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REVIEW

Prostate Cancer

Treatment sequencing in metastatic castrate-resistant prostate cancer

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Six different treatments have demonstrated improved survival in phase III trials targeted to patients with metastatic castration-resistant prostate cancer (mCRPC). Front-line therapeutic options for mCRPC include docetaxel, sipuleucel-T, abiraterone and radium-223. Post-docetaxel options include cabazitaxel, abiraterone, enzalutamide and radium-223. Despite much progress in recent years, much is yet unknown and debates occur over optimal treatment choices and sequences. None of the new agents have been compared to one another, thus physicians in practice today must make choices based on non-randomized comparisons, toxicity considerations and various assumptions. Abiraterone is now moving into the front line mCRPC space given recent regulatory approvals and enzalutamide will follow soon. Both of the hormonal agents have less toxicity when compared to chemotherapeutic options and both of these hormonal agents are expected to be used in a considerable number of mCRPC patients in the years ahead. Little data are available for the post-abiraterone or post-enzalutamide setting. In this review the currently available sequencing data are summarized and interpreted. It is now clear that cross resistance is a potential issue between various treatments, especially those agents that target the androgen axis. This review highlights the need for additional studies to optimize the current treatments for these patients.
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INTRODUCTION

Much progress has been made in metastatic castrate-resistant prostate cancer (mCRPC). Regulatory approvals have been numerous over the past two decades and now a variety of new therapies have become available for treatment of these patients. The availability of new therapies has yielded a conundrum as none of these new therapies have been directly compared to one another.

How can therapies for mCRPC best be utilized? Is there an optimal sequence of therapies? What therapy is best used in individual patients? Despite much progress, these questions are unanswered. Herein we make a brief review of the current literature and emphasize data that are relevant to sequencing and therapeutic selection. Despite many new trials, much is unknown. No comprehensive current review of sequencing data in mCRPC is available in the literature and the purpose of this manuscript is to provide such a review with a particular emphasis on an up to date perspective including abstracts at recent meetings.

To obtain data for this review we have comprehensively reviewed the literature for each of the approved mCRPC agents in Medline searches and also reviewed recent abstracts from the American Society of Clinical Oncology meetings, the American Society of Clinical Oncology Genitourinary Cancer meetings and meetings of the European Society of Medical Oncology.

BACKGROUND

Initially, prior to 2004, therapies provided palliative benefit but not overall survival (OS) benefit (**Table 1**). That changed in 2004 with the approval of docetaxel/prednisone for initial treatment of mCRPC. Two trials were pivotal for that approval, TAX327 and SWOG 9916.[1,2] Both used mitoxantrone/prednisone in the control group and both trials enrolled patients without prior chemotherapy. Both trials showed an OS benefit in favour of docetaxel, a taxane that binds to microtubules and inhibits microtubular polymerization. Docetaxel/prednisone became the standard of care for treating mCRPC. The docetaxel/estramustine combination has never been approved by any regulatory agency and the estramustine has side effects that can be avoided without compromising docetaxel effectiveness. Thus docetaxel/estramustine combinations are rarely used today.

After 2004, some trials adapted by clearly defining the "post-docetaxel" space (**Table 2**). The first trial to demonstrate an OS benefit in this space was the TROPIC[3] trial which compared the novel taxane cabazitaxel and mitoxantrone. Both arms also contained prednisone. Cabazitaxel also inhibits microtubular polymerization and this agent was approved in 2010. Subsequently, in 2011 and 2012, two additional trials were successful in prolonging survival in the post-docetaxel space. These included COU-301[4] and AFFIRM[5]. The active agents in these trials were abiraterone/prednisone and enzalutamide, respectively. The comparator arms were placebo/prednisone and placebo, respectively. Both of these trials conclusively demonstrated the value of further targeting androgen receptor (AR) signalling in "hormone-refractory" prostate cancer. Abiraterone inhibits androgen synthesis by binding to and inhibiting CYP17, a critical component of androgen synthesis pathways in the adrenal, testis, and tumor. Enzalutamide binds to the

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androgen receptor (AR) and serves as a potent androgen antagonist thereby preventing ligand-bound AR translocation into the nucleus. Given that both abiraterone and enzalutamide inhibit androgen signalling, instead of referring to patients progressing after castration as "hormone-refractory", the current preferred term is now "castrate-resistant".

Table 1: Regulatory approvals and endpoints in the United States in castrate-resistant prostate cancer

Year	*Agent*	*Endpoint*	*Control arm*	*Setting*
1981	Estramustine	Response	Diethylstilbestrol	CRPC
1993	Strontium-89	Pain	Placebo	Post-radiation
1996	Mitoxantrone/prednisone	Pain	Prednisone	Front line
1997	Samarium-153 lexidronam	Pain	Placebo	mCRPC
2002	Zoledronic acid+standard of care	Skeletal events	Placebo+standard of care	mCRPC
2004	Docetaxel/prednisone	Survival	Mitoxantrone/ prednisone	Front line
2010	Sipuleucel-T	Survival	Unstimulated immune cells	Mostly pre-docetaxel
2010	Cabazitaxel/prednisone	Survival	Mitoxantrone/ prednisone	Post-docetaxel
2010	Denosumab+standard of care	Skeletal events	Zoledronic acid+standard of care	mCRPC
2011	Abiraterone/prednisone	Survival	Prednisone	Post-docetaxel
2012	Enzalutamide	Survival	Placebo	Post-docetaxel
2012	Abiraterone/prednisone	Survival and Radiographic PFS	Prednisone	Pre-docetaxel
2013	Radium-223+standard of care	Survival	Placebo+standard of care	Pre- and post-docetaxel

PFS: progression-free survival; CRPC: castrate-resistant prostate cancer; mCRPC: metastatic castrate-resistant prostate cancer

Table 2: Trials demonstrating a survival benefit in metastatic castrate-resistant prostate cancer

Group	*Trial*	*Visceral disease allowed*	*HR*	*Survival (month)*
Front line				
Docetaxel/prednisone *vs* Mitoxantrone/ prednisone	TAX 327[1]	Yes	0.79	18.9 *vs* 16.5
Sipuleucel-T *vs* control	IMPACT[6]	No	0.78	25.8 *vs* 21.7
Abiraterone/ prednisone *vs* Placebo/ prednisone	COU-302[8]	No	0.75	Not reached *vs* 27.2
Enzalutamide *vs* Placebo	PREVAIL[9]	Yes	0.70	32.4 *vs* 30.4
Post-DOC				
Cabazitaxel/prednisone *vs* Mitoxantrone/ prednisone	TROPIC[3]	Yes	0.70	15.1 *vs* 12.7
Abiraterone/ prednisone *vs* Placebo/ prednisone	COU-301[4]	Yes	0.74	14.8 *vs* 10.9
Enzalutamide *vs* Placebo	AFFIRM[5]	Yes	0.63	18.4 *vs* 13.6
Front line and post-DOC				
Radium-223/BSC *vs* placebo/BSC	ALSYMPCA[7]	No	0.70	14.9 *vs* 11.3 overall 14.1 *vs* 11.3 post-DOC 16.1 *vs* 11.5 pre-DOC

BSC: best standard of care; DOC: docetaxel

Two additional trials, IMPACT and ALSYMPCA using sipuleucel-T[6] and radium-223[7], respectively, demonstrated an improvement in OS with trial designs distinct from those trials previously mentioned. The IMPACT trial utilized sipuleucel-T (an autologous cellular immunotherapy targeted to prostatic acid phosphatase) in patients with asymptomatic or minimally symptomatic mCRPC without visceral metastases. Patients could be enrolled whether or not docetaxel had been previously administered but the chemotherapy free interval had to be at least 3 months and the vast majority (85%) of patients were chemotherapy naïve. The control arm in IMPACT consisted of reinfusion of a portion of the patient's mononuclear cells that had been collected but unexposed to antigen stimulation. A crossover design allowed application of antigen exposed cells after documented radiographic progression.

In the ALSYMPCA trial using radium-223[7], both the eligibility and control groups were different from other trials. Radium-223 is a bone-seeking alpha particle emitter. Eligibility included only symptomatic mCRPC patients with bone metastases but no visceral metastatic disease. "Symptomatic" was defined simply as taking any form or analgesics (opiates or non-opiates) for pain. Patients with lymph nodes larger than 3 cm were also excluded. Patients enrolled could have been post-docetaxel, or refuse docetaxel, or have been judged unfit for docetaxel by their physician. Patients were randomized to six doses of radium or placebo. Standard of care (SOC) treatments were allowed in addition to the radium or placebo. SOC excluded radiopharmaceuticals, chemotherapy, and experimental agents but included various hormonal therapies and external beam radiation (except hemi-body fields). SOC therapies could be administered per investigator judgment. In the statistical analysis plan, a pre-specified analysis of OS was to be performed after stratifying for docetaxel use (yes/no) prior to trial entry. The trial demonstrated an overall OS benefit for radium treated patients. The stratified OS data demonstrated radium benefit regardless of docetaxel pre-treatment or not. Thus the regulatory approval did not specify docetaxel use for patients eligible for radium-223.

The COU-302[8] trial was the first trial to trigger regulatory approval in patients specifically and entirely dedicated to the pre-chemotherapy mCRPC space. Patients were asymptomatic or minimally symptomatic and had received no prior chemotherapy and had no visceral metastases. The trial had co-primary endpoints, radiographic progression-free survival (rPFS) and overall survival. The endpoint of rPFS was strongly positive at the time of an interim analysis ($P < 0.001$) but the overall survival endpoint was not formally met as the O'Brien-Fleming boundary was not breeched. The actual P value for OS at interim was 0.0097 and the pre-specified P value required by O'Brien-Fleming methodology was ≤0.0008. Secondary endpoints such as time to PSA progression, time to performance status (PS) decrease, time to opioids, and time to chemotherapy were significantly delayed in those receiving abiraterone/prednisone as compared to placebo/prednisone. We note that the time to chemotherapy in both arms, but especially in the abiraterone arm was quite long considering the time to PSA progression, PS decline, and radiographic deterioration. Regulatory authorities have approved abiraterone/prednisone in the pre-chemotherapy mCRPC space, and this is an important event that is currently changing patterns of care.

An additional regulatory approval is anticipated in 2014. The PREVAIL trial comparing enzalutamide and placebo in patients with asymptomatic and minimally symptomatic mCRPC patients with no prior chemotherapy. In contrast to the COU-302 trial, in PREVAIL patients with visceral metastases were eligible (except

brain metastases). A press release[9] from the company indicated that the data monitoring committee had stopped the trial at an interim analysis. Both primary endpoints (rPFS and OS) indicated efficacy of enzalutamide in this setting ($P < 0.001$ for each). In this case the O'Brien-Fleming boundary for the OS endpoint was breached. At the time of this manuscript submission, regulatory authorities have yet to opine on this trial but given the OS benefit it would be surprising if approval were not granted.

Taken together, present front-line mCRPC options in the United States shown to improve survival include docetaxel/prednisone, sipuleucel-T, abiraterone/prednisone, or radium (**Table 2**). Post-docetaxel options that prolong survival include cabazitaxel/prednisone, abiraterone/prednisone, enzalutamide, or radium-223. No agent has yet improved survival when co-administered with docetaxel/prednisone despite multiple attempts (including randomized trials with calcitriol, GVAX, atrasentan, zibotentan, aflibercept, bevacizumab, dasatinib, lenalidomide, strontium, and zoledronate).

PROBLEMATIC ISSUES WITH CURRENT DATA

The segmentation of CRPC treatments into a pre- and post-docetaxel space is artificial. This artificiality was simply built on the chronology of drug development and is not justified on a biological basis. It is noteworthy that none of the newer agents, either in the front-line or post-docetaxel space, have been compared head to head (see **Table 2**). Instead control groups consisted of mitoxantrone/prednisone, placebo, prednisone, or "standard or care". Each trial with a currently approved agent has utilized treatments in the control group that today are regarded as being sub-optimal. Further, we note that some trials include patients with visceral disease and others do not. This is delineated in **Table 2**. Taken together we conclude that the optimal front-line therapy and the optimal post-docetaxel therapy are debatable for mCRPC patients given lack of appropriate comparisons. Thus physicians in practice today must make choices based on non-randomized comparisons, an assessment of toxicities, and various assumptions rather than true "level one" data.

The optimal sequence of therapies is much discussed, but there is little consensus in expert opinion given the lack of data in settings other than post-docetaxel. Cabazitaxel/prednisone, abiraterone/prednisone, radium-223, and/or enzalutamide represent reasonable options for many docetaxel pre-treated patients. Abiraterone/prednisone, enzalutamide, sipuleucel-T, and/or radium-223 might represent alternatives to docetaxel/prednisone as a first line therapy.

Of note front-line abiraterone, sipuleucel-T, and radium-223 were tested in asymptomatic or mildly symptomatic patients without visceral metastases. The enzalutamide pre-chemotherapy trial included only those who were asymptomatic or minimally symptomatic but did not exclude those with visceral metastatic disease. The radium-223 phase III trial included only symptomatic patients without visceral disease but many patients receiving radium in the ALSYMPCA trial actually had minimal analgesic use and would have also been eligible for the front line trials with abiraterone/prednisone, enzalutamide, or sipuleucel-T. Docetaxel was tested in mCRPC patients both with and without symptoms, and in those with and without visceral metastases.

Since abiraterone/prednisone was approved as first line mCRPC therapy in the United States in 2012, the importance of the post-abiraterone setting is clear. If abiraterone therapy is first line, what therapy should follow? Enzalutamide in the pre-docetaxel space has very recently been shown to improve OS in this setting and it is now clear that enzalutamide will soon be available in this space as well. What therapies should follow after progression on enzalutamide? There is no current evidence, as no randomized trials have been performed in this setting.

CAVEATS REGARDING THE CURRENT SEQUENCING ERA

The amount of second-line efficacy data available in the situations other than the post-docetaxel space is limited and predominately retrospective at this time. Regardless, it is timely to review current data as it will be quite a long time before randomized trials are available and clinicians are obligated to make decisions for their patients at this time regardless of whether or not pristine data are available.

Attempting to review non-randomized trails is problematic from several perspectives. First there is no standardized reporting. Herein we attempt to capture PSA decline >50% rates, confirmed PSA >50% decline rates, no PSA response as best response, time to PSA progression, soft tissue response rates by RECIST, duration of therapy, and progression-free survival (PFS) (see **Table 3**). It is also important to highlight where there are some data and where there are no data. We have combined both phase II and III trials in our table and this is important for readers to note as the reliability of phase III data is generally much higher than phase II data. PFS is often measured quite differently from trial to trial and thus PFS is particularly problematic to compare. For instance, some trials utilized PSA as a marker of progression and some did not. Some trials used two new lesions on a bone scan, and some trials required additional progression on subsequent scans.

In this review, conceptual rather than exhaustive discussions are utilized. Regardless we believe that these findings are important in terms of understanding the current therapeutic landscape and for designing the next generation of trials. This review will be methodical, even though the datasets are small and mostly retrospective (see **Table 3**). Within any well designed sequencing trials, one must always be aware that the patients treated with the second therapy have more advanced disease and are more likely to have negative prognostic factors such as a reduced performance status, pain, visceral metastases, high lactate dehydrogenase (LDH), high PSA, and/or a low hemoglobin. Thus lower response rates for second line therapies may simply be due to a higher burden of disease and worse prognostic indicators. Further, in examining small single institution trials there are potential unknown biases in patient selection and followup that might or might not apply to a more general patient population.

POST-ABIRATERONE DATA

Given the importance of abiraterone/prednisone, particularly as an emerging front-line therapy, the sequencing discussions regarding this agent are particularly critical. As noted above, many clinicians now start abiraterone/prednisone as first line mCRPC therapy but the consequences of that decision on subsequent therapies are not well delineated.

Mezynski and colleagues from the de Bono group[10] have published a retrospective review of docetaxel in the post-abiraterone space suggesting the possibility of cross-resistance between these two agents. The response rate as measured by 50% PSA decline was 26% versus 45%-57% in other docetaxel trials.[1, 2, 11] The time to PSA progression (4.6 months) post-docetaxel in the Mezynski study whereas the time to PSA progression or progression from any cause was 6.3 months in the SWOG 9916 trial. Time to PSA progression was not stated in the TAX327 trial but the duration of PSA response was 7.7 months. The median number of docetaxel doses in the Mezynski report was 6 as compared to a median number of 9.5 in TAX327 trial. The best response as no PSA response was 34% for docetaxel in the post-

Table 3: Synopsis of selected first-, second- and third-line trials in metastatic castrate-resistant prostate cancer

Treatment and line of treatment	*PSA≥50 decline (%)*	*PSA≥50 % decline confirmed (%)*	*Best PSA response is no response (%)*	*Median treatment duration (month) (%)*	*RECIST response rate (%)*	*Radiographic PFS median (month)*	*Median PSA progression (months)*	*Phase*
First-line DOC[1]	NR	45	NR	6.6	12	NR	NR	III
First-line DOC[11]	57	NR	14	NR	NR	NR	NR	II
First-line ABI[8]	62	NR	NR	NR	36	16.8	11.1	III
First-line ABI[28]	79	67	10	14.5	69	NR	16.3	II
First-line ENZ[17]	62	NR	11	NR	36	NR	9.4	I/II
Second-line AB[4] (post-DOC)	NR	29	NR	8.0	14	5.6	10.2	III
Second-line ABI[22] (post-DOC)	51	45	11	5.5	27	NR	5.6	II
Second-line ENZ[5] (post-DOC)	NR	54	NR	8.3	29	8.3	8.3	III
Second-line ENZ[17] (post-DOC)	51	NR	17	NR	12	6.7	6.2	I/II
Second-line CBZ[3] (post-DOC)	NR	39	NR	4.1	14	NR	6.4	III
Second-line CBZ[14] (post-DOC)	52	NR	8	4.9	NR	NR	6.1	Retro
Second-line DOC[10] (post-ABI)	26	NR	37	4.1	11	NR	4.6	Retro
Third-line ABI[20] (post-DOC and post-ENZ)	8	NR	63	3.0	8	NR	2.7	Retro
Third-line ABI[21] (post-DOC and post-ENZ)	3	NR	78	3.0	0	NR	NR	Retro
Third-line ABI[14] (post-DOC and post-CBZ)	17	NR	28	3.8	NR	NR	2.7	Retro
Third-line ENZ[16] (post-DOC and post-ABI)	29	NR	49	4.9	3	NR	NR	Retro
Third-line ENZ[18] (post-DOC and post-ABI)	23	13	56	2.9	4	NR	2.7	Retro
Third-line CBZ[14] (post-DOC and post-ABI)	32	NR	22	2.8	NR	NR	4.1	Retro
Third-line CBZ[13] (post-DOC and post-ABI)	49	NR	NR	4.1	20	NR	NR	Retro
Third-line CBZ[15] (post-DOC and post-ABI)	30	NR	NR	NR	NR	NR	NR	Retro

ABI: abiraterone; CBZ: cabazitaxel; DOC: docetaxel; ENZ: enzalutamide; PFS: progression-free survival; Retro: retrospective study; NR: not reported

abiraterone setting[10] as compared to a recent trial which reports a 14% rate when docetaxel is given first line.[11] Interestingly of the 8 patients who did not respond to abiraterone (defined as "best PSA response" being progression), none responded to docetaxel post-abiraterone. In another, even smaller retrospective study of 14 patients presented by Aggarwal *et al.*[12] the PSA response rate was 43%, but the median time to progression was 4.2 months. Taken, though these data are derived from relatively small studies, taken together these data suggest a significant possibility of cross-resistance when docetaxel is given post-abiraterone.

POST-DOCETAXEL AND ABIRATERONE

Cabazitaxel has been evaluated as third line therapy in patients previously treated with both docetaxel and abiraterone in two retrospective studies. In a combined French/UK experience[13] reported in abstract form, a median of 6 cycles of cabazitaxel were administered (4.1 months), which is similar to data from the TROPIC trial. A total of 49% of these cabazitaxel patients had a >50% PSA decline, which compared to a confirmed >50% decline rate of 39% in the TROPIC study[3]. In the combined French/UK retrospective experience, of the 35 patients with RECIST evaluable disease, 7 (20%) had a partial response. This compares to a 14% RECIST response rate in TROPIC. These data suggest that the response to cabazitaxel are not impaired post-abiraterone however other studies (vide infra) may not be consistent with these observations.

A 68 patient Dutch study[14] recently reported in abstract form for third line cabazitaxel in patients previously treated with both docetaxel and abiraterone. This study also reported on cabazitaxel post-docetaxel giving a nice comparison of second and third line cabazitaxel. The median duration of third line cabazitaxel treatment was approximately 85 days (2.8 months) as compared to 150 days (4.9 months) for patients treated with cabazitaxel second line (post-docetaxel) in this study. In the phase III TROPIC[3] study, the median duration of cabazitaxel treatment was approximately 4.1 months. In the Dutch study, the biochemical PFS was approximately 4 months for third line cabazitaxel patients as compared to a PSA progression in TROPIC of 6.4 months. Best response equalled no response in approximately 22% of the third line cabazitaxel treated patients as compared to 8% of post-docetaxel patients treated with second line cabazitaxel in the Dutch study. PSA decline rates of >50% were not reported. Contrary to the initial French/UK report, these data suggest that abiraterone may induce some degree of cross-resistance with cabazitaxel. We point out that this conclusion is tempered by the fact that cabazitaxel was third line therapy in the Dutch study and second line therapy for the majority of patients in TROPIC.

In an Israeli retrospective analysis,[15] 24 patients received cabazitaxel after docetaxel and abiraterone. A median of 4 cycles of cabazitaxel were administered. The majority of these patients were treated with 20 mg m^{-2} of cabazitaxel instead of the FDA approved dose of 25 mg m^{-2}. The PSA response rate was 30%. PFS and other parameters of activity were not reported. This study may also suggest some degree of abiraterone induced cross-resistance with cabazitaxel, albeit it is difficult to interpret because of the lower dose of cabazitaxel used and the fact that again cabazitaxel was given third line in this small study.

Enzalutamide treatment as third line therapy after docetaxel and after abiraterone has been evaluated in three studies. In the first study[16], with data prospectively collected in a German "Named Patient Access Program", the activity of enzalutamide was clearly diminished post-abiraterone with "no PSA response" as best response in 49% of patients. This compares to only 17% of patients in a phase I/II study of enzalutamide post-docetaxel.[17] The >50% PSA decline rate with enzalutamide in this setting was 29% compared to 54% in the AFFIRM phase III trial conducted in the post-docetaxel setting. In a subset analysis of the Named Patient Access program, a >50% PSA decline to enzalutamide was observed in 7/16 (44%) patients previously achieving a >50% PSA decline with abiraterone. Of the patients with no decline in PSA as best response after abiraterone, 3/14 (21%) had a 50% decline in PSA after enzalutamide. Thus a "no response" to initial abiraterone treatment could not predict a "no response" to subsequent enzalutamide. The median PFS duration was not clearly stated in this study.

In a second retrospective study of enzalutamide[18] conducted in post-docetaxel patients also treated with prior abiraterone, 39 patients were treated and 22 (56%) had no PSA decline as their best response. A total of 9 patients (23%) had a PSA decline of >50% but only 5 of these patients had a confirmed >50% PSA decline. Thus many of the reported declines in PSA were short-lived. Of the 15 patients with a >50% PSA response after abiraterone, 2 had >50% PSA response to enzalutamide. Of the 22 patients without a response to abiraterone, 2 had a >50% PSA response to enzalutamide. The median duration of treatment was only 2.9 months and median time to progression was 2.8 months. This compares to a median time to progression of 8.3 months in the phase III post-docetaxel AFFIRM trial. In the AFFIRM trial the RECIST response rate was 29% as compared to a RECIST response rate of 4% in this retrospective analysis. Thus, although the data are minimal, there is clear evidence of cross-resistance between abiraterone and enzalutamide but one could not exclude a response to enzalutamide by looking at an individual's prior data while taking abiraterone. Regardless the duration of enzalutamide treatment in the third line setting is short, measuring less than 3 months.

In a third small review of enzalutamide[19] predominantly in the post-docetaxel, post-orteronel space, 20 patients received treatment in a Greek "Named Patient Access Program". Orteronel is another CYP17 inhibitor similar to abiraterone but not FDA approved. A number of these patients had also previously received additional chemotherapy including 4 patients with prior cabazitaxel treatment. In this heavily pre-treated patient population, 8/20 (40%) patients had no PSA response as their best response to enzalutamide but 9/20 (45%) had a >50% PSA decline. No PFS was reported. These data are consistent with the others, CYP17 inhibitors decrease enzalutamide responses but some patients can still respond as measured by PSA declines.

POST-ENZALUTAMIDE STUDIES

For the novel antiandrogen enzalutamide there are no published data evaluating use of docetaxel or cabazitaxel after enzalutamide. This is important given that the trial comparing enzalutamide to placebo (PREVAIL) in the chemotherapy-naïve setting will likely change the future paradigm of sequencing as this trial demonstrated an OS benefit for enzalutamide.

POST-DOCETAXEL AND ENZALUTAMIDE

Studies of abiraterone in patients previously treated with both docetaxel and enzalutamide have been reported in two separate retrospective studies.[20,21] Both of these report a dramatic decrease in the activity of abiraterone compared to that expected. PSA >50% decline response rates are far less than expected at 13% and 8% respectively versus 29%-51% expected from phase II-III studies with abiraterone in the post-docetaxel space.[4,22] PFS after abiraterone was reduced from expectations as well, measuring 2.7 months in the post-enzalutamide and post-docetaxel setting,[20] however PFS was not clearly defined in this third line study so direct comparisons are not possible with the phase III data. No PSA response as the best response to abiraterone in this setting was 63%-78% which compares to 11% in the phase II trial of abiraterone post-docetaxel.[22] These data need to be interpreted with caution because a high proportion of patients in these series were PS 2 (29% and 23% respectively). These data suggest that enzalutamide induces clear cross-resistance to abiraterone and that cross-resistance is near complete. Overall it would appear that the cross-resistance induced by prior enzalutamide treatment on subsequent abiraterone is greater than vice-versa.

POST-CABAZITAXEL STUDIES

The Dutch group of Wissing and colleagues[14] examined retrospectively the activity of abiraterone in the second line setting (post-docetaxel) or the third line setting (post-docetaxel and post-cabazitaxel). The activity or abiraterone was quite similar in both of these settings suggesting that that cabazitaxel induces little cross-resistance to abiraterone. The median treatment duration for abiraterone second line was approximately 130 days as compared to 110 days for third line treatment. The median biochemical PFS was 2.7 months for both second and third line cabazitaxel. The best response being no biochemical response was approximately 31% and 28%, respectively.

POST-RADIUM STUDIES

No formal post-radium studies have been reported. In one abstract a prospective analysis of chemotherapy safety post-radium was presented. Conclusions were limited as not all time points were available for analysis but there did not appear to be overt signs of excessive toxicity.[23] There is no reason to suspect from mechanistic studies that radium and the newer hormonal agents should provoke cross-resistance making these agents potentially quite amenable to combination therapy with non-overlapping toxicites.

OVERALL SYNOPSIS

We would like to fully acknowledge the limitations of this analysis. There is a paucity of prospective multi-institutional data. We have been careful to distinguish prospective from retrospective but have relied on retrospective data for much of this discussion. Much of the data cited herein are available in abstract but not in peer-reviewed form. Abstracts may represent incomplete data sets and many abstracts are never published in the peer-review because of various deficiencies. Individuals treated with subsequent therapies typically have more advanced disease and may have a lower PS as well; these factors may be important in the lower response rates for subsequent therapies.

Despite the limitations, several conclusions appear appropriate. Abiraterone and enzalutamide pre-treatments have a profound effect on the activity of one another. The activity of abiraterone after enzalutamide is quite minimal compared to what might otherwise be expected. The activity of enzalutamide post-abiraterone is diminished but some patients may have responses as measured by PSA. The duration of that response appears more limited than expected, suggesting cross-resistance. We point out that data to date for enzalutamide and abiraterone sequencing are in the post-docetaxel setting and if docetaxel were not used that it is possible that there would be differences in the current data. Data to date however suggest that whichever of these agents is used first will markedly diminish the activity of the second. We note that both enzalutamide and abiraterone target the ligand in the androgen-axis. Neither has a direct action on ligand independent androgen receptor activity. We suspect that splice-variants of the androgen receptor (which lack a ligand binding domain) are linked to resistance patterns for both of these agents.[24,25]

Abiraterone may diminish the activity of subsequent docetaxel but the studies are small and retro-spective and cannot be considered definitive at this time. In some studies, but not others, abiraterone may also diminish the activity of cabazitaxel. Clearly more clinical data are needed with cabazitaxel in this setting. Little is known about the activity of docetaxel or cabazitaxel in the post-enzalutamide space. This is clearly an area of unmet need given the lack of activity with abiraterone.

Preclinical data recently published describes impaired efficacy of docetaxel, cabazitaxel and enzalutamide in an abiraterone-resistant prostate cancer cell line and also impaired efficacy of docetaxel,

cabazitaxel and abiraterone in an enzalutamide resistant prostate cancer cell line. All four substances inhibited androgen receptor nuclear translocation *in vitro* what could be a possible explanation for partial cross-resistance of these drugs.[26] A possible important common mechanism of resistance might be AR splice variants that express a DNA binding domain but no ligand-binding domain. These variants are capable of ligand-independent AR mediated transcription and cause a particular transcriptional response that is distinct from full-length AR.[27]

Abiraterone and enzalutamide are clearly active in the post-docetaxel setting but even here there is some diminished effectiveness that we have not focused on herein. Abiraterone appears to be active in the third line setting after both docetaxel and cabazitaxel pre-treatments. Little data are available for enzalutamide in the third line setting.

This review underscores the potential importance of the sequencing of new therapies in CRPC but also highlights the fact that there is much we do not know. To date we have little in the way of prospective trials to address sequencing (except in the post-docetaxel setting). Given that abiraterone and enzalutamide are now taking a more front line role in metastatic CRPC, it is clear that more data are needed in both the post-abiraterone and post-enzalutamide space. There is an urgent need for prospective sequencing trials with the newer drugs to find if there is an optimal sequence. It is also clearly necessary to find predictive factors, either clinical or molecular, to assist the clinician in making better treatment decisions in an individualized manner.

Though we have emphasized sequencing in this brief review, it is important to recognize that the studies we have highlighted have implications for combination therapy as well. Effective combinations depend on some degree of independent mechanistic action and agents that do not induce cross-resistance to one another are likely to be the most-effective in combination therapy as well.

AUTHOR CONTRIBUTIONS

Both authors contributed to the conception, writing and final review of the manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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