While data was released for a number of disease sites at ASCO 2018, there were significant Canadian content updates in prostate cancer that have the potential to affect treatment. What follows is a multi-specialist analysis of Canadian led abstracts presented at ASCO 2018. CARE™ Perspectives are provided by select CARE™ Urology, Radiation Oncology and Medical Oncology Faculty members.
**Abstract #5015:** Phase 2 randomized cross-over trial of abiraterone + prednisone (ABI+P) vs enzalutamide (ENZ) for patients (pts) with metastatic castration resistant prostate cancer (mCPRC): Results for 2nd-line therapy.

Daniel Khalaf et al.

**Results:**
202 pts (101/arm) were accrued with median follow-up 22.3 months (m). 65 pts from arm A and 71 from arm B crossed-over to 2nd-line treatment and 30 pts (15/arm) stopped treatment without cross-over. Baseline characteristics at time of 2nd-line therapy were balanced: median age 75 (range 50-93), PSA 14.5 (6.6-62.1), alkaline phosphatase > upper limit of normal (ULN) in 39% of pts and bone/liver metastasis (mets) in 89%/9%. ECOG PS was 0-1 in 89% vs 76% of pts for arm A vs arm B (p = 0.044) and LDH was > ULN in 25% vs 8% (p = 0.013). PSA50 for 2nd-line therapy for arm A vs arm B was 34% vs 4% (p<0.001) and median time to PSA progression on 2nd-line therapy (TTPP) was 2.7 m vs 1.3 m (HR 0.38, 95% CI 0.26-0.56). For the intention-to-treat population, TT2P was 13.6 vs 11.9 m (HR 0.38, 95% CI 0.26-0.56). The sequence of ABI+P followed by ENZ was associated with superior PSA50 and TTPP on 2nd-line therapy. AR alterations associated with ABI+P and ENZ resistance were detectable in ctDNA. Clinical trial information: NCT02125357

**Conclusions:** The sequence of ABI+P followed by ENZ was associated with superior PSA50 and TTPP on 2nd-line therapy. AR alterations associated with ABI+P and ENZ resistance were detectable in ctDNA. Clinical trial information: NCT02125357

**Background:** ABI+P and ENZ have similar efficacy for 1st-line treatment of mCRPC but cross-resistance confounds treatment with the alternate agent at progression. The optimal sequencing has not been prospectively investigated and predictive biomarkers are needed.

**Methods:** A multi-centre trial of ABI+P followed by ENZ at PSA progression (arm A) vs ENZ followed by ABI+P (arm B). Primary endpoints were PSA decline > 50% (PSA50) on 2nd-line therapy and time to 2nd PSA progression (TT2P) (from start of 1st-line). Deep-targeted sequencing of serial samples of circulating tumour DNA (ctDNA) was performed.

**Results:** 202 pts (101/ arm) were accrued with median follow-up 22.3 months (m). 65 pts from arm A and 71 from arm B crossed-over to 2nd-line treatment and 30 pts (15/arm) stopped treatment without cross-over. Baseline characteristics at time of 2nd-line therapy were balanced: median age 75 (range 50-93), PSA 14.5 (6.6-62.1), alkaline phosphatase > upper limit of normal (ULN) in 39% of pts and bone/liver metastasis (mets) in 89%/9%. ECOG PS was 0-1 in 89% vs 76% of pts for arm A vs arm B (p = 0.044) and LDH was > ULN in 25% vs 8% (p = 0.013). PSA50 for 2nd-line therapy for arm A vs arm B was 34% vs 4% (p<0.001) and median time to PSA progression on 2nd-line therapy (TTPP) was 2.7 m vs 1.3 m (HR 0.38, 95% CI 0.26-0.56). For the intention-to-treat population, TT2P was 13.6 vs 11.9 m (HR 0.38, 95% CI 0.26-0.56). Median overall survival (OS) was not reached vs 24.3 m (HR 0.82, 95% CI 0.53-1.27). On multivariable analysis, factors associated with 2nd-line TTPP were: bone mets (HR 2.22, 95% CI 1.08-4.54), liver mets (HR 3.18, 95% CI 1.21-8.41) and treatment arm A vs B (HR 0.27, 95% CI 0.17-0.40). At progression, AR gene copy number increased in 14% of evaluable pts (7/49) and AR L702H/T878A(S) mutations were present in 8% of pts. ctDNA fraction ≥2% at baseline was associated with worse TT2P (HR 2.04, 95% CI 1.43 - 2.90) and OS (HR 4.07, 95% CI 2.40-6.91).

**Conclusions:** The sequence of ABI+P followed by ENZ was associated with superior PSA50 and TT2P on 2nd-line therapy. AR alterations associated with ABI+P and ENZ resistance were detectable in ctDNA. Clinical trial information: NCT02125357

"AA+P FOLLOWED BY ENZALUTAMIDE MAY YIELD A LONGER OVERALL PERIOD OF DISEASE CONTROL THAN THE REVERSE SEQUENCE."
CARE™ FACULTY PERSPECTIVES:
ABSTRACT #5015

CARE™ MEDICAL ONCOLOGY AND UROLOGY FACULTY
DR. SEBASTIEN HOTTE (JURAVINSKI) AND DR. ANIL KAPOOR (MCMASTER UNIVERSITY)

At last year’s ASCO meeting, Dr. Chi and his colleagues from the BCCA presented the data on first line therapy with either abiraterone acetate + prednisone (AA+P) or enzalutamide. Results suggested that both agents are fairly similar with regards to time to progression (PSA and radiographic) but there are differences in response rates and toxicity that may guide decision of which agent to use first. Patients who are unlikely to receive two lines of AR-targeted therapy, are those with poor prognostic factors such as:

- Elevated LDH
- Elevated alkaline phosphatase
- Low hemoglobin
- Presence of liver metastases
- Poor performance status
- Short period between start of primary androgen deprivation therapy (ADT) and CRPC

For these patients with poor prognostic factors who are unlikely to receive 2 lines of AR therapy, sequencing is of lesser importance and the first line comparison suffices to make decisions. However, in patients more likely to receive both AA+P and enzalutamide during their course of disease, optimal sequencing becomes more important.

Dr. Khalaf and colleagues present the first prospective data to help clinicians with this decision and suggest that AA+P followed by enzalutamide may yield a longer overall period of disease control than the reverse sequence. Potentially important caveats to this study are its moderate sample size and the fact that all but 30 men crossed over from one treatment to the other, which may not be representative of real world sequencing experiences. Once again, the BCCA group has also highlighted the incredible information that can be obtained via circulating tumour DNA (ctDNA). They should be commended for conducting this pragmatic yet informative study that has been highly enriched by an exceptionally rich translational research component.

CARE™ RADIATION ONCOLOGY FACULTY
DR. BRITA DANIELSON (U OF A)

There has been uncertainty regarding the utility of switching from one AR-targeted therapy to another in the setting of progression after first-line therapy for mCRPC. The abstract by Khalaf et al provides important information that may guide our sequencing decisions when two AR-targeted therapies are to be used in sequence. However, treatment choices must be made in the context of provincial drug funding, as such, access to therapies and sequencing possibilities may vary from province to province. As well, chemotherapy still has an important role to play in mCRPC, and needs to be considered in those patients who are fit for treatment.
Abstract #5028: Subsequent treatment after abiraterone acetate + prednisone (AA + P) in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC): Detailed analyses from the phase 3 LATITUDE trial.

Kim Chi et al.

Background: Pts with NDx-HR mCNPC quickly progress to castration-resistant disease when using androgen deprivation therapy (ADT) alone. The LATITUDE study found significant improvement in OS and rPFS when AA + P was added to ADT. Pts receiving placebo (PBO) could cross over after unblinding at the first interim analysis. We present details on subsequent therapies pts received after unblinding at this second preplanned analysis.

Methods: NDx-HR mCNPC pts were randomized 1:1 to AA (1 g QD) + P (5 mg QD) + ADT or PBOs + ADT. Secondary end points, median time to subsequent prostate cancer (PC) therapy and chemotherapy (chemo), and a post hoc exploratory end point, time to life-prolonging therapy, were analyzed by stratified proportional hazards model.

Conclusions: Adding AA + P to ADT delays the need for subsequent PC therapy vs ADT for pts with NDx-HR mCNPC. Time to subsequent and life-prolonging therapies (Table) were 37% and 26% on AA + P, and 58% and 45% on PBOs, respectively. Compared with PBOs, AA + P delayed time to subsequent PC therapy (HR [95% CI] 0.428 [0.361-0.507]), life-extending PC therapy (HR [95% CI] 0.398 [0.326-0.486]), and chemo (HR [95% CI] 0.471 [0.378-0.586]). Median duration of first life-prolonging therapy was 3.7 mo for AA + P (n = 155) and 5.7 mo for PBOs (n = 268).

Results: 1199 pts were enrolled (ITT). At median follow-up of 41.4 mo, median treatment exposure was 25.8 vs 14.4 mo (AA + P vs PBOs, respectively), and treatment was ongoing for 34% and 12% of pts receiving AA + P and PBOs, respectively. 60 PBOs pts crossed over to AA + P, with a median AA + P exposure of 2 mo (57/60 still on AA + P). The most common reason for discontinuation was progressive disease (AA + P, 40%; PBOs, 64%). Pts receiving subsequent and life-prolonging therapies (Table) were 37% and 26% on AA + P, and 58% and 45% on PBOs, respectively. Compared with PBOs, AA + P delayed time to subsequent PC therapy (HR [95% CI] 0.428 [0.361-0.507]), life-extending PC therapy (HR [95% CI] 0.398 [0.326-0.486]), and chemo (HR [95% CI] 0.471 [0.378-0.586]). Median duration of first life-prolonging therapy was 3.7 mo for AA + P (n = 155) and 5.7 mo for PBOs (n = 268).

Life-prolonging therapy

<table>
<thead>
<tr>
<th>Any, n (%)</th>
<th>AA + P (n = 597)</th>
<th>PBOs (n = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>127 (21)</td>
<td>207 (34)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>47 (8)</td>
<td>89 (15)</td>
</tr>
<tr>
<td>Radium-223</td>
<td>23 (4)</td>
<td>39 (6)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>17 (3)</td>
<td>42 (7)</td>
</tr>
<tr>
<td>AA + P</td>
<td>12 (2)</td>
<td>76 (13)</td>
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</tbody>
</table>
CARE™ MEDICAL ONCOLOGY FACULTY
DR. SEBASTIEN HOTTE (JURAVINSKI)

The optimal treatment of men with newly diagnosed metastatic castrate naïve prostate cancer (mCNPC) with evidence of high burden of disease has drastically evolved over the last five years. First, Dr. Christopher Sweeney and colleagues showed with CHAARTED that men with this disease could live on average close to two years longer if they received six cycles of docetaxel along with starting ADT. This was corroborated by the STAMPEDE investigators and docetaxel rapidly became the accepted standard of care. More recently, the LATITUDE investigators demonstrated similar survival benefits with the addition of abiraterone acetate and prednisone (AA+P). 5mg daily. For these patients, little data existed as to the choice of next therapy. This year, Dr. Kim Chi presented important data on subsequent therapy following progression with AA+P. Interestingly, only 45% of patients in the placebo group and 26% of patients on AA+P received subsequent life-prolonging therapy, which in my mind highlights the importance of not treating patients for too long for them to be able to tolerate and benefit from potentially helpful treatments. Most patients went on to receive docetaxel. These two factors really stress the fact that these patients are complex and often have aggressive disease, which should be managed in a multidisciplinary care setting. Furthermore, if the medical oncologist is not already involved in the care of these patients, early and timely referral to a medical oncologist is imperative.

CARE™ UROLOGY FACULTY
DR. ANIL KAPOOR (MCMASTER UNIVERSITY)

The current treatment for newly diagnosed high-risk metastatic castration naïve prostate cancer (NDx-HR mCNPC) includes androgen deprivation therapy (ADT) with the addition of either docetaxel (DOCE) or AA+P. Chi et al. presented an abstract at ASCO 2018 examining subsequent treatment after AA+P in patients NDx-HR mCNPC from the phase 3 LATITUDE study. This analysis showed that AA+P delayed the need for subsequent therapy, and that subsequent therapy most often was docetaxel, followed by enzalutamide, radium-223 and cabazitaxel, respectively. For urologists, the important implications for those of us that choose to treat NDx-HR mCNPC with AA+P, is early referral to our medical oncology colleagues once patients have progressed for consideration of docetaxel and subsequent therapies.

CARE™ RADIATION ONCOLOGY FACULTY
DR. BRITA DANIELSON (U OF A)

As a radiation oncologist, I am often the first physician at the cancer centre to see patients with newly-diagnosed metastatic castrate naïve prostate cancer (mCNPC), as they are often referred for consideration of palliative radiation therapy for bone pain. In addition to palliative radiotherapy, the traditional role of radiation oncology has been the initiation and supervision of androgen deprivation therapy. With additional systemic therapies now approved for mCNPC, I feel that my patients are best served by a consult with medical oncology regarding their options for treatment (e.g. AA+P, docetaxel, or clinical trial). I would be comfortable following patients on AA+P in this setting, with the understanding that referral back to my medical oncology colleagues is an always an option.
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