondary outcome analysis was restricted to the few patients who received cabazitaxel immediately post-docetaxel and was largely under-powered.

In this retrospective analysis, patients with an extended response to first ARPI did not seem to derive the same benefit from cabazitaxel. There was a nonsignificant trend toward lower OS and significantly shorter PFS with post-docetaxel cabazitaxel use, findings important for use of ARPI progression time in treatment decisions. Exceptional responders to an ARPI may similarly represent a qualitatively different biological disease state that retains sensitivity to ARPIs but is more resistant to cytotoxic agents. For example, patients with BRCA mutations have demonstrated improved first line ARPI response[32] yet also taxane resistance.[33] Given our study's retrospective nature, unmeasured prognostic differences in patients with PAR chosen to receive cabazitaxel must be considered, and some SAR patients will likely still benefit from cabazitaxel. As in CARD, a significant proportion of our patients received first ARPI after docetaxel, which may impact ARPI progression time; analyzing by a composite of time to progression of both ARPI and docetaxel may be a consideration in future studies.

Poor response to first ARPI was used to select patients in CARD,[14] but has not been extensively evaluated as a prognostic or predictive marker.[20] Other, more complex models to anticipate response have been studied,[34] and patients with poor prognostic features have been suggested to derive greater benefit from cabazitaxel.[20,22] In this study, PAR patients represented two-thirds of the cohort and had markedly lower OS, recognizing they also tended to have higher volume disease but proportionally less visceral disease. We note that the classification of high and low volume disease used here is better validated in castrate-sensitive settings, but could still offer insights to different phenotypes of disease. Trial populations differ from general clinical practice in many respects; indeed, over one-third of patients in this cohort would have been ineligible for the TROPIC trial. Accordingly, OS in prior real-world analyses has been shorter than clinical trial outcomes.[23]

During the study period and in the post-docetaxel setting, cabazitaxel was used less frequently and in later lines as compared to either abiraterone or enzalutamide. Clinicians preferred cabazitaxel in patients with good performance status and chemotherapy tolerance and in those who met TROPIC clinical trial criteria. In multiple tumor types, oral agents have been found to be preferred by patients over IV chemotherapy.[35,36] Although the CARD trial did not show increased grade 3 adverse events,[14] other randomized[22] and real-world[23] data suggest toxicities can be higher with cabazitaxel. Cabazitaxel use also seemed under-discussed by clinicians in our study. This study was conducted before the results of CARD were disseminated, and it is anticipated that discussions around cabazitaxel use may be more frequent now. At the same time, novel life-prolonging therapies such as lutetium-177-PSMA-617 and olaparib will add to the complexity of treatment decision making and sequencing, while external events such as the COVID-19 pandemic may alter IV versus oral therapy discussions.[37] We anticipate an evolving, more biomarker-driven approach to treatment sequencing, for which prior ARPI response should be considered.

Our study is limited by its retrospective nature. While real-world analyses have advantages in their less selected patient populations and generalizability of results, clinical outcomes seen in these analyses may be impacted by selection bias and other unmeasured variables. Similarly, determining oncologists' perceptions around cabazitaxel and precise reasons for treatment decisions, for example whether patients were symptomatic, was limited by the low rate of documentation of cabazitaxel discussions, and would be better evaluated in a prospective fashion. It is probable some SAR patients may benefit from cabazitaxel, and patients must be considered individually. Additionally, while equivalent proportions of each ARPI response group were exposed to cabazitaxel, and cabazitaxel dosing levels did not impact OS and PFS in the PROSELICA trial,[38] dose intensity was not explicitly gathered. Acknowledging these limitations, we demonstrated the most impressive benefit from cabazitaxel use in patients with PAR, corroborating the clinical rationale behind the CARD study. Sequencing data in retrospective studies are also at risk of immortal time bias. We attempted to address potential immortal time bias by limiting PFS and PSA analyses to subsets of the study, but this in turn limits statistical power, and thus many of the outcomes must be considered exploratory. The high degree of heterogeneity in treatment sequences prevented more detailed analysis by therapy-line, and larger cohorts may better delineate these factors.

Conclusion

In conclusion, these data from our real-world population support rapid progression on first ARPI as an important consideration in decisions around optimal cabazitaxel use.

Clinical Practice Points

- In the post-docetaxel treatment of metastatic castrate-resistant prostate cancer (mCRPC), the CARD trial showed cabazitaxel to have superior third line PFS and OS compared to androgen receptor pathway inhibitors (ARPIs) in patients who progressed within 12 months on first ARPI. ARPI progression time may be an important consideration as a selection factor in treatment sequencing. What was not clearly delineated by these results was assessment of cabazitaxel impact on patients with longer ARPI responses. Similarly, extending CARDs results to a real-world population, where comorbidities may limit cabazitaxel effectiveness, is vital. Finally, defining the population

for whom cabazitaxel was discussed and utilized by clinicians, and the pre-CARD factors that drove patient selection, are important to optimize its use going forward.

- The findings of this study corroborate a real-world benefit for cabazitaxel in poor ARPI responders (< 12 months), and importantly show that strong ARPI responders (>12 months) do not appear to benefit, with a trend towards harm. Cabazitaxel was less utilized compared to either funded ARPI, and while clinical trial fit, performance status and prior chemotherapy tolerance were all associated with its use, ARPI progression time was not.
- These data support progression time on first ARPI as an important consideration in decisions around optimal cabazitaxel use, while understanding practice patterns in cabazitaxel use to date will help support optimal use and guideline crafting going forward.

Disclosures

We have the following to declare. R.L.Y is a consultant for Janssen, Bayer, AstraZeneca and Sanofi, has research funding from Sanofi, and is part of a speakers bureau for Janssen. N.A. has a consulting or advisory role for Bristol Meyers Squib, Merck, Pfizer, EMD Serano and Seagen. A.W, R.G and E.B. have no competing interests to declare.

CRediT authorship contribution statement

Alexander S Watson: Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Richard Gagnon:** Investigation, Data curation, Formal analysis, Writing – review & editing. **Eugene Batuyong:** Investigation, Writing – review & editing. **Nimira Alimohamed:** Conceptualization, Writing – review & editing. **Richard Lee-Ying:** Conceptualization, Funding acquisition, Project administration, Methodology, Formal analysis, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.04.009.

References

1. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2012;368:138–148. doi:10.1056/NEJMoa1209096.
2. Rathkopf DE, Smith MR, Bono JSde, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol*. 2014;66:815–825. doi:10.1016/j.eururo.2014.02.056.
3. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *New England J Med*. 2014;371:424–433. doi:10.1056/NEJMoa1405095.
4. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *New England J Med*. 2011;364:1995–2005. doi:10.1056/NEJMoa1014618.
5. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13:983-992. doi:10.1016/S1470-2045(12)70379-0
6. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *New England J Med*. 2012;367:1187–1197. doi:10.1056/NEJMoa1207506.
7. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376:1147–1154. doi:10.1016/S0140-6736(10)61389-X.
8. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213–223. doi:10.1056/NEJMoa1213755.
9. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411–422. doi:10.1056/NEJMoa1001294.
10. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. *New England J Med*. 2021;0 nulldoi:10.1056/NEJMoa2107322.
11. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. *New England J Med*. 2020;383(24):2345–2357. doi:10.1056/NEJMoa2022485.
12. Caffo O, Maines F, Kinspergher S, Veccia A, Messina C. Sequencing strategies in the new treatment landscape of prostate cancer. *Future Oncology*. 2019;15(25):2967–2982. doi:10.2217/fon-2019-0190.
13. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, et al. The effects of new life-prolonging drugs for metastatic castration-resistant prostate cancer (mCRPC) patients in a real-world population. *Prostate Cancer Prostatic Dis*. 2021 Published online March 21. doi:10.1038/s41391-021-00344-1.
14. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381:2506–2518. doi:10.1056/NEJMoa1911206.
15. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. *Lancet Oncol*. 2019;20:1730–1739. doi:10.1016/S1470-2045(19)30688-6.
16. Cassinello J, Domínguez-Lubillo T, Gómez-Barrera M, et al. Optimal treatment sequencing of abiraterone acetate plus prednisone and enzalutamide in patients with castration-resistant metastatic prostate cancer: a systematic review and meta-analysis. *Cancer Treat Rev*. 2021;93:102152. doi:10.1016/j.ctrv.2020.102152.
17. van Soest RJ, de Morrée ES, Kweldam CF, et al. Targeting the androgen receptor confers in vivo cross-resistance between enzalutamide and docetaxel, but not cabazitaxel, in castration-resistant prostate cancer. *Eur Urol*. 2015;67:981–985. doi:10.1016/j.eururo.2014.11.033.
18. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *Eur Urol*. 2015;67:23–29. doi:10.1016/j.eururo.2014.06.045.
19. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol*. 2013;24:1802–1807. doi:10.1093/annonc/mdt138.
20. Oh WK, Cheng WY, Miao R, et al. Real-world outcomes in patients with metastatic castration-resistant prostate cancer receiving second-line chemotherapy versus an alternative androgen receptor-targeted agent (ARTA) following early progression on a first-line ARTA in a US community oncology setting. *Urol Oncol*. 2018;36 500.e1-500.e9. doi:10.1016/j.urolonc.2018.08.002.
21. Al Nakouzi N, Le Moulec S, Albigès L, et al. Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. *Eur Urol*. 2015;68:228–235. doi:10.1016/j.eururo.2014.04.015.

22. Annala M, Fu S, Bacon JVW, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2 trial. *Ann Oncol*. 2021 Published online April 6. doi:10.1016/j.annonc.2021.03.205.
23. Rouyer M, Oudard S, Joly F, et al. Overall and progression-free survival with cabazitaxel in metastatic castration-resistant prostate cancer in routine clinical practice: the FUJI cohort. *Br J Cancer*. 2019;121:1001–1008. doi:10.1038/s41416-019-0611-6.
24. Higano CS, Sternberg CN, Saad F, et al. Treatment patterns and outcomes for metastatic castration-resistant prostate cancer (mCRPC) in a real-world setting: a retrospective study of greater than 2500 patients. *JCO*. 2019;37(7_suppl):256. doi:10.1200/JCO.2019.37.7_suppl.256.
25. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26:1148–1159. doi:10.1200/JCO.2007.12.4487.
26. Buonerba C, Bosso D, De Placido S, di Lorenzo G. A randomized phase II study comparing cabazitaxel/prednisone to cabazitaxel alone for second-line chemotherapy in men with metastatic castrate resistant prostate cancer (mCRPC): CABACARE. *JCO*. 2018;36 6_supplTPS387-TPS387. doi:10.1200/JCO.2018.36.6_suppl.TPS387.
27. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *New Engl J Med*. 2015;373:737–746. doi:10.1056/NEJMoa1503747.
28. King CJ, Woodward J, Schwartzman J, et al. Integrative molecular network analysis identifies emergent enzalutamide resistance mechanisms in prostate cancer. *Oncotarget*. 2017;8:111084–111095. doi:10.18632/oncotarget.22560.
29. Smith R, Liu M, Liby T, et al. Enzalutamide response in a panel of prostate cancer cell lines reveals a role for glucocorticoid receptor in enzalutamide resistant disease. *Sci Rep*. 2020;10:21750. doi:10.1038/s41598-020-78798-x.
30. Alumkal JJ, Sun D, Lu E, et al. Transcriptional profiling identifies an androgen receptor activity-low, stemness program associated with enzalutamide resistance. *PNAS*. 2020;117:12315–12323. doi:10.1073/pnas.1922207117.
31. Maughan BL, Antonarakis ES. Does sequencing order of antiandrogens in prostate cancer matter? *Nat Rev Urol*. 2020;17:197–198. doi:10.1038/s41585-020-0289-9.
32. Antonarakis ES, Lu C, Luber B, et al. Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. *Eur Urol*. 2018;74:218–225. doi:10.1016/j.eururo.2018.01.035.
33. Nientiedt C, Heller M, Endris V, et al. Mutations in BRCA2 and taxane resistance in prostate cancer. *Sci Rep*. 2017;7:4574. doi:10.1038/s41598-017-04897-x.
34. Belderbos BPS, de Wit R, Hoop EOde, et al. Prognostic factors in men with metastatic castration-resistant prostate cancer treated with cabazitaxel. *Oncotarget*. 2017;8:106468–106474. doi:10.18632/oncotarget.22474.
35. Eek D, Krohe M, Mazar I, et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. *Patient Prefer Adherence*. 2016;10:1609–1621. doi:10.2147/PPA.S106629.
36. Catania C, Didier F, Leon ME, et al. Perception that oral anticancer treatments are less efficacious: development of a questionnaire to assess the possible prejudices of patients with cancer. *Breast Cancer Res Treat*. 2005;92:265–272. doi:10.1007/s10549-005-3376-y.
37. Schrag D, Hershman DL, Basch E. Oncology practice during the COVID-19 pandemic. *JAMA*. 2020;323:2005. doi:10.1001/jama.2020.6236.
38. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. *J Clin Oncol*. 2017;35:3198–3206. doi:10.1200/JCO.2016.72.1076.