GENITOURINARY FACULTY

CARE™ PERSPECTIVES
ASCO 2020
PROSTATE CANCER SECTION

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
MAY 29 - 31ST 2020

CARE Education
Community Academic Research Education
@weareCARE

www.CAREeducation.ca
info@careeducation.ca
CARE Education
www.facebook.com/weareCARE
The American Society of Clinical Oncology (ASCO) recently hosted the virtual annual meeting May 29th-31st, 2020. This CARE™ Update from ASCO focuses on trials presented in prostate cancer. Full abstract and session presentation content are available at: https://meetinglibrary.asco.org/browsemeetings/2020%20ASCO%20Virtual%20Scientific%20Program

In this chapter of the CARE™ Perspectives ASCO Conference Report:

01 - Prostate Cancer Oral Session Highlights
   - CONDOR
   - TheraP
   - Neoadjuvant apalutamide plus leuprolide in localized high-risk prostate cancer
   - HERO

02 - Other Important Trial Updates
   - Overall survival results:
     - ARAMIS
     - PROSPER
     - SPARTAN
   - Canadian spotlight: PC-BETS Trial
   - Request to participate in CARE™ COVID-19 needs assessment

Review and Canadian perspectives provided by CARE™ GU Steering Faculty members:

Dr. Brita Danielson  
Radiation Oncology  
University of Alberta (AB)  
CARE™ GU Faculty

Dr. Sandeep Sehdev  
Medical Oncology  
The Ottawa Hospital (ON)  
CARE™ GU Faculty

EDUCATION FRAMED FROM A CANADIAN PERSPECTIVE
**ASCO 2020 Abstract 5501.** Impact of PSMA-targeted imaging with 18F-DCFPyL-PET/CT on clinical management of patients (pts) with biochemically recurrent (BCR) prostate cancer (PCA): Results from a phase III, prospective, multicenter study (CONDOR).

Clinical trial information: NCT03739684.

Michael J. Morris et al.

**Trial Background/Summary:**
Current imaging modalities are inadequate for localizing and characterizing occult disease in men with BCR PCa, particularly in pts with low PSA (<2 ng/mL).

- 18F-DCFPyL (PyL) is a novel PET imaging agent that binds selectively with high affinity to PSMA, which is overexpressed in PCA.

The study achieved its primary endpoint: CLR (correct localization rate) of 84.8% to 87.0% among the three PyL-PET/CT readers; the LLCI (95% confidence interval) for CLR by all three reviewers was >77%.

Based on local radiology assessment, PSMA-avid lesion(s) were identified in 69.3% (142/208) of pts. 63.9% (131/205) had a change in intended management after PyL-PET/CT, of which 78.6% (103/131) were attributable to positive PyL finding(s) and 21.4% (28/131) to negative PyL scans.

**Study Conclusion:**
PSMA-targeted PyL-PET/CT detected and localized occult disease in most men with BCR presenting with negative or equivocal conventional imaging. PyL-PET/CT led to changed management plans in the majority of pts, thus providing evidence that clinicians find PSMA PET imaging useful in men with recurrent or suspected metastatic PCa.

**CARE™ Faculty Perspective:**
There is increasing evidence to support the use of PSMA PET in Canada, which is vitally important to validate its use as standard of care imaging. The CONDOR study showed that the majority of patients with biochemical recurrence (BCR) who undergo PSMA PET will demonstrate activity on the scan, which has a significant impact on management. Targeted therapies (i.e. SBRT) and systemic therapies may be optimized based on PET-avid disease, as opposed to our previous blanket approach of utilizing ADT alone for BCR.

**ASCO 2020 Abstract 5500.** TheraP: A randomised phase II trial of 177Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results (ANZUP protocol 1603).

Clinical trial information: NCT03392428.

Michael S Hofman et al.

**Trial Background/Summary:**
LuPSMA is a radiolabeled small molecule that delivers therapeutic β–radiation to PSMA-expressing tumours. The PSA50-RR (PSA response rate defined by ≥50% reduction) was higher in those assigned LuPSMA than cabazitaxel (65/99 [66%; 95%CI 56-75] vs 37/101 [37%; 95%CI 27-46], P<0.001).

At a median follow-up of 11.3 months, LuPSMA significantly improved PSA-PFS (HR 0.63, 95%CI 0.45-0.88, P=0.007; 143 events with next pre-specified analysis planned after 170 events).

- OS data remains immature (57 deaths).
- Grade III-IV adverse events (AEs) occurred in 31/98 (32%) LuPSMA-treated men vs 42/85 (9%) in cabazitaxel-treated men.

**Study Conclusion:**
LuPSMA was more active (PSA50-RR) than cabazitaxel in this setting with fewer G3-4 AEs and PSA-PFS favouring LuPSMA.

**ASCO 2020 Abstract 5504.** Neoadjuvant apalutamide (APA) plus leuprolide (LHRHa) with or without abiraterone (AA) in localized high-risk prostate cancer (LHRPC).

Clinical trial information: NCT03279250.

Eleni Efstathiou et al.

**Trial Background/Summary:**
Localized high-risk prostate cancer (LHRPC) is associated with a substantial risk of disease recurrence and prostate-cancer specific mortality.

- Novel androgen signaling inhibitors (ASI) with medical castration may improve outcomes in LHRPC.

**Study Conclusion:**
Treatment was well tolerated with Grade 3 hypertension in 7 (2 APA + LHRHa).
Presurgical PSA was ≤0.1 in 62/63 (98%). Organ confined disease (≤ypT2N0) found in 13/32 (41%) APA+LHRHa vs. 12/31 (39%) APA+AA+LHRHa treated. 2 (3%) had pathologic complete remission (APA+AA+LHRHa), 6 (10%) minimal residual disease (5 on APA +LHRHa).

Despite uniformity in PSA response, there was heterogeneity in measures of tumour viability: TV (tumour volume) (0-11.5cc), TC (tumour cellularity %) (1-80%), TEV (tumour epithelial volume) (0-6.1cc).

≤ypT2N0 associates with diagnostic biopsy positivity for the prespecified molecular signature (p <0.0001), PTEN expression (p: 0.004), absence of cribriform/ intraductal spread (p 0.002) but not with Gleason Score.

Study Conclusion:
Neoadjuvant Apalutamide plus LHRHa is tolerable and results in tumour regression in a subset of LHRPC patients. Dual ASI treatment does not further improve outcomes. Biopsy positive for a prespecified molecular signature, associated with response. Study results emphasize the need to consider biologic heterogeneity and pursue validation of predictors of response to improve therapeutic outcomes in LHRPC.

ASCO 2020 Abstract 5602. HERO phase III trial: Results comparing relugolix, an oral GnRH receptor antagonist, versus leuprolide acetate for advanced prostate cancer.

Clinical trial information: NCT03085095.
Neal D. Shore et al.

Trial Background/Summary:
Relugolix is the first oral GnRH receptor antagonist.

LHRH agonists are the mainstay for medical castration in advanced prostate cancer; however, they cause an initial testosterone (T) surge with a delayed onset of castration and require depot injection.

A total of 96.7% (95% CI: 94.9%, 97.9%) of men on relugolix achieved and maintained castration through 48 weeks compared to 88.8% on leuprolide.

The difference of 7.9% (95% CI: 4.1%, 11.8%) demonstrated non-inferiority (margin -10%) and superiority (P < 0.0001) of relugolix to leuprolide.

All key secondary efficacy endpoints tested demonstrated superiority over leuprolide (P < 0.0001) (In the testosterone recovery subset, median T levels were 270.76 ng/dL in the relugolix compared to 12.26 ng/dL in the leuprolide group 90 days after discontinuation of therapy.

In a prespecified analysis, the incidence of major adverse cardiovascular events (MACE) was lower in the relugolix group than in the leuprolide group (2.9% vs. 6.2%, respectively); otherwise the safety and tolerability profiles were generally similar.

Study Conclusion:
Relugolix achieved castration as early as Day 4 and demonstrated superiority over leuprolide in sustained T suppression through 48 weeks, faster T recovery after discontinuation and a 50% reduction in MACE. Relugolix has the potential to become a new standard for T suppression for patients with advanced prostate cancer.

CARE™ Faculty Perspective:
LHRH agonists have long been the backbone of management for high-risk, recurrent, and advanced prostate cancer. The HERO study has shown the safety and efficacy of a novel oral LHRH agonist, relugolix, which has the potential to dramatically change how we administer ADT. Avoiding subcutaneous or intramuscular injections, potentially decreasing cardiovascular effects and achieving durable testosterone suppression, relugolix may soon become the preferred option for ADT in Canada.
Overall Survival - SPARTAN, PROSPER, ARAMIS

The final survival results from three trials were presented during the poster discussion session titled: Genitourinary Cancer—Prostate, Testicular, and Penile.

The SPARTAN, PROSPER, and ARAMIS trials have been covered extensively by CARE™ Faculty since their initial findings reported improved metastasis-free survival with apalutamide, enzalutamide, and darolutamide respectively. Health Canada approval of these agents for high risk nmCRPC were based on these MFS findings, however, there was concern that delaying metastasis might not be clinically significant long-term and may not translate to an overall survival benefit.

The outcomes (or results) presented at ASCO provide valuable survival (and safety) data that supports the early use of these agents in the nmCRPC setting.

**ASCO 2020 Abstract 5516.** Final survival results from SPARTAN, a phase III study of apalutamide (APA) versus placebo (PBO) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC).

Clinical trial information: NCT01946204.

Eric Jay Small et al.

**Trial Background/Summary:**
With follow-up of 52.0 mo, 428 (of 427 required) OS events had occurred.

Median treatment duration: APA, 32.9 mo; PBO, 11.5 mo.
Median OS was significantly longer with APA + ADT vs PBO + ADT (73.9 vs 59.9 mo), (hazard ratio [HR], 0.784, Table).

- APA significantly lengthened TTCx (HR, 0.629).

Discontinuation rates (APA vs PBO) due to progressive disease were 42.7% vs 73.9%, and due to adverse events (AE) 15.2% vs 8.4%.

Safety was consistent with previous reports.

- 1 TEAE leading to death (myocardial infarction) was considered potentially APA related.

**Study Conclusion:**
In pts with nmCRPC, APA + ADT significantly improved OS compared with PBO + ADT, with median OS > 6 yr in the APA + ADT group and 14 mo improvement over PBO + ADT. Benefit from APA was observed despite a 19% crossover from PBO. The safety profile of APA was consistent with prior interim analyses.

**ASCO 2020 Abstract 5515.** Final overall survival (OS) from PROSPER: A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (nmCRPC).

Clinical trial information: NCT02003924.

Cora N. Sternberg et al.

**Trial Background/Summary:**
As of Oct 15, 2019 (median follow-up = 48 mo), there were 466 deaths (288 [30.9%] and 178 [38.0%] in the ENZA and PBO arms, respectively).

ENZA significantly prolonged OS compared with PBO (HR 0.73; 95% CI 0.61-0.89; P = .0011).

- Median OS was 67.0 mo (95% CI 64.0-not reached) in the ENZA arm and 56.3 mo (95% CI 54.4–63.0) in the PBO arm.

- Median duration of treatment was 33.9 mo vs 14.2 mo with ENZA vs PBO, respectively.

- Rate of discontinuation from any AE was 17% (6 per 100 patient-years) in the ENZA arm vs. 9% (6 per 100 patient-years) in the placebo arm.

- Grade ≥ 3 adverse events (AEs) were reported by 48% of men in the ENZA arm vs 27% in the PBO arm (16% vs 6% were drug related, respectively).

**Study Conclusion:**
ENZA treatment resulted in a statistically significant 27% reduced risk of death compared with PBO, demonstrating that initiation of ENZA + ADT before the onset of detectable metastasis improves OS in men with CRPC and rapidly rising PSA. This OS benefit persists despite crossover from the PBO arm to ENZA and higher rates of subsequent antineoplastic therapies in men from the PBO arm. Safety was consistent with previous clinical trials. This final OS analysis from PROSPER provides prospective validation of MFS as a potential surrogate endpoint for OS in nmCRPC and supports the continued use of ENZA + ADT as a standard of care in men with nmCRPC and rapidly rising PSA.
**ASCO 2020 Abstract 5514.** Overall survival (OS) results of phase III ARAMIS study of darolutamide (DARO) added to androgen deprivation therapy (ADT) for nonmetastatic castration-resistant prostate cancer (nmCRPC).

Clinical trial information: NCT02200614.

Karim Fizazi et al.

**Trial Background/Summary:**

DARO is a structurally distinct androgen receptor inhibitor with a favourable safety profile

Final analysis was conducted after 254 deaths were observed (15.5% of DARO and 19.1% of PBO patients).

DARO showed a statistically significant OS benefit (HR 0.69; 95% CI 0.53-0.88; P=0.003) corresponding to a 31% reduction in the risk of death compared with placebo.

- All other secondary endpoints were significantly prolonged by DARO, regardless of the effect of crossover and subsequent therapies on survival benefit.

Incidence of treatment-emergent adverse events (AEs) with ≥5% frequency were generally comparable between DARO and PBO.

Rate of discontinuation from any AE was 8.9% in the DARO arm, 8.7% in the PBO arm, and 4.7% in the PBO-DARO crossover arm.

**Study Conclusion:**

DARO showed a statistically significant OS benefit for men with nmCRPC. In addition, DARO delayed onset of cancer-related symptoms and subsequent chemotherapy, compared with PBO. With extended follow-up, safety and tolerability were favorable and consistent with the primary ARAMIS analysis (Fizazi et al, N Engl J Med 2019;380:1235-46).

**Table. Summary of SPARTAN, PROSPER, and ARAMIS OS Results**

<table>
<thead>
<tr>
<th>Final OS</th>
<th>SPARTAN (Apa + ADT vs. PBO + ADT)</th>
<th>PROSPER (Enza + ADT vs. PBO + ADT)</th>
<th>ARAMIS (Daro + ADT vs. PBO + ADT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (months)</td>
<td>73.9m vs. 59.9m (median f/u 52.0m)</td>
<td>67m vs. 56.3m (median f/u ~48m)</td>
<td>NR</td>
</tr>
<tr>
<td>HR</td>
<td>0.784</td>
<td>0.73 (061-0.89)</td>
<td>0.69 (0.53-0.88)</td>
</tr>
<tr>
<td>P Value</td>
<td>P=0.0161</td>
<td>P=0.0011</td>
<td>P=0.003</td>
</tr>
</tbody>
</table>

**Related abstract of Interest:**


Shan Jiang et al.

**Table. Safety outcomes of D vs. A or E**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall</td>
<td>-6.3*</td>
<td>0.6</td>
<td>-6.3*</td>
<td>0.4**</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-1.0</td>
<td>1.0</td>
<td>-4.9*</td>
<td>0.5</td>
</tr>
<tr>
<td>Mental-impairment</td>
<td>-2.6</td>
<td>0.4</td>
<td>-3.5*</td>
<td>0.3**</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-2.4</td>
<td>1.2</td>
<td>-3.9**</td>
<td>0.7</td>
</tr>
<tr>
<td>Rash</td>
<td>-16.0*</td>
<td>0.5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-4.4</td>
<td>0.9</td>
<td>-12.8*</td>
<td>0.6**</td>
</tr>
<tr>
<td>Severe Fatigue</td>
<td>-0.7</td>
<td>0.3</td>
<td>-2.2*</td>
<td>0.2</td>
</tr>
<tr>
<td>Fracture</td>
<td>-6.2*</td>
<td>0.4**</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

* All grades AEs with the exception of severe fatigue (grade 3+)
* Raw and multiplicity adjusted p-value <0.05
** Raw p-value <0.05 NR=not reported in PROSPER

**Study Conclusion:**

After adjusting for trial differences, D showed favorable safety profile in fall, dizziness, mental-impairment, hypertension, rash, fatigue, and fracture.

**CARE™ Faculty Perspective:**

These results confirm the idea that treatment of patients with high risk nmCRPC can optimize survival outcomes and supports MFS as a surrogate marker for OS in patients with advanced prostate cancer. This has the potential to impact clinical trial design and how drugs are approved for clinical use. We can also reflect on novel endpoints such as PFS2; will the demonstrated value of PFS2 translate into routine use as an endpoint in future clinical trials?

With these updated results showing similar survival advantages with all 3 agents, individual patient preferences and tolerability will inform choice of treatment. Although indirect comparisons can be useful in comparing these three trials, head-to-head trials are needed.
**Canadian Spotlight**

Prostate cancer biomarker enrichment and treatment selection (PC-BETS) study: A Canadian cancer trials group phase II umbrella trial for metastatic castration-resistant prostate cancer (mCRPC).

Clinical trial information: NCT03385655, NCT02905318.

Kim N. Chi, Som Mukherjee, Fred Saad, Eric Winquist, Michael Ong, Michael Paul Kolinsky, Adrian G. Sacher, Cristiano Ferrario, Muhammad Salim, Robyn Jane Macfarlane, Nayyer Iqbal, Sebastien J. Hotte, Matti Annala, Jelena Petrovic, Dongsheng Tu, Moira Katherine Rushton, Francisco Emilio Vera Badillo, Martin Smoragiewicz, Alexander William Wyatt

**Trial Background/Summary:**
Genomic characterization of mCRPC has identified commonly occurring alterations but also recurrently mutated genes at much lower frequencies.

250 pts were screened from two sequential trials over 29 months at 11 centers.

Commonly detected genomic alterations involved AR (49% gain, 24% mutation), TP53 (49%), PTEN/PI3K pathway (35%), DNA repair (23%: mismatch repair (5%), BRCA2 (8%), ATM (3%), CDK12 (5%), other (2%)) and CTNNB1/APC (14%).

**Study Conclusion:**
Prospective centralized screening of ctDNA to stratify mCRPC pts into a precision oncology trial is feasible. Activity was seen in 4 of 7 evaluable cohorts with darolutamide and adavosertib, meeting the threshold for expansion of these arms.

---

**CARE™ RESPONSE TO COVID-19:**
REQUEST TO PARTICIPATE

Canada’s health-care system is hard at work fighting COVID-19, but the 1 million Canadians living with prostate cancer face an extra challenge. The current pandemic is forcing clinicians to react rapidly and develop solutions to deliver healthcare.

In an effort to help understand clinician’s approach and needs Drs. Sandeep Sehdev and Brita Danielson, CARE™ GU Steering Faculty, have developed a short questionnaire with a focus on systemic and clinical impact of changes implemented due to COVID-19 both today and the near term.

Please access the assessment at: CAREeducation.ca/needs-assessments/

As a follow-up, participating CARE™ faculty are planning virtual meetings with colleagues from across the country to discuss the insights gained from this assessment. The aim of this collaboration is to share approaches for patient care and safety in Canadian prostate cancer practices in the absence of an effective vaccine for COVID-19.

Thank you in advance for your participation and stay tuned for more!
CARE™ (Community, Academic, Research, Education) Faculty is a Pan-Canadian group of leaders in their field who gather, discuss and address gaps in knowledge, to develop education initiatives that frame news from a Canadian perspective.

The vision of the CARE™ Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE™ Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

Learn more at CAREeducation.ca